Quantitative measurement of cerebral blood flow by ^{99m}Tc-HMPAO SPECT in acute ischaemic stroke: usefulness in determining therapeutic options

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Abstract

***Objective*—Early recanalisation by thrombolysis is a conclusive therapy for acute ischaemic stroke. But this therapy may increase the risk of intracerebral haemorrhage or severe brain oedema. The purpose was to evaluate usefulness of quantitative measurement of cerebral blood flow by single photon emission computed tomography (SPECT) in predicting the risk of haemorrhage or oedema, and determining the therapeutic options in acute hemispheric ischaemic stroke.**

***Methods*—The relation was studied retrospectively between initial regional cerebral blood flow (rCBF) quantitatively measured by technetium-99m-labelled hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) SPECT and final clinical and radiological outcome in 20 patients who presented hemispheric ischaemic stroke and were treated conservatively or received early recanalisation by local intra-arterial thrombolysis. The non-invasive Patlak plot method was used for quantitative measurement of rCBF by SPECT.**

***Results*—Regions where residual rCBF was preserved over 35 ml/100 g/min had a low possibility of infarction without recanalisation and regions where residual rCBF was preserved over 25 ml/100 g/min could be recovered by early recanalisation. However, regions where residual rCBF was severely decreased (< 20 ml/100 g/min) had a risk of intracerebral haemorrhage and severe oedema.**

***Conclusions*—A quantitative assessment of residual rCBF by ^{99m}Tc-HMPAO SPECT is useful in predicting the risk of haemorrhage or severe oedema in acute ischaemic stroke. Therapeutic options should be determined based on the results of rCBF measurement.**

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Keywords: acute ischaemic stroke; SPECT; regional cerebral blood flow

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In acute ischaemic stroke (within 12 hours after onset), technetium-99m labelled hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) single photon emission computed tomography (SPECT) is useful for predicting the outcome of patients.[1–4] Recently, intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA)[5–7] or more aggressive recanalisation using an endovascular technique[8–16] have been attempted in the treatment of acute hemispheric ischaemic stroke. Yet even if early recanalisation is achieved, some patients have cerebral infarction or symptomatic intracerebral haemorrhage.[9 11 15 17–20] The PROACT II (Prolyse in Acute Cerebral Thromboembolism II) randomised study showed that intra-arterial thrombolysis within 6 hours significantly improved the clinical outcome of acute ischaemic stroke caused by middle cerebral artery (MCA) occlusion. But symptomatic intracranial haemorrhage within 24 hours was five times more likely to occur in treated patients than in control patients.[21] Hence, it is important to identify patients who have increased risk of haemorrhage. The usefulness of SPECT in predicting haemorrhagic transformation by the evaluation of residual blood flow has been reported,[17 20] but the evaluation of cerebral perfusion by SPECT is usually based on qualitative assessment. Ueda *et al* showed semiquantitative criteria to predict haemorrhage from the analysis of two cerebral blood flow (CBF) parameters, the ratio of ischaemic regional activity to cerebellar activity and the asymmetry index in patients with complete recanalisation within 12 hours.[22] Recently, a simple non-invasive method for the quantitative evaluation of regional cerebral blood flow (rCBF) by SPECT has been developed.[23 24] In this study, we retrospectively studied the relation between initial rCBF quantitatively measured by ^{99m}Tc-HMPAO SPECT and the final radiological outcome in patients who showed hemispheric ischaemic stroke and were treated conservatively or received early recanalisation by local intra-arterial thrombolysis. From these results we considered the therapeutic options for acute ischaemic stroke based on quantitative measurement of rCBF by SPECT.

Subjects and methods

Twenty patients admitted to our hospital between December 1996 and November 1998 were studied retrospectively. When stroke patients are referred to our clinic, we usually perform CT initially. If haemorrhagic cerebrovascular disease is ruled out, we immediately perform ^{99m}Tc-HMPAO SPECT, and subsequent cerebral angiography in the case of broad hypoperfusion. In this study, we included patients if: (1) they showed hemiparesis and/or aphasia on neurological examination on

Table 1 Summary of clinical data for early consecutive 10 patients who were treated conservatively

Patient	Age/sex	Site of occlusion	Haemorrhagic transformation	Final clinical outcome	Final radiological findings
1	69/M	Rt ICA	−	SDis	Large basal ganglia infarct
2	81/F	Rt MCA	+	SDis	Large MCA infarct, mild haemorrhage
3	88/F	Rt ICA	−	D	Severe cerebral oedema
4	83/F	Rt MCA	−	SDis	Large MCA infarct
5	78/M	Lt ICA	−	SDis	Large basal ganglia infarct
6	63/M	Lt MCA	−	SDis	Posterior MCA infarct
7	77/F	Lt ICA	−	SDis	Medium MCA infarct
8	87/M	Lt MCA	−	SDis	Medium MCA infarct
9	70/M	Rt ICA	−	SDis	Large MCA infarct
10	82/M	Rt ICA	+	D	Severe cerebral oedema and haemorrhage

ICA=Internal carotid artery; MCA=middle cerebral artery; SDis=severely disabled; D=dead.

admission; (2) the time of occurrence was precisely known to us; (3) initial CT showed no apparent hypodensity areas or haemorrhage; (4) pretreatment ^{99m}Tc-HMPAO SPECT could be obtained within 6 hours after the onset; (5) occlusion of the internal carotid artery (ICA) or MCA was confirmed by cerebral angiography.

Clinical data of all patients are summarised in tables 1 and 2. The early 10 consecutive patients were treated conservatively after being diagnosed by CT, ^{99m}Tc-HMPAO SPECT, and cerebral angiography. They were managed by administration of the antiplatelet agent ozagrel (thromboxane synthase inhibitor) and dextran for the subsequent 14 days, after which ticlopidine was given. We performed angiography in four patients (1, 2, 5, and 6) afterwards and no spontaneous recanalisation was seen. By comparison, the later 10 consecutive patients underwent early recanalisation successfully by the endovascular technique immediately after diagnosis by CT, ^{99m}Tc-HMPAO SPECT, and cerebral angiography. They first received local intra-arterial thrombolysis with urokinase (120 000–720 000 IU) using a microcatheter, Fas Tracker (Target Therapeutics) and some patients received additional percutaneous transluminal angioplasty (PTA) using a Stealth balloon catheter (Target Therapeutics) for severe residual stenosis. The time interval between initial SPECT and recanalisation was within 2 hours in all patients. After recanalisation was achieved, all patients were managed by administration of heparin until the next day, ozagrel and dextran for 14 days after that, and ticlopidine thereafter. We performed angiography on the next day of recanalisation in most patients (except patient 12). No reocclusion was seen in the second angiography.

QUANTITATIVE MEASUREMENTS OF rCBF BY SPECT

The non-invasive method of Matsuda *et al* (Patlak plot method) was used for the quantitative measurement of regional CBF (rCBF) with ^{99m}Tc-HMPAO SPECT.[23 24] Briefly, intravenous radionuclide angiography was first performed by bolus injection of 740 MBq ^{99m}Tc-HMPAO from the right brachial vein, and afterward the usual brain perfusion SPECT image was obtained. The passage of the tracer from the aortic arch to the brain was monitored in a 64×64 format for 100 seconds at 1 second intervals using a rectangular large field gamma camera (Shimadzu SNC-500R). Regions of interest (ROIs) were drawn over the aortic arch and bilateral brain hemispheres and time-activity curves for these ROIs were processed. The brain activity curve was shifted to the left to match the peak times of both brain and aortic arch activity curves. The Patlak plot was established to obtain slope (k_u), then a hemispheric brain perfusion index (BPI) was determined as follows:

$$BPI=100\times k_u\times 10\ (ROI_{aorta}\ size)/(ROI_{brain}\ size)$$

The BPI was converted to the hemispheric mean CBF (mCBF) value measured by ^{133}Xe inhalation SPECT using Matsuda's regression equation. Regional CBF was calculated from mCBF using Lassen's correction algorithm. The unaffected cerebral hemisphere was used as a reference region in this process. As shown in figs 1 and 2, we retrospectively chose two SPECT axial cerebral slices which corresponded to those of CT images (level of anterior commissure and level of upper lateral ventricles). Then 20 ROIs (16 pixels, square shaped) were placed manually in grey matter areas of the two slices (18 ROIs in the cerebral cortex and two in the basal ganglia) and rCBF

Table 2 Summary of clinical data for the later consecutive 10 patients who received recanalisation

Patient	Age/sex	Site of occlusion	Time to recanalisation (h)	Haemorrhagic transformation	Final clinical outcome	Final radiological findings
11	74/F	Rt MCA	4	−	SD	Large basal ganglia infarct
12	71/M	Lt MCA	3	+	D	Massive haemorrhage and oedema
13	90/F	Lt MCA	5	−	SD	Temporal MCA infarct
14	75/F	Lt MCA	2	−	GR	No infarct
15	68/F	Rt ICA	3	−	GR	No infarct
16	50/F	Lt ICA	2	−	GR	No infarct
17	51/F	Lt ICA	6	−	SD	Large ACA and anterior MCA infarct
18	67/M	Rt ICA	5	−	GR	Small basal ganglia infarct
19	67/F	Lt MCA	4	−	SD	Large MCA infarct
20	74/M	Lt ICA	7	−	GR	No infarct

ICA=Internal carotid artery; MCA=middle cerebral artery; GR=good recovery; SD=severely disabled; D=dead.

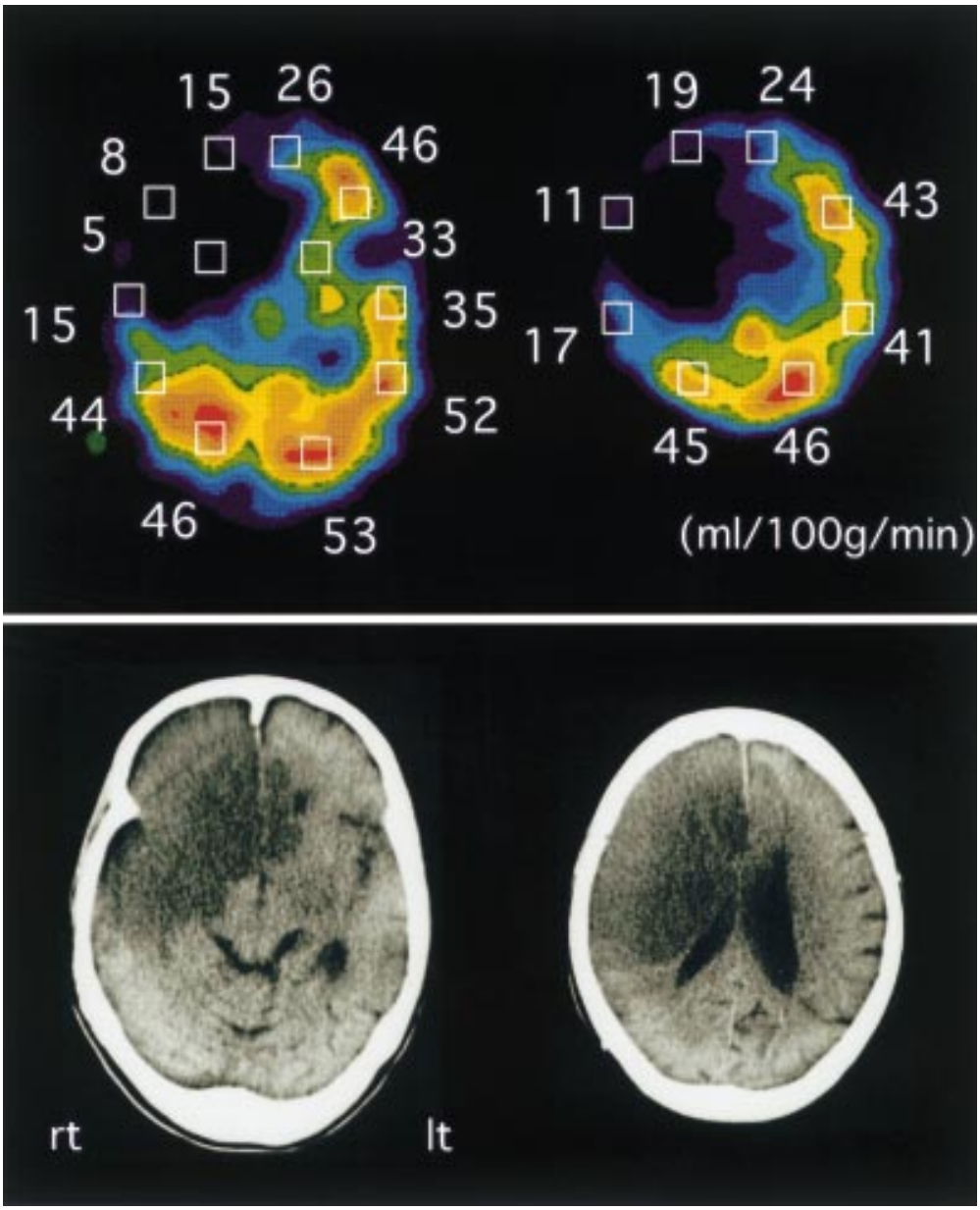

Figure 1 Patient 3. An 88 year old woman became suddenly unresponsive with left hemiplegia. An initial CT showed no abnormal findings but ^{99m}Tc-HMPAO SPECT showed hypoperfusion in the right internal carotid artery (ICA) territory. Regional CBF values in some regions were severely decreased to less than 10 ml/100 g/min (top). Angiography showed complete occlusion of the terminal of the right ICA but she was treated conservatively. Brain CT obtained 2 days after onset showed severe cerebral oedema in the right ICA territory (bottom). Finally she died of cerebral herniation 4 days after the onset.

was calculated in each ROI. A computer program linked with the gamma camera performed all of these operational steps.

ASSESSMENT OF CLINICAL AND RADIOLOGICAL OUTCOME

Follow up CT or MR images were obtained immediately after treatment, the next day, 1 and 2 weeks, and 1 month after treatment, and whenever otherwise clinically required. The final clinical and radiological outcome was assessed when the patient's symptoms stabilised, usually about 1 month after onset. The clinical outcome was assessed according to the Glasgow outcome scale (GCS).[25] The regions corresponding to ROIs placed on the pretreatment SPECT image in the affected hemisphere (10 regions in each patient) were judged as non-infarct or infarct (including haemorrhagic transformation) from the final CT or MR findings. The relation between the rCBF value and the radiological outcome was examined in each group.

Results

CONSERVATIVE TREATMENT

All (100%) patients treated conservatively had persistent neurological deficits and had poor clinical outcomes. They showed large cerebral infarction in the territory of the occluded artery. However, when the rCBF value was relatively well preserved by collateral circulation, the region escaped infarction even if the region was the territory of the occluded artery.

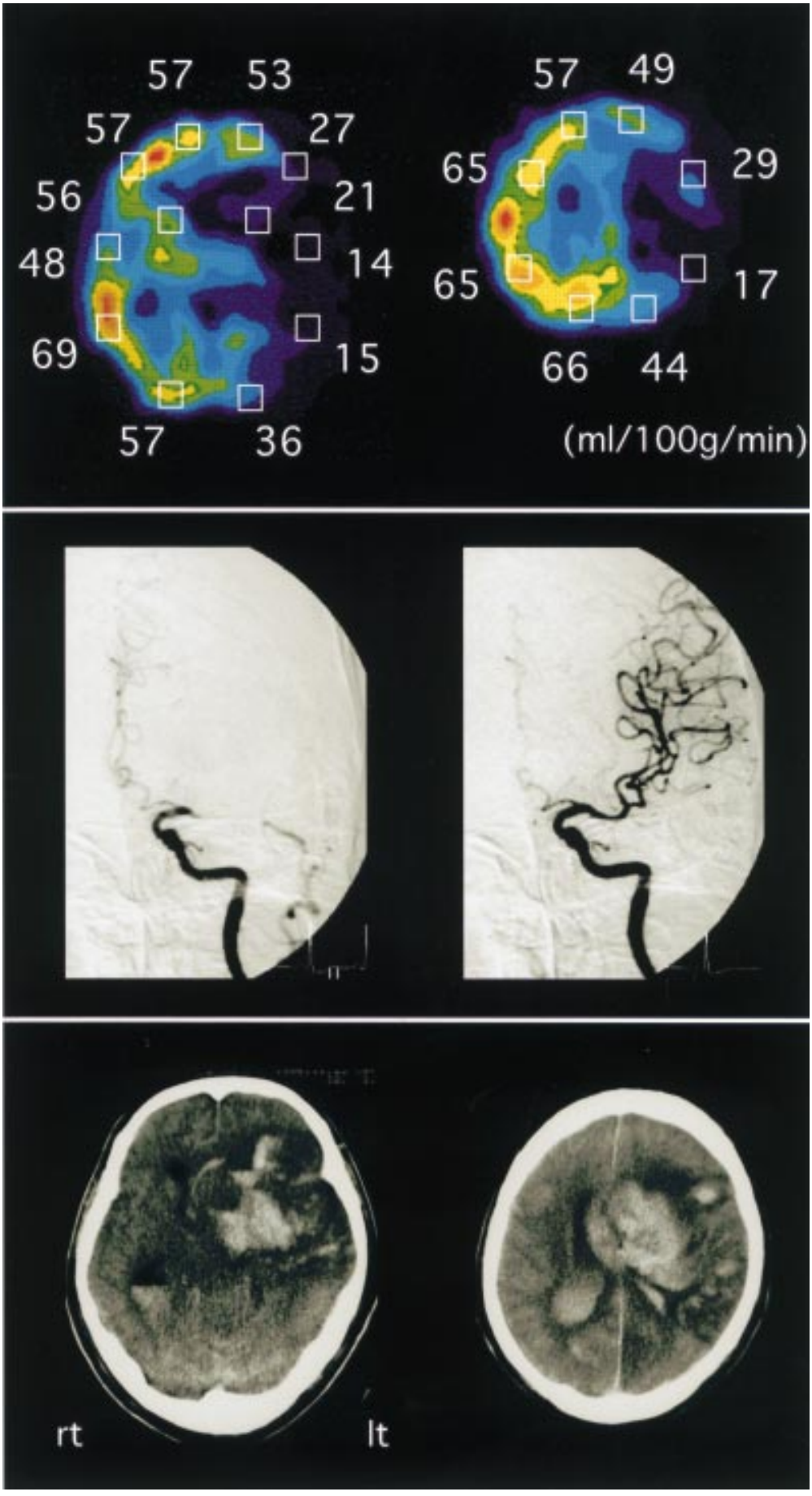

Figure 2 Patient 12. A 71 year old man suddenly developed aphasia and right hemiplegia. An initial CT showed no abnormal findings but ^{99m}Tc-HMPAO SPECT showed hypoperfusion in the left MCA territory. Regional CBF values in some regions were further decreased to less than 20 ml/100 g/min (top). Angiography showed complete occlusion of the left MCA at its origin (middle left). A local injection of 720 000 U urokinase successfully achieved recanalisation 3 hours after the onset (middle right). But his symptoms did not improve and his consciousness level suddenly deteriorated 12 hours after recanalisation. CT showed a massive intracerebral haemorrhage (bottom). He subsequently died of cerebral herniation.

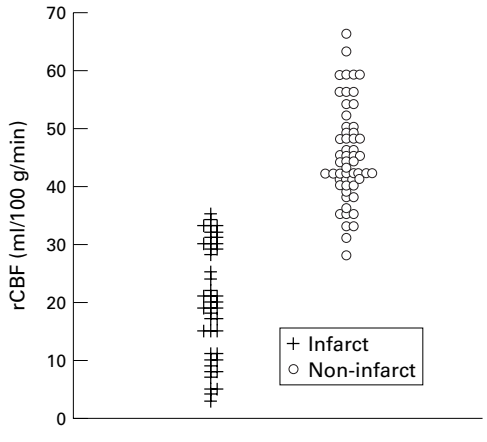

Figure 3 Relation between initial rCBF value and the radiological outcome of ROIs in the affected region in 10 patients who were treated conservatively. Initial rCBF threshold for infarction seemed to be between 30 and 35 ml/100 g/min.

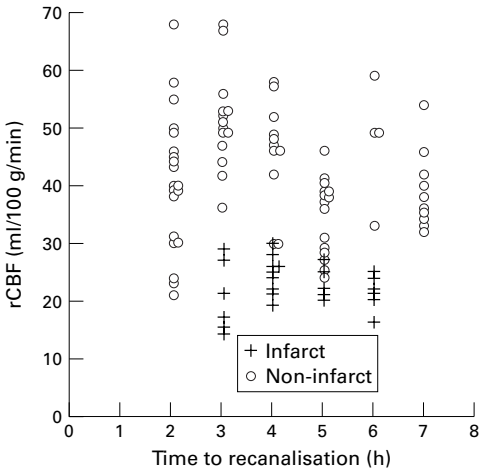

Figure 4 Relations between initial rCBF value and time to recanalisation, and the radiological outcome of ROIs in the affected region in 10 patients who received successful early recanalisation. The initial rCBF threshold for infarction seemed to be about 25–30 ml/100 g/min, when recanalisation was achieved 3–7 hours after onset.

The relations between the rCBF value and the radiological outcome of ROIs in the affected hemisphere are shown in fig 3. From these results, the initial rCBF threshold for infarction seemed to be between 30 and 35 ml/100 g/min when patients are treated conservatively. Therefore, regions where residual rCBF was preserved at over 35 ml/100 g/min had a low possibility of infarction without recanalisation.

One patient with right MCA occlusion (patient 2) showed late onset intracerebral haemorrhage in regions where initial rCBF values were particularly lowered to 11 or 17 ml/100 g/min, although the haemorrhage was not serious. Furthermore, two patients (3 and 10) died of cerebral herniation with acute severe cerebral oedema with or without intracerebral haemorrhage a few days after the onset. Their initial rCBF values were severely decreased to less than 10 ml/100 g/min (fig 1). Therefore, in conservative treatment, late onset intracerebral haemorrhage may occur in regions where initial rCBF decreases severely (<20 ml/100 g/min), and lethal acute cerebral oedema may occur in patients whose initial rCBF decreases even more (<10 ml/100 g/min).

RECANALISATION TREATMENT

In our series, the time period from onset to recanalisation was 2–7 hours. Even patients whose onset took place in our hospital required 2 hours to recanalise. Among 10 patients who received recanalisation, five (50%) recovered from their neurological deficits completely, but the other five (50%) had poor clinical outcomes despite early recanalisation. Relations between the rCBF value and the time to recanalisation, and the radiological outcome of ROIs in the affected hemisphere are shown in fig 4. One patient with left ICA occlusion (patient 20) fully recovered with no infarcted area on MRI by recanalisation even 7 hours after onset. His initial rCBF values obtained 5 hours after onset were more than 30 ml/100 g/min in all regions. On the other hand, most patients who had poor outcomes showed broad infarction in the territory of the recanalised artery. One patient with left MCA occlusion (patient 12) died of massive intracerebral haemorrhage and oedema after successful early recanalisation (3 hours after onset). His initial rCBF values in some regions were lowered to less than 20 ml/100 g/min (fig 2). It seems that the use of urokinase and anticoagulation therapy by heparin might seriously aggravate haemorrhage.

From these results, the initial residual rCBF value seemed to be a more important factor than the time to recanalisation in determining the radiological outcome. When recanalisation was achieved 3–7 hours after onset, the rCBF threshold for infarction seemed to be about 25 -30 ml/100 g/min. However, a patient whose residual rCBF was severely decreased had lethal intracranial bleeding despite early recanalisation.

Discussion

In cerebral ischaemia, it is inevitable that affected tissue develops infarction without early recovery of cerebral blood flow. Recently, intravenous thrombolysis with rtPA or endovascular recanalisation has been attempted as an accepted therapy for acute hemispheric ischaemic stroke, but the problems of symptomatic intracerebral haemorrhage have been mentioned.[5–16] When thrombolytic therapy is considered, it is important to identify patients who have increased risk of haemorrhagic transformation.

The usefulness of SPECT has been studied for this purpose because the risk of haemorrhage and severe brain oedema is generally correlated with the severity of the perfusion deficit.[2] Alexandrov *et al* showed that simple visual analysis of ^{99m}Tc-HMPAO SPECT within 24 hours after stroke onset could predict the risk of haemorrhagic transformation occurring spontaneously or during anticoagulant therapy.[26 27] Ueda *et al* retrospectively studied the relation between pretreatment ^{99m}Tc-HMPAO SPECT and the risk of haemorrhagic transformation in patients with complete recanalisation within 12 hours.[22] They showed

semiquantitative criteria to predict haemorrhage from the analysis of two CBF indices, the ratio of ischaemic regional activity to cerebellar activity, and the asymmetry index. But with the use of these visual and semiquantitative analyses, judgment is vague especially in patients who show diffuse hypoperfusion due to aging or in patients who have previous contralateral or cerebellar lesions. Hence, quantitative measurement of rCBF is needed to evaluate cerebral perfusion appropriately.

Positron emission tomography is probably the most reliable method for quantitatively assessing human cerebral perfusion, but it is not usually available for emergency cases.[28 29] Xenon-enhanced CT[30–32] or SPECT seems to be the most suitable tool for quantitative assessment of cerebral perfusion in typical clinical cases. The Patlak plot using ^{99m}Tc-HMPAO SPECT is a non-invasive method of quantitative measurement of rCBF developed by Matsuda *et al*,[23 24] which can quantify rCBF with the mere addition of an intravenous radionuclide angiography lasting 100 seconds. Furthermore, emergency examination can be made available with a technetium generator. In fact, it takes about 10 minutes to prepare the tracer, 25 minutes to obtain the SPECT image, and 15 minutes to analyse the data by computer in our hospital. Thus, the degree and the extent of ischaemia in patients with acute stroke who show no abnormal CT findings can be evaluated within an hour after admission.

In this study, we showed that the regions where residual rCBF was preserved at over 25 ml/100 g/min could be recovered by early recanalisation (within 7 hours after onset). However, the regions where residual rCBF was severely decreased (usually less than 20 ml/100 g/min) had a risk of haemorrhagic transformation, and the use of thrombolytic or anticoagulation agents would accelerate haemorrhage seriously in such cases. Ueda *et al* determined that the CBF threshold of the ischaemic region for the development of haemorrhage was about 35% of cerebellar CBF when recanalisation was achieved within 5 hours.[22] Assuming that cerebellar CBF is about 60 ml/100 g/min, this threshold is consistent with our result. Moreover, we showed that the region where residual rCBF was preserved at over 35 ml/100 g/min had a low possibility of developing infarction. Ueda *et al* also showed that ischaemic tissue with 55% of cerebellar flow still might be salvageable, even when treatment is initiated 6 hours after onset.[22] Shimosegawa *et al* showed that the lesion to contralateral radioactivity ratios distinguishing infarction and survival of brain tissue was 0.6 in patients without thrombolytic therapy by ^{99m}Tc-HMPAO SPECT performed within 6 hours after onset.[4] In addition, Firlik *et al* showed that the mean CBF in the symptomatic vascular territories of patients whose deficit was resolved was about 35 ml/100 g/min using Xe-enhanced CT.[32] These results also seem to be in good agreement with our own.

In regard to recanalisation treatment, our study was limited to patients who received local intra-arterial thrombolysis, and we required 2–7 hours to achieve recanalisation with these patients. This endovascular treatment is a better method of recanalisation, but requires more time in comparison with intravenous thrombolysis with rtPA. In our cases, one patient (14) who received recanalisation 2 hours after onset recovered despite lower residual rCBF (<25 ml/100 g/min). Therefore, if successful recanalisation is achieved within 2 hours after onset, the threshold could be further decreased. However, the application of rtPA for acute ischaemic stroke is not approved in Japan at this time. If intravenous rtPA could achieve recanalisation much earlier, the therapeutic ischaemic threshold could be much lowered. Nevertheless, it is difficult to achieve recanalisation within 2 hours after onset.

According to a PET study of acute ischaemic stroke, Furlan *et al* estimated that CBF in the penumbra ranged from 7 to 17 ml/100 g/min.[28] This result was consistent with that of previous animal studies.[33 34] In addition, Heiss *et al* demonstrated that critically hypoperfusued tissue (<12 ml/100 g/min on PET) could be preserved by early thrombolytic therapy.[29] Compared with these PET studies, our viability threshold with early recanalisation (25 ml/100 g/min) and oligemia threshold (35 ml/100 g/min) by SPECT are evidently high. Various methodological problems seem to be related to this discrepancy. At first, lower spatial resolution of SPECT may be the reason for the higher ischaemic threshold. As another possibility, the pharmacokinetics of ^{99m}Tc-HMPAO may be a cause of the overestimation of CBF in the ischaemic area. SPECT exaggerates the CBF in such areas by including the plasma activity in the dilated vascular component.[35]

Although our results cannot be directly compared with those using PET, the purpose of this study is to propose practical therapeutic criteria for acute ischaemic stroke based on quantitative rCBF measurement by ^{99m}Tc-HMPAO SPECT. The present results suggest that for patients whose residual rCBF is between 25 and 35 ml/100 g/min, recanalisation therapy by intravenous thrombolysis with rtPA or local intra-arterial thrombolysis should be considered. This decision should be made within 6 hours after the onset. On the other hand, recanalisation therapy is contraindicated for patients whose residual rCBF is less than 20 ml/100 g/min, due to the high risk of haemorrhage. Conservative treatment is recommended for these patients. However, the residual rCBF for recovery may be lowered if recanalisation is expected within 2 hours after onset. For patients whose residual rCBF decreased severely (<10 ml/100 g/min), other aggressive therapy, including hemicraniectomy or hypothermia treatment,[36 37] should be considered, to avoid cerebral herniation from haemorrhage or severe oedema. Finally, for patients whose residual rCBF is over 35 ml/100 g/min, urgent recanalisation therapy may not be needed, because the affected tissue does not develop infarction immediately. If needed, revascularisation in the chronic stage may be an option.

In actually applying these criteria, it will be difficult to determine the appropriate therapy in situations where some brain areas are salvageable but others are already irreversibly damaged and exposed to the risk of haemorrhage. Generally, recanalisation therapy is contraindicated for areas with risk of haemorrhage. But Heiss *et al* showed that morphological and clinical recovery is attributed to the volume of the severely hypoperfused region in thrombolytic therapy.[29] Therefore, if the area at risk for haemorrhage is extremely small compared with the salvageable area, recanalisation therapy may be an option. This will be the subject of further study.

This is a report concerning the relation between quantitative analysis of initial rCBF and the outcome of thrombolytic therapy for acute stroke. Although recanalisation therapy should not be delayed, an evaluation of residual blood flow is essential to avoid lethal intracerebral haemorrhage by thrombolytic therapy. For this purpose, ^{99m}Tc-HMPAO SPECT is the best clinical method at present because it permits quantitative measurement of rCBF easily in a short time and can be made available for emergency examinations. Further studies are needed to determine if quantitative SPECT can be used to identify patients who are likely to benefit from recanalisation therapy.

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