# Prediction of cerebral infarct sizes by cerebral blood flow SPECT performed in the early acute stage

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Cerebral infarct due to embolic stroke without recanalization was examined by cerebral blood flow (CBF) SPECT in the early acute stage, and the possibility of predicting the size it will reach in the later stages was evaluated. Twenty patients (67 ± 13 years) were examined by CBF SPECT with $^{99m}$Tc-ECD 4.5 ± 3.1 hours after the onset of cardiogenic cerebral embolism. The ratio of the antero-posterior length of the cerebral hemisphere to that of the severe ischemic region, which was defined as an area of clear-cut severe reduction in CBF as observed by SPECT, was calculated. One week after the onset, the cerebral infarct was measured in the same manner by CT, and the relationship between the two measurements was evaluated. The CBF in the region of severe ischemia and the surrounding region was determined by the Patlak plot method, and the affected/non-affected (A/NA) ratio was calculated. In severe ischemic regions the CBF ranged from 1.7 ml/100 g/min to 20 ml/100 g/min (mean, 11 ± 5 ml/100 g/min), whereas the A/NA ratio ranged from 4% to 45% (mean, 26 ± 11%). On the other hand, the CBF in the surrounding regions ranged from 20 ml/100 g/min to 52 ml/100 g/min (mean, 34 ± 8 ml/100 g/min) whereas the A/NA ratio ranged from 52% to 104% (mean, 77 ± 11%). The coefficient of correlation between the infarct size predicted by SPECT and that measured by CT was r = 0.986, and the correlation equation was Y = 1.047X − 2.969. CBF SPECT performed in the early acute stage can be used to predict the size of cerebral infarct.

**Key words:** SPECT, cerebral infarct, early acute stage, cerebral blood flow, $^{99m}$Tc-ECD

## INTRODUCTION

It is important to provide treatment for ischemic brain damage as soon as possible, and this has been recently emphasized in the case of intravenous thrombolytic therapy.[1–3] Therefore, determination of the size of the cerebral infarct and its diagnosis in the early acute stage have become all the more important in choosing a treatment and evaluating its effectiveness.

The methods used for imaging cerebral ischemia in the early acute stage are computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and angiography. It takes more than 12–24 hours to distinguish cerebral infarct regions as low density areas by CT.[4–6] On the other hand, images of infarcted regions can be obtained several hours after brain insult with diffusion MRI techniques.[7,8] PET and SPECT can theoretically image the regions and degrees of ischemia immediately after brain insult since they visualize and quantify CBF itself. For that reason, SPECT is one of the most useful diagnostic methods for assessing irreversible ischemic damage in the brain in the early acute stage.

It has been shown that regions showing a CBF under 15–20 ml/100 g/min as measured by PET[9] and SPECT[10] become infarcted areas. Measurement of CBF in the acute stage would therefore serve to predict the size of the cerebral infarct in the later stages.

In this study, cerebral ischemia was examined by CBF SPECT in the early acute stage, and the possibility of predicting the size of the cerebral infarct will reach in the later stages was evaluated.

## MATERIALS AND METHODS

The subjects were 20 patients (67 ± 13 years) who were examined within 6 hours after brain insult at the Outpatients' Critical Care Department, Ogaki Municipal Hospital, between August 1996 and December 1997 and underwent CBF SPECT in the early stage because cardiogenic cerebral embolism was suspected. Patients who showed rapid improvement in symptoms within 2 hours after the onset presumably due to recanalization, those who were likely to suffer a relapse within one week, and those who showed marked aggravation of symptoms, were excluded. Of the 20 patients evaluated, atrial fibrillation alone was observed in 12 patients, mitral stenosis in 1 patient, old myocardial infarction in 2 patients, and chronic heart failure in 5 patients. The arteries responsible for cerebral embolism were the middle cerebral artery in 18 patients, the anterior cerebral artery in 1 patient, and the posterior cerebral artery in 1 patient.

### Clinical assessment

Immediately after the anamnesis and neurological examination of the patient by a neurologist, cerebral CT was performed, to confirm the clinical diagnosis of cerebral infarct. From chest x-p, electrocardiographic, and echocardiographic findings, the patients were diagnosed as having cardiogenic cerebral embolism. Consciousness disorder was mild in 8 patients, moderate in 8 patients, and severe in 4 patients. All patients presented neurological symptoms such as hemiparesis and aphasia. CBF SPECT was immediately performed. It was started 1.0 hour at the shortest and 12 hours at the longest after the onset (mean, 4.5 ± 3.1 hours) of symptoms.

CT was performed about one week after the onset, and the presence of cerebral infarct reaching the cerebral cortex and hemorrhagic infarct was confirmed. Hemorrhagic infarct and recanalization were observed in all patients. After hospitalization, 400–600 ml/day glycerol and 10,000 unit/day heparin were administered as conservative therapy; thrombolytic therapy was not performed.

### SPECT

$^{99m}$Tc-ethyl cysteinate dimer (ECD) (740 MBq) was injected into the right cubital vein of the patients, who had their eyes covered with a mask and were resting in the supine position. Then dynamic images were obtained with a rotating gamma camera (601E, Toshiba). A low-energy versatile collimator was used for beam collection, and quantification was performed by the Patlak plot method reported by Matsuda et al.[11,12] Static images were obtained with a triple-headed SPECT system equipped with a high-resolution fan-beam collimator (GCA9300A/ HG, Toshiba). Data were collected in the continuous rotation mode (128 × 128 matrix) at 4 degrees for 20 min. The apparatuses used for data analysis were GMS55U and GMS5500U (Toshiba). The raw data were assessed by the triple energy window method for scatter correction, and prefiltered through a Butterworth filter; then 128 × 128 matrix images were reconstructed with a Ramp filter. Sorenson's attenuation correction was performed, and 6.9 mm thick transaxial images were constructed. Data parallel to the orbitomeatal line (OM line) of the patients were collected.

The mean CBF in the non-affected hemisphere was calculated by the Patlak plot method,[11,12] and the CBF in each region was determined by proportional allotment and expressed in rainbow colors with the maximum blood flow of 70 ml/100 g/min shown in red, the minimum blood flow of 0 ml/100 g/min shown in deep blue, and intermediate blood flow shown continuously in green and yellow (Figs. 1–3). CT images were obtained with a 10-mm slice thickness along the OM line by means of a CT (Quantex-RX, Yokogawa).

### Image analysis

Images were analyzed by two neurologists. At the time when no clear-cut abnormalities were detected by CT, regions showing a clear reduction in blood flow in the cerebral cortex, which were macroscopically seen as regions of deep to light blue on the SPECT images, were identified, and the borders between a severe ischemic region and its surroundings were marked (Fig. 1). The antero-posterior length of the severely ischemic region in the cerebral cortex and the cerebral hemisphere was manually measured, and the ratio was calculated (Fig. 1). Since it was difficult to measure the width of the ischemic region, it was not examined in this study. The slice of the CT images obtained at the time of hospitalization that best matched the SPECT image was chosen, and it was used in the follow-up CT examination.

The CBF in the non-affected hemisphere was measured by the Patlak plot method (Fig. 2), and the mean CBF in the regions of interest (ROIs) which were locally set was determined by proportional allotment. The ratio of the mean count in the ROIs in the affected area to that in their symmetric ROIs in the non-affected hemisphere (A/NA ratio) was calculated. Figure 2 shows the ROIs.
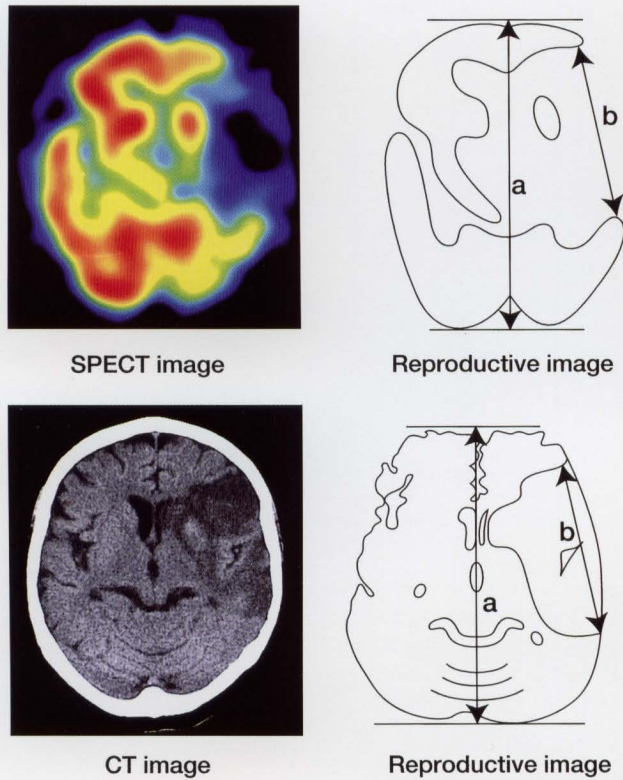
The antero-posterior length of the low density areas showing cerebral infarct was manually measured along the cerebral cortex on the CT images obtained about one week after the onset (Fig. 1), and its ratio to the antero-posterior length of the cerebral hemisphere was calculated. The sample slices were chosen from among the slices obtained of basal ganglia, lateral ventricle and white matter.

### Data analysis

The paired Student's t test was used to compare values of CBF and the A/NA ratios. SPECT and CT measurements were examined by regression analysis, and the correlation coefficient and equation were determined.

We will first describe a representative patient who presented with atrial fibrillation (a 67-year-old male). Right hemiplegia and aphasia suddenly occurred, and the patient was brought to our hospital 30 min after the onset of these symptoms. His level of consciousness was at E3V1M1 according to the Glasgow Coma Scale, and cerebral CT was immediately performed. The CT showed mild blurring of the left caudoputaminal area (Fig. 3a). Cerebral SPECT was performed 3 hours after the onset and revealed that the CBF in a large area of the left middle cerebral artery region was reduced (Fig. 3b). One week



SPECT image          Reproductive image

CT image          Reproductive image

Evaluation = b/a ×100 （%）

**Fig. 1**  Measurement of a severely ischemic region by SPECT (upper figure). The percent (%) ratio of the antero-posterior length of the cerebral cortex (b) in the region showing clear, marked reduction of blood flow to the antero-posterior length of the cerebral hemisphere (a). Measurement of cerebral infarction by CT (lower figure). The percent (%) ratio of the antero-posterior length of the cerebral cortex (b) in the low density areas of the CT image to antero-posterior length of the cerebral hemisphere (a).
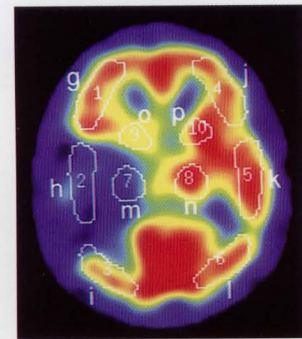


|  | CBF | A/NA ratio |
|---|---|---|
| Severe ischemic regions | · · · · h, m | $\frac{h}{k}$, $\frac{m}{n}$ |
| Surrounding regions | · · · · g, i, o | $\frac{g}{j}$, $\frac{i}{l}$, $\frac{o}{p}$ |

**Fig. 2**  Establishment of the regions of interest (ROIs) in the severely ischemic region and its surrounding regions by SPECT. The affected/non-affected (A/NA) ratio was determined as the ratio of the mean count in the ROIs in the lesion to that in their symmetric ROIs in the non-affected hemisphere. CBF: cerebral blood flow
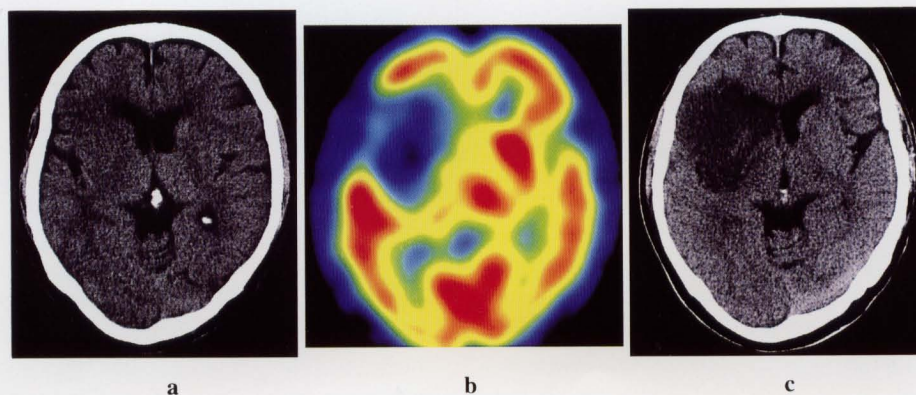


a          b          c

**Fig. 3**  A 67-year-old patient who had developed right hemiplegia accompanied by atrial fibrillation. Mild blurring of the left caudoputaminal area was observed by CT one hour after the onset (a). Three hours after the onset, clear reduction of the blood flow in the left middle cerebral artery areas was observed by SPECT (b), and cerebral infarction in the same areas was observed by CT (c).
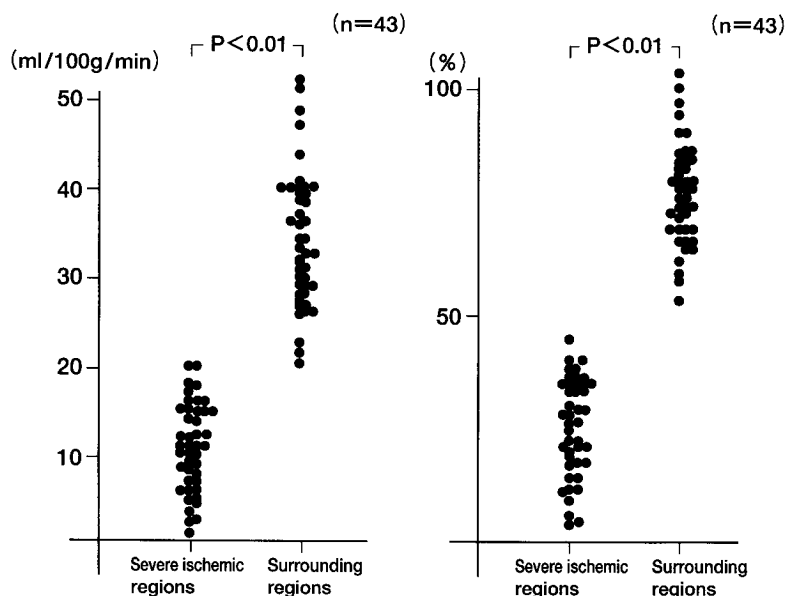
**Fig. 4** The CBF in the severely ischemic region and its surrounding region was determined by proportional allotment of the mean blood flow in the non-affected hemisphere (left figure). The ratio of the mean count in the ROIs in the severely ischemic region and its surrounding region to that in their ROIs in the non-affected hemisphere was calculated (right figure). Ratio = (mean count in the severely ischemic ROI/mean count in the non-affected ROI) × 100 (%). CBF: cerebral blood flow, ROI: region of interest
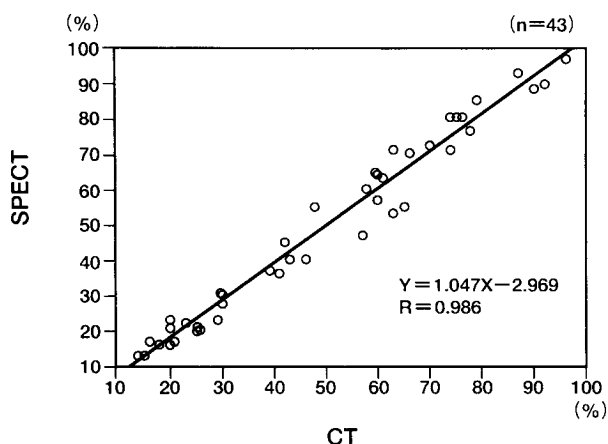


**Fig. 5** There was a close correlation between the size of the severely ischemic region and that of cerebral infarction (%) measured by SPECT and CT, respectively.

after the onset, hemorrhagic infarct was observed by CT in that area (Fig. 3c). The CBF in the severely ischemic region was 8.5 m*l*/100 g/min, that is, it was 17% of that in the non-affected hemisphere. The ratio of the antero-posterior length of the severely ischemic region and cortical infarct to that of the cerebral hemisphere was 30% both on the SPECT image and on the CT image, showing a good correlation between SPECT and CT images.

Two to three CT slices were chosen from each patient, and the mean individual CBF was calculated at selected ROIs (n = 43) within the infarct region showing low

density on the CT image and its surrounding region on each slice (Fig. 4, left). The CBF ranged from 1.7 m*l*/100 g/min to 20 m*l*/100 g/min in severely ischemic regions (mean, 11 ± 5 m*l*/100 g/min), whereas in the surrounding regions it ranged from 20 m*l*/100 g/min to 52 m*l*/100 g/min (34 ± 8 m*l*/100 g/min). There was a significant difference (p < 0.01) between CBF in severely ischemic regions and their surrounding region. As this figure indicates, cerebral infarction was subsequently detected on CT images of severely ischemic regions with a CBF of about 20 m*l*/100 g/min or less. On the other hand, no infarction developed in regions with a CBF of about 25 m*l*/100 g/min.

Figure 4 (right) shows the percentage of the mean count in the ROIs in the severely ischemic regions relative to that in their symmetric ROIs in the non-affected hemisphere. The percentage ranged from 4% to 45% (mean, 26 ± 11%) in severely ischemic regions on the SPECT images. On the other hand, the percentage in the surrounding regions ranged from 52% to 104% (mean, 77 ± 11%). There was a significant difference (p < 0.01) between the A/NA ratio of a severely ischemic region and its surrounding region, so that transition to infarction was observed on CT images in severely ischemic regions showing values about 50% than those of the corresponding regions in the non-affected hemisphere, but not in regions showing values about 60% or more than those of the corresponding regions.

Figure 5 shows the correlation between the percentage size of a severely ischemic region on the SPECT images

(Y) and cerebral infarction on the CT images (X). The size of the infarct ranged from a small one measuring 2.4 cm in the cerebral cortex to a large one (11.2 cm) encompassing the entire hemisphere on the CT image. The percentage size of the infarct and severely ischemic regions was 14 to 96% on the CT images and 13 to 96% on the SPECT images. The correlation coefficient was r = 0.986, and the correlation equation was Y = 1.047X − 2.969. The correlation was good in the case of small infarcts in the cerebral cortex as well as in large ones, but manual measurement of severely ischemic regions under 2 cm on SPECT images was difficult and bound to be inaccurate.

## DISCUSSION

In clinical practice, CBF SPECT is superior to CT, MRI and angiography for a qualitative evaluation of cerebral ischemia and assessment of its sizes. In the early stage, cerebral infarction could be detected by CT. For instance, changes such as a sign indicating middle cerebral artery hyperintensity (MCH) and blurring of the image of the lenticula can be detected by CT several hours after its onset,[13,14] but it takes more than 12–24 hours after its onset to clearly assess the extent of the infarction.[4–6] Therefore, CT is not useful for a final diagnosis of cerebral infarction in the very early stages.

On the other hand, assessment of cerebral infarction by MRI in relatively early stages has become possible.[15–17] It is necessary to wait for more than 8 hours after the occurrence of infarction before examining the infarcted region by conventional MRI;[18] and diffusion MRI, which has recently been drawing attention, can be performed at no less than 2 hours after its occurrence.[7] But it has been reported that images sufficiently clear for an accurate measurement of the size of cerebral infarction cannot be obtained by diffusion MRI. With this method clear images of infarcts cannot be obtained until several hours after the brain insult.

Imaging of cerebral ischemic regions by SPECT is theoretically possible immediately after brain insult. As shown in Fig. 3, cerebral ischemia could be clearly imaged by SPECT in a patient 3 hours after the brain insult, and the size of the severely ischemic region could also be measured. In this patient, the size of the severely ischemic region was similar to that of the cerebral infarction measured later by CT. Although the spacial resolution of SPECT is very inferior to that of MRI and CT, the degree and region of ischemia could be clearly established by SPECT. It has recently been reported that the specificity (95%) and sensitivity (93%) of SPECT regarding the detection of cortical infarction within 48 hours from the onset are not inferior to those of CT,[19] indicating that the inferiority of SPECT in space-resolution is not a disadvantage for the detection of cortical infarction.

Differences among neuroperfusion tracers in their accumulation in cerebral infarct lesions have been sug-

gested. For example, $^{99m}$Tc-HMPAO induces hyperperfusion in reperfused areas, and visualization of real infarct regions is difficult.[20] On the other hand, $^{99m}$Tc-ECD is insensitive to luxury perfusion,[21] and therefore, appears to be superior in predicting infarct areas. In addition, Shimosegawa et al.[20] reported overlapping of blood flow in infarct and non-infarct areas with $^{99m}$Tc-HMPAO, whereas only slight overlapping was detected with $^{99m}$Tc-ECD in this study (Fig. 4), also suggesting the superiority of $^{99m}$Tc-ECD.

We examined whether the size of a cerebral infarct measured by CT in the later stage could be predicted with SPECT in the early acute stage. To our knowledge, there have been no reports on this question. In humans, the CBF in infarct regions is reported to be under 15–20 m$l$/100 g/min and the A/NA ratio to be 48 ± 14%[20] and 39–43%.[22] In the present study, similar values were obtained.

On the other hand, the CBF value in the regions surrounding the infarction was reported to be 22–41 m$l$/100 g/min[10] or 33–36 m$l$/100 g/min,[22] and the A/NA ratio was reported to be 75 ± 10%,[20] which were similar to the values we obtained in the present study. If the CBF remains at 15–20 m$l$/100 g/min in the early acute stage, cerebral infarction will result.[23] In the present study, to test this assumption, the size of severely ischemic regions and that of cerebral infarct areas were determined by SPECT in the early acute stage and by CT one week later. As shown in Fig. 5, it was possible to accurately predict the size of the infarct. Of course, there were exceptions. Previous studies have shown that the establishment of cerebral infarction depends on time in regions with a CBF of 20 m$l$/100 g/min or less, and that infarction develops after a few hours in these regions.[24–26] These reports suggest that necrosis can be prevented by early reperfusion. For instance, we often encounter patients who experience spontaneous recanalization of the obstructed vessel in the early stage (about 1 hour) after the onset of symptoms and recover rapidly. In such cases, only a mild decrease in CBF will be observed by SPECT, and it will be difficult to predict the size of the cerebral infarct based only on images obtained by SPECT in the acute stage. Despite these limitations, compared with CT and MRI, SPECT performed in the early acute stage provides a good means to predict transition to cerebral infarction in the later stages in patients who undergo conventional treatments.

When the size of the areas in which ischemia will progress to infarction is reduced by treatment, such as thrombolytic therapy, this can be visually confirmed by comparing SPECT performed before treatment with CT performed at a later stage. The results of this study may contribute to the evaluation of the effects of treatment for cerebral infarction performed in the early stage.

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