Presence of Early Ischemic Changes on Computed Tomography Depends on Severity and the Duration of Hypoperfusion
A Single Photon Emission–Computed Tomographic Study

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Background and Purpose—To evaluate the clinical significance of early ischemic change (EIC) on computed tomography (CT), pertinent factors that contribute to the appearance of EIC.

Methods—Both CT and technetium-99m hexamethylpropylene amine oxime were performed on a total of 53 patients (34 men, 19 women, mean 69.7 years old) with acute embolic stroke within 6 hours of onset. Patients were excluded if they showed definite clinical recovery or were administered thrombolytic agents. EIC was evaluated using Alberta Stroke Program Early CT Score (ASPECTS). Residual cerebral blood flow (CBF) was determined on SPECT. Variables that were considered pertinent were patients’ age, gender, neurological severity, symptom duration, and residual CBF. Using significant pertinent factors for EIC, separate analyses of brain swelling without hypoattenuation and parenchymal hypoattenuation were performed.

Results—Patients with EIC (n = 37) showed severe neurological deficits, a longer duration and severe hypoperfusion. A positive correlation was observed between ASPECTS and residual CBF (P=0.002; Kruskal-Wallis test). A logistic-regression analysis revealed that both symptom duration (r=0.024, P=0.006) and severity of hypoperfusion (r=12.167, P=0.006) are independent factors related to EIC. Symptom duration and residual CBF were significantly different among patients with parenchymal hypoattenuation (n=32), brain swelling without hypoattenuation (n=5), and no EIC (P=0.018 and P=0.001, respectively; one-way ANOVA).

Conclusions—The presence of EIC is determined by the duration and the degree of hypoperfusion. This finding supports the hypothesis that tissue damage may be evaluated by a combination of onset time and the presence of EIC. (Stroke. 2005;36:000-000.)

Key Words: ischemia • ischemic stroke • thrombolytic therapy • tomography, x-ray computed • hypoattenuation, x-ray computed
thought to be more benign and reported to suggest ischemic penumbral or oligemic tissue. These EIC subtypes should be evaluated separately, and pertinent factors for the presence of each EIC may be different.

Therefore, we have conducted a retrospective study to clarify the clinical significance of EIC observed within 6 hours of onset. Pertinent factors for the presence of EIC were evaluated using cerebral blood flow (CBF) studies on single photon emission–computed tomography (SPECT) with technetium-99m hexamethylpropylene amine oxime ($^{99m}$Tc–HMPAO). We also evaluated the difference in pathological background between the 2 EIC subtypes.

 Patients and Methods

Patients

Patients presenting either to the Saiseikai Kumamoto Hospital or to the Kumamoto University Hospital during the period of January 1997 through December 2004 were recruited for this study. Neurological scores using the National Institute of Health Stroke Scale (NIHSS) were recorded on admission. Patients or their next of kin were asked to participate in the study immediately after the emergent CT brain scan in order to provide an option of thrombolytic therapy. After informed consent was obtained, the SPECT study was performed. During the study period, thrombolysis was attempted by an intraarterial approach if the patient showed a residual CBF of $35\%$ to $70\%$ of the contralateral hemisphere, were $80$ years old, and could be administered the thrombolytic agent within 6 hours of onset.

Inclusion criteria for the study were patients with supratentorial embolic stroke attributable to cardioembolism or large artery atherosclerosis, a documented time of onset, and both the baseline CT scan and SPECT scan performed within 6 hours of onset. Exclusion criteria were patients with reversible ischemic neurological deficit, definite clinical neurological improvement, or evidence of early reperfusion. In addition, patients were excluded if they had either a history or neuroimaging evidence of a previous contralateral stroke. Patients who were administered thrombolytic therapy were also excluded. These criteria were designed to exclude patients in whom the residual CBF was likely to have changed during the time period between the baseline CT, SPECT, and outcome CT scans.

A total of 1338 patients with acute ischemic stroke was admitted to the 2 hospitals. Of these, 122 patients fulfilled the inclusion criteria. Among them, 32 patients were excluded because of the rapid clinical recovery with (n=21) or without (n=11) the use of thrombolytic agents. Ipsilateral hyperperfusion on SPECT was documented in 9 patients. Another 28 patients had evidence of previous stroke on the contralateral hemisphere. As a result, 53 patients (34 men, 19 women) with an age range of 35 to 88 years old (mean 69.7 years) were enrolled into the study. The study was approved by the review board of Graduate School of Medical Sciences, Kumamoto University (Kumamoto, Japan).

CT Studies

Each patient underwent a noncontrast CT scan on arrival to the emergency department using either a Toshiba X-Vigor Real (Toshiba Medical Systems Corp) or General Electric Lightspeed QX/i scanner (GE Yokogawa Medical Systems Inc). The scanning parameters were nonhelical, $120$ kV, 200 mA, and 1 second for a slice. The average pixel size of the reconstructed image was $0.92 \times 0.92$ mm, and the slice thickness was 8 mm for both systems. All the baseline CT were retrospectively assessed for the presence and location of EIC using ASPECTS (Figure 1). ASPECTS was calculated from 2 standard axial CT slices, 1 at the level of the thalamus and basal ganglia and the other at the level of the sylvian fissure. ASPECTS scores range from 0 to 10, with higher scores indicating more extensive ischemic injury. The study was approved by the review board of Graduate School of Medical Sciences, Kumamoto University (Kumamoto, Japan).

![Baseline CT](image1.png)

**Baseline CT**

![SPECT](image2.png)

**SPECT**

![Outcome CT](image3.png)

**Outcome CT**

**Figure 1.** Example of image analysis (Patient 43). A indicates anterior circulation; P, posterior circulation; C, caudate nucleus; L, lentiform nucleus; IC, internal capsule, genu and posterior limb only; I, insular ribbon; M1, anterior MCA cortex anterior to the sylvian fissure; M2, MCA cortex lateral to the insular ribbon (opercular cortex); M3, posterior inferior MCA cortex (posterior temporal lobe); and M4, M5, and M6 refer respectively to anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3 and rostral to the basal ganglia. The baseline ASPECT score (Left; 4 hours after onset) was 2. Points were taken off for the insula, lentiform nucleus, M1, M2, M3, M4, M5, and M6 regions. An outcome CT scan (Right) showing an ASPECT of 3. Points were taken off for the insula, M1, M2, M3, M4, M5, and M6. Severe hypoperfusion of the right MCA territory is described on brain SPECT (Center). Residual blood flow was calculated on the M2 region using the region of interest method. The radioisotope uptake of the region of interest (L) where the final infarct area was documented on the outcome CT, is compared with the contralateral region of interest (C). The L/C ratio was used as the residual blood flow.
ganglia, and 1 just rostral to the ganglionic structures, with appropriately narrow window width and center level (60 and 30 Hounsfield units, respectively) by 2 stroke neurologists (T.H. and T.Y.) who had completed the European Co-operative Acute Stroke Study (ECASS) training program.\textsuperscript{20} They assessed with knowledge of the patients' symptoms but without knowledge of the SPECT findings or outcome CT. Disagreements between the observers were decided by consensus after reevaluation of baseline CT applying variable window width on the monitor.\textsuperscript{21}

The CT was repeated on day 1, at least 12 hours after the onset, and this was referred to as the outcome CT. Location and extent of final infarction were defined using ASPECTS. Presence of hemorrhagic transformation was also evaluated on outcome CT.

**SPECT Studies**

\textsuperscript{99m}Tc-HMPAO SPECT was performed among the candidates for thrombolysis or among patients needed to decide therapeutic option, using a double-headed Toshiba GCA7200A/PI (Toshiba Medical Systems Corp) or a triple-headed Shimadzu Prism 3000 scanner (Shimadzu Corp). \textsuperscript{99m}Tc-HMPAO (15–25 mCi; Cerebrotec-Nihon Mediphysics) was injected as soon as possible after the baseline CT scan had been performed. As this study was conducted during the hyperacute stage, therapeutic option was the top priority at any time. Therefore, once tracer was given, the SPECT scan was started within 2 hours of tracer injection, after determination of the treatment plan. SPECT acquisition parameters for the scanners were as follows: 90 frames and a matrix of 64x64 pixels (1 pixel = 4.3 mm) for the GCA7200A/PI system; 120 frames and a matrix of 128x128 pixels (1 pixel = 1.93 mm) for the Prism3000 system. Slice thickness was 4 pixels for the GCA7200A/PI system and 3 pixels for the Prism 3000 system. The full-width half-maximum (FWHM) resolution was 12.0 mm for the GCA7200A/PI system and 3.1 mm for the Prism3000 system. The data were reconstructed using standard Butterworth filtered back projection.

**Analysis of CT and SPECT**

Local CBF was calculated on 2 of the SPECT slices corresponding to each ASPECTS slice. Symmetrical rectangular regions of interest of 25.0 mm x 25.0 mm were placed at the area where final infarction was described on the outcome CT (L: lesion side) and the symmetrical mirror area (C: contralateral side). The radioactivity ratio (L/C ratio) was calculated and was used to represent the local CBF (Figure 1). The symptom duration was calculated from the documented time of symptom onset to the time of the baseline CT scan.

The subtypes of EIC (PH and BS) were evaluated separately. PH was defined as a region of abnormally low attenuation of brain structures relative to attenuation of other parts of the same structures or the contralateral hemisphere. On the other hand, BS was defined as any focal narrowing of the cerebrospinal-fluid space attributable to compression by adjacent brain structures, such as effacement of the cortical sulci or ventricular compression, without concomitant PH.

**Statistical Analysis**

Univariate analyses were performed for differences in patients' age, NIHSS score, symptom duration, and residual CBF between the EIC positive and negative patients using a two-tailed unpaired t test. The score of baseline ASPECT was compared with NIHSS, residual CBF, and symptom duration using Kruskal-Wallis test. \(\chi^2\) test was used to evaluate the difference of gender. Differences were considered significant at \(P<0.05\). Thereafter, a logistic regression analysis model was employed using the significant factors in the univariate analysis. The significant pertinent factors, which determine the presence of EIC, were clarified using this model.

Regarding the subtype of EIC, pertinent factors were compared for PH and BS using one-way ANOVA, and post hoc analyses consisted of the Scheffe F statistic for significant difference between pairs of 3 groups of patients exhibiting PH, BS, and negative EIC. Results were considered statistically significant at \(P<0.05\). All the statistical analyses were performed using Dr. SPSS II for Windows 11.01J software (SPSS Inc).

**Results**

**Patients’ Characteristics**

Baseline CT was performed at 20 to 340 minutes (mean 119.3 minutes), and SPECT was performed at 48 to 360 minutes (mean 203.1 minute) after the symptom onset. The time interval between the baseline CT and the tracer injection was 87.1±59.8 minutes for the positive group, and 75.9±44.0 minutes for the negative group (\(P=0.452\); unpaired t-test). The stroke subtype was cardioembolism in 47 patients, and large artery atherosclerosis in 6.

**CT Evaluation**

EIC was positive in 37 patients. Among them, BS was observed in 5 patients (13.5%). The details of the presence, subtype, and distribution of EIC, and locations where residual CBF was determined are summarized in Table 1. The median baseline and outcome ASPECT scores were 9 and 5, respectively. The interobserver k value for the baseline ASPECT score was 0.74.

**Pertinent Factors Contributed to Early Ischemic Change on CT**

Results of univariate analysis are summarized in Table 2. A significant negative correlation was observed between the baseline ASPECT score and NIHSS score (\(P=0.044\); Kruskal-Wallis test). The baseline ASPECT score also showed significant positive correlation with residual CBF (\(P=0.002\); Figure 2), but not with symptom duration (\(P=0.235\)). Figure 3 shows the distribution of EIC positive (both PH and BS) and negative patients in regard to the degree and the duration of hypoperfusion. Patients with low residual CBF or long symptom duration tended to have EIC. The two dotted lines approximate EIC threshold.

A logistic regression analysis model was developed using the 3 independent variables shown to be significant on the univariate analysis: NIHSS, symptom duration, and residual CBF. As a result, symptom duration and residual CBF were 2 independent factors that determined the presence of EIC (Table 2).

**EIC Subtype Analysis**

Symptom duration and residual CBF were compared among 3 groups of patients: patients with PH, BS, and negative EIC (Figure 4). Because results of one-way ANOVA for symptom duration and residual CBF were both significant (\(P=0.018\) and \(P=0.001\), respectively), Scheffe post hoc analyses were performed. Symptom duration was significantly longer in patients with PH (mean, 142.5±70.3 minutes) compared with negative patients (85.8±75.3 minutes; \(P=0.040\)). However, patients with BS (78±54.4 minutes) showed no statistically different with PH (\(P=0.176\)) or negative patients (\(P=0.977\)). On the other hand, residual CBF was significantly lower in patients with PH (0.4485±0.1774; \(P=0.002\)) and BS (0.4195±0.0797; \(P=0.040\)) compared with patients with negative EIC (0.6301±0.1241), although no significant difference was observed between BS and PH (\(P=0.929\)).
Discussion

We have conducted a retrospective study to evaluate the clinical significance of EIC evaluated by ASPECTS, and found that the time from onset to CT and residual CBF are 2 independent factors that contributed to the presence of EIC. Regarding the subtype of EIC, BS was observed within 3 hours and consisted of 13.5% of all EIC. Symptom duration and residual CBF were significantly different among patients.

Table 1. Summary of the Patients

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<th>No.</th>
<th>Age</th>
<th>Gender</th>
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<th>Infarct Location</th>
<th>Location and Type of Early Sign</th>
<th>ASPECTS, Baseline</th>
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</table>

**Note:**
- M, men; F, women; NIHSS, National Institute of Health stroke scale; Rt, right; Lt, left; ASPECTS, Alberta Stroke Program Early CT Score; C, caudate nucleus; L, lentiform nucleus; IC, internal capsule, genu and posterior limb only; I, insular ribbon; M1, anterior MCA cortex anterior to the insular ribbon (opercular cortex); M3, posterior inferior MCA cortex (posterior temporal lobe); and M4, M5, and M6 respectively to anterior, lateral, the sylvian fissure; M2, MCA cortex lateral to and posterior to MCA territories immediately superior to M1, M2, and M3 and rostral to the basal ganglia; A, anterior circulation; P, posterior circulation; N, negative early sign; PH, parenchymal hypoattenuation; BS, brain swelling without parenchymal hypoattenuation; CBF, cerebral blood flow; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; H/T, hemorrhagic transformation; +, positive; --, negative; CE, cardioembolism; LAA, large artery atherosclerosis; DSA, digital subtraction angiography; TCD, transcranial Doppler; MRA, magnetic resonance angiography.
with PH, BS, and no EIC. Thus, BS seems to associate with mild brain tissue damage compared with PH.

Although the clinical importance of EIC has been argued,\textsuperscript{14,15,22,23} only 1 previous positron emission tomographic study\textsuperscript{10} focused on residual CBF. In that study, the presence of EIC was correlated with severe ischemia and not related to symptom duration. On the other hand, the frequency of EIC in the ECASS II cohort\textsuperscript{5} was 58% for the first hour, 66% for the second, and 65% for the third hour. Moreover, a reevaluation of baseline CT scans obtained from the NINDS recombinant tissue plasminogen activator study\textsuperscript{14} showed that EIC was significantly associated with time from stroke onset to baseline CT scan. In this study, EIC was shown to indicate that tissue was subjected to severe hypoperfusion with considerable duration. If the precise onset time was documented, the state of ischemic process in the brain tissue may be estimated by evaluating the presence of EIC.

TABLE 1. Continued

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<tr>
<th>Symptom, Duration (min)</th>
<th>Time of Tracer, Injection (min)</th>
<th>Residual CBF</th>
<th>Location, CBF Measured</th>
<th>ASPECTS, at 24 Hours H/T</th>
<th>Stroke Subtype</th>
<th>Vascular Occlusion</th>
<th>Modality</th>
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Regarding the subtype of EIC, BS is suggested as an effect of compensatory vasodilation and is not closely associated with brain tissue damage.\textsuperscript{22,24} In this study, BS was found in patients with proximal arterial occlusion (1 patient with internal carotid artery occlusion, 2 each with horizontal portion and branch occlusion of middle cerebral artery) and might be caused by the opening up or widening of collateral circulation.\textsuperscript{18} On the other hand, PH indicates net uptake of tissue water caused by severe focal ischemia. In animal models, a 1% increase in tissue water content corresponded to a 1.8 decrease in Hounsfield unit.\textsuperscript{25} It takes 2 to 3 hours until the drop in x-ray attenuation becomes visible on CT scans after MCA occlusion. Therefore, we speculated that brain tissue swelling without hypoattenuation was observed within early hours of onset and then accompanied by concomitant PH. It is suggested that PH detected earlier than 2 hours after stroke onset means a more severe ischemic damage causing earlier brain edema.\textsuperscript{26}

Several problems with this study need to be addressed. First, one of the regions of interest corresponding to the lowest CBF within the final infarction was used to represent the patient’s residual CBF. We know that the distribution of

\begin{table}[ht]
\centering
\caption{Results of the Statistical Analysis}
\begin{tabular}{|l|c|c|c|}
\hline
Variables & Univariate Analysis & & Multivariate Analysis & \\
\hline
 & Positive Group & Negative Group & P & R & Odds 95% CI & P \\
\hline
Age & 71.5±9.5 & 65.4±14.1 & 0.1305$ & & & \\
Gender, men/women & 22/15 & 12/4 & 0.2834# & & & \\
NIHSS & 15.6±6.6 & 10.3±7.6 & 0.0236$ & & & \\
Symptom duration, min & 133.8±71.3 & 85.8±75.3 & 0.0395$ & & & \\
Residual CBF & 0.45±0.17 & 0.63±0.12 & 0.0001$ & & & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{$,}$, unpaired t test; \textsuperscript{#}, \chi^2 test.
the level of hypoperfusion differs gradually from the core of ischemic tissue to the periphery. The brain tissue showing EIC has been reported as the “tip of an iceberg” in an extended volume of critically hypoperfused brain tissue. Furthermore, patients with extended volume of EIC (ie, lower ASPECT score) corresponded with severe hypoperfusion (Figure 2). Therefore, we believe that it is reasonable to use the lowest local CBF to represent the patient’s residual CBF in order to evaluate the presence of EIC.

Second, this study assumes that the residual CBF is stable during the period when the ischemic process is completed. The absence of clinical improvement, no use of thrombolytic drugs, and no evidence of reperfusion were taken as circumstantial evidence to support this assumption. Although we carefully selected patients with relatively stable residual CBFs, the level of local CBF may have changed during the hyperacute stage. Thus, the retrieved result from this analysis was based on the crude assumption of unchanged levels of perfusion during the time period that EIC was established.

Another issue is the level of residual CBF that induced cerebral infarction. Although previous studies reported CBF threshold as L/C ratio of 0.6027 or lesion-to-cerebellar activity ratio of 0.35, some of our patients with residual CBF around 0.80 resulted in infarction when it continued. The main reason for this discrepancy is probably the difference in study populations. They included patients with various patterns of CBF (ie, patients with reperfusion therapy or hyperperfusion). On the other hand, we carefully selected the patients with stable CBF conditions. In a previous SPECT study based on the similar patient population, individual ischemic threshold value ranged as 0.53 to 0.77.

In summary, we found that EIC reflects the severity of ischemia (a product of the duration and level of hypoperfusion). PH is more closely associated with a severe ischemic damage compared with BS.

**Acknowledgements**

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**References**


**Figure 4.** Comparison of the pertinent factors related to early ischemic signs. Symptom duration and residual CBF are compared among patients with negative early sign (NEG; n = 16), BS (n = 5), and PH (n = 32). Patients with PH have significantly long symptom duration (P = 0.040; one-way ANOVA with Scheffe post hoc analysis) and severe hypoperfusion (P = 0.002) compared with early sign negative patients. Patients with BS showed significant hypoperfusion compared with early sign negative patients (P = 0.040).


Presence of Early Ischemic Changes on Computed Tomography Depends on Severity and the Duration of Hypoperfusion. A Single Photon Emission-Computed Tomographic Study

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