Discrepant $^{99m}$Tc-ECD images of CBF in patients with subacute cerebral infarction: A comparison of CBF, CMRO$_2$ and $^{99m}$Tc-HMPAO imaging

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Three patients with subacute ischemic cerebral infarction examined by SPECT with $^{99m}$Tc-ECD and PET within the same day showed signs of luxury perfusion in the subacute phase, which is between 9 to 20 days after the onset. A $^{99m}$Tc-HMPAO SPECT study was also performed within 2 days of the ECD-SPECT study.

ECD-SPECT images of three patients displayed a focal decreased uptake in the infarcted lesions, while in infarcted foci, there was almost equivalent or increased CBF compared to normal and unaffected areas, decreased CMRO$_2$, and high HMPAO uptake. The ECD-SPECT results were similar to those of CMRO$_2$ rather than CBF, though the HMPAO-SPECT image was similar to that of CBF. In one patient, HMPAO images revealed hyperfixation of the tracer. In the chronic phase and in the acute phase before 5 days after the onset, there were no discrepancies among the ECD-SPECT, CBF, HMPAO-SPECT, and CMRO$_2$ images.

These observations indicated that $^{99m}$Tc-ECD is a good indicator of damaged brain tissues in subacute ischemic infarction. They also suggested that $^{99m}$Tc-ECD is a potential agent with which to evaluate cerebral tissue viability in some pathological states of cerebrovascular disease. The characteristics may be suitable for confirming the effects of thrombolytic therapy in acute ischemia, because these conditions often show signs of luxury perfusion when the therapy is successful.

Key words: $^{99m}$Tc-ECD, $^{99m}$Tc-HMPAO, cerebral infarction, luxury perfusion, CBF, CMRO$_2$

INTRODUCTION

TECHNETIUM-99m labeled Ethyl Cysteinate Dimer ($^{99m}$Tc-Tc-bicisate, $^{99m}$Tc-ECD) has been developed as a brain perfusion tracer for single photon emission computed tomography (SPECT), with which to assess various neurological diseases. Early studies have shown a good correlation between the distribution of $^{99m}$Tc-ECD and that of cerebral blood flow tracers such as $^{99m}$Tc-HMPAO (hexamethylpropyleneamine oxime), $^{123}$I-IMP (N-isopropyl-$^{123}$I-iodoamphetamine), $^{133}$Xe, and $^{15}$O-CO$_2$ in normal volunteers and in patients with chronic stroke. However, images of subacute cerebral infarctions obtained by means of $^{99m}$Tc-ECD SPECT and CBF by positron emission tomography (PET) in our preliminary study, appeared discrepant.

In this paper, we describe three patients with subacute stroke who showed uncoupling of blood flow and oxygen metabolism—so-called "luxury perfusion"—by comparing three imaging methods with SPECT and $^{99m}$Tc-ECD.

MATERIALS AND METHODS

Patients

Three patients with subacute cerebral infarctions were investigated by means of PET with $^{15}$O-CO$_2$, $^{15}$O-O$_2$ and $^{15}$O-CO, as well as by SPECT with $^{99m}$Tc-ECD and $^{99m}$Tc-HMPAO, 9–20 days after onset. Three stroke patients were examined during the acute phase, and one was in the acute and chronic phase. Comparing these three patients, PET and SPECT studies of nine patients with chronic infarctions were performed. The clinical features of the patients are summarized in Table 1.
Table 1  Patient list

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>Time from onset</th>
<th>Procedures</th>
<th>Clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) discrepancies between ECD-SPECT and CBF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>67/M</td>
<td>9d</td>
<td>PET + HMPAO (11d)</td>
<td>cerebral infarction in the left MCA territory</td>
</tr>
<tr>
<td>2</td>
<td>63/M</td>
<td>11d</td>
<td>PET + HMPAO (13d)</td>
<td>cerebral infarction in the left MCA territory</td>
</tr>
<tr>
<td>3</td>
<td>59/M</td>
<td>20d</td>
<td>PET</td>
<td>cerebral infarction in the left parietal lobe</td>
</tr>
<tr>
<td>(2) no discrepancies between ECD-SPECT and CBF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>70/M</td>
<td>2d</td>
<td>PET + HMPAO (1d)</td>
<td>cerebral infarction in the right MCA territory</td>
</tr>
<tr>
<td>5</td>
<td>78/F</td>
<td>2d</td>
<td>PET + HMPAO (42d)</td>
<td>cerebral infarction in the right MCA territory</td>
</tr>
<tr>
<td>6</td>
<td>77/M</td>
<td>5d</td>
<td>HMPAO (5d)</td>
<td>cerebral infarction in the right MCA territory</td>
</tr>
<tr>
<td>7</td>
<td>54/M</td>
<td>25d</td>
<td>PET</td>
<td>cerebral infarction in the right MCA territory</td>
</tr>
<tr>
<td>8</td>
<td>68/F</td>
<td>79d</td>
<td>PET</td>
<td>cerebral infarction in the right MCA territory</td>
</tr>
<tr>
<td>9</td>
<td>65/M</td>
<td>3mo</td>
<td>PET + HMPAO (3mo)</td>
<td>cerebral infarction in the right MCA territory</td>
</tr>
<tr>
<td>10</td>
<td>67/M</td>
<td>1yr</td>
<td>PET</td>
<td>multiple small cerebral infarctions</td>
</tr>
<tr>
<td>11</td>
<td>51/M</td>
<td>1yr</td>
<td>PET</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>66/M</td>
<td>3yrs</td>
<td>HMPAO (3yrs)</td>
<td>cerebral infarction due to basilar artery occlusion</td>
</tr>
</tbody>
</table>

d: days, mo: months, yr: year, MCA: middle cerebral artery.

Methods
X-ray computed tomography (CT), ECD-SPECT and PET measurements were performed within the same day. First, we performed CT. Next, cerebral blood flow (CBF) and oxygen metabolism (CMRO₂) were measured with PET by means of the O-15 steady state method with a HEADTOME IV. Immediately after the PET study, about 555–740 MBq (15–20 mCi) of ⁹⁹ᵐTc-ECD was injected intravenously. SPECT data were collected from 5 to 32 minutes thereafter, with a HEADTOME II, which is a ring type multidetector SPECT system that can examine 3 slices simultaneously. We obtained 9 slices in this study. HMPAO-SPECT was also performed on two patients within 2 days of the ECD-SPECT and PET studies. The HMPAO-SPECT measurements were similar to those obtained in the ECD-SPECT study. We obtained X-ray CT images in the same planes from each of the patients. The imaging patterns were visually evaluated.

RESULTS
There were discrepancies between the ECD-SPECT and CBF images from all three patients, and in two of them, the ECD and HMPAO images disagreed. The uptake of ECD was lower than those of CBF and HMPAO images in the lesions of the three patients. The distribution of ECD resembled that of CMRO₂. These three patients were studied 9–20 days after the onset of stroke. On the other hand, during the chronic and acute phases less than 5 days after onset, ECD-SPECT, CBF, CMRO₂, and/or HMPAO images were in good agreement. In one patient (Patient 2) there were discrepancies between CBF and ECD, and between CBF and HMPAO images. The relative uptake of HMPAO was higher than that shown by the CBF images.

Patient 1
A 67-year-old man had global aphasia and right hemiparesis. He was admitted to our hospital 6 hours after the onset. CT revealed low density areas in the left middle cerebral arterial territory. Magnetic resonance angiography (MRA) revealed an occlusion of the horizontal portion of the left middle cerebral artery (MCA).

PET and ECD-SPECT were performed 9 days after the insult, and HMPAO-SPECT was performed 2 days after the PET study. These images are shown in Figure 1. There was a low density area (LDA) in the left MCA territory, and high density spots were evident in the LDA. There was markedly high CBF and high uptake of HMPAO in the lesion. CMRO₂ and ECD uptake was decreased in the same regions.

Patient 2
A 63-year-old man was admitted to our hospital because of right hemianopsia 3 days after the onset. He had another attack of aphasia and right hemiplegia 10 days after admission. PET and ECD-SPECT were performed 11 days after the second onset (Fig. 2).

CT revealed a faint LDA in the left frontal lobe supplied by the left anterior cerebral artery (ACA). This CT finding was the so-called “fogging effect.” CBF, CMRO₂ and ECD uptake was decreased in the left ACA territory. However, there was markedly high uptake of HMPAO in the lesion. The CBF in the lesion was relatively higher than ECD uptake and CMRO₂.

Patient 3
A 59-year-old male was admitted to our hospital within a day of the onset of right hemiparesis and sensory aphasia. The CT study revealed no responsible lesions at this time. Cerebral angiography performed after the first CT revealed an embolic occlusion of the posterior branch of the
left middle cerebral artery. He was treated with an intra-arterial infusion of 720000 units of urokinase, but the occlusion was not recanalized and the symptoms did not change.

Twenty days after the onset, we performed ECD-SPECT, PET and CT (Fig. 3). The latter CT revealed a wedge-shaped low density area in the left parietal lobe. ECD-SPECT demonstrated a defect as a similarly shaped lesion. However, the CBF in the lesion appeared to be almost normal, which was similar to that of the contralateral cortex. The CMRO$_2$ in the lesion was low, and that of the contralateral region was almost normal. The distribution of $^{99m}$Tc-ECD resembled that of the CMRO$_2$, rather than the CBF image.

DISCUSSION

$^{99m}$Tc-ECD is a neutral lipophilic complex, and its characteristics make it suitable for use in brain SPECT. It is rapidly taken up by the brain and it is rapidly cleared from arterial blood. High quality SPECT imaging results from the optimal physical characteristics of $^{99m}$Tc and the
favorable biodistribution of ECD that results in low background activity, high photon flux and high brain uptake.

Some groups\textsuperscript{5-8} have reported a similar brain distribution of \textsuperscript{99m}Tc-ECD and CBF SPECT tracers such as \textsuperscript{133}Xe, \textsuperscript{99m}Tc-HM-PAO and \textsuperscript{123}I-IMP in normal volunteers and in chronic stroke patients, but our preliminary observations revealed that ECD-SPECT images were similar to those of CMRO\textsubscript{2} and not CBF in the lesions as shown by "luxury perfusion."\textsuperscript{17,8} Lassen and Sperling\textsuperscript{9} have reported that \textsuperscript{99m}Tc-ECD images failed to show reflow hyperemia in 7 patients with subacute stroke in multicenter trials, comparing \textsuperscript{133}Xe CBF and ECD measured by SPECT. Nakagawara et al.\textsuperscript{10} have also reported that \textsuperscript{99m}Tc-ECD uptake was underestimated in 10 patients with reflow hyperemia comparing \textsuperscript{99m}Tc-HM-PAO, \textsuperscript{123}I-IMP, and/or \textsuperscript{133}Xe studies.

Here we reported that ECD failed to show reflow of the infarcted lesions in three patients with subacute infarctions with uncoupled blood flow and metabolism, and that the ECD images were similar to those of CMRO\textsubscript{2} measured by PET. This reflow phenomenon is considered to be evidence of the re-opening of the occluded vessels due to
thrombolysis, and subacute stroke patients often have reflow due to thrombolysis. Though we cannot confirm evidence of the re-opening of occluded vessels by cerebral angiography, CT demonstrated typical findings of reflow due to thrombolysis such as hemorrhagic infarction and fogging effects.

The retention of $^{99m}$Tc-ECD activity in the brain is related to in vivo metabolism. $^{99m}$Tc-ECD was metabolized rapidly in the brain by a specific enzymatic pathway to a polar complex that is trapped. The hypofixation is due to slowness of deesterification in the infarcted lesion. From this perspective, the retention of $^{99m}$Tc-ECD may be affected by the severity of tissue damage or metabolism under some pathological conditions where metabolism and blood flow are uncoupled (luxury perfusion, or reflow hyperemia). On the other hand, the uptake of HMPAO in
the lesion of one patient was high, while CBF in the lesion was relatively low. The discrepancies between ECD and HMPAO images include the cause of hyperfixation of HMPAO in the infarcted lesion.12

Although our observations were limited to three patients, these findings suggested that Tc-99m ECD is a useful SPECT tracer for assessing cerebral tissue viability in patients with reflow hyperemia or luxury perfusion. Although additional studies are required to confirm these findings and speculations, ECD-SPECT images may be useful for studying cerebral function or tissue viability. The characteristics of Tc-99m ECD may be suitable for confirming the clinical, but not angiographical, effects of thrombolytic therapy, because these conditions often manifest luxury perfusion when the therapy is successful.

REFERENCES