Early and Delayed Brain SPECT with Technetium-99m-ECD and Iodine-123-IMP in Subacute Strokes

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The brain distribution of ^{99m}Tc-ECD versus ^{123}I-IMP was compared in patients with subacute stroke in order to compare diagnostic accuracy. **Methods:** A total of 25 patients with subacute stroke underwent early and delayed SPECT imaging with ^{99m}Tc-ECD and ^{123}I-IMP. Washout of ^{99m}Tc-ECD was calculated and a differential percentage of activity (DPA) of ischemic versus normal zones was assessed. Images were analyzed twice by five independent observers. **Results:** Technetium-99m-ECD clearance was 12.5% from the whole brain during early imaging. Ischemic parietal zones had higher clearance than normal parietal zones. Technetium-99m-ECD images showed larger differences between abnormal and normal brain activity than ^{123}I-IMP images. Detection accuracy was slightly, but not significantly, higher for ^{99m}Tc-ECD and ^{123}I-IMP (sensitivity: 73.8% as 66.6%; specificity: 81.7% as 81.6%). Reproducibility among observers was similar for ^{99m}Tc-ECD and early ^{123}I-IMP. **Conclusion:** Technetium-99m-ECD demonstrates high diagnostic accuracy during subacute stroke, similar to ^{123}I-IMP, but with more intense, better delineation of the perfusion defects.

Key Words: technetium-99m-ECD; iodine-123-IMP; subacute strokes; brain SPECT

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Recently a neutral lipophilic complex, ^{99m}Tc-ethyl cysteinate dimer (ECD), was introduced as a tracer for brain perfusion imaging (*1,2*) because of its high cerebral retention (6.5%) (*3*). First studies performed in normal volunteers demonstrated that normal brain clearance was very slow with two exponential components (40% 1.3 hr, 60% 42.3 hr) (*4–6*). Technetium-99m-ECD was found to be highly sensitive in stroke patients for diagnosis and assessment of cerebral ischemia (*6–8*).

Cerebral ^{123}I-isopropyliodoamphetamine (IMP) distributes evenly to regional brain perfusion only during the early period after injection and there is a constant redistribution of the tracer with time (*9*). The redistribution pattern correlates closely with the cerebral metabolic rate of oxygen ($CMRO_2$) (*10*) and with clinical outcome (*11*). The peripheral area zone observed around the hypodensity on the CT scan is a major clue for prognosis (*12*).

Perfusion cerebral tracers have different brain retention mechanisms. Iodine-123-IMP binds to serotonine receptors (*13*) and is dealkylated to iodoamphetamine (*14*). A subsequent oxydation of iodoamphetamine leads to a reactive product which covalently binds to microsomal proteins coupled with the mitochondrial cytochrome P-450 (*15,16*). Technetium-99m-HMPAO is retained by a steric transformation of the chelate perhaps linked to glutathione activity (*17,18*). Technetium-99m-ECD is hydrolized in polar metabolites after crossing the blood-brain barrier (*19*). The first two perfusion neurotracers have a different brain biodistribution over time, especially in ischemic areas. Iodine-123-IMP fills into the lesion, whereas ^{99m}Tc-HMPAO clears out of the same area. The brain distribution of ^{99m}Tc-ECD versus time in normal and ischemic tissues at the subacute phase of stroke has not yet been studied.

The purposes of our study were to:

1. Assess the total brain clearance of ^{99m}Tc-ECD activity versus time and validate the SPECT imaging technique independently of time after injection.
2. Determine changes in regional biodistribution of ^{99m}Tc-ECD over time in ischemia and infarction.
3. Evaluate intra- and interobserver variability for interpreting early and delayed SPECT images with the two tracers.
4. Compare sensitivity and specificity of ^{99m}Tc-ECD and ^{123}I-IMP SPECT imaging on early and delayed images in patients experimenting the subacute phase of stroke.

This study was a part of a phase III international multicenter trial, previously presented (*7,19*). The protocol has been reviewed and accepted by the institutional ethic com-

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mittee of our university and written informed consent was obtained from each patient or a "caregiver."

METHODS

Radiopharmaceutical Preparation

Iodine-123-IMP was prepared using iodine exchange reaction with a commercial kit (IK-3 CIS Bio-International BP 32 91192 GIF/Yvette, France) as previously described (*20*). Each vial contained 10 mg of lyophilized ^{123}I-IMP and copper sulfate, and was filled with 180 MBq of ^{123}I (p,2n) and acetate buffer (pH 3.6) and heated for 45 min at 130°C to dryness. Chromatography was performed using thin-layer chromatography (TLC) on silica gel plates 60 F254 Merck and solvent (85% chloroform, 15% methanol, acetic acid) with a labeling efficiency greater than 95%.

Technetium-99m-ECD was prepared from a kit and labeled with 925 MBq of [^{99m}Tc]pertechnetate. The specific radioactivity was tested by TLC using Baker-Flex silica gel IBF plates and a solvent system of ethyl acetate. Labeling efficiency was consistently higher than 95%.

Imaging Protocol and Data Acquisition

The imaging studies were carried out using a conventional tomographic rotating gamma camera. Data acquisition was performed in 64 projections with a 64 × 64 matrix. The gamma camera was fitted with a high-resolution, low-energy (160 keV maximum) collimator for ^{99m}Tc and ^{123}I studies. Blindfolded supine patients received the radiopharmaceuticals intravenously in a quiet room. Early SPECT acquisition started 87 min ± 27 s.d. (range 50–120 min) and delayed acquisition 255 min ± 78 s.d. (range 130–420 min) after injection of 740 MBq of ^{99m}Tc-ECD. The following day, early SPECT acquisition started 29 min ± 13 s.d. (range 20–60 min) and delayed one 209 min ± 58 s.d. (range 90–330 min) after the injection of 250 MBq of ^{123}I-IMP. The imaging time was 30 sec per projection for ^{99m}Tc-ECD, 40 sec for ^{123}I-IMP, collecting more than 2.5 million counts per examination.

By subtracting background activity on each projection representing the scattering outer activity of the head, tomographic images were reconstructed by filtered backprojection using a Sheep-Logan filter. The axial slices were reoriented parallel to a orbitomeatal line joining the inferior limit of the frontal and occipital lobes. Coronal, sagittal and transverse slices were analyzed after data smoothing using a matrix two pixels deep.

Phantom Studies

In order to evaluate contrast and resolution characteristics of the two radiotracers, the standard cylindrical 20-cm diameter Phelps phantom with a plastic wall 1 cm deep, a 3-cm central metacrylate rod and six peripheric metacrylate rods (0.5–2.5 cm diameter) placed at 3.7 cm off the border was used for SPECT studies (*21*). For ^{99m}Tc, the phantom was filled with 74 MBq and the tomographic imaging time was 15 sec per projection. For the ^{123}I study, 25 MBq was used and data were acquired during 20 sec per projection. Both studies were containing more than 7.5 million counts. For each study, three reconstructions were performed using the same filter than for this brain study without attenuation correction, with Bellini correction (*22*) and with first order Chang correction (*23*). The image contrast was defined as the ratio of counts in the cold rods areas-to-maximum counts in the slice. The mean of four slices was calculated for each peripheral cold rod diameter.

Control Subjects and Patients

Control Subjects. Ten age-matched normal human subjects (6 male, 4 female, range: 44–69 yr; mean age 61.3 yr ± 9.4 s.d.) with no history of psychiatric, neurologic or vascular disease were injected with ^{99m}Tc-ECD SPECT using the same imaging protocol. Seven age-matched normal human subjects (4 males and 3 females with a mean age of 56 yr ± 11 s.d.) were explored with ^{123}I-IMP and reported elsewhere (*11*). The pattern of ^{99m}Tc-ECD brain uptake in normal subjects was similar to that observed with ^{123}I-IMP (*24*).

Patients. A group of 25 patients with cerebral ischemia (mean age: 70 yr ± 15.7 s.d.; range 24–91 yr; 16 males and 9 females) was included in the study. All patients had ^{99m}Tc-ECD and ^{123}I-IMP SPECT studies during the subacute phase of their stroke, i.e., no later than 14 days after onset (range: 6–14 days, mean delay: 11.2 days ± 2.8 s.d. for the first SPECT). CT images showed a focal hypodensity compatible with the diagnosis of ischemic stroke in all patients. They were classified as cortical strokes (*15*) and subcortical strokes (*10*) according to clinical and CT data.

Cortical stroke referred to stroke involving the cortical and/or subcortical area of the middle cerebral or posterior cerebral arteries territory. Cerebral ischemia in the left middle cerebral artery territory was observed eight times, six times in the right middle cerebral artery territory, and only once in the left posterior cerebral artery territory. Subcortical ischemia was found in 10 patients, all in the middle cerebral artery territory (5 involving the RMCA and 5 involving the LMCA).

The classification of Yatsu et al. (*25*) was used for the etiological diagnosis of stroke. The total group included 1 lacunar infarction, 10 cardioembolic strokes, 4 thromboembolic strokes and 10 ischemic strokes of undefined origin. All the patients underwent CT scanning within the period of the SPECT examination (mean 4.6 days ± 7.2 s.d. before the first SPECT).

Technetium-99m-ECD Brain Biodistribution

Regions of interest (ROIs) were drawn interactively around the skull on the ^{99m}Tc-ECD images and counts measured on the first and on the last projection (64) acquired with a 45-min lag phase (including 32 min for projection acquisition and 7 min for interprojection intervals). Correction of physical decay was performed and the percentage of biological decay was calculated to measure the clearance per hour. Measurements were done on early SPECT scans of control subjects (10) and early and delayed SPECT scans of patients (50) and results plotted versus time. Three groups were analyzed: 35 studies (25 + 10 early determinations) between 50 to 120 min; 18 studies between 130 and 285 min and 7 studies between 325 and 440 min.

Regions of interest (25-pixel area or more) were drawn on three representative slices in each hemisphere over the left and right frontal, temporal parietal and occipital lobes, white matter, basal ganglia and cerebellum. After correction for physical decay, the clearance of ^{99m}Tc-ECD between early and delayed SPECT was computed for each region. The results were analyzed for the 13 enrolled subjects. Normal and ischemic areas were computed separately and the analysis was split into two groups: Group 1 consisted of early SPECT scans starting 60–80 min postintravenous injection and Group 2 consisted of SPECT scans starting 90–115 minutes after injection.

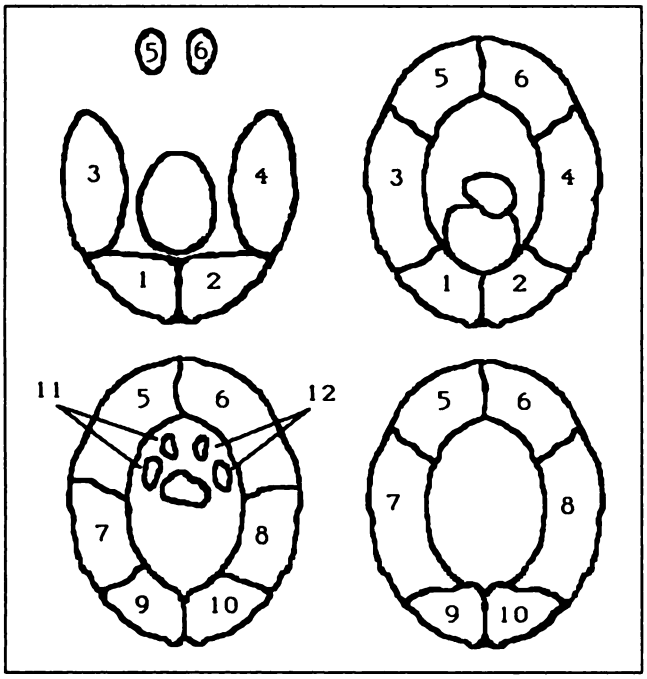

FIGURE 1. Drawing of the 12 ROIs visually analyzed on 4 transverse slices of early and delayed ^{99m}Tc-ECD and ^{123}I-IMP SPECT imaging. 1: right cerebellum; 2: left cerebellum; 3: right temporal lobe; 4: left temporal lobe; 5: right frontal lobe; 6: left temporal lobe; 7: right parietal lobe; 8: left parietal lobe; 9: right occipital lobe; 10: left occipital lobe; 11: right striatum; and 12: left striatum.

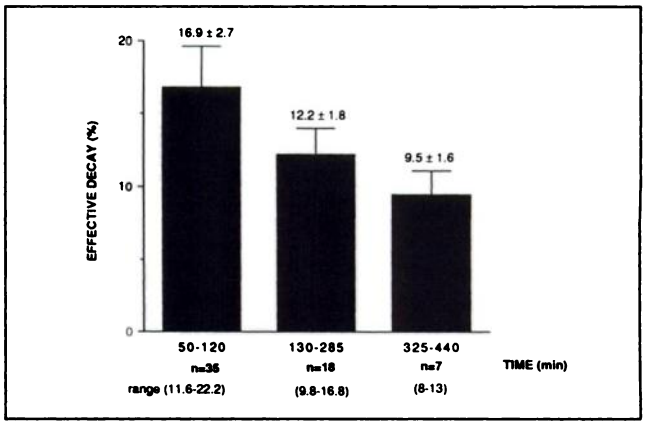

FIGURE 3. Effective decay of 45-min acquisition of ^{99m}Tc-ECD with the course of time on total head.

Data Analysis for Comparison of ^{99m}Tc-ECD and ^{123}I-IMP SPECT Images

Visual Analysis. SPECT images were analyzed by five readers blinded to the clinical data and the results of the other imaging studies. This interpretation was performed twice with a 1-wk interval to assess intra-observers reproducibility. The readers evaluated two paired sets of transverse, coronal and sagittal slices from the SPECT scans (early and late ^{99m}Tc-ECD versus early ^{123}I-IMP from the same patient). Based on this analysis, each reader had to localize abnormal zones in 12 areas drawn on four transverse slices (Fig. 1).

For that comparison, observers reviewed three SPECT data sets: early (ECD 1) and delayed (ECD 2) ^{99m}Tc-ECD and early (IMP 1) ^{123}I-IMP, because the delayed ^{123}I-IMP SPECT images were not relevant for diagnosis due to the redistribution process.

Sensitivity and specificity of ^{99m}Tc-ECD and ^{123}I-IMP SPECT were calculated using cross-matching between areas noted as normal or abnormal (more than 5 times in 10) by the readers compared to normal and abnormal areas according to clinical data and CT results. Intra- and interobserver reproducibility were evaluated for each SPECT examination and each reader.

Finally, each reader classified the quality of the ^{99m}Tc-ECD and ^{123}I-IMP SPECT images.

Semiquantitative Analysis. After completion of the visual analysis, two unblinded readers used two pooled consecutive transverse slices demonstrating abnormal cerebral activity to calculate the left-right differential percentage of activity (DPA) between symetrical ROIs using a previously published method (*11*). All the data were expressed as mean ± s.d.

A semiquantitative analysis was performed on images from control subjects by studying two slices and three areas per slice (frontal, parietal and occipital) and calculating the DPA. Taking into account the corresponding regions in left and right hemisphere, six areas were compared per subject (60 areas for the 10 controls).

RESULTS

Phantom Studies

Figure 2 shows the image contrast as a function of the cold rod diameter for each method, reconstruction without and with attenuation correction. Image contrast results were equivalent for ^{99m}Tc and ^{123}I independently of the reconstruction method used.

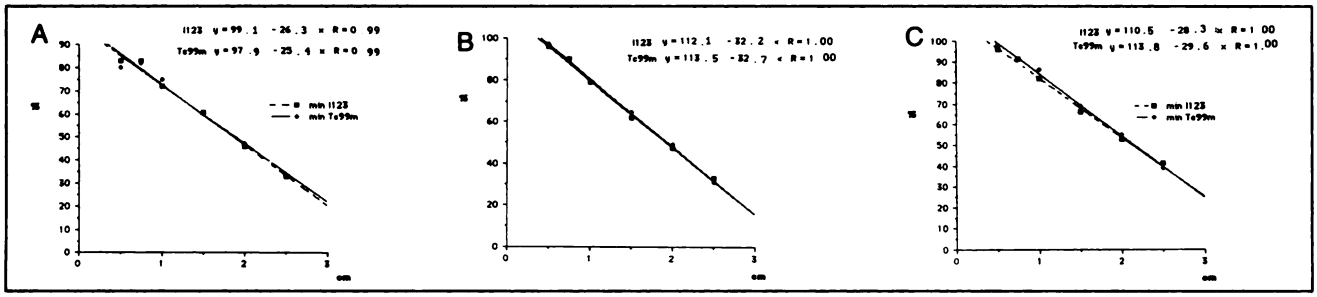

FIGURE 2. Diagrams of contrast obtained on cylindrical 20 cm Phelps phantom filled with ^{99m}Tc or with ^{123}I in hypoactive areas drawn on rod images of different diameters (0.5 to 2.5 cm) (A) without attenuation correction (B) with Bellini correction and (C) with first order Chang correction.

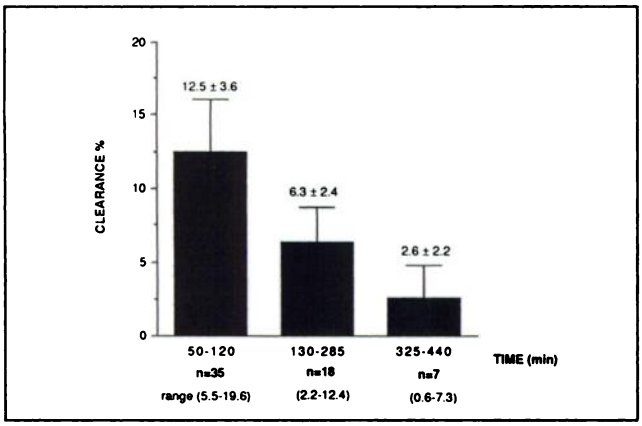

FIGURE 4. Biological clearance decay of ^{99m}Tc-ECD with the course of time on total head.

TABLE 1
Sensitivity and Specificity Determined on 15 Cortical and 10 Subcortical Strokes According to Clinical and CT Data

	Total n = 25	Cortical strokes n = 15	Subcortical strokes n = 10
Sensitivity (%)			
ECD1	73.8	85.4	43.7
ECD2	72.7	80	50
IMP1	66.6	78	31
Specificity (%)			
ECD1	81.7	83.7	79.8
ECD2	80.3	83.8	76.9
IMP1	81.6	85.3	76.9

ECD1 = early ^{99m}Tc-ECD imaging; ECD2 = delayed ^{99m}Tc-ECD imaging; and IMP1 = early ^{123}I-IMP imaging

Technetium-99m-ECD Brain Biodistribution

The differential activity for the whole head (i.e., variation of the content of the first and the last projection) during the SPECT acquisition was 16.9% at 50 min and 9.5% at 440 min after injection (Fig. 3).

Technetium-99m-ECD clearance per hour was 12.5% at 50–120 min after injection and 2.6% at 325–440 min after injection for the whole brain (Fig. 4).

Regional clearances are displayed on Figure 5 for normal and ischemic zones. Clearance is smaller for inner cerebral areas than for the whole head. Significant differences were also found according to the time of SPECT. The largest clearance was in the parietal cortical area and the smallest was in the frontal cortex. Significant differences were found between normal and ischemic zones only in the parietal lobe where the clearance in the lesion was significantly greater ($p < 0.035$) than in normal brain in early imaging periods (50–80 min) but not significantly different ($p < 0.13$) afterwards (90–115 min).

Visual Analysis

Based on visual analysis, SPECT images were abnormal for all patients except one who had no abnormality on ^{123}I-IMP SPECT. One patient had an abnormal hyperactive focal lesion on ^{99m}Tc-ECD and ^{123}I-IMP, all others had hypoactive lesions.

Overall SPECT sensitivity was not significantly different for the two tracers (Table 1) (ECD1/ECD2 $p = 1$; ECD1/IMP1 $p = 0.66$; ECD2/IMPI $p = 0.7$). Sensitivity was significantly higher for cortical strokes than for subcortical strokes, regardless of the imaging agent used (ECD1 $p < 0.007$, ECD2 $p < 0.05$, IMP1 $p < 0.003$).

Specificity values were also not significantly different (ECD1/ECD2 $p = 0.91$; ECD1/IMP1 $p = 1$; ECD2/IMPI $p = 0.91$). Specificity was slightly higher but not significantly for cortical compared to subcortical strokes (Table 1) (ECD1 $p = 0.91$; ECD2 $p = 0.91$; IMP1 $p = 0.67$).

Matching performance was slightly better for cortical strokes than for subcortical strokes but not significantly different (ECD1/IMP1 $p = 0.84$; ECD2/IMP1 $p = 0.92$) (Table 2). The kappa concordance index (*26*) between SPECT images and radioclinical findings was 0.485 for ECD1; 0.46 for ECD2 and 0.435 for IMP1 (Table 2).

The intra- and interobserver reproducibilities were not different for ECD1, ECD2 and IMP1 (Table 3). The subjective quality of SPECT images was better in term of contrast for ECD1 and ECD2 than for IMP1.

Semiquantitative Analysis

In control subjects, the mean differential percentage of activity (DPA) was 1.7% ± 4 s.d. (n = 42, range 0–9.5%) for ^{123}I-IMP (7 patients) and 5.2% ± 2 s.d. (n = 60, range 0–8.6%) for ^{99m}Tc-ECD (10 patients). Therefore potential

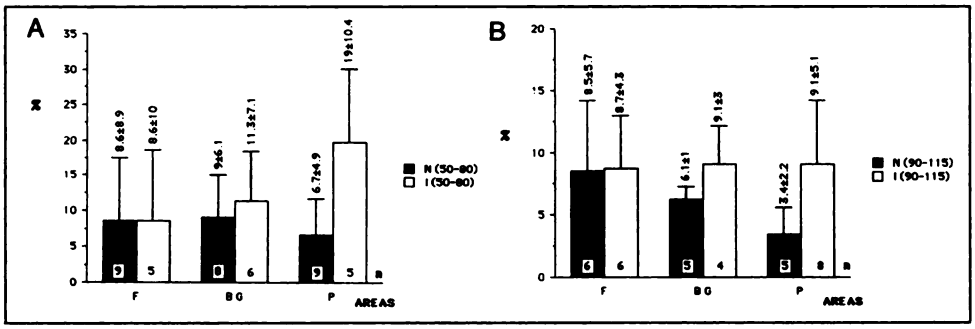

FIGURE 5. Comparison of regional clearance (F: frontal; BG: basal ganglia; and P: parietal) of ^{99m}Tc-ECD between different normal and ischemic zones of brain in 13 cortical strokes when acquisition time was set at (A) 50–80 min postinjection and (B) 90–115 min postinjection.

TABLE 2
Matching Percentage and Kappa Concordance Index Applied to 15 Cortical and 10 Subcortical Strokes

Results of matching (%)	Total n = 25	Cortical strokes n = 15	Subcortical strokes n = 10
ECD1/IMP1	91.3	93.2	89.2
ECD2/IMP1	92.3	93.3	90.8
Kappa concordance index (26)	ECD1 0.485	ECD2 0.46	IMP1 0.435

ECD1 = early ^{99m}Tc-ECD imaging; ECD2 = delayed ^{99m}Tc-ECD imaging; and IMP1 = early ^{123}I-IMP imaging

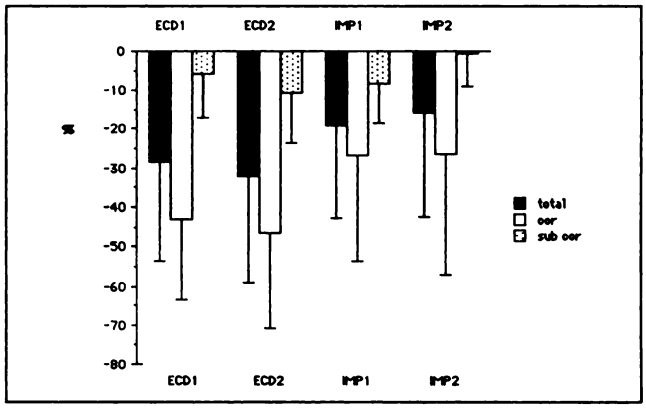

FIGURE 6. Differential percentage of activity (lesion/normal heterolateral area) on early SPECT with ^{99m}Tc-ECD and ^{123}I-IMP (ECD1, IMP1) and delayed SPECT with ^{99m}Tc-ECD and ^{123}I-IMP (ECD2, IMP2).

pathological areas were considered abnormal when DPA was larger than 10%.

Mean DPA was significantly larger in ischemic zones for delayed ECD2 than for early ECD1 ($p < 0.0001$) and was significantly higher for ECD1 and ECD2 than for IMP1 ($p < 0.02$, $p < 0.08$) for the total cohort of patients enrolled (Fig. 6) while the difference was highly significant for cortical strokes ($p < 0.001$) it did not reach statistical significance for subcortical strokes ($p < 0.3$, $p < 0.2$).

DISCUSSION

During the 50–120-min postinjection period, there is a difference of activity (mean 16.9%) between the first projection image and the last one (Fig. 3). This could be a drawback for an accurate SPECT reconstruction. To avoid these limits, one could remark that most of the activity decreasing in the early time was localized in background facial tissue (*5*) and that the regional structures were washing out at the same rate (Fig. 5) in normal patients. However there were differences in clearance in ischemic parietal zones and normal brain (Fig. 5) that could induce uncertainty in early SPECT reconstruction. To avoid these potential risks, it would be advisable to acquire projections after 2 hr.

TABLE 3
Interobservers and Intraobserver Visual Interpretation Reproducibility Performed Twice by Five Independent Blinded Medical Readers on SPECT Images

	Interobservers agreement (%) n = 5		
	Total n = 25	Cortical strokes n = 15	Subcortical strokes n = 10
ECD1	61.3 ± 15	66.5 ± 12	53.4 ± 15
ECD2	65.2 ± 18	70.9 ± 19	57.6 ± 10
IMP1	63.8 ± 16	69.3 ± 12	55.5 ± 18

Intraobserver agreement (%) n = 2		
ECD1	ECD2	IMP1
63.8 ± 8.8	69.1 ± 7.4	66.3 ± 7.3

ECD1 = early ^{99m}Tc-ECD imaging; ECD2 = delayed ^{99m}Tc-ECD imaging; and IMP1 = early ^{123}I-IMP imaging

The DPA of ischemic versus normal areas was significantly larger for ^{99m}Tc-ECD than for ^{123}I-IMP providing better contrast images improving significantly with time (Fig. 7). This imaging contrast was proved by phantom studies not to be due to physical interferences. In parietal strokes, the cortical border zones seemed to shrink on the delayed SPECT.

This phenomenon was supposed to be related to abnormal permeability of the blood-brain barrier (BBB) to ECD metabolites. This higher contrast of ^{99m}Tc-ECD SPECT images gave a higher confidence in image interpretation.

This "filling out" phenomenon was of less importance than with ^{99m}Tc-HMPAO in stroke (*27*). All the lesions in our study were hypoactive. Therefore, ^{99m}Tc-ECD could be considered more as a functional tracer linked to cell viability, similar to ^{123}I-IMP, whereas ^{99m}Tc-HMPAO mirrors perfusion (*24*). In several instances, ^{123}I-IMP SPECT displayed low activity in some ischemic cortical areas whereas ^{99m}Tc-ECD SPECT was not depicting these regions which were found completely inactive. Interpretation of this discrepancy could be explained by: (1) a low uptake of ECD due to a lower extraction coefficient than ^{123}I-IMP in low flow ischemic situation; (2) a lack of retention in neuronal cells unable to achieve the enzymatic transformation of ^{99m}Tc-ECD in polar EC, due to a loss of viability linked to hypoaerobic conditions; and (3) a leakage of polar metabolites in regions where the BBB was disrupted, especially in parietal lobes.

The mechanism of retention is different for ^{99m}Tc-ECD and ^{123}I-IMP. Retention of ^{123}I-IMP depends upon local pH for uptake and binding on receptors to be trapped within the cells, therefore the resulting images are not matching in ischemic areas. It would be interesting to promote a PET imaging study measuring O_2 and glucose consumption with ^{99m}Tc-ECD versus ^{123}I-IMP images.

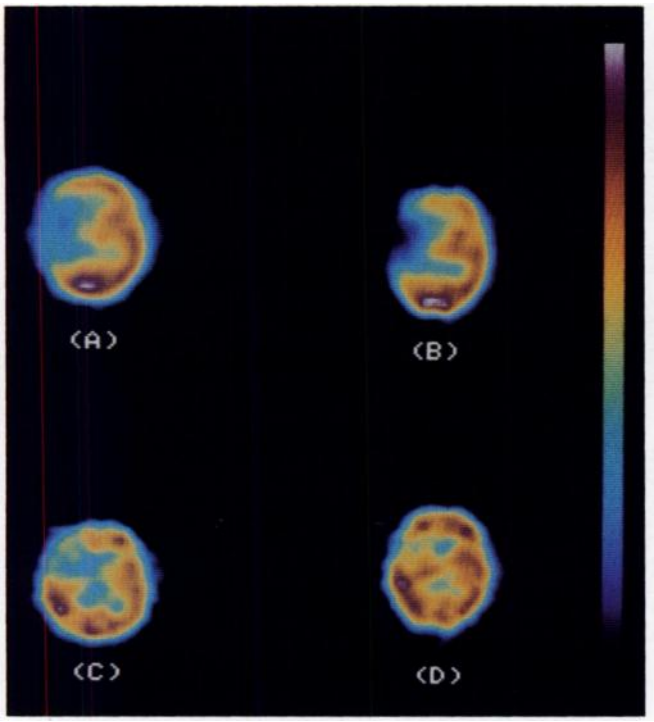

FIGURE 7. SPECT images obtained with ^{99m}Tc-ECD (top row) 60 min (A), 215 min (B) and with ^{123}I-IMP 25 min (C) and 185 min postinjection in a 71-yr-old female patient suffering from left hemiplegia and left lateral hemianopasia. It was a right middle cerebral artery stroke from cardiac origin. Early ECD 1 (A) displayed a large lesion with a differential hypoactivity versus normal parenchyma of −43%. Delayed ECD 2 (B) displayed a broader lesion with a higher differential activity of −64%. Early IMP 1 (C) showed a smaller sized lesion with a differential activity of −27.5% and a delayed IMP 2 (C) with a incomplete redistribution (−17%). This image displayed a washin (redistribution) with IMP and a washout with ECD.

This study demonstrated that ^{99m}Tc-ECD showed excellent matching with ^{123}I-IMP on subacute stroke defects, with about the same sensitivity and specificity even though ^{99m}Tc-ECD demonstrated deeper defects than ^{123}I-IMP facilitating delineation of lesions and diagnosis of small, particularly subcortical lesions. Even if the SPECT images are improving versus time, accurate diagnosis is not affected by early imaging (1 hr postinjection). So early imaging with ^{99m}Tc-ECD may be used routinely to explore ischemic diseases instead of ^{123}I-IMP taking in account that its clearance may slightly interfere in some cases.

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