Acetazolamide Challenge and Technetium-99m-ECD Versus Iodine-123-IMP SPECT in Chronic Occlusive Cerebrovascular Disease

Takashi Ohnishi, Takao Yano, Shinichi Nakano, Seishi Jinnouchi, Shigeki Nagamachi, Leo II Flores, Hiroshi Nakahara and Katsushi Watanabe

Department of Radiology, Internal Medicine and Neurosurgery, Junwa Memorial Hospital; Department of Radiology, Miyazaki Medical College, Miyazaki, Japan

We compared the acetazolamide challenge test using ^{99m}Tc-ECD SPECT and ^{123}I-IMP SPECT images in patients with chronic occlusive cerebrovascular disease. We also evaluated the usefulness of linearization correction for acetazolamide challenge test of ^{99m}Tc-ECD SPECT. **Methods:** Twenty patients with unilateral chronic occlusive cerebrovascular disease (10 patients had middle cerebral arterial lesion and 10 had internal carotid lesion) were included in the study. Split-dose (a dose fractioning was 1:2), and sequential SPECT technique was used for ^{99m}Tc-ECD SPECT studies while only acetazolamide challenge test studies for ^{123}I-IMP SPECT were performed. Permeability surface area product model (PS model) and back-diffusion model (Lassen's correction) were used for linearization correction of acetazolamide challenge with ^{99m}Tc-ECD SPECT. **Results:** Six of 16 patients with reduced vasodilatory capacity in ^{123}I-IMP SPECT were underestimated by ^{99m}Tc-ECD SPECT acetazolamide challenge test. Relative ECD uptake normalized by cerebellar uptake compared with IMP uptake showed a nonlinear relationship, indicating relatively less uptake in high flow range. The underestimations of limited vasodilatory capacity observed in ^{99m}Tc-ECD SPECT without linearization correction was modified by linearization algorithm. However, the effect of correction based on PS model was superior than that of Lassen's correction. The corrected ^{99m}Tc-ECD uptake ratio, based on PS model, and IMP uptake ratio demonstrated a better linear relationship than that of Lassen's correction. **Conclusion:** Technetium-99m ECD SPECT corrected based on the PS model is a better method of linearization for evaluating cerebrovascular reserve using acetazolamide challenge.

Key Words: technetium-99m ECD; acetazolamide challenge; linearization correction

J Nucl Med 1997; 38:1463–1467

During the past several years, substantial research has been conducted to develop a ^{99m}Tc-labeled radiopharmaceutical to evaluate regional cerebral blood flow (rCBF) with SPECT. The first commercially available ^{99m}Tc-labeled flow tracer was ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO), and it has been widely used. Characteristics of this tracer are high cerebral extraction with long retention in the brain (*1*). Since ^{99m}Tc-HMPAO is unstable in an aqueous solution, it must be administered within 30 min after reconstitution (*2*). The recently developed ^{99m}Tc-N,N′-(1,2-ethylenediyl)bis-L-cystein diethyl ester (ECD) demonstrated a rapid blood clearance of labeled metabolite, slow washout from the brain and negligible intracerebral redistribution, and it appears to be stable (*3*). The distribution of ^{99m}Tc-ECD in the brain correlated with rCBF under conditions of normal and reduced perfusion (*4,5*). However, Nakagwara et al. reported that ^{99m}Tc-ECD demonstrated poor contrast between high- and low-flow regions when compared to ^{123}I N-isopropyl-p-iodoamphetamine (IMP) in acetazolamide challenge test (*6*).

The nonlinear relationship of rCBF and ^{99m}Tc-ECD accumulation, especially at high blood flow areas, results in considerable underestimation of rCBF after acetazolamide challenge. The underestimation of rCBF on ^{99m}Tc-ECD SPECT at high flow lesion could be due to either the limited first-pass extraction of the tracer or backdiffusion of the tracer from the brain. In this study, we compared acetazolamide challenge using ^{99m}Tc-ECD and ^{123}I-IMP SPECT images. We also applied the permeability surface area product model (PS model) and backdiffusion model (Lassen's correction) for linearization corrections of acetazolamide challenge using ^{99m}Tc-ECD SPECT and evaluated the usefulness of these corrections.

MATERIALS AND METHODS

Subjects

Twenty patients (13 men, 7 women; mean age 69 yr, range 56–82 yr) having unilateral chronic occlusive cerebrovascular disease were included in the study. All patients had a previous history of minor strokes or transient ischemic attacks. Conventional angiography or digital subtraction angiography (DSA), brain MRI and MR angiography were performed in all patients before SPECT studies were done. The grade of arterial stenosis on cerebral angiogram was classified as mild (luminal narrowing under 30% in diameter), moderate (luminal narrowing of 30%–70% in diameter) and severe (luminal narrowing over 70% in diameter). With cerebral angiogram, unilateral atherosclerotic vascular lesions were noted on the trunk of the middle cerebral artery (MCA) in 10 patients (five occlusions and five severe stenoses) and internal carotid artery (ICA) in 10 patients (four occlusions, two severe stenoses, one moderate stenoses and two mild stenoses). Lacunar infarctions in the basal ganglia and white matter in the MCA territory were observed in all patients without cortical infarction.

SPECT Imaging Protocol

SPECT images were obtained using a dual-headed gamma camera system (OPTIMA, GE-YMS, Tokyo, Japan) with high-resolution collimators (FWHM = 11 mm). SPECT acquisition was performed in 64 steps, 360° and with a 128 × 128 matrix. Transaxial, sagittal and coronal images were reconstructed by filtered backprojection using both Butterworth and Ramp filters (cutoff frequency 0.45 cycle/cm for ^{99m}Tc-ECD and 0.42 cycle/cm for ^{123}I-IMP, respectively) with attenuation correction (Sorenson 0.11 cm^{-1} for ^{99m}Tc-ECD and 0.067 cm^{-1} for ^{123}I-IMP, respectively). The ^{99m}Tc-ECD SPECT studies were performed using the split-dose technique. A first dose of 370 MBq ^{99m}Tc-ECD was administered at resting state. Ten minutes after administration of first dose, 1000 mg of acetazolamide was injected while the first

Received Jun. 12, 1996; revision accepted Nov. 27, 1996.

For correspondence or reprints contact: Takashi Ohnishi, Department of Radiology, Junwa Memorial Hospital, 1199 Komatsu, Miyazaki, 880-21, Japan.

SPECT study (rest image) with 15 sec per step was being performed. Without repositioning the patient, an additional 740 MBq ^{99m}Tc-ECD was injected immediately after the first SPECT acquisition. Ten minutes after the second injection of ^{99m}Tc-ECD, another SPECT study of 15 sec per step was started. Acetazolamide challenge images were obtained by subtracting the first SPECT images from the second SPECT images. In ^{123}I-IMP SPECT studies only acetazolamide challenge studies were performed. At first, 1000 mg of acetazolamide were administered then 7 min later 222 MBq ^{123}I-IMP was injected. SPECT acquisition of 20 sec per step was started 10 min after ^{123}I-IMP injection.

Data Analysis

The limitation of vasodilatory capacity in the affected area was estimated by asymmetry index (AI) on the acetazolamide-challenged image. AI was calculated with the formula 100 × Ca/Cu, where Ca is the mean reconstructed counts for the affected area and Cu is the mean reconstructed counts for the contralateral unaffected area. Reduced vasodilatory capacity in the affected area was classified into three grades as follows: Grade 0 (AI: 90%–100%), Grade I (AI: 75%–90%) and Grade II (AI: 60%–75%) (*6*). The ratio of the value in each cortical region to that in the cerebellum (C/Cr) was compared between ^{99m}Tc-ECD SPECT images and ^{123}I-IMP SPECT images.

The ROIs were placed on cerebral cortices (30 × 30 mm) and cerebellar hemispheres (30 × 30 mm) in ^{99m}Tc-ECD SPECT images and ^{123}I-IMP SPECT images. In each patient, 8 ROIs were placed in frontal, temporal, parietal and occipital cortices in the bilateral hemisphere. The ROIs in the cerebellar hemisphere were placed ipsilateral to the cerebral lesion to exclude the effect of crossed cerebellar diaschisis or hypoperfusion. The correlation between C/Cr ratios on ^{123}I-IMP SPECT and those on ^{99m}Tc-ECD SPECT were analyzed by simple linear regression model. This analysis was performed using the JMP Macintosh program (SAS Institute Inc., NC).

Linearization Procedures

Linearization Based on Permeability Surface Area Product (Ps) Model. We applied the same linearized correction based on the PS model that was reported by Yonekura et al. (*4*). Assuming no backdiffusion of the tracer, regional uptake of ^{99m}Tc-ECD in the brain region (C) can be expressed with the equation:

$$C = F \times E \int_0^T Ca(t)\,dt, \qquad \text{Eq. 1}$$

where F is CBF (ml/min/100 g), E is the first-pass extraction and Ca(t) denotes the arterial input function. Based on the PS model, E can be expressed as a function of F and PS:

$$E = 1 - \exp(-PS/F). \qquad \text{Eq. 2}$$

Assuming identical input function to various regions in the brain in the same subject, the SPECT count ratio to the reference region (C/Cr) can be expressed as a function of low ratio (F/Fr) and PS as:

$$\frac{C}{Cr} = \frac{F}{Fr} \times \frac{1 - \exp(-PS/F)}{1 - \exp(-PS/Fr)}. \qquad \text{Eq. 3}$$

This equation can be simplified as:

$$Y = [X(1 - Z^{1/x})]/(1 - Z), \qquad \text{Eq. 4}$$

where X = F/Fr, Y = C/Cr, and Z = exp (−PS/Fr). The estimated Z value and averaged cerebellar blood flow (Fr) reported by Yonekura et al. were 0.243 and 50 ml/min/100 g, respectively (*4*). Correction of SPECT counts was performed by the table look-up method using the PS value. To simplify the correction, fourth-order polynomial curve-fitting for calculation of X from a given Y was applied:

$$X = f(Y) = \sum_{i=0}^{4} K^i Y^i \qquad \text{Eq. 5}$$

$$X = 0.04 + 0.675y + 0.365y^2 - 0.623y^3 + 0.583y^4, \qquad \text{Eq. 6}$$

which was used for the correction of SPECT counts.

TABLE 1
Estimation of Reduced Vasodilatory Capacity Using Iodine-123-IMP and Technetium-99m-ECD Under Acetazolamide-Activated Condition

Limitation in vasodilative capacity	IMP	ECD (no correction)	ECD (Lassen)	ECD (PS model)
Grade 0	4	6	4	4
Grade I	8	10	10	9
Grade II	8	4	6	7

Backdiffusion Correction

The backdiffusion correction algorithm for ^{99m}Tc HMPAO (Lassen's linearization correction) was applied for the backdiffusion correction for ^{99m}Tc-ECD (*7*). The correction assumes that the extraction of ^{99m}Tc-ECD is the same for all brain regions, K2 (backdiffusion rate constant) is varying with blood flow (F), and K3 (lipophilic to hydrophilic conversion rate constant) is the same in all regions. The SPECT count ratio to the reference region (C/Cr) can be expressed as a function of flow ratio (F/Fr) as follows:

$$F/Fr = [(C/Cr)\,a]/[1 + a - (C/Cr)], \qquad \text{Eq. 7}$$

where a = K3/K2 for reference region. Friberg et al. reported that a was 2.59 and Fr (cerebellar blood flow) was 50 ml/min/100 g in this formula (*7*).

RESULTS

Table 1 shows the estimation in vasodilatory capacity using ^{123}I-IMP and ^{99m}Tc-ECD using the acetazolamide challenge. The acetazolamide challenge of the ^{123}I-IMP SPECT study demonstrated a Grade I limitation of vasodilatory capacity in eight patients and Grade II in eight patients. Without linearization correction 4 on eight patients with Grade II in acetazolamide challenge of ^{123}I-IMP SPECT study were underestimated as Grade I, and two of eight patients with Grade I were underestimated as Grade 0 in ^{99m}Tc-ECD SPECT study. These underestimations were corrected by a linearization algorithm, such as Lassen's correction or linearization correction based on the PS model. With Lassen's correction, two of eight patients with Grade II in acetazolamide challenge of ^{123}I-IMP SPECT were underestimated as Grade I with ^{99m}Tc-ECD SPECT. With the PS model linearization correction, only one of eight patients with Grade II in acetazolamide challenge of ^{123}I-IMP SPECT were underestimated as Grade I in ^{99m}Tc-ECD SPECT. Figure 1 A, B and C show the comparison between ^{99m}Tc-ECD uptake ratio and ^{123}I-IMP uptake ratio in patients having chronic occlusive cerebrovascular disease with acetazolamide challenge. Comparison of C/Cr ratios of ^{99m}Tc-ECD SPECT without linearization correction and those of ^{123}I-IMP SPECT (Fig. 1 A) demonstrated a good linear relationship when C/Cr ratio range are low. This linear relationship changes when the C/Cr ratio is high. Figure 1B demonstrates the effect of Lassen's linearization correction on the acetazolamide challenge of ^{99m}Tc-ECD SPECT. The corrected

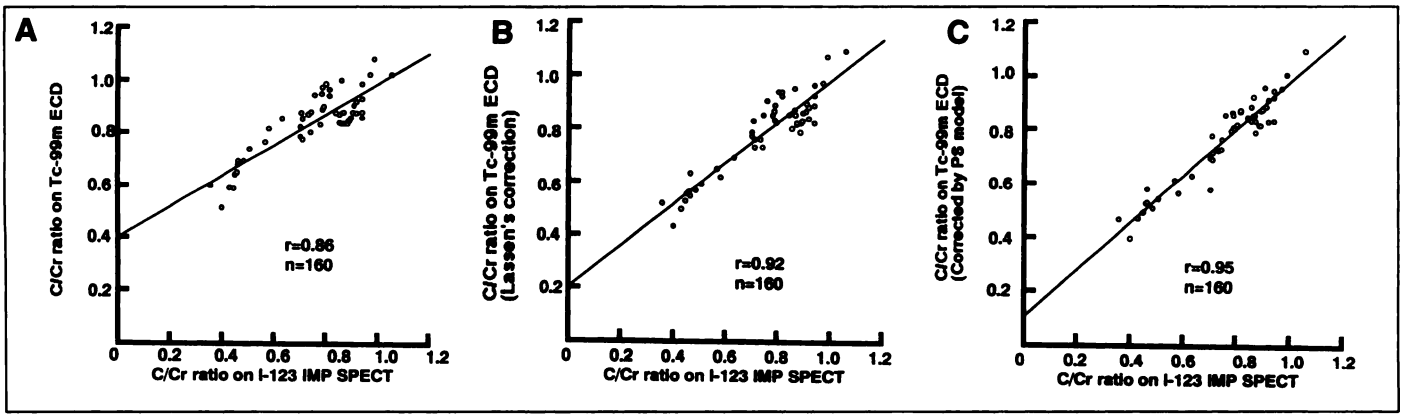

FIGURE 1. (A) Comparison of ^{99m}Tc-ECD uptake ratio and ^{123}I-IMP uptake ratio in patients having occlusive cerebrovascular disease with acetazolamide challenge, demonstrating a nonlinear relationship. (B) Relationship of linearization by Lassen's correction on the of ^{99m}Tc-ECD uptake ratio and ^{123}I uptake ratio. The corrected ^{99m}Tc-ECD uptake ratio demonstrated a good linear relationship with the ^{123}I-IMP uptake ratio. (C) Relationship of linearization based on the PS model on the ^{99m}Tc-ECD uptake ratio and ^{123}I uptake ratio. The corrected ^{99m}Tc-ECD uptake ratio demonstrated a better linear relationship with the ^{123}I-IMP uptake ratio.

^{99m}Tc-ECD uptake and IMP uptake ratio demonstrated a good linear relationship ($y = 0.21 + 0.78$ X, $r = 0.92$). Figure 1C demonstrates the effect of linearization correction based on the PS model on the acetazolamide challenge of ^{99m}Tc-ECD SPECT. The corrected ^{99m}Tc-ECD uptake based on the PS model and IMP uptake ratio demonstrated an excellent linear relationship ($y = 0.09 + 0.89$ X, $r = 0.95$). Figure 2 shows acetazolamide challenge SPECT images (^{123}I-IMP SPECT, ^{99m}Tc-ECD SPECT without correction, ^{99m}Tc-ECD SPECT with Lassen's correction and ^{99m}Tc-ECD SPECT with PS model correction) in a patient with right MCA occlusion. The acetazolamide challenge of ^{123}I-IMP SPECT images demonstrated reduction of vasodilatory capacity in right MCA territory. Technetium-99m-ECD SPECT images without correction also demonstrated reduction of vasodilatory capacity in the right MCA territory; however, there was poor contrast between affected and unaffected area when compared to ^{123}I-IMP SPECT images. This poor contrast is enhanced in SPECT images with linearization corrections. The contrast of corrected SPECT images by the PS model is better than that of Lassen's linearization correction.

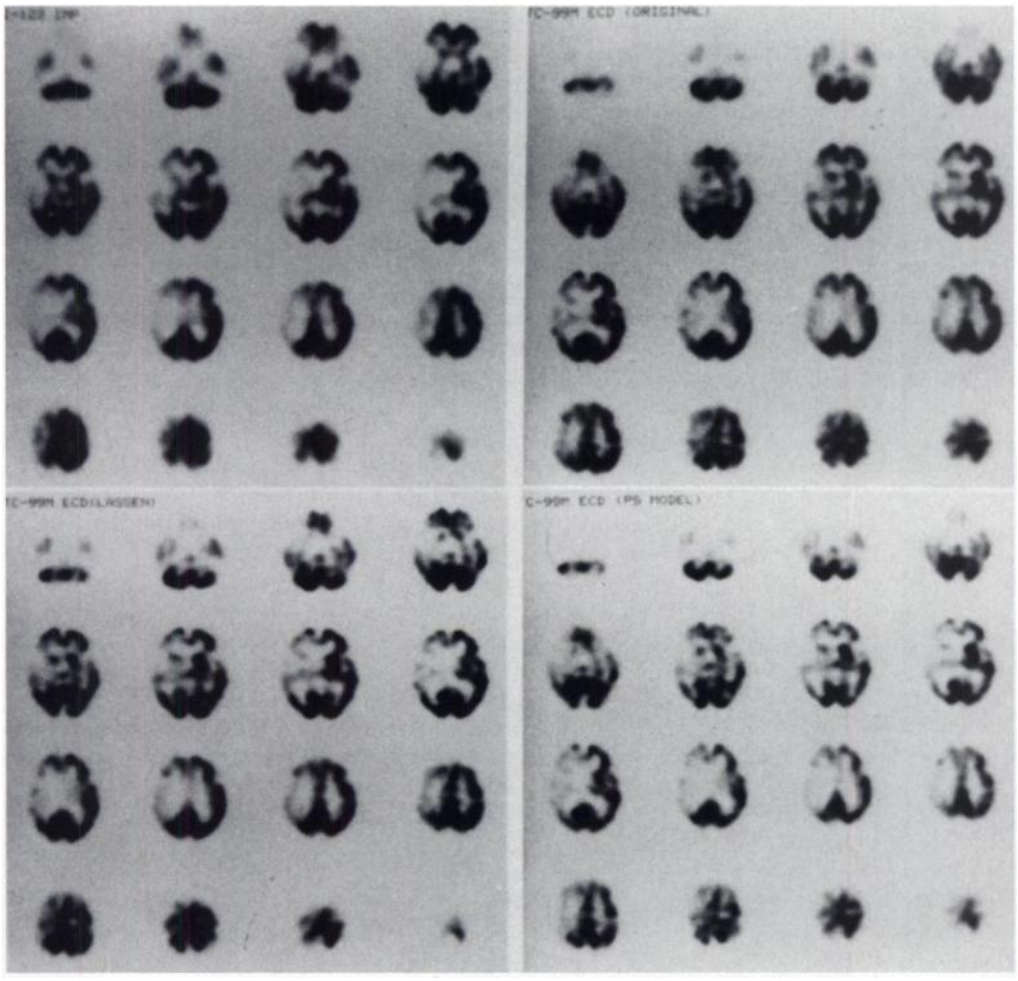

FIGURE 2. An 82-yr-old woman with left hemiparesis diagnosed as having minor stroke. A right common carotid angiogram reveals an occlusion of the right MCA. A T2-weighted MR image shows right putamen infarcts without cortical infarction. Acetazolamide challenge of ^{123}I-IMP SPECT image demonstrated a reduction in vasodilatory capacity of the right MCA territory (left top). Acetazolamide challenge of ^{99m}Tc-ECD SPECT image demonstrated a reduction vasodilatory capacity of the right MCA territory (right top). Underestimation of reduced vasodilatory capacity in the right MCA area is noted when compared with the ^{123}I-IMP SPECT image. This poor contrast is modified in SPECT images with linearization corrections. The contrast of corrected SPECT images by the PS model (right bottom) is better than that of Lassen's linearization correction (left bottom).

DISCUSSION

In patients having atherothrombotic stroke, the estimation of perfusion reserve using the acetazolamide challenge is a useful method for managing a relapse of stroke (*8–11*). It has been used to estimate the perfusion reserve of the brain with rCBF-SPECT, PET and stable Xe CT (*11*). PET is the gold standard for assessing cerebral perfusion due to its potential in quantifying rCBF, cerebral blood volume and fractional oxygen extraction. However, the expense and technical complexity exclude the PET technique for routine clinical use. SPECT technique with tracers for rCBF measurements, such as ^{123}I-IMP, ^{99m}Tc-HMPAO and ^{99m}Tc-ECD, has been widely used for assessing cerebral perfusion.

Technetium-99m-ECD has several advantages over ^{99m}Tc-HMPAO as a rCBF tracer (*2,12*). ECD is more stable for many hours after reconstitution, and it has less backdiffusion when compared to HMPAO (*2,12*). These characteristics of ^{99m}Tc-ECD make it suitable for estimating vasodilatory capacity using sequential SPECT with split-dose technique. Nakagawara et al. (*6*) reported that a retention of ^{99m}Tc-ECD in the unaffected area with an increased rCBF under acetazolamide activation could be superior to that of ^{99m}Tc-HMPAO, and ^{99m}Tc-ECD SPECT might be suitable for estimating perfusion reserve using acetazolamide challenge.

However, they also reported that ^{99m}Tc-ECD demonstrated poor contrast between high- and low-flow regions when compared to ^{123}I-IMP under acetazolamide challenge (*6*). In our study, image contrast in acetazolamide challenge of ^{99m}Tc-ECD SPECT images without linearization correction was inferior to that of ^{123}I-IMP SPECT. Six of 16 patients with reduced vasodilatory capacity (Grades I and II) in ^{123}I-IMP SPECT were underestimated in acetazolamide challenge of ^{99m}Tc-ECD SPECT. Relative ECD uptake, normalized by cerebellar uptake against that of IMP, showed a nonlinear relationship, indicating relatively less uptake in high-flow range areas. Therefore, we thought a linearization correction algorithm was essential in estimating the limitation of vasodilatory capacity using acetazolamide challenge or carbon dioxide inhalation.

The underestimation of vasodilatory capacity with ^{99m}Tc-ECD could be explained by limited first-pass extraction of ^{99m}Tc-ECD or backdiffusion of the tracer from the brain to the blood or both. In this study, we applied two models (Lassen's correction and correction based on the PS model) for linearization correction in ^{99m}Tc-ECD SPECT. The correction based on the PS model corrects the nonlinear relationship due to the limited extraction of the tracer while Lassen's correction corrects the backdiffusion of the tracer from the brain to the blood. The underestimated limitation of vasodilatory capacity observed in ^{99m}Tc-ECD SPECT without linearization correction was corrected by linearization algorithm. However, the effect of correction based on the PS model was superior to that of Lassen's correction. And the corrected ^{99m}Tc-ECD uptake ratio based on the PS model and IMP uptake ratio demonstrated a better linear relationship than that of Lassen's correction. Technetium-99m-ECD was reported to have a lower extraction fraction below 70% (*2*). On the other hand, IMP was reported as having over 90% (*2,12*). Technetium-99m-ECD shows rapid conversion from a lipophilic compound to hydrophilic metabolites in brain and blood (*13*). The arterial input in the brain is limited for a short period after intravenous administration. These findings suggest that the PS model could account for the nonlinear relationship between ^{99m}Tc-ECD uptake and ^{123}I-IMP uptake. Yonekura et al. reported that the comparison of ^{99m}Tc-ECD SPECT and CBF PET measurement (O^{15} steady-state method) demonstrated a nonlinear relationship of the tissue count of ^{99m}Tc-ECD and CBF. The corrected SPECT count-based PS model showed an excellent linear relationship (*4*). We suppose that underestimation of the limitation of vasodilatory capacity on ^{99m}Tc-ECD SPECT is due to underestimation of increased rCBF in the unaffected area mainly due to the limited first-pass extraction of the tracer. The linearization correction based on the PS model may be suitable for ^{99m}Tc-ECD SPECT.

The poor image contrast between low- and high-flow regions on ^{99m}Tc-HMPAO is due to the flow-dependent backdiffusion of lipophilic tracer from the brain, and the linearization correction applied was based on backdiffusion correction of Lassen's correction (*14–16*). Technetium-99m-ECD shows a gradual decrease in activity of the brain after several hours; however, the elimination rate is the same for high- and low-flow regions (*17*). The kinetic analysis also demonstrated a relatively small backdiffusion of ^{99m}Tc-ECD compared to that of ^{99m}Tc-HMPAO, and there was no relationship between backdiffusion rate and CBF (*18*). These observations indicate that the elimination of ^{99m}Tc-ECD from the brain is independent from blood flow, as opposed to ^{99m}Tc-HMPAO. The correction based on the PS model is more appropriate than backdiffusion correction for ^{99m}Tc-ECD.

Iodine-123-IMP was reported to have a high extraction fraction of about 96% and has no backdiffusion (*12*). Its linear uptake follows a wide range of flow assessed by microspheres (*19*). This causes ^{123}I-IMP to have a better linear relationship of ^{123}I uptake and rCBF in high-flow regions, and thus it is more suitable for the acetazolamide challenge test than ^{99m}Tc-labeled rCBF tracers. To estimate vasodilatory capacity by acetazolamide challenge, repeated SPECT studies with and without drug administration, are necessary. Furthermore, in the test/retest studies, the assumption is that the original distribution pattern is still the same during the second SPECT image acquisition. However, ^{123}I-IMP demonstrates a homogenous washout pattern. Due to the heterogenous washout pattern, a test/retest protocol would introduce significant error, therefore a two-day protocol is preferable (*12*). The two ^{123}I-IMP SPECT studies should be performed at an interval of at least several days. Recently, Hashikawa et al. (*20*) reported a split-dose and sequential ^{123}I-IMP SPECT protocol that enabled quantitative CBF measurements with and without acetazolamide challenge. However, this method requires dynamic SPECT with a high-sensitivity collimator, collimator change and arterial catheterization (*20*). The split-dose technique using ^{99m}Tc-ECD does not require special equipment, and images can be acquired by simple subtraction method.

Holm et al. (*21*) reported that the non-negligible washout of ^{99m}Tc-ECD between the two dose administrations limited the usefulness of split-dose SPECT technique for activation studies (visual stimulation). They found that the substantial and inhomogeneous washout of the tracer over a 100-min period was a significant problem for split-dose activation studies (*21*). Moretti et al. (*22*) reported that during the 50–120 min postinjection period, the regional structures were washing out at the same rate in normal brain tissue; however, there were differences in clearance in ischemic parietal zones and normal brain. This may be a potential pitfall in split-dose and sequential SPECT method with ^{99m}Tc-ECD. In our study, the SPECT protocol finished within 60 min, and CBF increase caused by acetazolamide challenge is greater than that of visual stimulation, unlike Holm's study. Moretti et al. (*12*) reported that ^{99m}Tc-ECD had the same uptake and retention characteristics of HMPAO and it was suitable for test/retest protocol. Our preliminary

data demonstrated that the heterogenous washout of ^{99m}Tc-ECD within 60 min could be negligible (Flores L II, *personal communication*). The influence of inhomogeneous washout of the tracer is thought to be small in our ^{99m}Tc-ECD SPECT protocol.

CONCLUSION

The vasodilatory capacity under acetazolamide challenge was underestimated with ^{99m}Tc-ECD when compared to ^{123}I-IMP. However, this underestimation could be corrected by the PS model. Technetium-99m-ECD SPECT that is corrected based on the PS model may be a useful method for evaluating cerebrovascular reserve using acetazolamide challenge.

REFERENCES

1. Kung HF, Ohmomo Y, Kung MP. Current and future radiopharmaceuticals for brain imaging with single-photon emission computed tomography. *Semin Nucl Med* 1990; 20:290–302.
2. Greenberg JH, Lassen NA. Characterization of ^{99m}Tc bicisate as an agent for the measurement of cerebral blood flow with SPECT. *J Cereb Blood Flow and Metabol* 1994;14(suppl 1):S1–S3.
3. Knudsen GM, Anderson AR, Sommier FE, et al. Brain extraction and distribution of ^{99m}Tc bicisate in humans and in rats. *J Cereb Blood Flow and Metabol* 1994;14(suppl 1):S12–S18.
4. Yonekura Y, Tsuchida T, Sadato N, et al. Brain perfusion SPECT with ^{99m}Tc bicisate: comparison with PET measurement and linearization based on permeability-surface area product model. *J Cereb Blood Flow and Metabol* 1994;14(suppl 1):S58–S65.
5. Shishido F, Uemura K, Murakami M, et al. Cerebral uptake of ^{99m}Tc bicisate in patients with cerebrovascular disease in comparison with CBF and CMRO2 measured by positron emission tomography. *J Cereb Blood Flow and Metabol* 1994;14(suppl 1):S66–S75.
6. Nakagawara J, Nakamura J, Takeda R, et al. Assessment of postischemic reperfusion and diamox activation test in stroke using ^{99m}Tc-ECD SPECT. *J Cereb Blood Flow and Metabol* 1994;14(suppl 1):S49–S57.
7. Friberg L, Anderson AR, Lassen NA, et al. Retention of ^{99m}Tc bicisate in the human brain after intracarotid injection. *J Cereb Blood Flow and Metabol* 1994;14(suppl 1):S19–S27.
8. Vorstrup S. Tomographic cerebral blood flow measurements in patients with ischemic cerebrovascular disease, and evaluation of the vasodilatory capacity by the acetazolamide test. *Acta Neurol Scand* 1988;77:5–48.
9. Vorstrup S, Brun B, Lassen NA. Evaluation of the cerebral vasodilatory capacity by the acetazolamide test before EC-IC bypass surgery in patients with occlusion of the internal carotid artery. *Stroke* 1986;17:1291–1298.
10. Hirano T, Minematsu K, Hasegawa Y, et al. Acetazolamide reactivity on I-123 IMP single-photon emission computed tomography in patients with major cerebral artery occlusive disease: correlation with positron emission tomography parameters. *J Cereb Blood Flow Metabol* 1994;14:763–770.
11. Yamashita T, Hayashi M, Kashiwagi S, et al. Cerebrovascular reserve capacity in ischemia due to occlusion of major arterial trunk: studies by Xe-CT and the acetazolamide test. *J Comput Assist Tomogr* 1992;16:750–755.
12. Moretti JL, Caglar M, Weinmann P. Cerebral perfusion imaging tracers for SPECT: which one to choose? *J Nucl Med* 1995;36:359–363.
13. Walovitch RC, Hill TC, Garrity ST, et al. Characterization ^{99m}Tc-L,L-ECD for brain perfusion imaging, part 1: pharmacology of ^{99m}Tc-ECD in nonhuman primates. *J Nucl Med* 1989;30:1892–1901.
14. Lassen NA, Anderson AR, Friberg L, et al. The retention of ^{99m}Tc d, l-HMPAO in the human brain after intracarotid bolus injection: a kinetic analysis. *J Cereb Blood Flow and Metabol* 1988;8:S13–S22.
15. Inugami A, Kanno I, Uemura K, et al. Linearization correction of ^{99m}Tc-labeled hexamethyl-propylene amine oxime (HMPAO) image in terms of regional CBF distribution: comparison to C15 O2 inhalation steady-state method measured by positron emission tomography. *J Cereb Blood Flow and Metabol* 1988;8:S52–S60.
16. Yonekura Y, Nishizawa S, Mukai T, et al. SPECT with ^{99m}Tc d,l-hexamethylpropylene amine oxime (HMPAO) compared with regional cerebral blood flow measured by PET: effects of linearization. *J Cereb Blood Flow and Metabol* 1988;8:S82–S89.
17. Léveillé J, Demonceau G, Walovitch RC. Intersubject comparison between ^{99m}Tc-ECD and ^{99m}Tc-HMPAO in healthy human subjects. *J Nucl Med* 1992;33:1902–1910.
18. Murase K, Tanada S, Inoue T, et al. Kinetic behavior of ^{99m}Tc-ECD in the human brain using compartment analysis and dynamic SPECT: comparison with ^{99m}Tc-HMPAO [Abstract]. *J Nucl Med* 1992;33:909.
19. Kuhl DE, Barrio JR, Huang SC, et al. Quantifying local cerebral blood flow by N isopropyl p 123 iodoamphetamine (IMP) tomography. *J Nucl Med* 1982;23:196–203.
20. Hashikawa K, Matsumoto M, Moriwaki H, et al. Split-dose ^{123}I-IMP SPECT: sequential quantitative regional cerebral blood flow change with pharmacological intervention. *J Nucl Med* 1994;35:1226–1233.
21. Holm S, Madsen PL, Sperling B, et al. Use of ^{99m}Tc bicisate in activation studies by split-dose technique. *J Cereb Blood Flow and Metabol* 1994;14(suppl 1):S115–S120.
22. Moretti JL, Tamgac F, Weinmann P, et al. Early and delayed brain SPECT with ^{99m}Tc-ECD and ^{123}I-IMP in subacute strokes. *J Nucl Med* 1994;35:1444–1449.

Viable Neurons with Luxury Perfusion in Hydrocephalus

Ching-yee Oliver Wong, Mark G. Luciano, William J. MacIntyre, Richard C. Brunken, Joseph F. Hahn and Raymundo T. Go

Departments of Nuclear Medicine and Neurosurgery, The Cleveland Clinic Foundation, Cleveland, Ohio

A woman with hydrocephalus due to aqueductal stenosis had functional imaging of cerebral perfusion and metabolism to demonstrate the effects of endoscopic third ventriculostomy–a new form of internal surgical shunting. Technetium-99m-ECD SPECT and ^{18}F-FDG PET showed regional luxury perfusion at the left frontal region. Three months after a successful third ventriculostomy, a repeated imaging of cerebral perfusion and metabolism showed resolution of luxury perfusion and global improvement of both perfusion and metabolism. This concurred with postoperative clinical improvement. The paired imaging of cerebral perfusion and metabolism provides more information than just imaging perfusion or metabolism. Thus, the detection of perfusion and metabolism mismatch may open a new window of opportunity for surgical intervention.

Key Words: hydrocephalus; perfusion and metabolism mismatch

J Nucl Med 1997; 38:1467–1470

The link between cellular viability and functional outcome after surgical intervention has been demonstrated in the myocardium with coronary artery disease by imaging myocardial perfusion and metabolism using $^{13}NH_3$ and ^{18}F-FDG (*1*) and by $H_2{}^{15}O$ and ^{11}C-acetate (*2*) PET. Recent studies using ^{123}I-labeled benzodiazepine receptor antagonist (*3–5*) and paired studies with ^{99m}Tc-HMPAO and ^{18}F-FDG (*6*) have opened a new quest into neuronal viability in cerebrovascular disease. However, little is known about neuronal viability and function in hydrocephalus, in which there is net accumulation of cerebrospinal fluid (CSF) within the cerebral ventricles with resultant dilatation (*7*). The constant pressure on cortical cells causes reduction of cerebral perfusion (*8,9*) and metabolism (*10–12*) that can be imaged noninvasively in humans by radionuclide emission tomography such as PET and SPECT. The structural changes are displayed by anatomical imaging such as x-ray CT or MRI as dilatation of ventricular system and thinning of the cortex. It is presumed that irreversible cerebral cortical damage has occurred when ventricles become dilated and metabolism shuts down. Therefore, the viability of the cortical neurons

Received Jul. 29, 1996; revision accepted Oct. 23, 1996.

For correspondence or reprints contact: C. Oliver Wong, MBBS, PhD, Department of Nuclear Medicine, Gb3, The Cleveland Clinic Foundation, Cleveland, OH 44143.