Annals of Nuclear Medicine Vol. 10, No. 1, 161–164, 1996

Quantifying brain tumor blood flow by the microsphere model with N-isopropyl-p-[^{123}I]iodoamphetamine super-early SPECT

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Regional cerebral blood flow was quantitatively measured in 6 patients with brain tumor by the microsphere model with N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) "super-early" single photon emission computed tomography (SPECT) images obtained 4–6 min after IMP injection with a three-head rotating gamma camera. The ratio of radioactivities (counts/pixel/min) in the "early" SPECT images (taken 25–55 min after IMP injection) to the "super-early" images of the brain tumors was 1.47 ± 0.13 (mean $\pm$ SD, $n = 6$), which was significantly lower than the ratio in the normal cerebral cortices (1.93 ± 0.25) ($p < 0.01$). This indicates faster clearance of IMP from the tumor tissue than that from the normal brain tissue. Blood flow values for the brain tumors obtained by the microsphere model based on the "super-early" SPECT images were 39.3 ± 12.4 m*l*/100 g/min, which was similar to the blood flow values for normal gray matter and in agreement with previous studies with positron emission tomography.

Key words: cerebral blood flow, brain tumor, [^{123}I]IMP, SPECT, microsphere model

INTRODUCTION

N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) has been used as a tracer for measuring cerebral blood flow (CBF) with single photon emission computed tomography (SPECT).[1] The relatively high first-pass extraction fraction and long retention in the brain tissue also allow quantitative CBF measurement based on the microsphere model.[1,2] "Early" SPECT images (usually from data acquired over 30 min after injection) have been used for this CBF quantification, but significant clearance of IMP from the brain tissue is believed to affect the delayed SPECT images.[3,4] Brain tumors usually appear as a "perfusion defect" in the "early" SPECT images, probably because clearance of IMP from tumor tissue is much faster than that from normal brain tissue. In the present study, we took "super-early" SPECT images, obtained 4–6 min after IMP injection, to avoid the effect of clearance of IMP from the tumor tissue and applied the microsphere model for quantitative measurement of the blood flow in brain tumors.

Received August 14, 1995, revision accepted October 19, 1995.

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MATERIALS AND METHODS

The study included six patients with brain tumor (four metastatic brain tumors, one glioblastoma, and one meningioma, Table 1). All the brain tumors were located above the tentorium (five in the cerebral cortex, one in the thalamus). All patients underwent X-ray CT or MRI with contrast enhancement and histological diagnosis was based on tumor specimens obtained at surgery.

Patients were placed on the table with the eyes covered with an eye-mask in a quiet environment. Under local anesthesia with 1% xylocaine, a cannula was inserted in the right dorsalis pedis artery for continuous blood sampling. Arterial blood gas analysis data (pO_2, pCO_2, pH), obtained just before IMP injection, were all within normal limits. Patients were injected intravenously with 222 MBq of [^{123}I]IMP (Nihon Medi-Physics, Nishinomiya, Hyogo) over 10–15 sec and continuous sampling of arterial blood was performed for 5 min after the initiation of IMP injection (Fig. 1). SPECT images were obtained with a three-head rotating gamma-camera (GCA

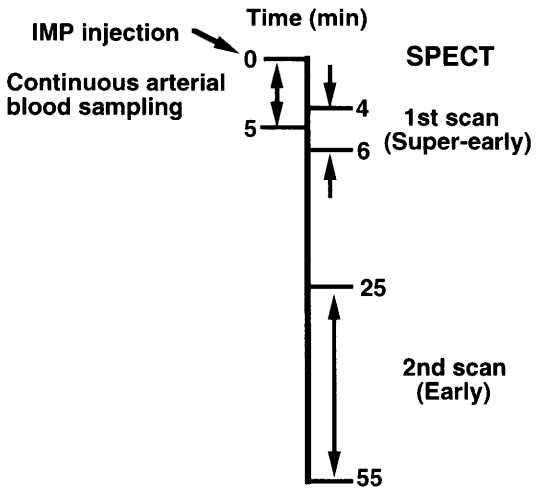

Fig. 1 Time schedule of the study.

9300A; Toshiba, Tokyo) with a high resolution fan beam collimator. The first data acquisition was started 4 min after IMP injection and continued for 2 min ("super-early" images) with two returns of pendulous rotation at an angle of 120 degrees, and the second from 25 to 55 min after IMP injection ("early" images). Since the head position of the patients did not change between two SPECT scans, the regions of interest were determined in the "early" SPECT images, which had much better image quality than the "super-early" images, and were then applied to both the "super-early" and "early" images for quantitative measurement of the radioactivity in the regions. The ratio of radioactivities (counts/pixel/min) in the "early" SPECT images to that in "super-early" images (early/super-early count ratio) was calculated for each brain region for each patient. The ratios in the brain tumors were compared with those in the normal or edematous brain tissues by grouped t-test.

The CBF was quantitatively measured in the brain tumor and peritumoral edema tissue based on the microsphere model using the "super-early" SPECT images and the arterial blood sample taken 5 min after IMP injection.[1] The CBF was also measured in the contralateral frontal cerebral cortex, contralateral basal ganglia, and ipsilateral cerebellar cortex as normal brain tissues. A fixed value for the octanol extraction fraction (0.8) was used.

RESULTS

The early/super-early count ratio in the brain tumors was 1.47 ± 0.13 (mean $\pm$ SD, n = 6), which was significantly lower than that in the normal cerebral cortices (1.93 ± 0.25, $p < 0.01$). The blood flow value in the brain tumors obtained with the microsphere model by using the "super-early" SPECT images was 39.3 ± 12.4 ml/100 g/min, which was similar to or a little lower than the blood flow values for normal gray matter (Table 2). MRI and SPECT images in a case of a metastatic brain tumor are shown in Figure 2.

Table 1 Clinical materials

Case	Age (y)/Sex	Diagnosis	Tumor location
1	59/M	Metastasis (lung)	Frontal
2	44/F	Metastasis (lung)	Parasagittal
3	72/M	Metastasis (colon)	Parietal
4	19/M	Metastasis (osteosarcoma)	Occipital
5	66/F	Glioblastoma	Thalamus
6	69/F	Meningioma	Frontal

Table 2 Early/super-early count ratio and regional cerebral blood flow

Region	Early/super-early count ratio	CBF (ml/100 g/min)
Tumor	1.47 ± 0.13*	39.3 ± 12.4
Peritumoral (edema)	1.92 ± 0.15	21.3 ± 3.8
Contralateral frontal	1.93 ± 0.25	42.2 ± 2.7
Contralateral basal ganglia	2.10 ± 0.25	38.3 ± 3.8
Ipsilateral cerebellum	1.89 ± 0.19	43.2 ± 7.5

The values are means $\pm$ SD (n = 6)
*Significantly lower than the values of other brain regions ($p < 0.01$).

DISCUSSION

Quantitative blood flow studies with positron emission tomography have shown that the blood flow values in most brain tumors are almost as high as those in gray matter.[5,6] In contrast, most IMP-SPECT studies have shown lower IMP uptake in tumors than in normal gray matter, and tumors with high IMP uptake are rather rare.[7-9] But low IMP uptake does not always result from low blood flow in brain tumors, but is rather due to rapid clearance of IMP from the tumors causing a lower IMP concentration during data acquisition. Dynamic SPECT studies have shown that clearance of IMP from the tumors started immediately after intravenous IMP injection.[10] In the present study, we attempted to measure tumor blood flow quantitatively by means of SPECT with IMP, which had not been achieved before, based on acquisition of the SPECT images before significant amounts of IMP were cleared from the tumors.

SPECT images of the brain can be obtained within a few minutes with a newly developed multi-detector SPECT system.[11] Clearance of IMP from the brain is known to be negligible during the 5 min after intravenous IMP injection, so the "super-early" SPECT images were acquired between 4 and 6 min (2 min scan) after IMP injection. Since the "super-early" images were not of good quality,

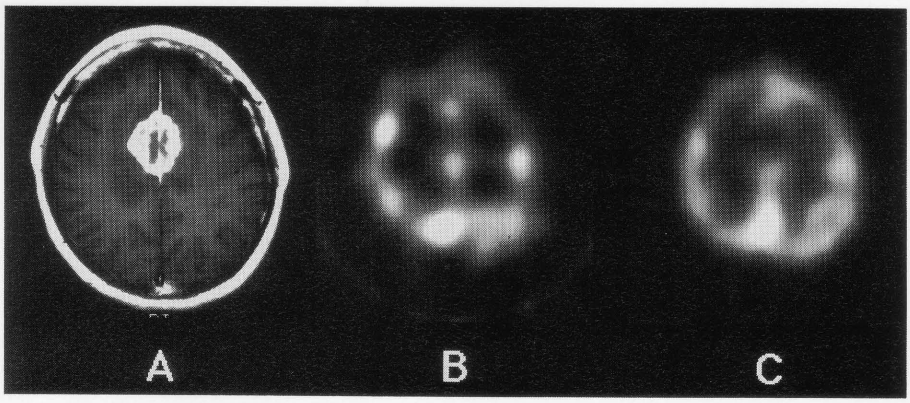

Fig. 2 MRI (A), "super-early" SPECT (B), and "early" SPECT (C) of a 44-year-old woman with a metastatic brain tumor from lung cancer. IMP uptake in the tumor region, which was decreased in the "early" image, was as high as that in the surrounding brain tissue in the "super-early" image. The early/super-early count ratio of the tumor in this case was 1.43 and blood flow value obtained by the microsphere model using the "super-early" SPECT image was 33.0 ml/100 g/min.

the "early" SPECT images (25 to 55 min, 30 min scan) were used as a guide for detecting brain structures. The early/super-early count ratio was significantly lower in the tumor tissue than in the normal cerebral cortex, indicating that the "super-early" and "early" SPECT images of brain tumor were different. Therefore, the quantification methods which employ "super-early" SPECT images extrapolated from "early" images by simple proportion of the total brain radioactivities of two scans[2] are inaccurate.

The blood flow value in brain tumors obtained with the "super-early" SPECT images and the microsphere model was 39.3 ± 12.4 (ranging from 27.2 to 55.5) ml/100 g/min, which was similar to or a little lower than the CBF values for normal gray matter and agreed with the values obtained in previous studies with positron emission tomography.[5,6] Clearance of IMP is negligible during the first 5 min after IMP injection in the normal brain, but it is not known if this is also true in tumor tissues. Since time activity curves vary from tumor to tumor, the optimal scanning schedule for the "super-early" SPECT scan, allowing adequate time for IMP to be distributed over the brain and before significant loss of IMP from the tumors occurs, may have to be determined for each type of tumor by dynamic SPECT studies.

Recent studies of IMP dynamics in the brain by means of two-compartment[3] or three-compartment[4] model analysis showed that clearance of IMP was already significant 30 min after intravenous IMP administration even in normal brain tissue, suggesting that SPECT data should be acquired as early as possible after IMP injection. Because the high-resolution SPECT equipment used in the present study is becoming widely available, "super-early" SPECT images will be routinely taken in many institutions in the near future. Quantitative CBF measurement can then be performed based on "super-early" IMP-SPECT images and the microsphere model, which is theoretically the simplest model and is applicable to various diseases of the central nervous system including brain tumors where the behavior of IMP is not fully understood.

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