INVESTIGATIVE NUCLEAR MEDICINE

Single-Photon Tomographic Study of Regional Cerebral Blood Flow After Stroke: Concise Communication

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Groups of normal volunteers and patients with cerebral vascular disease and stroke have been studied with a new single-photon emission computerized tomograph (SPECT), which displays regional cerebral blood flow in three transverse tomographic sections following 4 min of inhalation and washout of Xe-133.

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Since the early reports of Kety and Schmidt (*1*) there has been considerable interest in the measurement of cerebral blood flow by the diffusible indicator method. This approach seemed well suited to radionuclide tracer techniques, with the substitution of radioisotopes of several of the noble gases for Kety and Schmidt's original tracer, nitrous oxide. Considerable work was reported by Lassen, Ingvar, Sveinsdottir, and their associates, as they developed increasingly sophisticated scintillation multiprobe devices for the estimation of regional cerebral blood flow (rCBF) (*2–4*). These investigators realized, however, that observations with a multiprobe system were essentially limited to the brain's surface. They therefore decided to construct a device that would provide a three-dimensional representation of rCBF, and, working with one of us (EMS), they designed a single-photon emission computerized tomographic device (SPECT), the development and theory of which have been reported elsewhere (*5*). The prototype instrument was constructed at the University Hospital (Rigshospitalet) in Copenhagen, Denmark. We have secured a duplicate instrument,* and have used it in the study of stroke and cerebral vascular disease in a group of volunteer subjects.

MATERIALS AND METHODS

The detector of SPECT consists of 64 NaI(Tl) scintillation crystals in four groups of 16 (Fig. 1). Adjacent pairs of the 14 × 2 × 1.3 cm crystals are observed by three photomultiplier tubes with one-dimensional positioning capability. Three tomographic slices, approximately 2 cm in thickness with their centers 4 cm apart, are defined by fitting each crystal with three interchangeable focused lead collimators whose septa are appropriate in thickness and length for the 81-keV emission of Xe-133, the tracer used in these studies. Collimator design and specifications are described in greater detail by Stokely et al. (*5*).

The four sets of detectors are arranged in a square configuration (Fig. 1) and this array is mounted on a rotatable wheel. In practice a complete set of projections is obtained over a 360° rotation in 10 sec (6 rpm).

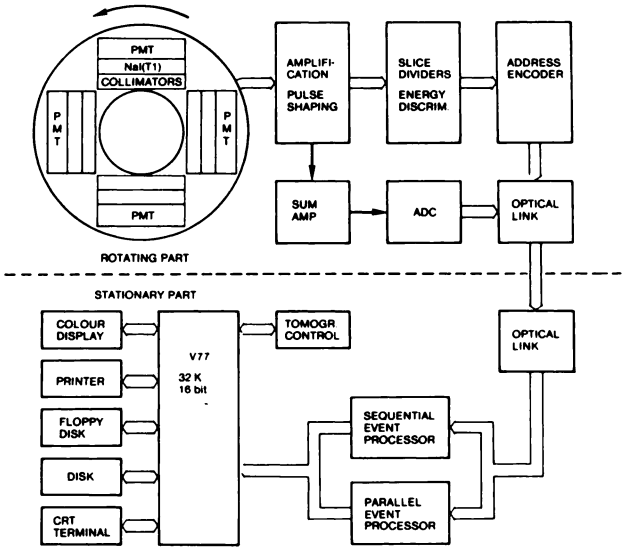

FIG. 1. Block diagram of single-photon emission computerized imaging unit used for dynamic determination and tomographic display of regional cerebral blood flow.

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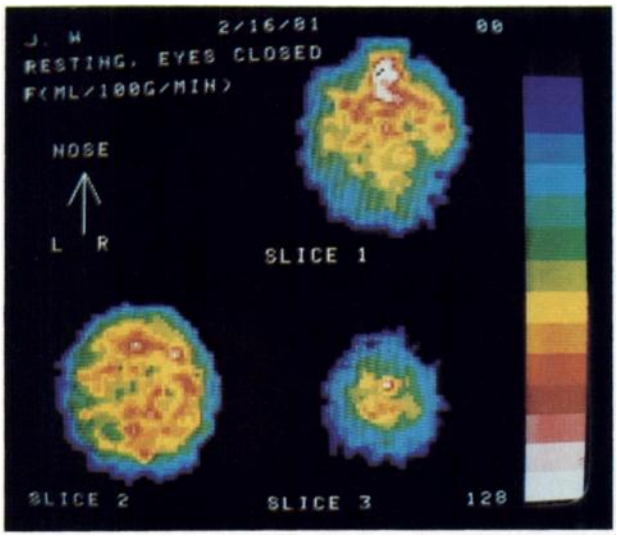

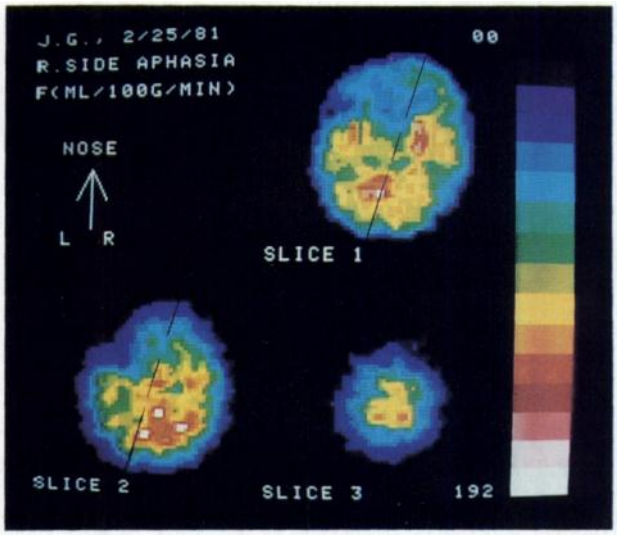

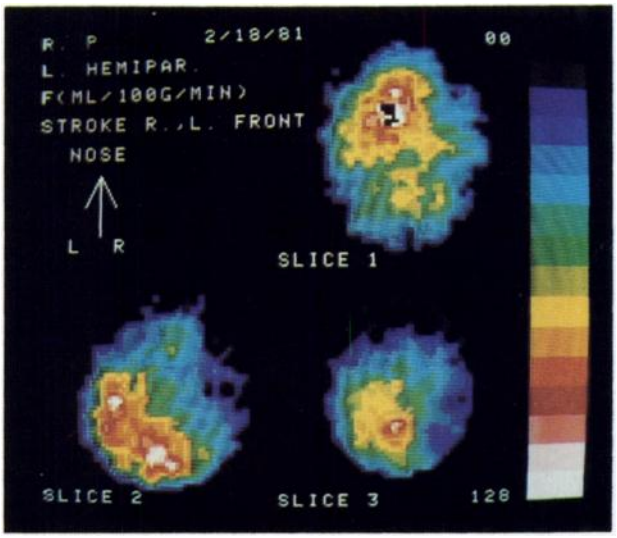

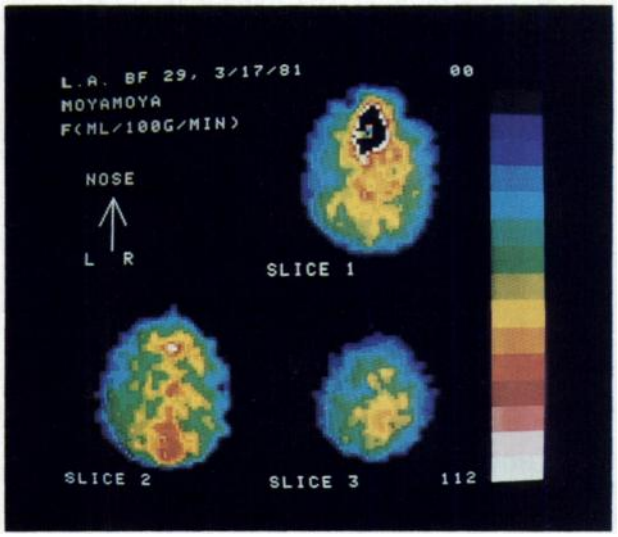

FIG. 2. Xe-133 study of regional cerebral blood flow in a "normal" volunteer in resting state with eyes closed. Three tomographic sections (Slices 1–3) are displayed in 16-color scale representing flow values from 0 (dark blue) to a maximum of 128 ml/100 g/min (white). In upper left-hand corner are subject's data and an orientation symbol. Flow patterns of the three slices are within normal limits. (Subject 1)

FIG. 3. Tomographic rCBF study of 58-yr-old hospitalized patient (Subject 2) with history of past left frontal and recent right strokes. rCBF patterns are abnormal.

FIG. 4. Tomographic study of a 54-yr-old man (Subject 3), a hospitalized patient who had had a stroke 10 days before this examination. His head is rotated 15° to his right, and the midline is marked with a dashed stripe. Flow patterns are abnormal.

FIG. 5. Tomographic study of a 29-yr-old woman (Subject 4) who had history of progressive cerebral vascular disease, with probable stroke 5 yr before examination. Clinical and arteriographic diagnoses were moyamoya, and the flow patterns are markedly abnormal.

The detector's electronics are located on the rotating part of the tomograph (Fig. 1). Included are circuits for amplification and shaping of the output pulses from the photomultiplier tubes, as well as energy discrimination and slice definition. An analog-to-digital converter (ADC) for 6-bit pulse-height analysis gives the energy of the event, and an 8-bit address encoder provides the address of the 64 × 64 channels representing the event's position. These data are sent to the tomograph's stationary electronic components through a 10-bit-wide optical link capable of 30 million bits/sec, located on the axis of rotation. Events are processed sequentially, and the address is sent to a computer. After energy discrimination, events are recorded in a 1-bit buffer and transmitted to the computer in negligible time. A data rate of 1 million counts/sec can be accommodated with negligible loss (1%). Images are reconstructed by a filtered back-projection method that utilizes the arithmetic means of opposing ray sums, multiplied by a correction factor for attenuation effects. Image data are stored on a single-sided, single-density flexible diskette, with system and operating programs recorded on diskettes as well.

Resolution of the SPECT system, determined with

various phantoms charged with Xe-133, varies from about 1.0 cm at the periphery of the head to 1.7 cm at the center in the transverse-section dimension. Resolution in the dimension of a coronal slice is almost constant at 1.9 cm across the slice. The system sensitivity, measured using Xe-133 in water in a cylindrical phantom 17 cm in diameter, is 19,145 cts/μCi-ml for each slice (57,434 total). The slice-to-slice crosstalk is 9% for a point source in a scattering medium, and adjacent-crystal crosstalk is less than 2%.

During a study the subject's head is placed within a plastic shield that lines the detection space. He breathes a xenon-oxygen-air mixture containing 10 mCi/l Xe-133 for 1 min, and ordinary air during a washout period of 3 min. The detector records four 1-min measurement periods, while at the same time, a collimated scintillation probe provides for a Xe-133 curve over the upper portion of the right lung as an input function. The method of Kanno and Lassen (*6*), used to calculate rCBF, is based on a monoexponential pulse response in each voxel, assuming a single well-mixed compartment in each voxel volume.

Since the input function is complex and is described by the inhalation of the tracer, the concentration of Xe-133 in each voxel is given by

$$C(t) = K_p \int_0^t C_a(x)\, e^{-p(t-x)}dx,$$

where K is a constant relating to the tracer's specific activity and the sensitivity of the detectors to the quantity of tracer, $C_a(x)$ is the arterial input function of tracer into all voxels, p is the desired perfusion rate in units of flow per unit weight of brain tissue, and x is a variable of integration. The equation is then solved for p. Flow values for each voxel are calculated by a "table lookup" method described by Kanno and Lassen (*6*).

Values of rCBF are displayed in a 64 × 64 matrix on a television monitor, using a linear scale that may be rendered either as 16 shades of gray from white to black, or 16 colors from white through red to deep blue, maximum to minimum (see Figs. 2–5). In practice the interpretation of rCBF tomographic sections is facilitated by use of the color scale, since visual separation of the black-and-white scale is difficult even for those skilled in analysis of radiographic images.

In most studies the tomographic sections parallel the cantho-meatal line (CML), which is a line drawn from the outer canthus of the eye to the midpoint of the external auditory meatus. The center of the lowest, or first, slice is usually located 2 cm above the CML. The center of the second slice is 6 cm above the CML, and the third slice is centered 10 cm above the CML. Alignment of the head during studies and reduplication of positioning in subsequent studies is carried out with the aid of transparent templates and positioning photographs.

Studies on four volunteer subjects will be reported.

Subject 1 was a 40-yr-old right-handed woman who was in good health, and was a part of a group of "normal" individuals who volunteered for baseline studies. During the 4-min measurement period she lay supine and motionless. Her eyes were closed. Ambient light and sound were kept at low levels.

Subject 2 was a hospitalized patient, age 58, who one week before the examination had suffered an extensive stroke involving much of the right cerebral hemisphere. She was known to have had a left frontal stroke in the past. She exhibited left hemiparesis and slurring of speech. During examination she lay supine with her eyes open. Ambient light and sound were kept at a low level.

Subject 3 was a 54-yr-old man who was hospitalized at the time of examination. He had had a stroke 10 days before the study, and it had produced a right hemiparesis and aphasia. A Tc-99m DTPA brain scan was positive for a lesion in the left frontoparietal area. TCT scan was not available. The subject was supine and had his eyes open during the examination. Ambient sound and light were as above.

Subject 4 was a 29-yr-old woman who had a history of progressive cerebral vascular disease, with a probable stroke 5 yr earlier. She had bilateral weakness of the extremities and marked slowness of speech. She had been studied extensively during her hospital stay, and had had numerous tests, including bilateral internal-carotid arteriography that had shown almost complete absence of filling of the middle cerebral arteries and their branches, with residual flow evident in anterior and posterior cerebrals, together with the formation of a rete mirabile, a network of small communicating vessels in the region of the basal ganglia. TCT studies suggested diffuse atrophy and a new right posterior infarct.

RESULTS

Figure 2 shows the general appearance of a SPECT study of rCBF in a normal individual (Subject 1). Slice 1, centered 2 cm above and parallel to the CML, shows its highest activity in the anterior midline, due to the presence of Xe-133 in the nasal passages, sinuses, and nasopharynx. Anatomic structures represented in this slice include the bony orbits anteriorly and the base of the skull laterally and posteriorly, accounting for the relatively low peripheral flow in these areas. Perfused structures anteriorly represent the inferior portions of the frontal and temporal lobes. In the midline of this slice, from anterior to posterior, are shown blood-flow values for basal ganglia and other midline structures. Posteriorly in the midline, rCBF may be seen in the pons and cerebellum. In many resting, right-handed individuals preponderant flow may be seen in the inferior portions of the right frontal and temporal lobes. This is not conclusively demonstrated in this subject.

Slice 2 shows the higher perfusion values to be in the

frontal and in the right parietal and temporal lobes peripherally, with lower rCBF values on the left side. This is a common pattern in the resting, right-handed, normal subject. Anatomic structures represented in Slice 2 include frontal, parietal, temporal, and occipital lobes peripherally, while central activity is thought to represent perfusion of such structures as thalamus, internal capsule, splenium, and inferior corpus callosum, front to back. In some individuals, areas of low flow corresponding to the lateral ventricles may be seen, and there is generally higher flow in the periphery of the hemispheres (gray matter) than in the more central portions (white matter).

Slice 3, centered 10 cm above the CML, cuts tangentially through cortical gray matter. As in this individual, it is often not an especially useful view. Some of the structures whose perfusion patterns are included in this slice are the frontal, precentral, postcentral, and angular gyri.

Other information displayed in Fig. 2 includes clinical data, seen in the upper left-hand corner, a symbol showing the orientation of the patient, and, along the color scale on the right, the values of minimum and maximum rCBF in ml/100 g/min.

Subject 2, whose study is seen in Fig. 3, was known to have had at least two episodes of stroke, whose effects can be seen in all three slices. In Slice 1 there is asymmetry of the anterior pattern, with marked reduction of flow to the inferior portions of the right frontal and temporal lobes. The posterior pattern is thought to be within normal limits. In Slice 2 there is no evidence of the normal pattern seen in Fig. 2, Slice 2. Instead there is residual perfusion of left parietal and temporal lobes, and the occipital lobe. This person was examined in a lighted room, and her eyes were open throughout the study. Some of the elevated rCBF seen in the occipital region involves a stimulated visual cortex. Elsewhere there is reduced flow to the entire frontal region and the right side, except for the occipital area. Even in Slice 3 there is asymmetry, with deletion of the right side of the usually rather symmetrical third-slice pattern.

Subject 3, whose study is seen in Fig. 4, turned his head approximately 15° to the right just before the beginning of the study. The midline is marked with a dashed black stripe. In Slice 1 there is evidence of diminution of rCBF in the inferior frontal and left temporal lobes, while Slice 2 shows a deep, wedge-shaped defect in the flow pattern of the left frontoparietal region. It was in this area that a wedge of increased radionuclide uptake had been seen on brain scintigrams. Blood flows are also reduced in the left parietal and temporal areas, compared with the right side. The patient was examined with his eyes open in a lighted room, but this does not account for all of the high flow values seen in the occipital area. As can also be seen in Slice 2 of Fig. 3, when large-scale redistribution of rCBF has occurred after cerebral vascular accidents, chaotic flow patterns may appear, and areas of high flow may be identified in anomalous locations. The appearance of Slice 3 is not remarkable.

Subject 4, whose study is seen in Fig. 5, had had a long history of mental impairment preceding her stroke 5 yr previously, and came to us for examination with the clinical diagnosis of moyamoya. This entity was first identified by Japanese neurologists and radiologists (*7,8*), but is now seen with increasing frequency in this country and elsewhere around the world. It is characterized by progressive occlusive disease of the middle cerebral arteries and their branches, with the development of a basal network of collateral vessels. In view of the nature and extent of her disease, the findings in Fig. 5 are not surprising. In Slice 1 there is relative reduction of perfusion in the most lateral aspects of the inferior frontal and temporal lobes, with relative preservation of midline perfusion. Note the anterior midline artifact due to radioxenon in the nasal passages.

Slice 2 also shows diminution in perfusion of the peripheral portions of both cerebral hemispheres. The mid portions of the frontal lobes, the basal ganglia, and the occipital lobes maintain perfusion at or above median levels, being supplied by anterior and posterior cerebral arteries and the basal communicating network. In Slice 3 the remaining perfusion seems to be centered posteriorly, as might be expected. The profound change in distribution of cerebral blood flow in the presence of this vascular occlusive disease becomes even more apparent when Slice 2 in Fig. 5 is compared with Slice 2 in Fig. 2.

DISCUSSION

The cases described above are part of an on-going assessment of the capabilities of a dynamic single-photon emission computerized tomograph (SPECT) designed for the noninvasive determination of rCBF using an inhaled radiotracer such as Xe-133 (see Appendix). It is evident that qualitative changes in the rCBF pattern, readily recognizable as significant deviations from normal, may be produced by extensive cerebral vascular disease such as that present in three of our subjects (Figs. 3–5). In our present experience there is concurrence between SPECT and rCBF studies and TCT scans when vascular disease has produced anatomic changes. However, cases such as that seen in Fig. 5 suggest that important changes in rCBF may be detected by this method before development of positive TCT findings. Similar results have recently been published by Lassen et al. (*9*) based upon their study of ten patients who had had strokes. Lassen et al. performed their rCBF determinations with the SPECT system that was the prototype of our unit.

During this pilot study no effort was made to evaluate

variables that might influence rCBF during a determination. However, we now measure blood pressure and expired CO_2 before and after each test in order to assist us in determining the statistical significance of differences in regional flow, and in whole-slice mean flow values.

We believe that SPECT determination of rCBF might be of value in the study of patients with other disease entities that affect brain perfusion, and that it should be evaluated carefully for its potential application to routine patient care.

FOOTNOTE

* Tomomatic 64, Medimatic A/S, Gersonvej 7, DK 2900 Hellerup, Denmark.

APPENDIX

The tracer used in determination of rCBF with SPECT is Xe-133, which has a 5.3-day half-life and decays to Cs-133. It emits negative beta particles of 35 and 50 keV maximum energy, and photon radiation at 81 keV, emitted with a frequency of 35% (*10*). When administered in doses of 10 mCi/l during one minute of rebreathing, Xe-133 may be expected to give lung doses of 0.1-0.2 rad and total-body doses of the order of 0.01 rad (*11*,*12*). The highest dose would be received by the mucosa of the upper airways, which might receive from 1 to 5 rads per procedure.

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