Revival of Clinical Nuclear Medicine Brain Imaging

The struggle for survival of single-photon tomography, championed by a few strong and persistent proponents, now appears not to be in vain, as evidenced by the paper on regional cerebral blood flow in this issue of *The Journal of Nuclear Medicine* (*1*) and another corroborative study (*2*). As is well known to most readers of this *Journal*, the clinical use of emission transverse-section tomography dates from the early 1960s, when the first transverse-section tomograph was developed by Kuhl and Edwards (*3*). Later, the emission longitudinal tomographic scanner for limited-angle tomography was developed by Anger (*4*). Noteworthy efforts to develop or adapt instrumentation and algorithms for single-photon tomography can be found in IAEA symposia on medical scintigraphy (*5,6*), and in symposia on tomographic imaging using single photons (*7–9*).

Enthusiasm among nuclear medicine clinicians has waxed and waned with the hopes and disappointments of innovations such as coded apertures, including Fresnel and seven-pinhole embodiments of longitudinal tomography (*9*), and the adaptation of single- or dual-headed Anger cameras to rotating gantries for transverse-section tomography. The disappointments of longitudinal tomography and the associated coded-aperture approach result from the inadequacies of sampling over a limited angular range (*10*). The frustrations with the commercial single-headed devices can be attributed to poor sensitivity and less-than-optimal algorithms to correct for attenuation and scatter.

Though a number of single-headed, single-photon tomographs are now being offered by commercial companies, these devices fall short of being practical instruments for tomography owing to poor sensitivity and poor resolution. In fact, the commercial systems using one or two state-of-the-art gamma cameras for conventional projection imaging and tomography seem not to have improved from the previous experience of a number of investigators (*11–17*).

Three instrumental approaches that do not have the major limitations of poor sensitivity, inadequate resolution, and restricted angular range of sampling are:

(1) Four detector banks placed as closely as practical to the subject (Fig. 1-B): Mark IV (*3*) and Tomomatic-64 (*1,2,18*).

(2) Harvard Scanning Multidetector Brain System, which is a modification of a device built initially by Union Carbide (*19–22*).

(3) Circular array of crystals with rotation and moving collimator fins—Headtome (*23*).

The sensitivities of these systems are compared in Table 1 with those of positron tomographs, the Anger camera, and a fully three-dimensional system using 200 high-purity germanium detectors of intermediate sensitivity, low resolution, but good accuracy for rCBF (*24*).

The Mark IV, perfected by Kuhl and his late associate Roy Edwards, has sensitivity and resolution that allow practical studies of the brain. It is competitive with positron tomography for brain imaging in the 1- to 2-cm resolution range. The imaging characteristics of this device can be improved even further. The Tomomatic-64, used by Bonte and Stokely (*1*) for studies reported in this issue, was designed for rapid sequential imaging in order to observe xenon washout tomographically for calculation of regional cerebral blood flow (rCBF). The reported resolution of the Mark IV is 1.8 cm FWHM at the center and 1.6 cm FWHM at 9 cm from the center. The reported resolution of the Tomomatic-64 is 1.7 cm, although the xenon images appear to have poorer resolution.

The Harvard Scanning Multidetector Brain System, until recently marketed by Union Carbide Corp., has a resolution capability of 10 mm and a sensitivity $\frac{1}{3}$ that of the PET devices with the same resolution and section thickness. This system does not perform the angular sampling fast enough for xenon washout studies, but it has the potential for imaging relative rCBF, if radiopharmaceuticals that are extracted in proportion to blood flow become widely available. Unfortunately for Union Carbide, just as these agents became available (*25–28*), the firm ceased the evaluation and commercial development of this system. Fortunately, researchers at Harvard Medical School took over the instrument and are pursuing improvements in hardware and software.

From results with the Mark IV (*29,30*) and with the Harvard multidetector system (*21,22,31,32*), it now appears that static imaging by these brain tomographs can give data on

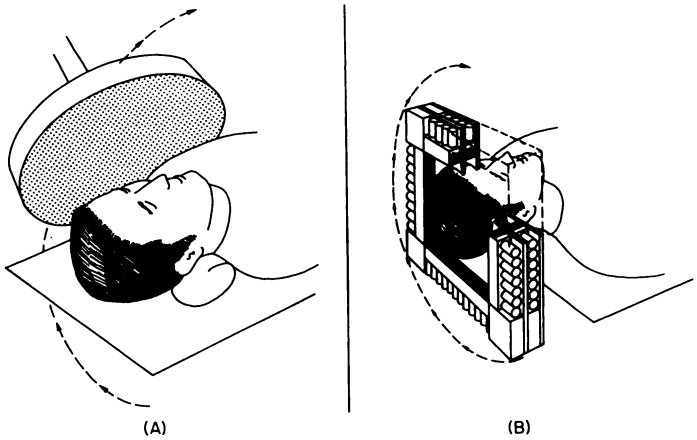

FIG. 1. Single-photon tomographic imaging approaches: (A) rotating Anger scintillation camera; (B) rotating four-sided scanner yet to be developed, with detecting head consisting of scintillators or solid-state detectors.

rCBF competitive with PET using iodine-123-substituted phenylalkylamines (e.g., iodo-isopropyl amphetamine). Note that although these phenylalkylamines have an affinity for dopamine receptors, they also readily penetrate the blood-brain barrier as lipophilic compounds. Contrary to the behavior of freely diffusible compounds (e.g., iodoantipyrine, H_2O, noble gases, etc.), the phenylalkylamines become trapped, perhaps by the fact that the partition coefficient changes significantly with a change in pH (*26*). Thus, for compounds that are avidly extracted and do not wash out readily, a relative rCBF can be evaluated by quantitating the relative distribution of the administered tracer after the initial uptake period of a few minutes, just as one would proceed with microsphere relative-flow analysis.

Thus we have within the grasp of any clinical department either the xenon-washout method or the extraction method for evaluating rCBF in ischemic disease with a sensitivity probably greater than that of contrast-enhanced TCT. Both depend on a proper instrument that is not one of the commercial single-headed, single-photon rotating devices (Fig. 1A), but an instrument similar to that in Fig. 1B or some modification of the Harvard Multidetector Scanning Brain System.

The possibility that the xenon-washout technique will be far more sensitive in the early detection of brain disorders seems evident from the case presentations in the Bonte-Stokely article in this issue of the *Journal* and in case reports by Lassen et al. (*1*,*2*). The method used by their device (Tomomatic-64) for the quantification of regional blood flow involves inhalation of xenon through a convenient and easy-to-operate device. Emission data are acquired over a period of 4 min, during which time the head scanner rotates at a rate of 180°/5 sec in order to acquire multiple angles for computed tomographic reconstruction. The input function—i.e., availability of a xenon tracer to the cerebral vascular bed—is evaluated by a detector over the chest. The regional cerebral blood flow is calculated in terms of volume/minute per unit mass of brain tissue, and color scales are used to relate the spatial distribution of flow to numerical values. The development of this device by Danish investigators was based on the objective of achieving a high count rate using inhalation

TABLE 1.

Device	Sensitivity (cts sec^{-1} μCi^{-1} cc^{-1})	Resolution	
		Transverse (mm)	Axial (mm)
Positron Tomographs (BGO)	50,000–75,000	7.5–9	15
Mark IV (*3*)	15,400	17	17
Harvard Scanning Multidetector Brain System (*20*)	14,000	10	13
Tomomatic-64 (*18*)	17,000	17	23
Headtome (*23*)	21,000	10	20
200-element HP Germanium (*24*)	2,400*	20	20
Anger camera	~600	11	<11

* Estimated from 12,600 cps/μCi/cc in 1,640 cm^3 phantom.

or injection of Xe-133, and at the same time circumventing the problem of superposition that invalidates the quantification of ischemic areas deep within the brain.

From the experience of the Danish investigators and the group at Southwestern Medical School in Dallas, it appears that there is at least one practical, single-photon, commercial device that can conveniently depict changes in cerebral blood flow and even measure twenty-percent changes in blood flow associated with motor cognitive activity (*2*). There are a number of improvements that one can anticipate in the next generation of the present commercial instrument. First, it appears that the resolution is worse than 1.7 cm and that there are artifacts associated with inadequacies in the method of data collection, scatter correction, and the method of compensation for attenuation. From discussions with the developers and users of the Tomomatic-64, it appears that substantial improvements can be made even in the present machine by software developments. Thus, the results reported by two pioneering papers (*1*,*2*) can be expected in the near future to be even better, and we hope the device will be generally available to nuclear medicine departments within a year. In addition, by substituting Xe-127 for Xe-133, a sixfold advantage in usable photon/rad dose to the lungs can be realized.

There are encouraging prospects for evaluating rCBF, regional blood volume, and permeability changes in the blood-brain barrier using a practical instrument similar to the Mark IV (Fig. 1B), but no commercial machine exists at present. An article by Thomas Hill and co-workers, due to appear in an upcoming issue of *The Journal of Nuclear Medicine*, will corroborate findings of Kuhl et al. (*3*) regarding single-photon imaging of relative rCBF. Arguments why a four-sided system is optimal (*10*) and arguments to support the contention that the sensitivity of a single-photon device is not impractically low (*10*) have been substantiated by experimental results on single-section devices. The sensitivity of these devices is $\frac{1}{3}$ to $\frac{1}{4}$ that of single-section PET devices, as shown in Table 1.

The development of an instrument that allows imaging of multiple contiguous sections without gaps between them will require clever design if scatter rejection is maintained. Nevertheless, with an availability of pure I-123 compounds, Tc-99m chelates, and techniques for the use of Tc-99m-labeled red blood cells, a one- or two-section tomograph should give the practicing nuclear medicine diagnostician the tool he can apply with crucial measurement capabilities for brain disorders with 10-mm resolution.

The objective of this editorial is to call attention to our present capability to measure or infer regional cerebral blood flow using single-photon tomography in the clinical nuclear medicine department without any extraordinary training or requirements on personnel. The radiopharmaceuticals are available. All that is required is the acquisition of a proper single-photon tomograph for the head. A previous editorial by Thomas Hill (*33*) and a review of the status of single-photon tomography in 1980 by Cowan and Watson (*34*) also present the clinical advantages of single-photon tomography. Oldendorf has recently presented cogent arguments which support the contentions of this editorial (*35*, *36*). For either the Xe-washout rCBF (absolute) or the static rCBF (relative) approach, the device should involve about $\frac{1}{4}$ the cost of a positron tomograph. We can hope that commercial systems will be designed to do what can be done in terms of sensitivity, resolution, uniformity, and reliability.

"Brain scanning" may yet be the procedure of choice for central nervous system lesions in clinical diagnostic medicine.

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