Quantitative Iodine-123 IMP Imaging of Brain Perfusion in Schizophrenia

Marvin B. Cohen, Ralph R. Lake, L. Stephen Graham, Michael A. King, Arthur S. Kling, L. Jaime Fitten, James O'Rear, Gabriella A. Bronca, Manju Gan, Roger Sevrin, and Leslie Yamada

Nuclear Medicine Service, Pharmacy Service, and Psychiatry Service, V. A. Medical Center, Sepulveda, California; and University of California at Los Angeles and the University of Massachusetts, Worcester, Massachusetts

Decreased perfusion in the frontal lobes of patients with chronic schizophrenia has been reported by multiple observers using a variety of techniques. Other observers have been unable to confirm this finding using similar techniques. In this study quantitative single photon emission computed tomography brain imaging was performed using p,5n [^{123}I]IMP in five normal subjects and ten chronically medicated patients with schizophrenia. The acquisition data were preprocessed with an image dependent Metz filter and reconstructed using a ramp filtered back projection technique. The uptake in each of 50 regions of interest in each subject was normalized to the uptake in the cerebellum. There were no significant confirmed differences in the comparable ratios of normal subjects and patients with schizophrenia even at the $p = 0.15$ level. "Hypofrontality" was not observed.

J Nucl Med 30:000–000, 1989

Decreased perfusion of the frontal lobes in patients with chronic schizophrenia was first observed in 1974 by Ingvar and Franzen (*1–2*). This so called "hypofrontality" has also been reported by other investigators using xenon-133 (^{133}Xe) counting and imaging plus other single photon emission computed tomography (SPECT) and position emission tomography (PET) techniques (*3–13*). Several PET laboratories, however, have been unable to demonstrate the presence of "hypofrontality" in schizophrenia (*14–17*). The latter studies, however, measured glucose metabolism rather than regional cerebral blood flow (rCBF) or perfusion. Decreased perfusion of the frontal lobes in chronic schizophrenia is theoretically expected because many of the symptoms in these patients represent a loss of normal functions associated with the prefrontal cortex (*18*). We have studied brain perfusion in ten patients with chronic schizophrenia and five normal subjects using quantitative SPECT imaging of N-isopropyl p-iodoamphetamine- (IMP) labeled with p,5n iodine-123 (^{123}I).

Received Dec. 20, 1988; revision accepted May 18, 1989.

For reprints contact: Marvin B. Cohen, MD, Nuclear Medicine Service (115), V. A. Medical Ctr., Sepulveda, CA 91343.

MATERIALS AND METHODS

The cold IMP (Medi-Physics, Richmond, CA) is labeled in our laboratory by a modification of the Baldwin Method with p,5n ^{123}I (Crocker Laboratories, University of California at Davis), which is devoid of iodine-124 and other high-energy contaminants (*19–20*). This use of p,5n ^{123}I permits us to utilize a high resolution, low-energy collimator. Tracer injection of all subjects is performed under ambient conditions of light and sound in a quiet area. Acquisition is obtained with a 14-cm radius of rotation for 50 sec at each of the 60 views. The full width at half maximum (FWHM) at this distance is 1.3–1.5 cm. At the completion of the acquisition of the primary data sets, a thin technetium-99m- (^{99m}Tc) filled plastic tube is taped to the left orbito-meatal (OM) line and imaged in the lateral view. Transverse slices parallel to the OM line may then be obtained via software by transformation of the original transverse sections. Sagittal and coronal slices are obtained from the transformed transverse data set. Well-defined areas of cortex and basal ganglia are identified by systematically matching landmarks on these thin SPECT images to slices in a textbook of tomographic anatomy. We utilized "An Atlas of the Human Brain for Computerized Tomography" 1978 by T. Matsui and A. Hirano to obtain well-defined regions with no overlap into other cortical areas.

Ten chronically medicated patients with well-characterized (DSM III) schizophrenia (S) and five normal subjects (N) were imaged for 50 min with a single-head SPECT camera (Siemens ROTA Camera) and a high resolution collimator beginning

20 min after the i.v. injection of 5 mCi [^{123}I]IMP. Preprocessing using an image dependent Metz filter (*21–22*) and reconstruction using a ramp filter plus attenuation correction by the Chang Method were performed with a PDP 11/84 computer. The reconstructed images were then reoriented by three-dimensional interpolation into transverse images parallel to the OM line, coronal images perpendicular to the OM line and sagittal images. Each image represents a slice of 0.6-cm thickness.

Perfusion of cortical structures and basal ganglia was quantitated by marking a small ROI (minimum of 10 pixels in a 64 by 64 pixel image) around a portion of the image which on comparison to the reference atlas was known to represent only the desired structure without overlap into adjacent structures. Since gray matter structures have the highest activity in these images, the mean value of the five "hottest" pixels within the region of interest (ROI) was used to represent the structure, thus minimizing the influence of ROI extent into lower activity areas. The statistical uncertainty related to sampling only 5 pixels is minimized by the use of filtered images. This value was then expressed as a fraction of the uptake measured in the cerebellum. All ROIs were marked by a single observer. The coefficient of variation among repeated determinations on the same subject averages 5%. Perfusion was determined in each of 50 ROIs marked in the transverse (30), coronal (14), and sagittal (6) views. For those well-defined structures which were consistently visualized in multiple slices, the average uptake in two adjacent slices was used, resulting in 27 separate regions for analysis.

The study population consisted of six patients with paranoid schizophrenia, four patients in the residual phase of schizophrenia and five normal subjects. All patients were 26–56-yr-old male veterans with history of chronic schizophrenia and long-term therapy with neuroleptics. The mean age was 36 yr (paranoid), 46 yr (residual) and 34 yr (normal). The mean duration of illness for the paranoid group was 16 yr and for the residual group was 21 yr. The range was 13 to 25 yr. Diagnostic subtyping for the two groups of schizophrenic patients was based on the Diagnostic and Statistical Manual of Mental Disorders, Version III-R, (DSM-III-R). Data utilized to complete the diagnostic subtyping checklist was derived from extensive clinical interviews with each patient and include: the Structured Clinical Interview for DSM-111-R (SCID), the Maine Paranoid Scale (MPS), the Scale for Assessment of Negative Symptoms (SANS), and the Brief Psychiatric Rating Scale (BPRS). Clinical history, sociodemographic characteristics and social and occupational functioning was assessed using the Psychiatric and Social History Questionnaire. Prospective subjects were excluded from the study of schizophrenia if any of the following conditions were found during the initial evaluation: (a) a recent history (within the past 6 mo) of alcohol or drug abuse/dependence; (b) CNS disease; (c) other significant medical problems requiring regular medication or treatment; (d) the individual requires dietary restriction. Normal control subjects were staff personnel at the Sepulveda VAMC who were age and sex-matched to the paranoid group. Normal controls underwent a clinical screening to confirm the absence of any psychiatric or neurologic disorder.

A blinded, subjective reading of the same images used for quantitative analysis was performed by three experienced observers. They were allowed to see the entire set of images, but were asked to evaluate the same ROIs in the transverse view that were evaluated by the computer for each of the ten patients and five normal subjects. ROC instructions were given and ROI were evaluated on a 0 (definitely normal) to 4 (definitely abnormal) scale by each of the three readers. Structures in adjacent 0.6-cm slices were combined and given a single score. Each of the three readers derived scores for a total of 105 areas.

RESULTS

For each of the 27 structures analyzed the average perfusion for normal and schizophrenic subjects is shown in Tables 1 and 2. In all three projections, differences in the frontal regions between normal and schizophrenic subjects were not significant even at the $p = 0.15$ level. If all frontal areas are averaged together there is still no significant difference ($p = 0.26$). Thus "hypofrontality" was not observed in this population. Our results were not affected by dividing the patients into subgroups: six paranoid schizophrenia and four residual schizophrenia.

The only structures which demonstrated significant differences between normal and schizophrenic subjects

TABLE 1
Cerebral Perfusion Ratio Schizophrenia (10) vs. Normal (5)

Region transverse slices	DX	Mean ratio*	s.e. of mean	p Value
Right inf. temporal pole	S	0.788	0.028	0.043
	N	0.659	0.057	
Left inf. temporal pole	S	0.633	0.055	0.535
	N	0.561	0.102	
Right inf. frontal cortex	S	0.833	0.021	0.514
	N	0.859	0.034	
Left inf. frontal cortex	S	0.820	0.030	0.281
	N	0.871	0.036	
Right temporal cortex	S	0.862	0.021	0.055
	N	0.810	0.017	
Left temporal cortex	S	0.834	0.019	0.002
	N	0.912	0.017	
Right parietal cortex	S	0.820	0.023	0.391
	N	0.791	0.024	
Left parietal cortex	S	0.882	0.022	0.789
	N	0.874	0.021	
Right sup. frontal cortex	S	0.836	0.018	0.243
	N	0.863	0.014	
Left sup. frontal cortex	S	0.850	0.022	0.420
	N	0.881	0.031	
Occipital cortex	S	0.958	0.029	0.970
	N	0.957	0.023	
Right caudate	S	0.804	0.043	0.833
	N	0.793	0.026	
Left caudate	S	0.800	0.046	0.486
	N	0.747	0.057	

* Normalized to cerebellum.

TABLE 2
Cerebral Perfusion Ratio Schizophrenia (10) vs. Normal (5)

Region	DX	Mean ratio*	s.e. of mean	p Value
Coronal slices				
Right inf. frontal cortex	S	0.807	0.026	0.767
	N	0.796	0.023	
Left inf. frontal cortex	S	0.837	0.015	0.697
	N	0.853	0.039	
Right temporal cortex	S	0.835	0.023	0.646
	N	0.814	0.040	
Left temporal cortex	S	0.827	0.024	0.279
	N	0.869	0.031	
Right parietal cortex	S	0.800	0.023	0.568
	N	0.778	0.032	
Left parietal cortex	S	0.836	0.020	0.923
	N	0.839	0.018	
Right sup. frontal cortex	S	0.827	0.022	0.821
	N	0.833	0.016	
Left sup. frontal cortex	S	0.832	0.015	0.702
	N	0.845	0.031	
Right basal ganglia	S	0.800	0.030	0.272
	N	0.740	0.046	
Left basal ganglia	S	0.778	0.022	0.980
	N	0.780	0.041	
Sagittal slices				
Right inf. front cortex	S	0.826	0.030	0.708
	N	0.808	0.037	
Left inf. frontal cortex	S	0.855	0.035	0.339
	N	0.815	0.023	
Right occipital cortex	S	0.881	0.048	0.091
	N	0.972	0.024	
Left occipital cortex	S	0.966	0.032	0.763
	N	0.976	0.032	

* Normalized to cerebellum.

at the p = 0.05 level were in the temporal lobes. While normal subjects showed a significant difference between right and left temporal lobes, this difference was not seen in schizophrenics. In schizophrenic patients as a group perfusion was relatively decreased in the left temporal cortex and increased in the right inferior temporal pole on the transverse images (Table 1). However, these differences were not confirmed in the coronal images (Table 2). This may be due at least in part to the statistically small sample of normal subjects (N = 5) and the injection of tracer under conditions of ambient noise.

The perfusion ratio in the peripheral cortex tended to be symmetrical and varied from ~0.8 to 0.9. Next to the cerebellum, the occipital cortex had the highest ratio, but this may have been due to the fact that patients were injected in ambient lighting. The lowest ratio was seen in the inferior temporal poles. No effort was made to determine if these chronically medicated patients were actively hallucinating at the time of injection of the [^{123}I]IMP, but perfusion of the basal ganglia was less than perfusion in the peripheral cortex. Transverse images of a patient and a normal subject are seen in Figure 1. Normal and relatively symmetrical uptake of IMP is seen in all cortical and subcortical areas. Minor asymmetries are a normal finding.

The failure to detect decreased perfusion of the fron-

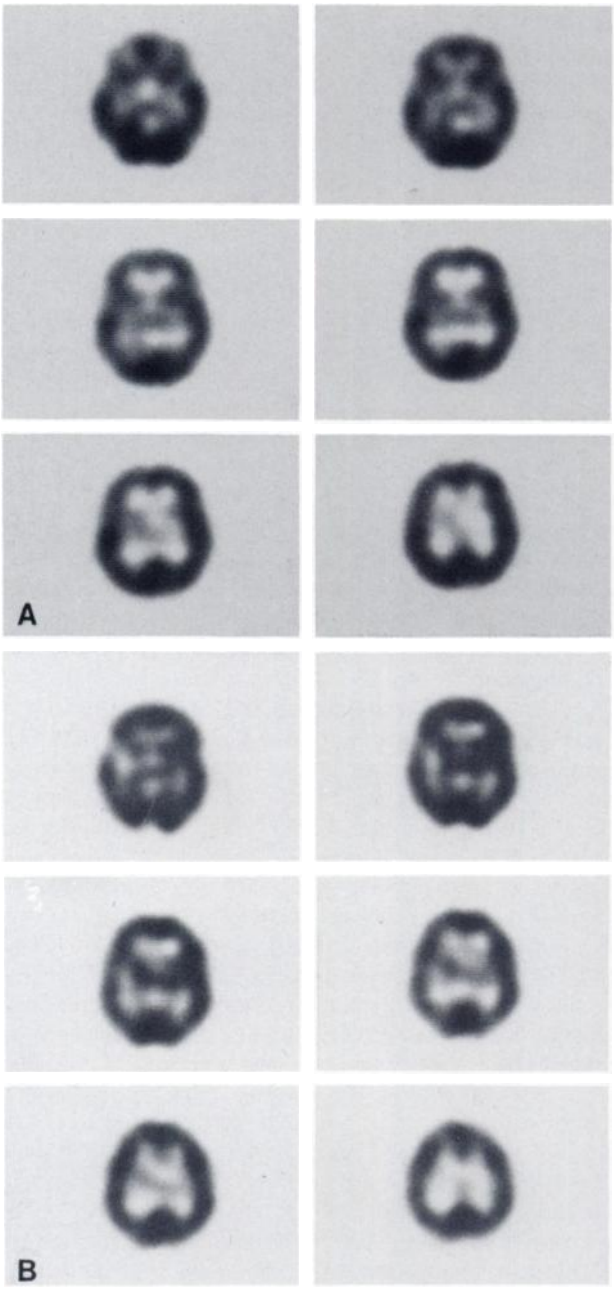

FIGURE 1
Representative transverse images of a normal subject (A) and a schizophrenic patient (B). The images are oriented parallel to the orbito-meatal line at comparable levels in each patient. Note the uniform tracer uptake in the frontal area in both images. The slight asymmetries in tracer activity seen in both sets of images are normal.

tal lobe prompted a blinded, subjective reading of the films by three experienced observers (RS, RL, and AK), but this also revealed no evidence of "hypofrontality". Consensus was reached on the interpretation of the uptake in each ROI, except for six areas. One reader raised a question of abnormality in three areas of one normal subject which were rated as definitely normal (0) by the other two readers. Each of the three readers rated as possibly abnormal (2) a single ROI which was rated by the other two readers as definitely normal (0) or probably normal (1). While only occasional ROIs were rated as probably abnormal (3), no ROI in any patient or normal subject was rated as definitely abnormal (4).

DISCUSSION

"Hypofrontality" is not merely something that has been reported from imaging studies in patients with schizophrenia. It is also expected on theoretical grounds in the frontal lobe as an expression of a negative symptom, especially in patients with paranoid schizophrenia. Symptoms of schizophrenia are classified as being either negative or positive. Negative symptoms are the result of a loss or diminution in function and are considered an expression of neuronal hypoactivity. The positive symptoms of schizophrenia are considered to be due to neuronal hyperactivity and include such things as hallucinations and agitated behavior (*18*).

Ingvar and Franzen (*1–2*) first observed "hypofrontality" using a nonimaging technique with ^{133}Xe. Mathews (*3–4*), Gur (*5*), and others (*6–7*) also observed "hypofrontality" in patients with schizophrenia by this xenon technique. SPECT imaging of CBF using ^{133}Xe has also demonstrated "hypofrontality" in schizophrenia in the left frontal lobe and especially in patients with the paranoid type (*8–9*). Frackowiak (*23*) pointed out potential sources of error in the ^{133}Xe method, which measures perfusion in the superficial cortex only. The counts collected are limited by the low solubility of xenon and the short time for acquisition. Uncertainties regarding local partition coefficients create problems in quantitation. The relatively poor spatial resolution obtained with 80 keV gamma rays plus interference by xenon activity in the frontal sinuses and soft tissue also affect the accuracy of this technique.

The outstanding and continually improving spatial resolution of PET has been utilized to study both cerebral glucose metabolism and blood flow, which remain coupled in schizophrenia and most other diseases. Increased blood flow and glucose metabolism has been observed by PET imaging in the basal ganglia of symptomatic, unmedicated patients with schizophrenia (*24–25*). O'Connell (*26*) has made similar observations with SPECT imaging using [^{123}I]IMP. However, he reported that the increased perfusion of the basal ganglia in schizophrenia was correlated with the presence of symptoms and did not appear to be secondary to medication. Matsuda (*27*) has observed increased uptake of [^{123}I] IMP in the auditory cortex of a patient with auditory hallucinations. Decreased glucose metabolism in the frontal lobes has been reported by several investigators (*10–13*). However, other PET researchers have found normal glucose metabolism in the frontal lobes of patients with schizophrenia (*14–17*). Jones (*14*) also found normal cerebral blood flow in schizophrenia using oxygen-15 with the PET technique.

The decreased perfusion in the left temporal cortex in our patients with schizophrenia is consistent with the findings in a PET study using fluorine-18 flurodeoxyglucose in which a tendency to reduced metabolism was observed in the left temporal cortex (*17*). Our findings, however, should be viewed with caution until confirmation is obtained with additional patients under controlled conditions.

The spatial resolution of SPECT is less than that of the state of the art PET equipment, but spatial resolution of SPECT with [^{123}I]IMP is better than obtained with ^{133}Xe (*28–29*). The spatial resolution obtained in our SPECT images is now comparable to that reported using older PET systems. SPECT is more clinically available than PET, but has only recently been utilized with [^{123}I]IMP to study schizophrenia.

Simon (*9*) has observed "hypofrontality" in patients with schizophrenia using [^{123}I]IMP as the imaging agent. Nevertheless, we have been unable to confirm the presence of "hypofrontality" in our group of patients with schizophrenia. The failure of several groups to confirm the presence of "hypofrontality" in schizophrenia may be related to the different techniques that have been utilized and the environmental conditions that were present at the time of injection of the tracer. If "hypofrontality" is a real phenomenon, it may be more readily demonstrated under as yet undefined conditions. Devous (*8*) reported that the use of a functional task induced decreased perfusion of the frontal lobe in seven patients with paranoid schizophrenia but not in four patients with nonparanoid schizophrenia. The use of a cognitive task designed to stimulate the frontal cortex under standardized conditions may be required to reliably evaluate blood flow and metabolism in the frontal lobe of patients with schizophrenia. The Continuous Performance Test and the Wisconsin Card Sorting Test are two such procedures (*18*).

ACKNOWLEDGMENTS

This study was funded by the Research Service, Veterans Administration Medical Center.

The authors thank Karen Greenwell for technical assistance and Barbara Ruccione for editorial assistance.

REFERENCES

1. Ingvar DH, Franzen G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatr Scand* 1974, 50:425–462.
2. Ingvar DH, Franzen G. Distribution of cerebral activity in chronic schizophrenia. *Lancet* 1974, 2:1484–1486.
3. Mathew RJ, Meyer JS, Francis DJ, et al. Regional cerebral blood flow in schizophrenia: a preliminary report. *Am J Psychiatr* 1981, 138:112–113.
4. Mathew RJ, Duncan GC, Weinmann ML, et al. Regional cerebral blood flow in schizophrenia. *Arch Gen Psychiatr* 1982, 39:1121–1124.
5. Gur RE, Skolnick BE, Gur RC, et al. Brain function in psychiatric disorders. I. Regional cerebral blood flow in medicated schizophrenics. *Arch Gen Psychiatr* 1983, 40:1250–1254.
6. Ariel RN, Golden CJ, Berg RA, et al. Regional cerebral blood flow in schizophrenia. *Arch Gen Psychiatr* 1983, 40:258–263.
7. Kurachi M, Kobayashi K, Matsubara R, et al. Regional cerebral blood flow in schizophrenic disorders. *Eur Neurol* 1985, 24:176–181.
8. Simon T, Paulman R, Homan R, et al. Single photon emission computed tomography of the brain with xenon-133 and iodoamphetamine. *J Nucl Med* 1987, 28:570.
9. Devous MD Sr, Raese JD, Herman JH, et al. SPECT determination of regional cerebral blood flow in schizophrenic patients at rest and during a mental task [Abstract]. *J Nucl Med* 1986, 27:P734.
10. Buchsbaum MS, Ingvar DH, Kessler R, et al. Cerebral glucography with positron tomography. *Arch Gen Psychiatr* 1982, 39:251–259.
11. Buchsbaum MS, DeLisi LE, Holcomb HH, et al. Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch Gen Psychiatr* 1984, 41:1159–1166.
12. DeLisi LE, Buchsbaum MS, Holbomb HH, et al. Clinical correlates of decreased anteroposterior metabolic gradients in positron emission tomography (PET) of schizophrenic patients. *Am J Psychiatr* 1985, 142:78–81.
13. Wolkin A, Jaeger J, Brodie JD, et al. Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. *Am J Psychiatr* 1985, 142:564–571.
14. Jones T. The application of PET. In: Ell PJ, Holman BL. *Computed emission tomography.* New York: Oxford Press, 1982.
15. Reivich M, Gur RE, Resnick SM, et al. Local cerebral glucose consumption in schizophrenics on and off medication [Abstract]. *J Nucl Med* 1987, 28:702.
16. Volkow ND, Brodie JD, Wolf AP, et al. Brain metabolism in patients with schizophrenia before and after acute neuroleptic administration. *J Neurol Neurosurg Psychiatr* 1986, 49:1199–1202.
17. Kling AS, Metter EJ, Riege WH, et al. Comparison of PET measurement of local brain glucose metabolism and CAT measurement of brain atrophy in chronic schizophrenia and depression. *Am J Psychiatr* 1986, 143:175–180.
18. Andreasen NC. Brain imaging: applications in psychiatry. *Science* 1988, 239:1381–1388.
19. Baldwin RM, Lin TH, Wu JL. Synthesis and brain uptake of isomeric I-123 iodoamphetamine derivatives. *J Labeled Comp Radiopharm* 1982, 19:1305–1306.
20. Cohen MB, Graham LS, Yamada LS. [123I] Iodoamphetamine SPECT imaging. *Internat J Appl Rad Isotopes* 1986, 37:749–763.
21. King MA, Glick SJ, Penny BC, et al. Interactive visual optimization of SPECT prereconstruction filtering. *J Nucl Med* 1987, 28:1192–1198.
22. Graham LS, King MA, Cohen MB, et al. Use of Metz filters for preprocessing I-123 iodoamphetamine ECT brain images [Abstract]. *J Nucl Med* 1987, 28:677.
23. Frackowiak RSJ, Pozzili C, Legg NJ, et al. Regional cerebral oxygen supply and utilization in dementia. *Brain* 1981, 104:753–778.
24. Alavi A, Gur RE, Resnick S, et al. Prominence of basal ganglia metabolic activity in schizophrenia [Abstract]. *J Nucl Med* 1986, 27:901.
25. Early TS, Reiman EM, Raichle ME, et al. Left globus pallidus abnormality in never-medicated patients with schizophrenia. *Proc Natl Acad Sci* 1987, 84:561–563.
26. O'Connell RA, Van Heertum RL, Holt AR, et al. Single photon emission computed tomography (SPECT) in psychiatry [Abstract]. *Clin Nucl Med* 1987, 12 (suppl 13):9.
27. Matsuda H, Gyobu T, Il M, et al. Increased accumulation of N-isopropyl-(I-123) p-iodoamphetamine in the left auditory area in a schizophrenic patient with auditory hallucinations. *Clin Nucl Med* 1988, 13:53–55.
28. Lassen NA, Henriksen L, Holm S, et al. Cerebral blood-flow tomography: Xe-133 compared with isopropylamphetamine I-123. *J Nucl Med* 1983, 24:17–21.
29. Matsuda H, Seki H, Ishida H, et al. Regional cerebral blood flow changes during finger movement and reading aloud: comparison between N-isopropyl-p-[123] iodoamphetamine intravenous injection and ^{133} xenon inhalation methods. *Kaku Igaku* 1984, 21:859–865.