Sensitivity of Measurements of Regional Brain Activation with Oxygen-15-Water and PET to Time of Stimulation and Period of Image Reconstruction

Nora D. Volkow, Nisar Mullani, Lance K. Gould, Stephen S. Adler, and Samuel J. Gatley

Medical Department and Chemistry Department, Brookhaven National Laboratory, Upton, New York, Department of Psychiatry, SUNY at Stony Brook, Stony Brook, New York, and Division of Cardiology, University of Texas Health Science Center, Houston, Texas

Measurement of oxygen-15- (^{15}O) water uptake with positron emission tomography (PET) is a sensitive technique to monitor regional brain activation secondary to stimulation paradigms. In order to investigate data acquisition times that show maximal changes in regional activation and to assess the optimal time for stimulus presentation, we investigated 10 controls with ^{15}O-water and PET during baseline and stroboscopic light stimulation. Sequential scans were done varying the time of stimulus presentation. The images were reconstructed using three different periods of data acquisition: uptake phase (initial 30–35 sec), washout phase (40 sec following peak activity in brain), and total activity (3 min). The images reconstructed during the uptake phase showed the largest changes in occipital cortex from stimulation. Maximal changes in occipital cortex were obtained when the visual stimulus was maintained during the uptake phase only.

J Nucl Med 1991; 32: 58–61

The use of positron emission tomography (PET to measure regional cerebral blood flow (rCBF) (*1*) has been shown to be a sensitive method to measure regional brain activation secondary to specific task stimulation (*2,3*). Oxygen-15-labeled water (^{15}O-water) is the most common PET rCBF tracer. A simplified method that obviates the need of arterial blood sampling has been developed and can be used to obtain changes in relative CBF (*4,5*). This strategy has proven to be very useful in mapping functional systems within the brain (*6,7*). Within this context it is important to develop activation strategies and acquisition protocols that maximize the signal from the stimulation paradigms. The CBF measurement with ^{15}O-water is very sensitive to the total time of data accumulation of the tracer concentration in the brain (*8,9*) and has been shown to lead to large errors for long data acquisition time. In order to minimize these errors, imaging times of less than 60 sec have been recommended since longer scanning intervals allow for rapid redistribution and equilibration of water between the high- and low-flow areas (*1,5,8*).

However, neither the optimal period for demonstration of changes in regional ^{15}O-water uptake after activation, nor the optimal period for stimulation have been determined.

In order to evaluate the sensitivity of uptake of ^{15}O-water to the timing of PET measurements and activation paradigms, we compared the values obtained by reconstructing the images using different periods of time, for scans taken both during baseline and during stroboscopic visual stimulation. We also evaluated the sensitivity of the method to the timing of stimulation by varying the period of time over which stimulation was presented.

MATERIALS AND METHODS

Ten healthy, right-handed male volunteers, age range 20–30 yr of age, were selected for the study. The guidelines of the Committee for the Protection of Human Subjects at the University of Texas in Houston were followed for this investigation. PET studies were carried out using the University of Texas TOFPET positron camera (*10*). This camera collects nine simultaneous image planes, with reconstruction resolution of 12 mm full width at half maximum (FWHM) in plane and 11 mm (FWHM) in the axial direction. Image plane separation is 10.8 mm, and most of the brain can be imaged at one time.

Prior to the emission scans, the subjects underwent a transmission scan using a ring filled with gallium-68 to correct for attenuation. Emission scans were obtained immediately after injection of 20–30 mCi of ^{15}O-water, which was delivered as a bolus over a 3-sec interval. For all of the emission scans, the

Received Apr. 26, 1990; revision accepted Jul. 6, 1990.
For reprints contact: Nora D. Volkow, MD, Medical Department Brookhaven National Laboratory, Upton, NY 11973.

data was collected using the list mode acquisition, where every detected event is stored sequentially on a computer disk for subsequent analysis. The time-activity curve of the radiotracer in the brain was then used to select the period of the scan corresponding to the uptake phase (period corresponding to the entry of the radiotracer in brain until peak counts) and the initial washout (period corresponding to the 40 sec after peak counting was achieved). The uptake phase usually corresponded to 35 sec and began 15–20 sec after injection. Images for the uptake and washout phases were then reconstructed. Images were also obtained by integrating the activity over the whole length of the scan (3 min). In addition, for one of the studies, we reconstructed 10-sec interval images to monitor the regional kinetics of the tracer throughout the scan.

Seven of the subjects underwent three sequential emission scans at 10-min intervals. The first and third emission scans were obtained with the subjects under baseline conditions (eyes open, ears unplugged), and the second scan was done while the subjects were under visual stimulation with a stroboscopic light (10 Hz), placed 45 cm from the subject's eyes. Stimulation was started 30 sec before injection of the tracer and was continued for a total of 3 min. Subjects remained in the camera during the procedure to avoid errors from mispositioning.

The other three subjects had five sequential emission scans. The first and fifth scans were done under resting conditions with no stimulation (Baselines 1 and 2). The second scan was done with stroboscopic stimulation, which was started 30 sec before injection of the tracer and was continued until peak counting was achieved in the brain (stimulation in uptake phase). The third scan was done with stroboscopic stimulation, which was started 30 sec before injection and was continued throughout the uptake and washout phases. The fourth injection was done with stimulation starting at peak counts and continued throughout the washout phase.

Regions of interest (ROIs) for the occipital cortex were drawn directly on the PET scan image in two contiguous slices, using as reference the neuroanatomical atlas by Matsui and Hirano (*11*). The regions were drawn in the uptake images obtained during baseline, and these same coordinates were then used to define the ROI for the other reconstructions. Relative values of ^{15}O concentration were obtained by averaging the values in the occipital regions and dividing by the average radiotracer concentration in the three central brain slices. These relative values were obtained for the images reconstructed during the uptake phase, during the washout phase and for the integrated scan. Differences were evaluated using paired t-tests.

RESULTS

Dynamics and Stability of CBF Measurements

Figure 1 shows the kinetics of ^{15}O-water for the central slice of the two baseline scans, which demonstrate very good reproducibility.

Comparison of kinetics of ^{15}O-water in the occipital cortex between baseline and continuous visual stimulation (Fig. 2) shows that the largest difference in concentration is seen during the uptake phase. In the washout phase, clearance of the tracer in the stimulated occipital cortex is faster than in the nonstimulated occipital cortex leading to a decrease in the contrast between baseline and visual stimulation scans for occipital cortex.

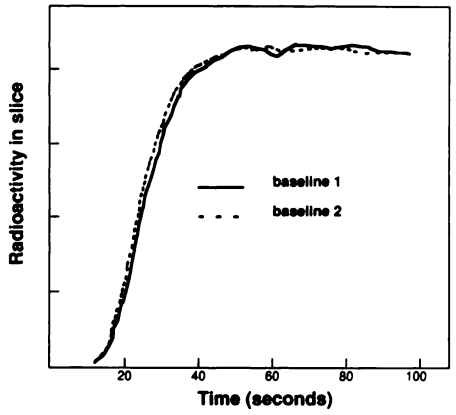

FIGURE 1
Kinetics of ^{15}O-water for the central slice for the two baseline scans.

Figures 3A-B show the individual relative CBF values in the occipital cortex for the images obtained using the uptake and washout reconstructions, respectively, for the scans taken during Baselines 1 and 2 and during visual stimulation. Stability in the measurements of ^{15}O concentration was tested by comparing the values from Baseline 1 to those for Baseline 2. Baseline values were not significantly different for either the uptake reconstruction (Baseline 1, 1.08 ± 0.06; Baseline 2, 1.09 ± 0.05) or the washout reconstruction (Baseline 1, 1.14 ± 0.10; Baseline 2, 1.14 ± 0.08). Differences in ^{15}O concentration for occipital cortex between the baseline and the visual stimulation were larger for images reconstructed during the uptake phase (1.26 ± 0.06, $p \leq 0.0001$ when compared with baseline) than for the washout phase (1.20 ± 0.12, $p \leq 0.09$ when compared with baseline). Uptake reconstructions were better in

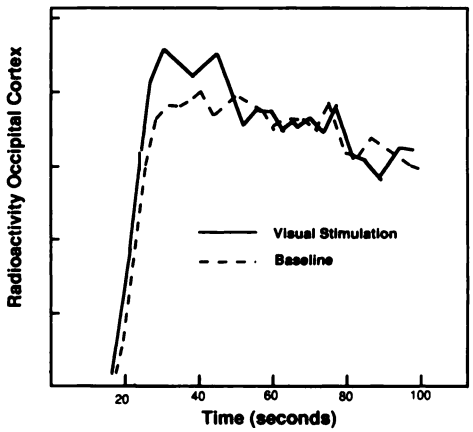

FIGURE 2
Kinetics of ^{15}O-water in occipital cortex for a baseline scan and for a scan taken during continuous visual stimulation.

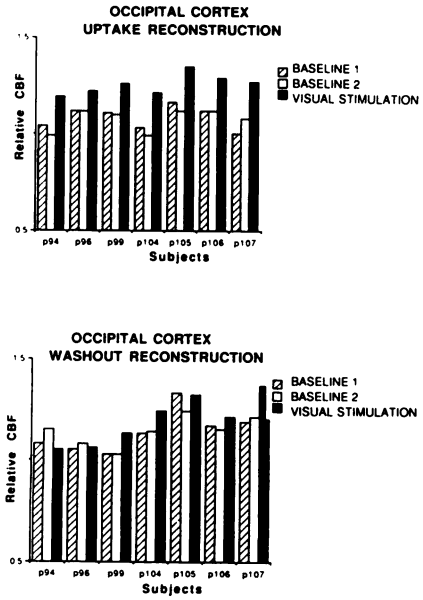

FIGURE 3
Individual values for relative CBF in the occipital cortex during two baseline scans and during visual stimulation. (A) The values obtained when using the uptake phase to reconstruct the images and (B) when using the washout phase. Relative values represent the average activity in occipital cortex divided by the average activity in the three central slices of the brain.

discriminating baseline from visual stimulation than were washout reconstructions.

Stimulation Time

Table 1 shows the percent change in occipital cortex for the images obtained using the uptake, the washout, and the integrated reconstructions during the different times of stimulus presentation. As with the previous experiment, maximal changes in occipital cortex, secondary to visual stimulation, were seen in the images reconstructed during the uptake phase. For all of the images, irrespective of the reconstruction period used, maximal stimulation in occipital cortex was observed when the subjects were stimulated only during the uptake phase. Visual stimulation of the subject during the washout phase only did not increase occipital concentration of labeled water. When using the integrated scan to reconstruct the images, significant differences were seen only when stimulation was carried out during the uptake phase.

DISCUSSION

The present work assesses the sensitivity to time of data collection of measurements of regional brain activation by visual stimulation using PET and ^{15}O-water. Images obtained using the initial 35–40 sec after arrival of the tracer in brain were more sensitive in detecting changes in occipital cortex, secondary to visual stimulation than images obtained using later phases of the scan or using longer intervals of acquisition. The high extraction fraction of H_2O in the brain (*12*) predicts that only a minimal amount of tracer has left the brain during the first 40 sec and that the sensitivity for measuring flow should be highest during that time (*1*). The study also shows that the initial washout phase of the tracer does not represent a steady-state condition and can be affected by stimulation during this period as shown by the decreased concentration of the tracer in the occipital cortex when the subjects were stimulated continuously throughout the scan (Fig. 2).

Increased clearance of radioactivity from the areas of high blood flow after the uptake phase would be expected. This effect was accentuated when stimulation was maintained throughout the whole scan as seen by the lower concentration of tracer in the occipital cortex, when stimulation was maintained throughout the washout phase.

In deciding optimal imaging time with these techniques, however, it is important to consider the statistical error due to the low count rates when scanning for short periods (*13*) and the errors due to the sensitiv-

TABLE 1
Percent Change in Relative CBF of Occipital Cortex Between the Images Taken During Baseline and the Images Taken During the Different Visual Stimulation Paradigms

Stimulation paradigm	Uptake reconstruction	Washout reconstruction	Integrated reconstruction
Uptake stimulation	20% ± 4%†	13% ± 3%*	8% ± 2%*
Uptake and washout stimulation	13% ± 1%†	9% ± 2%*	5% ± 3%
Washout stimulation	3% ± 2%	2% ± 7%	2% ± 2%
Baseline 2	1% ± 1%	2% ± 4%	1% ± 1%

Changes from the images taken during Baseline 2 are shown as reference. The stimulation paradigms were uptake stimulation = visual stimulation maintained through the uptake phase only, uptake and washout stimulation = visual stimulation maintained through the uptake and the washout phase, and washout stimulation = visual stimulation maintained throughout the washout phase only. The table shows the changes seen for the images using the uptake, the washout, and the integrated reconstructions (Paired t-test: * $p \leq 0.05$, † $p \leq 0.01$).

ity of this phase to dispersions in the input function (*14*).

The goal of our work was to optimize the strategies for regional brain activation secondary to stimulation, and not to accurately quantitate CBF. The early period in uptake studies contains a significant contribution from changes in regional blood volume (*15*) as well as rCBF.

In summary these studies suggest that the phase corresponding to the uptake of the ^{15}O-water is the most sensitive for detecting regional changes secondary to activation. It also shows that stimulation should continue only until the uptake phase. Timing of stimulation is particularly relevant for scans of more than 60 sec in that continuous stimulation could increase the clearance of the tracer.

ACKNOWLEDGMENTS

Research supported in part by the U.S. Department of Energy under Contract No. DE-AC02-76CH000016 and in part as a joint collaborative project with the Clayton Foundation for Research in Houston.

REFERENCES

1. Raichle ME, Martin WRW, Herscovitch P, Mintun MA, Markham J. Brain blood flow measured with intravenous $H_2{}^{15}O$. II. Implementation and validation. *J Nucl Med* 1983;24:790–798.
2. Celesia G, Polcyn RD, Holden JE, et al. Visual evoked potentials and positron emission tomographic mapping of regional cerebral blood flow and cerebral metabolism. *Electroencephalography Clin Neurophysiol* 1982;54:243–256.
3. Fox PT, Raichle ME. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. *J Neurophysiol* 1984;51: 1109–1120.
4. Fox PT, Mintun MA, Raichle M, Herscovitch P. A noninvasive approach to quantitative functional brain mapping with $H_2{}^{15}O$ and positron emission tomography. *J Cereb Blood Flow Metab* 1984;2:89–98.
5. Mazziotta JC, Huang S-C, Phelps M, et al. A noninvasive positron computed tomography technique using oxygen-15-labeled water for the evaluation of neurobehavioral task batteries. *J Cereb Blood Flow Metab* 1985;5:70–78.
6. Posner MI, Petersen SE, Fox PT, Raichle ME. Localization of cognitive operation in the human brain. *Science* 1988;240:1627–1631.
7. Petersen SE, Fox PT, Rosner ML, Mintun M., Raichle ME. Positron emission tomographic studies of the cortical anatomy of single word processing. *Nature* 1988;331:585–589.
8. Howard BE, Ginsberg MD, Hassel WR, Lockwood AH, Freed P. On the uniqueness of cerebral blood flow measured by the in vivo autoradiographic strategy and positron emission tomography. *J Cereb Blood Flow Metab* 1983;3:432–441.
9. Gambhir SS, Huang SCh, Hawkins RA, Phelps MA. Study of the single compartment tracer kinetic model for the measurement of local cerebral blood flow using ^{15}O-water and positron emission tomography. *J Cereb Blood Flow Metab* 1987;7:13–20.
10. Mullani NA, Wong NM, Hartz RK, Yerian K, Philippe EA, Gould KL. Design of TOPFPET: a high resolution time of flight positron camera. *IEEE Trans* 1982;29:31–34.
11. Matsui T, Hirano A. *An atlas of the human brain for computerized tomography.* Stuttgart: Gustav Fischer; 1978.
12. Herscovitch P, Raichle ME, Kilbourn MR, et al. Measurement of cerebral blood flow and water permeability with positron emission tomography using O-15-water and C-11-butanol. *J Cereb Blood Flow Metab* 1984;5(suppl 1):567–578.
13. Volkow ND, Mullani N, Bendriem B. PET instrumentation and clinical research. *Am J Physiol Imaging* 1988;3:142–153.
14. Iida H, Kanno I, Miura S, et al. Error analysis of a quantitative cerebral blood flow measurement using $H_2{}^{15}O$ autoradiography and positron emission tomography, with respect to the dispersion of the input function. *J Cereb Blood Flow Metab* 1986;6:536–545.
15. Koeppe RA, Hutchings GD, Rothley JM, Hichwa RD. Examination of assumptions for local cerebral blood flow studies in PET. *J Nucl Med* 1987;28:1695–1703.