Optimal Scan Time of Oxygen-15-Labeled Water Injection Method for Measurement of Cerebral Blood Flow

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We investigated the optimal scan time for obtaining the maximal signal-to-noise (S/N) ratio in cerebral blood flow (CBF) measured by PET imaging following ^{15}O-water bolus injection. We performed sequential measurements with dynamic scans of six subjects injected at rest while listening to white noise. Each dynamic data set was edited into images corresponding to different scan times and were calibrated to CBF images by the table look-up method. For each scan time, we evaluated a pixel-by-pixel standard deviation of the CBF for sequential measurements. The S/N-ratio of CBF in the gray matter was 10.2 ± 1.7 and 13.6 ± 2.9 at a 40 and 120 sec scan time, respectively. The gain of the 120-sec over 40-sec scan time corresponds to an 80% increase in the number of trials to reach the same S/N-ratio in a stimulation-activation study. The simulation study supported the results, in which the maximal S/N-ratio of the CBF was demonstrated to be 90 and 120 sec at a CBF of 80 and 60 ml/100 ml/min, respectively. It is concluded that the optimal scan time of the ^{15}O-water bolus injection method is in the interval from 90 to 120 sec.

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Oxygen-15-labeled water ($H_2{}^{15}O$) and PET for measuring cerebral blood flow (CBF) have been widely used as a tool of neurophysiologic stimulation studies (*1,2*). However, as the CBF images are vulnerable to a poor signal-to-noise (S/N) ratio, it is essential to maximize the information in each collection of stimulation trials in an individual subject.

The scan time determines not only the counts of the accumulation integral but also the curvature of the relationship between the CBF and the time integral. Therefore, statistical noise in the raw image of the accumulation integral will not directly be reflected on the CBF image. Hitherto, a shorter scan time (e.g., 40 sec) has been used and recommended often (*3*), but no systematic investigation has previously been made to optimize the scan time for maximal S/N ratio. In this study, we have tested this relationship employing human PET measurements and computer simulations.

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METHODS

Serial $H_2{}^{15}O$ dynamic scans with a 20-min scan interval were measured in six normal subjects. Four dynamic scans of 180-sec length were repeated for five subjects and six dynamic scans of 195-sec length were repeated for one subject. The subjects laid on a couch in a resting state with eyes closed and listened to white noise through small earphones during the study. The injected dose was 35–40 mCi (~0.5 mCi/kg). Images were acquired with a PET scanner (HEADTOME IV) (*4*) with seven simultaneous slices of 13 mm interval and a 9-mm effective reconstruction full-width at half-maximum (FWHM). Scanning commenced 20–25 sec after the bolus injection of $H_2{}^{15}O$ (*5*). Counts assessed in the first 90 sec were 600–800 × 10^3 per slice. Arterial input function via the radial artery was measured with a 5 ml/min withdrawal speed using a beta detector (*5*). Informed consent was obtained from all subjects.

After the dynamic raw data were edited images were obtained corresponding to different scan times (40, 60, 90, 120, 150 and 180 sec or 40, 60, 90, 120 and 195 sec) from each scan. CBF was calculated by an autoradiographic method using the arterial input function and the table look-up method based on the Kety equation (*5*). Curvatures of the nomograms used in the table look-up method were more bent with increasing scan time (Fig. 1). A partition coefficient of 1.0 was used. For each scan time, the mean and standard deviation of the CBF were calculated. Signal and noise were defined as the CBF mean and the CBF standard deviation, respectively. Regions of interest (ROIs) were selected at the sylvian fissure and occipital cortex and at the centrum semiovale for determination of S/N ratios in the gray and white matter, respectively. Elliptical ROI (8 × 16 mm and 6 × 24 mm) were used, respectively.

In addition, a simulation study was performed to estimate the relationship between the S/N ratio and scan time. A typical arterial input curve measured in a human study was used. Tissue curves for various ranges of CBF (20, 40, 60, 80 and 100 ml/100 ml/min), assuming a partition coefficient of 1.0, were calculated. An integration for different scan times (40, 60, 90, 120, 150 and 180 sec) was then obtained, and the CBF standard deviation as a product of the square root of the accumulation integral and the reciprocal of the slope of the nomogram curvature between CBF and integral was estimated. Finally, a relative S/N ratio as a ratio

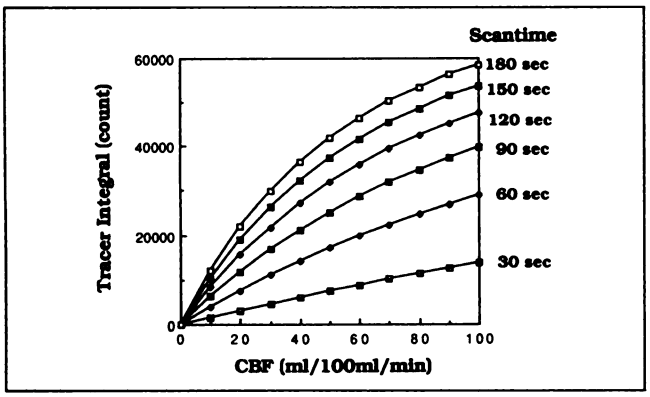

FIGURE 1. Nomograms of the relationship between CBF and tracer integral. By varying the scan time from 30 to 180 sec, the integral becomes higher and at the same time the nonlinearity of the curve increases.

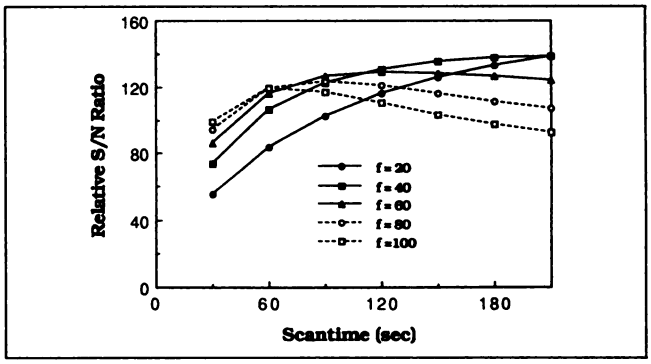

FIGURE 3. S/N ratio obtained from six serial measurements performed on a normal subject at rest listening to white noise. Dynamic PET data were edited into each scan time from 40, 60, 90, 120, and 195 sec scan time. ROIs were selected in the gray (the sylvian fissure and occipital cortex) and white matter (centrum semiovale).

of the given CBF to the above CBF standard deviation was obtained.

RESULTS

Figure 2 shows the CBF standard deviation images calculated from the six CBFs measured in one subject. Noise was diffusely higher in the 40-sec image than in 90-sec image. Gray matter structures emerging in the 90-sec CBF standard deviation image reflected an enhanced nonlinear relationship of the CBF and integral. The nonlinearity was more dominant in the gray matter than in the white matter. The S/N ratio defined as the ratio of CBF mean to CBF standard deviation is shown in Figure 3. CBFs obtained from six subjects at a 40-sec scan time were 61.3 ± 7.2 and 32.5 ± 12.8 ml/100 ml/min in the gray and white matter, respectively. S/N ratios were 10.2 ± 1.7 (7.5 ± 1.6) and 13.6 ± 2.9 (11.9 ± 2.3) in the gray (white) matter at 40 and 120 sec scan times, respectively (Table 1).

The simulation study results agreed well with the above observations in the subject study (Fig. 4). With 20 ml/100 ml/min in CBF, the S/N ratio increased as the scan time increased in the simulated scan time range (<180 sec). On the other hand, with 80 ml/100 ml/min in CBF, the S/N ratio peaked at a scan time of approximately 100 sec and slowly decreased thereafter, (Fig. 4).

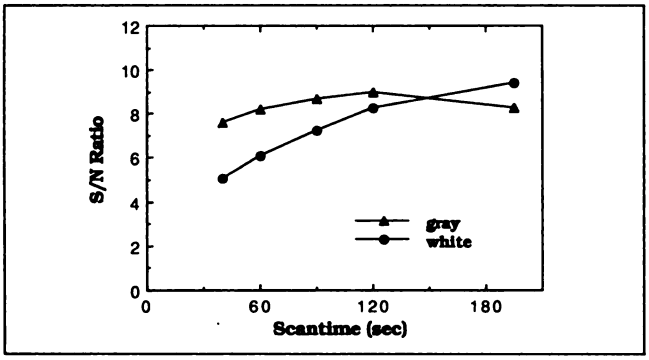

FIGURE 2. Mean CBF and standard deviation (SD) images for a 40- and a 90-sec accumulation scan time edited from dynamic PET data. Standard deviation was calculated from six serial CBF measurements on a normal subject at rest and listening to white noise.

DISCUSSION

We have previously demonstrated that a longer scan time would improve the quantitation of CBF while reducing errors caused by the dispersion and time-shift of the input function (*5,6*). In the present study, we investigated scan time with emphasis on improvement of the S/N ratio. The S/N ratio is more relevant to stimulation-activation studies than the quantitative property of CBF. The results of the present study again showed that the longer the scan time the better the performance.

We searched for an optimal scan time for the $H_2{}^{15}O$ bolus injection method for CBF measurement. It has been widely believed that in high flow regions the tissue radioactivity at 40 sec after injection includes little information on CBF (*3*), and longer scan times reduce flow informa-

TABLE 1
CBF and S/N Ratio at 40-sec and 120-sec Scan Time Determined in Six Subjects

Accumulation scan time		40 sec	120 sec
Gray matter*	CBF†	61.3 ± 7.2	59.5 ± 10.8
	S/N ratio‡	10.2 ± 1.7	13.6 ± 2.9
White matter§	CBF	32.5 ± 12.8	30.6 ± 13.3
	S/N ratio	7.5 ± 1.6	11.9 ± 2.3

* The ROI was selected at the sylvian fissure and the occipital cortex.

† The unit is ml/100 ml/min.

‡ Dimensionless signal and noise were given by CBF mean and CBF standard deviation, respectively.

§ The ROI was selected at the centrum semiovale.

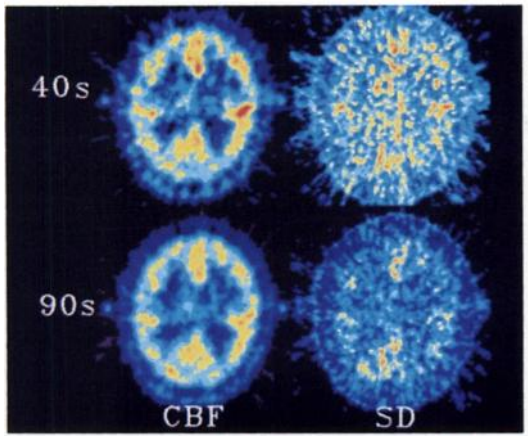

FIGURE 4. S/N ratio estimated by the simulation study, shown as a function of scan time for various blood flows (f) (20, 40, 60, 80 and 100 ml/100 ml/min). For f ≤ 60 ml/100 ml/min (solid lines), the longer the scan time the higher the S/N ratio, except for f ≥ 80 ml/100 ml/min (dashed lines).

tion, due to washout of the tracer from the tissues (*7*). However, the present study clearly demonstrates that this is not the case. From the standpoint of the S/N ratio, we showed that the optimal scan time would range from 90 to 120 sec, longer than the 40 sec previously described (*3*) or the 70 sec as suggested for the largest S/N ratio for activation of the visual cortex (*7*).

Our result is intuitively reasonable because the physiologic half-life of tissue $H_2{}^{15}O$ at a flow of 50 ml/100 ml/min is longer than 80 sec even with input of the unit impulse, and that with intravenous bolus injection it is much more than 200 sec. Therefore, the largest fraction of tracer accumulation reflects washin rather than washout. In other words, the $H_2{}^{15}O$ bolus injection method uses the principle of the indicator fractionation (*10*) rather than tracer clearance. Under the circumstances an accumulation time greater than 90 sec will still increase statistical information and hence improve the S/N ratio of CBF. The 40-sec scan time cannot be the optimum.

Volkow et al. recently described that a shorter scan time provided the larger change in photic activation (*11*). However, they discussed changes only in the raw images. This evaluation could cause substantial underestimation of flow change with increasing scan time (Fig. 1). Comparing separate images of the uptake phase and the washout phase during actual stimulation could mislead us to conclude that a shorter scan time would provide higher sensitivity for detecting stimulation foci compared to a longer scan time. The comparison only tells us that the uptake phase image includes more information on flow than the washout phase image, but this does not mean that a longer scan time will mean a loss of the flow information. On the other hand, the present paper demonstrates that extending the scan time increases the information content by improving the S/N ratio.

The only drawback of the longer scan time is an increase in the partial volume effect (PVE) due to tissue mixture (*5*). This effect mainly reduces the CBF mean rather than CBF standard deviation, hence reducing the S/N ratio with increasing scan time. Therefore, the PVE may shift the optimum point to a shorter scan time. The results of Figs. 2 and 3, however, already include this effect. Only with the extreme case of high CBF > 100 ml/100 ml/min, the optimal scan time will become as short as 60 sec (Fig. 4). Normally, CBF > 80 ml/100 ml/min is rare. Therefore, with $H_2{}^{15}O$ and the current resolution with PET, PVE is not as important for the S/N ratio as the scan time.

In interpreting human studies, we must take into account the physiologic fluctuation of brain function at rest. We hypothesized that physiologic fluctuation of CBF at rest was steady over the whole period of the study. Conrad and Klingelhöfer demonstrated using Doppler sonography that CBF fluctuated with uniform frequency over the current time scales of interest (e.g., a few seconds through a few minutes) during both rest and visual stimulation (*8*). Thus, it is estimated that physiologic fluctuation may contribute to the production of an equal offset in CBF standard deviation obtained with the present schedule of the measurement. We have in part confirmed it by comparison with two injection schedules (i.e., the bolus and slow) which resulted in no significant difference in the regional CBF standard deviation at rest between the two schedules (*9*).

In the simulation study, we assumed that the standard deviation of a regional value of the raw image was proportional to its square-root. This assumption is valid only in an ideal situation, in which the random and scatter contributions are uniform over the whole scan length, and where the distribution pattern of the tracer is unchanged over the whole scan length. The first condition was met with the present injection dose and scan setting. However, this may not be the case for the second condition. Nevertheless, the cortex ROI values may roughly correlate to the total counts of the image because most raw counts before the attenuation correction are measured from this area. Therefore, the assumption can be accepted under the circumstances of this study.

In this study we used a partition coefficient of 1.0. However, Iida et al. suggested that the distribution volume, (i.e., a product of partition coefficient and diffusible tissue fraction) was about 0.7–0.9 (*12*). The use of a larger partition coefficient than the true value will straighten the curvature of the relationship between the CBF and the integral, and therefore cause underestimation of both CBF mean and CBF standard deviation each cancelling out the S/N ratio. Finally, the use of a larger partition coefficient than the true value may not be reflected substantially on the S/N ratio.

The improvement in S/N ratio of CBF will reduce the number of the desired trials needed to obtain significant statistics. This gain is evaluated by the square of S/N ratios, since the signal is unchanged and the variance (square of standard deviation) of measurements is in-

versely proportional to the number of measurements. This implies that CBF at a 120-sec scan time in gray matter is equivalent to $(13.6/10.2)^2$ equaling 1.8-fold trials of those by a 40-sec scan time, that is, the 120-sec scan time corresponds to an 80% gain in the number of trials as compared to the 40-sec scan time.

In conclusion, the optimal scan time of PET using the $H_2{}^{15}O$ method is between 90 and 120 sec. The gain of the 120-sec scan time over the 40-sec scan time corresponded to an 80% increase in the number of stimulation trials needed to provide the same statistical significance.

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REFERENCES

1. Petersen SE, Fox PT, Posner MI, Mintun MA, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 1988;331:585–589.
2. Posner MI, Petersen SE, Fox PT, Raichle ME. Localization of cognitive operations in the human brain. *Science* 1988;240:1627–1631.
3. 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.
4. Iida H, Miura S, Kanno I, Murakami M, Yamamoto S, Amano M. Design and evaluation of HEADTOME-IV, a whole-body positron emission tomograph. *IEEE Trans Nucl Sci* 1989;NS-37:1006–1010.
5. Kanno I, Iida H, Miura S, et al. A system for cerebral blood flow measurement using an $H_2{}^{15}O$ autoradiographic method and positron emission tomography. *J Cereb Blood Flow Metab* 1987;7:143–153.
6. Iida H, Kanno I, Miura S, Murakami M, Takahashi K, Uemura K. 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.
7. Mintun MA, Raichle ME, Quarles RP, Length of PET data acquisition inversely affects ability to detect focal areas of brain activation. *J Cereb Blood Flow Metab* 1989;9:349.
8. Conrad B, Klingelhöfer J. Dynamics of regional cerebral blood flow for various visual stimuli. *Exp Brain Res* 1989;77:437–441.
9. Kanno I, Iida H, Murakami M, et al. Comparison of slow-infusion autoradiography method with bolus injection autoradiography method for measurement of CBF using $H_2{}^{15}O$ and PET [Abstract]. *J Cereb Blood Flow Metab* 1991;11:S574.
10. Landau WM, W.H. Freygang J, Roland LP, Sokoloff L, Kety SS. The local circulation of the living brain: Values in the unanesthetized and anesthetized cat. *Trans Am Neurol Assoc* 1955;80:125–129.
11. Volkow ND, Mullani N, Gould LK, Adler SS, Gatley SJ. Sensitivity of measurements of regional brain activation with oxygen-15-water and PET to time of stimulation and period of image reconstruction. *J Nucl Med* 1991;32:58–61.
12. Iida H, Kanno I, Miura S, Murakami M, Takahashi K, Uemura K. A determination of the regional brain/blood partition coefficient of water using dynamic positron emission tomography. *J Cereb Blood Flow Metab* 1989;9:874–885.

EDITORIAL

Optimization of Regional Cerebral Blood Flow Measurements with PET

Several methods for measuring regional cerebral blood flow (rCBF) with PET and ^{15}O-water have been developed, evaluated and applied. These include the ^{15}O equilibrium method (*1*), the autoradiographic method (*2*), and other techniques which will be referred to, generically, as dynamic methods (*3–7*). The common theoretical basis for these techniques is the Kety model, which assumes a homogenous tissue volume with respect to blood flow and tissue type, complete first-pass extraction of a diffusible, inert tracer, and uniform distribution of tracer within the tissue volume. More detailed models of the tissue volume have been proposed, but have not been widely applied. The Kety model has two adjustable parameters, blood flow and the tissue-to-blood partition coefficient. Optimization of blood flow measurements, per se, can be accomplished by varying: (1) the total observation period, (2) the scan and blood sampling protocol, and (3) the type and magnitude of tracer administration. For example, sharp bolus injection and continuous administration of tracer are the two extremes for the shape of input function. Choosing the continuous inhalation of $C^{15}O_2$ gas and the equilibrium method permits a longer observation period and higher precision at the expense of increased radiation dose. Making a specific choice of observation period and the method of tracer administration inevitably involves a trade-off among accuracy, precision, temporal resolution, and radiation dose to the subject.

An example of a CBF optimization scheme is provided in the report by Kanno et al. in this issue of the *Journal*, which shows that increasing the scan time in the autoradiographic method from 40 to about 100 sec improved the signal-to-noise (S/N) ratio of flow measurements while holding the radiation dose to the subject constant. The value of improved S/N ratio must be balanced against the loss of temporal resolution. In some activation studies, where it is necessary to maintain physiologic steady-state in the face of habituation, better temporal resolution may outweigh improved S/N ratio. It is also important

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