7. Muzic RF, Nelson AD, Miraldi F. Temporal alignment of tissue and arterial data and selection of integration start times for the H_2O^{15} autoradiographic CBF model in PET. *IEEE Trans Med Imag* 1993: in press.
8. 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.
9. Muzic RF, Nelson AD, Miraldi F. Mathematical simplification of a PET blood flow model. *IEEE Trans Med Imag* 1990;9:172–176.
10. Herscovitch P, Raichle ME, Kilbourn MR, Welch MJ. Positron emission tomographic measurement of cerebral blood flow and permeability-surface area product of water using [^{15}O]water and [^{11}C]butanol. *J Cereb Blood Flow Metab* 1987;7:526–542.
11. Berridge MS, Adler LP, Nelson AD, et al. Measurement of human cerebral blood flow with [^{15}O]butanol and positron emission tomography. *J Cereb Blood Flow Metab* 1991;11:707–715.
12. Celsis P, Goldman T, Henriksen L, Lassen NA. A method for calculating regional and cerebral blood flow from emission computed tomography of inert gases concentrations. *J Comp Assist Tomgr* 1981;5:641–645.
13. Koeppe RA, Holden JE, Polcyn RJ, Nickles RJ, Hutchins GD, Weese JL. Quantitation of local cerebral blood flow and partition coefficient without arterial sampling: theory and validation. *J Cereb Blood Flow Metab* 1985; 5:214–223.
14. Meyer E. Simultaneous correction for tracer arrival delay and dispersion in CBF measurements by the $H_2{}^{15}O$ autoradiographic method and dynamic PET. *J Nucl Med* 1989;30:1069–1078.
15. Iida H, Higano S, Tomura N, et al. Evaluation of regional differences of tracer appearance time in cerebral tissues using [^{15}O]water and dynamic positron emission tomography. *J Cereb Blood Flow Metab* 1988;8:285–288.

EDITORIAL

Practical Procedures and Pharmacological Applications of Quantitative PET

As nuclear medicine continues to merge the principles of imaging with those of modern biochemistry, biology and pharmacology, more demanding criteria are placed on measurements being made. The performance of analytical imaging assays of biological processes requires that the methods used have a definable quantitative foundation, whether the end result is a quantitatively reported result in μmole/min/g of tissue or a qualitatively reported clinical evaluation. Although this editorial focuses on the particular issue of ^{15}O-water studies of blood flow with PET, this is an objective for planar gamma and positron cameras, SPECT and PET imaging in nuclear medicine.

There are two levels of quantitation in PET. The first is quantitation of tissue radioactivity concentration as represented by images measured directly by PET scanners. The second is the quantitation of PET images in terms of biological parameters in tissue. The first level involves the consideration of many instrumentation and imaging issues, including scattered radiation, random coincidence, deadtime, photon attenuation, detector efficiency normalization, spatial resolution (intrinsic and reconstructed) and calibration (*1*). The second level requires, in addition, the accurate measurement of time-activity curves (TACs) of labeled compounds in blood/plasma that, combined with the quantitative measurement of radioactivity concentration in tissue and a validated tracer kinetic model, can provide quantitative information on biological parameters of interest in local tissues (*2*).

The measurement procedure of blood TACs is usually invasive, frequently requiring arterial blood sampling that is cumbersome and complex, and deters people from using it on a routine basis. Moreover, it could potentially create unnecessary patient anxiety and thus affect the normal state of the subject being studied. Many approaches have therefore been investigated to make the measurement of blood TACs less invasive and more practical. The paper by Nelson et al. (*3*) is an example of such an approach to minimize the invasiveness of the procedure. The authors used a scintillation probe over the superior aspect of the right lung during a bolus injection ^{15}O-water cerebral blood flow (CBF) study to measure the shape of the ^{15}O-water TAC in arterial blood. The measured TAC was then calibrated to radioactivity concentration units with a calibration study that equated the probe measurement with an equilibrium blood concentration (measured from blood samples with a well counter) following inhalation of ^{15}O-carbon monoxide.

With some clever, but somewhat ad hoc data processings to remove the background and to correct the time shift and dispersion, the probe-measured curve was shown to give estimates of CBF comparable to those obtained using direct arterial blood samples. The use of the probe measurement for ^{15}O-water CBF studies in normals is thus shown to be quite successful.

Some limitations associated with the lung probe approach, however, exist. Some can be easily improved, whereas solutions for others are not so trivial. For example, the use of a separate ^{15}O-carbon monoxide study and blood sampling for calibration is somewhat awkward and the use of ^{15}O with a short half-life of 2 min for calibration is very sensitive to timing errors and background radiation. Although the use of ^{15}O-water for calibration, as suggested by Nelson et al. (*3*), may eliminate the need of the ^{15}O-carbon monoxide inhalation, the high error sensitivity of the calibration due to the short half-life of ^{15}O remains.

The probe measurement for ^{15}O-water CBF studies in normals has been carefully validated by Nelson et al. (*3*). Extension of the approach for studies in patients, with other tracers, or for other organs, however, requires the validation to be repeated for each case, because the applicability of the approach relies on certain special features of the ^{15}O-water tracer that are not common to other tracers/studies.

Received Mar. 5, 1993; revision accepted Mar. 5, 1993.

For correspondence or reprints contact: S.C. Huang, Dept. of Pharmacology, UCLA School of Medicine, Los Angeles, CA 90024-1721.

For example, if the tracer has some specific uptake and retention in the lung tissue, the probe measurement would not be representative of the activity in blood. If a longer time interval for the blood curve is needed (i.e., >2 min), the uptake of a diffusible tracer like ^{15}O-water in the chest wall would begin to affect the shape of the probe-measured curve and the discrepancy between the distribution of ^{15}O-carbon monoxide and ^{15}O-water in the lung and in the adjacent tissues would become more significant and lead to larger errors in the estimation of the blood TAC.

For quantitative PET studies, there are other approaches with different advantages and limitations that one can consider for measuring blood TACs without arterial blood samplings. The "arterialization" of venous blood from a heated hand has been used successfully for FDG studies (*4*). This approach is usable if the tracer has a relatively low tissue extraction from blood and the quantitation method is based on the kinetics over a long time interval (e.g., >30 min in the case of FDG) that can tolerate a small timing delay and dispersion at the early time of the TAC.

In cardiac studies, there is a strong desire to use the imaged radioactivity level (as obtained by defining a region of interest (ROI) on PET images) in the cardiac chambers to provide the blood TAC (*5*). This approach does not require any blood sampling and there is no scanner-to-well counter calibration involved. The spillover of activity from the myocardium to the cardiac chamber and the relatively high noise level of the measurement can, however, pose significant problems, of which many solutions are available (*6–10*). The approach also has been extended to liver and kidney PET studies by using ROIs over the imaged cross-section of the abdominal aorta to give the shape of the blood TAC (*11–13*). Imaging of smaller arteries to provide the blood TAC also has been suggested (*14*). The large partial volume effect and the spillover of radioactivity from adjacent soft tissue are major concerns in cases where the surrounding tissue-to-blood activity concentration increases. All approaches that use ROIs on PET images give the total radioactivity concentration in blood. If there are labeled metabolites in blood or there are different distributions of the tracer between whole blood and plasma, additional measurements and corrections will need to be made (*9,15*).

For certain volatile tracers, the blood TAC can be approximated from the measured radioactivity in the expired air of the subject. This approach has been used by Holden et al. (*16*) for measuring CBF with ^{18}F-methyl- fluoride. The simplest approach of all is probably the use of the total administered dose per body weight of the subject to normalize the imaged tissue radioactivity. An underlying assumption of this approach is that the intersubject variability of the blood TAC after normalization to the administered dose and body weight is small. These variations are due to variable rates of lipophilic and hydrophilic tissue composition or variable systemic concentrations of tissue components that bind the tracer per unit of body weight. Furthermore, it is assumed that tissue uptake is directly related to the area of the blood TAC and the biological process being measured. For most PET studies, however, this assumption is far from the reality and the approach does not usually yield reliable quantitative results (*17*).

The studies by Nelson et al. (*3*) and their group (*18*) on the effects of the enoxacin on global CBF clearly demonstrate that the second level of PET quantitation (i.e., quantitation of biological and biochemical parameters in absolute units) is necessary to provide the critical information in many PET studies. Images of radioactivity distribution in tissue alone do not provide information about global stability or absolute changes in CBF or other biological processes. These investigators' use of quantitative PET also illustrates an important and growing application of PET in pharmacology. In this case, PET is used to study drug-induced biological changes that provide an objective means to assess the effect of a drug on an endogenous process in specific tissue in the living patient.

Another type of PET application in pharmacology is to examine the transport, metabolism, clearance and mechanism of drugs in tissue. Molecular drug action can be traced and studied using the tracer principle in nuclear medicine. An example of the usefulness of such studies was demonstrated in the examination of the effects of carbidopa on L-DOPA uptake in the human brain (*19,20*). By using FDOPA as an analog tracer of L-DOPA, it was shown that its transport across the blood-brain barrier (BBB) and the uptake process of the drug in the human brain is not directly affected by the use of carbidopa, which is used to inhibit the action of aromatic amino acid decarboxylase (AADC). Instead, carbidopa was found to inhibit only the decarboxylation activity of AADC in the periphery and thus increases and maintains the concentration of FDOPA (or L-DOPA) in plasma for uptake in the striatum. This finding is quite different from those based on experiments in rats (*21,22*) and illustrates yet another advantage of PET in allowing direct evaluation of drug action/mechanism in man. By eliminating the unreliable and often inaccurate extrapolation of results from animals to man (*23,24*), quantitative PET is expected to help facilitate greatly the evaluation process in the development of new drugs. This of course is taking place for numerous ligand-receptor assays developed for use in PET and SPECT. These analytical assays are providing the means to titrate blocking doses of drugs to their specific site of interaction in tissue in living humans with diseases for which the drugs are targeted (*25*). In addition to receptor blockage, this approach has targeted the monitoring of pharmacological modification of enzyme concentrations. For example, the ^{11}C-deprenyl tracer assay has been used to determine the percent depletion of monoamine oxidase-B (MAO-B) by pharmacologic dose schedules of deprenyl, as well as the slow rate of synthetic

recovery of MAO-B after stopping the drug (*26,27*). An alternative pharmacologic approach to modulating the concentration of MAO-B in the brain has employed the reversible inhibitor of MAO-B, RO19-6327, developed by Hoffman-LaRoche, Ltd. Again, ^{11}C-deprenyl has been used as a tracer to established the percentage of MAO-B blockage as a function of pharmacologically delivered doses of RO19-6327, as well as the recovery rate of the enzyme after drug delivery is stopped (*27,28*).

With rapid advances in chemistry, genetics and molecular and cellular biology, the target of drug design, is shifting to molecular mechanisms of such processes as signal transduction, second messengers, gene transcription and protein translation. Biological imaging of nuclear medicine will synergistically work with modern drug development so that the latter's objective is to modify the function of a biological process and former's is to image the function of that process. With this realization, drug development and biological imaging will work together to support each other to achieve a common objective in assessing the requirements and efficiency of drugs to provide molecular corrections of the biological nature of disease processes.

The continued commitment to refining and defining the necessary limits of analytical imaging techniques in nuclear medicine will further advance this new and fertile field of biological imaging. Improvement of the practical aspect of quantitative PET is also one of the critical areas that needs special attention and more concentrated efforts. The expected widespread use of quantitative PET will depend on the success of these efforts.

S. C. Huang
M. E. Phelps
UCLA School of Medicine
Los Angeles, California

REFERENCES

1. Hoffman EJ, Phelps ME. Positron emission tomography: principles and quantitation. In: Phelps M, Mazziotta J, Schelbert J, eds. *Positron emission tomography and autoradiography: principles and applications for the brain and heart*. New York: Raven Press; 1986:237–286.
2. Huang SC, Phelps ME. Principles of tracer kinetic modeling in positron emission tomography and autoradiography. In: Phelps M, Mazziotta J, Schelbert H, eds. *Positron emission tomography and autoradiography: principles and applications for the brain and heart*. New York: Raven Press; 1986:287–346.
3. Nelson AD, Miraldi F, Muzic RF, et al. Noninvasive arterial monitor for quantitative oxygen-15-water blood flow studies. *J Nucl Med* 1993;34:1000–1006.
4. Phelps ME, Huang SC, Hoffman EJ, et al. Tomographic measurement of local cerebral glucose metabolic rate in man with (^{18}F) fluorodeoxyglucose: validation of method. *Ann Neurol* 1979;6:371–388.
5. Weinberg IN, Huang SC, Hoffman EJ, et al. Validation of PET-acquired input functions for cardiac studies [published erratum appears in *J Nucl Med* 1988;29:1304]. *J Nucl Med* 1988;29: 241–247.
6. Henze E, Huang SC, Ratib O, et al. Measurements of regional tissue and blood-pool indicator concentrations from serial tomographic images of the heart. *J Nucl Med* 1983;24:987–998.
7. Hutchins GD, Schwaiger M, Rosenspire KC, et al. Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. *J Am Coll Cardiol* 1990;15:1032–1042.
8. Chen K, Huang SC, Yu DC. Effects of measurement errors in plasma radioactivity curve on parameter estimation in PET. *Phys Med Biol* 1991;36:1183–1200.
9. Choi Y, Huang SC, Hawkins RA, et al. A simplified method for quantification of myocardial blood flow using N-13-ammonia and dynamic PET [Abstract]. *J Nucl Med* 1993;34:488–497.
10. Lin KP, Huang SC, Choi Y, et al. A method for correcting myocardium to blood-pool spillover in dynamic cardiac PET FDG studies [Abstract]. *J Nucl Med* 1992;33:882.
11. Chen BC, Huang SC, Germano G, et al. Noninvasive quantification of hepatic arterial blood flow with nitrogen-13-ammonia and dynamic positron emission tomography. *J Nucl Med* 1991;32:2199–2206.
12. Chen BC, Germano G, Huang SC, et al. A new noninvasive method for quantification of renal blood flow with N-13 ammonia, dynamic PET and a two-compartment model. *J Am Soc Nephrol* 1992;3:1295–1306.
13. Germano G, Chen BC, Huang SC, et al. Use of the abdominal aorta for arterial input function determination in hepatic and renal PET studies. *J Nucl Med* 1992;33:613–620.
14. Rajeswaran S, Bailey D, Hume S, et al. 2D and 3D imaging of small animals and the human radial artery with a high resolution detector for PET. In: *Conference Record, IEEE nuclear science symposium*. 1990:1308–1312.
15. Huang SC, Barrio JR, Yu DC, et al. Modelling approach for separating blood time-activity curves in positron emission tomographic studies. *Phys Med Biol* 1991;36:749–761.
16. Holden JE, Gatley SJ, Hichwa RD, et al. Cerebral blood flow using PET measurements of fluoromethane kinetics. *J Nucl Med* 1981;22: 1084–1088.
17. Choi Y, Huang SC, Hawkins RA, et al. Comparison of methods for quantification of myocardial blood flow using N-13 ammonia and PET [Abstract]. *J Nucl Med* 1992;33:881.
18. Green JA, Weikart C, Lebsack M, et al. A study of the effects of enoxacin on cerebral blood flow and metabolism. *Pharmacotherapy* 1991;11:267.
19. Hoffman JM, Melega WP, Hawk TC, et al. The effects of carbidopa administration on 6-[^{18}F]fluoro-L-DOPA kinetics in positron emission tomography. *J Nucl Med* 1992;33: 1472–1477.
20. Huang SC, Yu DC, Barrio JR, et al. Kinetics and modeling of L-6-[^{18}F]fluoro-DOPA in human positron emission tomographic studies. *J Cereb Blood Flow Metab* 1991;11:898–913.
21. Hardebo JE, Owman C. Barrier mechanisms for neurotransmitter monoamines and their precursors at the blood-brain interface. *Ann Neurol* 1980;8:1–11.
22. Hardebo JE, Emson PC, Falck B, et al. Enzymes related to monoamine transmitter metabolism in brain microvessels. *J Neurochem* 1980; 35:1388–1393.
23. Barrio JR, Satyamurthy N, Hoffman JM, et al. In vivo binding of F-18 fluoroethylspiperone (FESP) to dopamine-D2 receptors: from rodents to human [Abstract]. *J Cereb Blood Flow Metab* 1987;7:S357.
24. Barrio JR, Huang SC, Phelps ME. In vivo assessment of neurotransmitter biochemistry in humans. *Ann Rev Pharmacol Toxicol* 1988;28: 213–230.
25. Sedvall G. The current status of PET scanning with respect to schizophrenia. *Neuropsychopharm* 1992;7:41–54.
26. Arnett CD, Fowler JS, MacGregor RR, et al. Turnover of brain monoamine oxidase measured in vivo by positron emission tomography using L-[^{11}C]deprenyl. *J Neurochem* 1987;49: 522–527.
27. Bench CJ, Price GW, Lammertsma AA, et al. Measurement of human cerebral monoamine oxidase type B (MAO-B) activity with positron emission tomography (PET): a dose ranging study with the reversible inhibitor RO19-6327. *Eur J Clin Pharmacol* 1991;10:169–173.
28. Fowler JS, Volkow ND, Logan J, et al. Monoamine oxidase B (MAO-B) inhibitor therapy in Parkinson's disease: the degree and reversibility of human brain MAO-B inhibition by RO19-6327. *Neurology* 1993:in press.