CONCLUSIONS

Dynamic PET imaging with ^{13}N-ammonia allowed the quantitative assessment of rHABF, which correlated well with values obtained by independent microsphere technique (rHABF = 0.92 × MS + .04, r = 0.98) in canine studies under various flow conditions. The same quantification performed on normal human volunteers yields a mean rHABF of 0.26 ± 0.07 cc/min/g, which is in agreement with the literature values. Further studies in patients with severe hepatocellular disease but normal cardiac output as compared to patients with normal liver function but low cardiac output will be needed to show the interrelationship of the pump and blood flow reserve.

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EDITORIAL

The Development and Application of Mathematical Models in Nuclear Medicine

The introduction and application of more sensitive and specific radiopharmaceuticals is a major component of scientific progress in nuclear medicine. Each tracer is targeted to measure a certain physiologic parameter of interest (e.g., blood flow, metabolism, receptor content) in one or more organs or regions. PET and SPECT instrumentation can produce high quality three-dimensional images of the radioactivity distribution of each tracer. With proper corrections for the various physical effects in emission tomography (e.g., attenuation, scatter), quantitatively accurate measurements of regional radioactivity concentration can be obtained. These quantitative images of tracer distribution can be useful, both clinically and scientifically. The use of tracer kinetic modeling techniques, however, can substantially improve their quality and utility (*1*). The model defines the quantitative connection between the radioactivity levels and all of the physiologic parameters that affect the uptake and metab-

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olism of the tracer. Ideally, the image signal will be dominated by the biologic parameter under study. An appropriate tracer kinetic model can account for the remaining biologic factors and provide direct quantitative estimates of the underlying physiologic parameters of interest.

The development of a model is by no means a trivial endeavor. There are no hard-and-fast rules defining what are the essential components of a model. In fact, a successful model is a blend of physiology, instrumentation, statistics and mathematics, and practical logistics. To determine the ultimate form of a useful model, a wide variety of factors must be considered and judicious compromises must be made. The complexity of a 100% complete model may make it impractical for routine use. A simpler but "less accurate" model may prove to be much more useful.

The majority of tracer models in PET and SPECT have employed the methods of compartment modeling. Such models will often require iterative estimation algorithms in order to determine the parameters of interest. In some cases, various simplifying assumptions can be applied that allow a more direct measurement of a subset of the original parameters. One general method of this type that has gained popularity is graphical analysis, also known as the Patlak plot (*2*). Under the special assumptions of this analysis, the slope of the resulting straight line graph represents the net influx rate constant of the tracer. For many investigations, the Patlak plot provides an appropriate compromise between the complexities of a comprehensive compartment model and no model at all. For any tracer, the ultimate form of a useful model will depend upon the biologic questions under study. It may even be that a simple, empirical method, such as using the concentration ratio of target region to an appropriate reference region, may be the most appropriate way to use a new tracer. However, interpretation of significant differences in tracer uptake between patient populations may be problematic without a good model-based understanding of the physiology and biochemistry of the tracer (*3*).

The primary factor affecting the form of a model is the nature of the tracer itself. Usually, a priori information can be used to predict some or all of the relevant metabolic fates of the tracer in tissue. It is usually necessary, however, to perform in vitro and in vivo animal studies to explore the nature of the tracer in more detail. Ideally, these studies not only provide the time course of total radioactivity in plasma and in the target organ, but also differentiate between the original tracer and its metabolites. In addition, through appropriate intervention studies, the sensitivity of the radioactivity concentration at various times postinjection to the physiologic parameter of interest can be demonstrated.

In addition to the biologic characteristics of the tracer, many other factors must be considered in the development of a model. The characteristics of the instrumentation to be used for measurement of tissue radioactivity are critical. These include the ultimate accuracy of the reconstruction algorithm and its corrections and the noise level in the measurements (determined by injected dose, camera sensitivity and scan time). It may be pointless to develop a sophisticated multi-compartment model in the presence of significant inaccuracies in the radioactivity concentration data due to improper corrections for attenuation or scatter. The noise level in the data affects the number of parameters that may be estimated from the data and usually is the primary determinant of the precision in the estimated parameters.

Within the constraints of the tracer and the instrumentation, a number of tradeoffs must be evaluated in determining the final form of the model. Is it practical to measure the input function? Can this be done by direct arterial samples, venous samples, or image values from the heart chambers, or can input function data be inferred from a reference region? Are radioactive metabolites important and can they be measured or estimated? What is a practical data collection period that is compatible with both the scanner requirements and the characteristics of the patients? Is a single scan sufficient or are multiple scans required? Are multiple injections under different conditions required? How many parameters can be determined directly from the measured data? Can parameter estimates be calculated easily on a pixel-by-pixel basis to generate a functional image of the parameter of interest or must iterative non-linear methods be applied to region of interest data? What assumptions are required to reduce the number of parameters to a workable set that can be determined with reasonable precision? How valid are these assumptions under normal and pathologic conditions?

In the process of developing and selecting a suitable model formulation and methodology, it is useful to perform validation studies to determine the precision and accuracy of model estimates, verify the legitimacy of the model assumptions, and help choose between various approaches. These studies are most useful if performed with human subjects, although many must be performed with large animals due to experimental and radiation dosimetry constraints. The simplest test is reproducibility, i.e., what is the variability of the model parameters under identical conditions, either on the same day or different days. Next are intervention studies to verify that the model parameters of interest change in the proper direction and by an appropriate magnitude in response to a variety of biologic stimuli. In addition, it is useful to test whether the parameters of interest do *not* change in response to a perturbation in a different factor, e.g., does an estimate of receptor number remain unchanged when blood flow is increased. Where possible, the assumptions made by the model should be tested, either by explicit experimentation or at least by computer simulation. The

latter approach is useful because it defines the magnitude of error in the parameters of interest due to errors in various assumptions. The limitation of simulation analysis is that it is only as good as the model on which it is based.

Finally, the absolute accuracy of model parameters can be tested by direct comparison with a "gold standard." This last validation step, while very appealing, is often very difficult to achieve. There is often no gold standard available for the measurement of interest. If such a standard is available, the comparison may often require careful matching of the scan data with tissue sample data. If the regions being compared are small, the effects of inaccurate registration and scanner resolution can make evaluation of the model's accuracy difficult at best.

In the preceding article (*4*), Chen et al. presented a model for the measurement of hepatic arterial blood flow with PET. This paper illustrates many of the important steps in the production and validation of a useful model. The authors first developed the model with animal studies and validated their approach using microspheres. They then applied the method to humans. In developing the model, the authors determined the relevant time period of measurement, and in so doing, demonstrated that it was unnecessary to measure plasma metabolites routinely. By comparison with microsphere data in the animal studies, the authors determined a value for a parameter [p(1), the permeability-surface area product] that would be used, but not measured, in the human studies. In the animal studies, results using arterial input functions measured both from blood samples and from region of interest data were compared in order to support the use of the simpler ROI method in humans. Simulation analysis was also performed to evaluate the effects of inaccuracies in model assumptions (the presence of vascular radioactivity, the assumed value for tissue volume of distribution) on the final estimates of blood flow.

In summary, a good and useful model will provide a mathematical description that is sufficient to predict the tracer's physiology and biochemistry within the limitations of available instrumentation and the logistics of a practical procedure appropriate for the relevant patient populations. In addition, the assumptions and limitations of the technique must be clearly delineated. Ideally, use of such a model will significantly improve the physiologic significance of the resultant data and may also improve the sensitivity of the tracer to the underlying physiologic processes under study.

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