EDITORIAL

Noninvasive Estimation of Cerebral Blood Flow

The quantitative aspects of PET, which allow regional measurements of the concentration of radioactivity to be made in absolute units, are well known. To extract quantitative information about physiological entities from a PET measurement or series of measurements (dynamic study), both a tracer kinetic model and an input function are required. The model is a mathematical description of the fate of the tracer within the body, in particular within the tissue under study, in terms of the relevant physiological parameters. However, these physiological parameters can only be quantified if, apart from the tissue response curve, the delivery of tracer to the tissue (input function) is also known.

In PET studies, measurement of the input function usually requires arterial cannulation and sampling, ideally with continuous withdrawal and on-line counting. In most cases, venous sampling is unsatisfactory because of uptake in the peripheral tissues and delay and dispersion within the circulation. The necessity to collect arterial blood is seen as a drawback of quantitative PET. It requires a greater commitment from both patient and doctor. In particular, it can be a negative factor in the recruitment of normal controls. In activation studies, the presence of an arterial cannula and the manipulation of the blood lines during a run could be confounding factors.

Wherever possible, techniques have been developed aimed at avoiding blood sampling altogether. The most obvious situation is that in which the heart is in the field of view of the scanner. This provides the opportunity to measure the input function with regions of interest (ROIs) within the left atrium or ventricle (*1*). For example, this has been applied to the measurement of myocardial blood flow (*2*). In the brain, a reference tissue model has successfully been applied to receptor studies (*3,4*). In this case, a region devoid of receptors is used as an indirect input function to a receptor-rich region to measure the binding parameters. However, it is clear that this type of model cannot be used for cerebral blood flow (CBF) studies.

The measurement of CBF was one of the first quantitative techniques to be implemented in the use of PET (*5*). Over the years, a number of different methods have been described (*6–9*) with the intent of increasing the accuracy of the measurement while maintaining functional flow maps (i.e., calculation of CBF on a pixel-by-pixel basis). The latter property is important for activation studies; it allows statistical tests to be performed on images of CBF. However, all these methods involve arterial blood sampling. As mentioned earlier, especially in the study of normal volunteers, this can be a limiting factor in the recruitment of subjects. Because many studies are directed toward the location of centers of activation rather than the measurement of the absolute change in flow, at present, most activation studies are performed without blood sampling. Instead, statistical tests are applied to the integral count images, which are normalized to a global flow of 50 ml/dl/min. A linear local relationship (i.e., over a small range of global activities) is assumed between counts and flow. Although for very short scan durations the relationship between flow and counts is almost linear, in practice, even for bolus injections, the maximum signal-to-noise ratio is obtained for a scan duration of approximately 90 sec. This results in a significant degree of nonlinearity. In theory, nonlinearity could affect local regressions (*10*) and thereby decrease the sensitivity for actual changes. For CBF studies that are performed as part of a receptor or metabolism study, quantitation is more important, and arterial blood sampling has to be performed. However, this is somewhat unsatisfactory if the receptor study itself can be analyzed with a reference tissue model.

Mejia et al. (*11*) attempted to quantify CBF without blood sampling. Their approach is different from the reference tissue method mentioned before in that they do not use a reference tissue with special characteristics. Instead, they have taken the innovative approach of using the whole brain as a reference and assuming that global CBF is 50 ml/dl/min, an assumption which is reasonably valid, at least for normal brain (*12*). Mejia et al. (*11*) show a good correlation between their method and the autoradiographic method (Table 1 and Figs. 8 and 9). Although the autoradiographic method probably cannot be used as the "gold standard," the comparison nevertheless demonstrates similar performance levels of both methods in this series of 10 studies. In other words, flow maps, similar to those obtained from the autoradiographic method, can be generated without blood sampling. An increased linearity between these flow values and "true" flow compared with integrated counts and "true" flow would be advantageous for activation studies. Apart from the theoretical higher sensitivity, the magnitude of changes can be quantified more reliably with this technique than from count images approaches. Although the patients' results have been obtained with a dynamic scanning sequence, the simulation studies (Fig. 4) would indicate that, in practice, at least for activation studies, the number of frames could be reduced dramatically. Whether noninvasive CBF images have any advantages over the present activation studies that use integrated count images needs to be addressed in the future.

The method reported by Mejia et al.

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(*11*) would be a real breakthrough if it would allow for an absolute quantitation of CBF. However, this has not been achieved yet. First, there is a strong dependence on the actual flow in the whole brain ROI. This means that the method cannot be applied in patients in whom a change in global CBF might be expected. Even in patients in whom global flow might be 50 ml/dl/min, errors can occur, which depend on the selection of the whole brain ROI. Perhaps a more serious concern is based on the assumption that the volume of distribution of water (V_d) is 1 for all regions. Apart from the fact that the V_d is different for gray and white matter, it is well known that the V_d for a heterogeneous region, such as the whole brain, is substantially lower than the true value when it is measured with nonlinear regression of the tissue time-activity curve (*9,13*). The advantage of curve fitting, which allows both CBF and V_d to be determined, is that tissue heterogeneity is primarily reflected in a bias of V_d, not CBF. On the other hand, if V_d is fixed, tissue heterogeneity will be expressed as a bias in CBF. Although the results of their initial study (Table 1) are promising, further studies will be required to test whether the approach proposed by Mejia et al. (*11*) can be truly quantitative. If quantitative studies without blood sampling can be achieved for CBF, application to other tracers could be considered.

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