EDITORIAL

Cerebral Blood Flow Quantitation in Clinical Routine Studies: How Far Have We Now Come?

Ito et al. describe a simple method for calculating cerebral blood flow (CBF) in absolute units with SPECT and [^{123}I]isoprophyl-iodoamphetamine (IMP) (*1*). It is based on the table look-up approach of Iida et al., in which a standard input curve is scaled by a single arterial blood sample (*2*). In their careful study, Ito et al. document that little error is added when using a venous blood sample collected from a hand vein.

IMP was the first brain retained tracer designed for measuring CBF (*3*). As shown in dog experiments by comparison to labeled microspheres, the initial blood-to-brain clearance of IMP practically equals blood flow for all brain regions (*4*). This means that, in normal brain, IMP has a very high extraction fraction of almost unity and negligible back-diffusion within the initial 5 min of the study. The ^{99m}Tc-labeled brain retained tracers developed subsequently, HMPAO and ECD, have obvious advantages over IMP. Their retention in the brain, however, is only about 40% to 50% and it varies with CBF (*5–7*). One cannot therefore calculate CBF with these tracers, even if the exact arterial input curve were measured. So, IMP is clearly the best of this group of tracers, provided the scanning can be accomplished within the first few min.

Most SPECT systems require recording times of 20 min or longer, however, to yield good images, and in this situation backdiffusion of IMP becomes a significant factor. Iida and his group, of which Ito was a member, showed (*2*) that one can correct for backdiffusion of IMP by using the table look-up procedure developed in 1979 by Kanno and Lassen for measuring CBF by ^{133}Xe (*8*). The method requires knowing the arterial input curve. Instead of determining this curve by collecting a series of arterial samples for each patient individually, Iida et al. proposed to use a standard curve obtained from a group of subjects. This curve was then scaled to the individual patient by a single arterial sample collected at 10 min, the time point when least error was introduced (*2*).

The study of Ito et al. shows that a single venous sample suffices to scale the standard input curve. The authors analyzed many samples of venous blood collected from the cubitus, the forearm and the dorsum of the hand in a large group of subjects. It was clear that the veins of the dorsum of the hand gave the best results, but heating of the hand did not improve the results further. The best agreement with arterial sampling at 10 min was obtained by sampling venous blood 15–20 min after IMP injection (*1*).

The method proposed by Ito et al. is attractively simple: a single SPECT scan of 30 to 60 min duration is taken starting 10 min after tracer injection, and one sample of whole blood, taken as described, is counted. Then, using the standard curve of Iida et al., and also their correction for hydrophillic metabolites, the input curve is obtained and rescaled by proper cross-calibration to express the values with the same counting efficiency as that of the SPECT scanner (*11,12*).

Does this mean, that the problems of routinely quantitating CBF are now solved? Of course not. Iodine-123 is not as good a tracer as ^{99m}Tc for SPECT imaging. Technetium-99m gives better images at lower radiation exposure and at considerably lower cost. Thus, unless the clinical value of absolute quantitation (IMP) compared to relative quantitation (HMPAO or IMP) can be clearly demonstrated, we shall probably continue to use ^{99m}Tc compounds to a considerable extent. Forgetting this aspect, it sounds appealingly rigorous to estimate the input function to scale the SPECT image pixel-by-pixel in absolute units of flow (ml/100 ml/min). This represents a form of parametric imaging that should be the standard for many procedures in nuclear medicine. Yet, how reliable can such a method be? This is hard to say, as we have no independent gold standard that could be applied simultaneously with IMP and in a wide spectrum of disease states. It is likely that in some diseases it would be necessary for good quantitation to use both early and late IMP images, as originally proposed by Iida et al. (*9*), so that variations of the distribution volume of IMP could be taken into account.

On a more basic level, it should be pointed out that the method presupposes that one can determine the brain concentration of ^{123}I in all regions; i.e., that one can correct accurately for attenuation and scatter, as well as for partial volume effects. This is clearly impossible. When using a standard whole-blood arterial input curve and also a standard curve for correcting for hydrophillic metabolites, it is probably correct that it is practically the same whether one uses one arterial or venous blood for scaling. There are, as outlined here, a multitude of other factors of systematic and random nature contributing to the overall error. This also means, however, that one should not take quantitation to be more than a fairly crude approximation to what we aim at measuring.

The new method is likely to work best if two measurements in the same subject are compared, as when studying the effect of acetazolamide on CBF to evaluate the hemodynamic affect of occlusion or tight stenosis on the internal carotid artery. In this sit-

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uation, however, the problem of correcting the second study for the remaining radioactivity of the first must be solved. Here, the rapid elimination of ^{133}Xe presents a distinct advantage. The ^{133}Xe method for measuring CBF (*8,10*), on the other hand, has several shortcomings such as poor spatial resolution and patient discomfort due to the necessity of using a face mask or a mouth piece combined with a nose clip. Thus, while allowing CBF quantitation without any blood sampling, the ^{133}Xe method has not gained wider use, despite its lower radiation exposure compared to that of tracers retained in the brain.

Are there not other methods we could use instead? Transcranial Doppler, while useful for monitoring purposes in particular, is clearly unable to measure tissue perfusion locally. The use of nonradioactive (cold) xenon for enhancement of x-ray CT scans does allow one to measure CBF quantitatively with good resolution. The method is, however, very sensitive to slight movements of the head and has a much less favorable signal-to-noise ratio than SPECT techniques. For this reason, and others as well, the "cold" xenon method has not gained wider acceptance, despite the fact that proper instrumentation is available in most hospitals.

Then, what about MRI? This is not the place to discuss all attempts to develop a CBF method for MRI. Suffice to say that no such method has yet gained acceptance for routine use. Thus, at the moment we have to stay with the SPECT techniques. They are not perfect, but they do work. So let us welcome the small but significant methodological advance, the venous sampling IMP method of Ito et al. (*1*) and see how we can best make practical use of it.

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