Brain Function Measured by SPECT:  
Cerebral Blood Flow and Neuroreceptor Quantitation

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A basic tool for quantifying blood flow or neuroreceptors is the convolution integral described by Kety in 1951 for a single tissue compartment. It is commonly called the autoradiographic equation as it was first used for this purpose in animal studies. It is now also widely used for quantitating SPECT and PET studies in man. The approach can be described as a *Bolus Distribution Principle* in that the observed counting rate for every pixel in a single image is linearized by correcting for loss of tracer and scaled by knowing the input. Another approach also of basic importance is the clearance principle, also called the *Sequence of Pictures Principle*, where the convolution equation is used to evaluate the relative change in a given pixel as observed in several images taken sequentially, a change solely influenced by the wash-out rate the tracer, the clearance from tissue to blood.

For measuring cerebral blood flow CBF using SPECT the most reliable tracer available is Xenon-133. At first the sequence of pictures principle was used as described by Kanno and Lassen in 1971. This resulted, however, in an overestimation of low flow levels. Hence a hybrid algorithm combining the sequence principle with the bolus distribution principle was devised by Celsis, Goldman, Henriksen and Lassen in 1981, correcting for the error mentioned, an error mainly due to Compton scatter, CBF is obtained in absolute units of ml/100 g/min using the Xe-133 curve recorded over the lung or end-expiratory air curve as an input function, which is proportional to the true input.

Several brain retained tracers have been developed for measuring CBF distribution by SPECT. Of these "chemical micro-emboli" the Iodine-123 labelled isopropyl-iodo-amphetamine (IMP) and Technetium-99m labelled compounds, (HMPAO and ECD) are most widely used. The image obtained can be linearized by correcting for back diffusion by Kety’s equation. An algorithm based on the approach and applicable for HMPAO and ECD was described by Lassen et al. in 1988 and its general validity has been verified by comparison to Xe-133 or to CBF recorded by PET. Absolute quantitation of blood flow with such tracers is usually not being attempted, as it requires arterial sampling and making certain assumptions that cannot be verified. We usually combine the lower resolution, but quantitative, Xe-133 CBF with the brain-retained tracers so as to obtain absolute calibration in an atraumatic and easy manner.

SPECT ligands for neuroreceptor studies in vivo have recently been developed based on Iodide-123 labelled tracers of high specific activity. The best studied ligand is, sofar, I-123 labelled Iomazenil, a benzodiazepine receptor ligand. Brain images of high quality can be obtained using properly shielded SPECT systems. Image quantitation is based on the single com-
partment model of Kety. With this model the blood to brain clearance, $K_1$, and the wash-out rate $k_2$ is determined pixel by pixel by analyzing the sequence of pictures (Koepe et al. 1991). Then the volume of distribution per unit volume of brain $V_d$ is obtained for every pixel as $V_d = K_1/k_2$. Since unspecific uptake is of negligible importance this gives, after a simple correction for protein binding, a map of the Binding Potential, the $B_{\text{max}}/K_d$ ratio. By performing two such studies one with and one without partial receptor blockages $K_d$ can be assessed (Lassen 1962, Lassen & Lassen 1994). The same parametric imaging approach can be used with IMP for calculating $K_1$, essentially the blood flow (Iida et al. 1994).

Other Iodine-123 labelled neuroreceptor ligands have been developed for SPECT. In particular the Iodine-123 benzamide derivative IBZM, a dopamin receptor ligand, should be mentioned. It binds to the $D_2$ receptor in the basal ganglia. However, the uptake in the brain cortex is higher than expected for a selective $D_2$ ligand. This suggests a more complex binding profile and one cannot, hence be quite clear how to interprete the observed images, and parametric imaging has not been attempted. A muscarinic postsynaptic receptor for acetylcholine Iodine-123, QNB also been described. But, due to its very high receptor affinity one cannot readily record the wash-out rate in receptor rich regions. This jeopardizes parametric quantitation in terms of $V_d$ or $B_{\text{max}}$. Other Iodine-123 labelled neuroreceptor ligands for SPECT use are currently being developed, in particular ligands for the presynaptic reuptake transporter systems. It is important, however, to achieve parametric imaging, i.e. images displaying the distribution of physiologically well defined parameters such as blood flow, $V_d$ or $B_{\text{max}}$ as can be obtained by the quantitation approaches outlined in this abstract, not simply “early and late” images or “cortex to cerebellar ratio images”.

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