ARE PET STUDIES SUITED TO SELECT EFFECTIVE STRATEGIES FOR CONTROLLED CLINICAL TRIALS IN STROKE?

W.-D. Heiss, M.D.
Max-Planck-Institut für Neurologische Forschung
and Neurologische Universitätsklinik Köln, FRG

Current concepts of the development of ischemic cell damage derived from animal experiments suggest a time window for the initiation of interventional therapy to prevent or ameliorate permanent neurologic deficits (Heiss 1983, Raichle 1983, Siesjö and Bengtsson 1989, Ginsberg 1990). The transfer of these experimental findings to the clinical routine of stroke treatment, however, is difficult since studies comparable to those in animal experiments are scarce in the acute stage of cerebral ischemia. With positron emission tomography (PET) several physiologic variables affected in the early phase of ischemia can be investigated affording the assessment of the severity of perfusional and/or metabolic disturbance and—by certain criteria—of the viability of brain tissue (Heiss 1990). By PET utilizing various tracers several questions pertinent to treatment of ischemic stroke can be attacked:

1. Viability of tissue after ischemia

In previous multitracer PET studies (Kuhl et al. 1980, Frackowiak and Wise 1983, Powers et al. 1985, Baron 1987) the criteria suggesting viability of tissue (severely decreased blood flow, slightly impaired oxygen consumption, increased oxygen extraction fraction) were defined, but systematic follow-up studies on the final fate of the involved tissue compartments are still lacking. Therefore, CBF, CMRO₂, OER, CVA and CMRG₁ were measured in 14 patients with ischemic stroke in the MCA territory within 6 to 48 hours (mean 23 hours) and again 13—26 days (mean 17 days) after the onset of symptoms. As can be expected, CBF and CMRO₂ was lowest in the center of the infarct (defined as CMRO₂ < 60 µmol/100 g/min), and further deteriorated during the observation period. In the surrounding of the infarct, 30.1% increased OEF (CMRO₂ reduced by 10.4, CBF by 21.9% compared to contralateral region) indicated viability of tissue. However, in these regions CMRO₂ (~15.7%) and OER (~6%) deteriorated despite CBF (9.5%) increased in the course suggesting the progression to necrosis of this originally viable tissue. Increase of CBF above the metabolic demand (hyperperfusion) could not prevent the progressive derangement, nor could this be achieved by unproportional increase of glucose uptake (anaerobic glycolysis). This study demonstrates that tissue is viable in an ischemic region up to 48 hours after the attack, but that this tissue can not be prevented from changing into necrosis by presently applied therapeutic strategies.

2. Evaluation of treatment effects

Large scale controlled clinical trials are the only means to prove the efficacy of treatment. Since such trials are extremely costly and time consuming PET studies of treatment effect on flow or metabolism can help to select drugs with a potential of effectiveness. In a randomized, double blind, placebo controlled study of 23 matched patients with acute (<48 h) ischemic stroke, the effect on rCMRG₁ of the Ca²⁺-channel blocking agent nimodipine was investigated (Heiss et al. 1990). Patients were randomly assigned to receive either nimodipine (2 mg/h constant infusion for 5 days, 120 mg/d orally for another 16 days) or carrier/placebo. Glucose metabolism was studied by PET before and after the 3 weeks treatment period. The clinical course was followed for 6 months using the Mathew Score for early and the Barthel Index for late assessment. While the infarct showed comparable rCMRG₁ changes in both groups, the metabolic changes in the other regions (contralateral infarct mirror region, ipsi- and contralateral cerebral gray matter, contra- and ipsilateral cerebellar hemispheres) differed significantly between treatment groups (side × region × treatment interaction, p<0.025), with improvements of up to 17% in the nimodipine group.
Progress of rehabilitation was significantly (p<0.05) better in the nimodipine treated patients (median change of Barthel Index=40 vs 2.5). These results agree with the findings of a multicenter trial (Gelmers et al. 1988) and additionally demonstrate that PET data obtained in the first few weeks correlate to the long term effects of treatment in ischemic stroke.

3. Estimation of prognosis

Clinical recovery of neurologic deficits are mainly determined by location and size of infarcts, but may additionally depend on the functional state of adjacent brain tissue, where neuronal loss and deactivation may affect flow and metabolism, and where the ability to respond to stimulation by appropriate neuronal recruitment may be impaired. Therefore, the degree of resting hypometabolism and reduced responsiveness to functional activation may provide a measure of prognosis. In 16 patients (age 43 ± 13.6 years) with mild to moderate aphasia consequent to infarction in the dominant hemisphere rCMRGl was measured at rest and during spontaneous speech. During follow-up (3–9 months), 8 patients improved considerably, achieving good to satisfactory language abilities while the others had a poor aphasic outcome. Hypometabolism of the non-infarcted tissue in the left cerebral hemisphere at rest was significantly (p<0.0042) more severe in the 8 cases with poor prognosis (28.2 ± 5.88 μmol/100 g/min) than in the 8 cases achieving good language recovery (37.8 ± 4.04 μmol/100 g/min). During speech the two groups differed (ANOVA, p<0.05) in their activation pattern: While those eventually showing poor recovery primarily recruited the cerebral hemisphere contralateral to the infarct, the patients with good prognosis activated equally metabolism in both cerebral and cerebellar hemispheres, including areas related to primary language processing and also the supplementary motor area. The significantly more severe hypometabolism in tissue surrounding an infarct in patients with poor prognosis indicates substantial neuronal loss, as previously found in experimental focal ischemia (Mies et al. 1983), which impairs the capacity for functional recovery and diminishes metabolic recruitment during task performance. In patients with good outcome, the mild hypometabolism is mainly due to deactivation by disconnection (“diaschisis”, Feeney and Baron 1986); this tissue responds to stimulation and — since neuronal networks are intact — is capable of functional recovery.

These are only a few selected examples of the application of PET to the study of various aspects related to treatment of ischemic stroke. These preliminary results indicate that PET will be helpful in the selection of effective treatment strategies and also in the selection of patients with a potential to benefit from these therapies.

REFERENCES
1) Heiss WD: Stroke 14, 329—331, 1983
2) Raichle ME: Ann Neurol 13, 2—10, 1983
4) Ginsberg, MD: Cereb Vascul Brain Metab Rev 2, 58—93, 1990
13) Feeney DM, Baron JC: Stroke 17, 817—830, 1986