

Hepatic metabolism of glucose analogues measured by dynamic positron emission tomography and interpreted by compartment models

With special reference to the hepatic dual-input function

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ABSTRACT

The PhD dissertation presents investigations carried out at the PET Center, Aarhus University Hospital. The hepatic metabolism of glucose analogues was quantified by tracer kinetic models that relate the time course of the tracer radioactivity in tissue to that in blood supplying the organ. Regional tissue time-activity curves (TACs) are detected externally by dynamic positron emission tomography (PET), whereas the organ input function is usually measured by arterial blood sampling. Kinetic parameters are estimated by model regression against data.

The brain and other organs are supplied solely by arterial blood, whereas liver has a dual blood supply, via the hepatic artery and portal vein (PV). In a pig study, kinetic parameter estimates using an arterial input function were compared to those using the hepatic dual-input function. Using the dual-input function, parameters describing the fast blood-tissue exchange and the vascular volume were in agreement with other measurements of liver blood volume and perfusion. In contrast, these parameters were clearly underestimated when using an arterial input function. However, estimates of the net metabolic clearance were unaffected by the choice of input function, and for this analysis an image-derived input function could be used. For 3-O-[¹¹C]-methylglucose (¹¹C-MG), there was no net metabolic clearance, in agreement with the expected lack of metabolism. For 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (¹⁸FDG), we found a metabolic clearance indicating metabolic steps beyond the formation of 2-[¹⁸F]-fluoro-2-deoxy-D-glucose-6-phosphate (¹⁸FDG-6P). This was further examined in a liver biopsy experiment, where two metabolites were identified after ¹⁸FDG injection, which shows that ¹⁸FDG-6P is a substrate for glucose-6-phosphate dehydrogenase in the liver.

The dual-input function is a prerequisite for full kinetic analysis of dynamic liver PET studies, but it cannot be measured directly in human subjects. Therefore, alternative non-invasive approaches to estimate the hepatic dual-input function were examined. A model was developed to predict portal venous TACs from arterial TACs based on pig experimental data, which would allow reconstruction of the dual-input based on arterial blood samples. The PV model had a clear physiologic interpretation in terms of the distribution of transit times. For both intravascular ¹⁵O-carbon monoxide and dif-

fusible ¹¹C-MG, the prediction of the PV TAC was shown to benefit from constraining the model by independent estimates of the mean transit time. This was strong evidence for the physiologic relevance of the PV model, which includes asymptotically a simple power law. The asymptotic form described PV TACs well for both tracers and will be useful to describe the PV TAC in the study of the human liver.