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POSITRON COMPUTED TOMOGRAPHY: CURRENT STATE, CLINICAL RESULTS AND FUTURE TRENDS

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Emission computed tomography has become an attractive new means for the nontraumatic study of physiologic processs. Introduced in 1963[1] this imaging modality overcomes many of the limitations inherent to conventional imaging. Ideally, emission tomography should permit external visualization of the three dimensional distribution of radioactive tracers in organs in form of tomographic images with a resolution that is independent of depth, represent the local distribution of radioactive tracers quantitatively and, hence, provide a capability comparable to in vitro counting of tissue samples or autoradiography[2]. For studies of the brain these criterias can be largely met by single photon emission tomography[3] while cardiac studies with this imaging device have been limited by a lack of satisfactory correction for photon attenuation and by the depth dependent resolution[4]. By contrast, positron computed tomography (PCT) permits direct measurements of and correction for photon attenution on the emission images[2]. Moreover, due to the electronic collimation the resolution of PCT images is depth independent. Thus, positron emission computed tomography is at present superior for studies of the heart. In addition, positron emitting radiopharmaceuticals have become available that trace metabolic pathways in a known and well defineable manner and allow, through quantitative imaging, the nontraumatic measurement of local organ function. On the other hand, a drawback for PCT is the need for an on site cyclotron and the relatively high cost.

Positron emitting indicators

Design of single photon emitting radiopharmaceuticals that trace physiologic processes has been difficult in the past. Labeling of Tc-99m, I-123 or I-131 to physiologically active substances often modified their kinetics so that they no longer were useful for studying a specific physiologic process. By contrast, positron emitting O-15, C-11, N-13 or F-18 can be labeled to metabolically active substrates such as glucose, free fatty

acids (FFA) or amino acids without significantly altering their biologic properties. C-11 palmitate as a primary substrate of myocardial energy metabolism for example has permitted the study of regional myocardial FFA uptake, its subsequent breakdown through β-oxidation and storage in form of triglycerides or neutral lipids. This has been possible because of the relatively slow clearance of this substrate from myocardium. Evaluation of carbohydrate metabolism may however be more difficult. Although glucose can be labeled with C-11, it is rapidly metabolized in tissues. The tissue C-11 activity recorded with PCT therefore represents a complex distribution of C-11 metabolic intermediates that changes with time and is difficult to use for quantitative measurements of glucose metabolism.

This emphasizes the need for substrate analogs that trace metabolic pathways or representative steps in a known and well-defineable manner. F-18 2-fluoro 2-deoxy-glucose (FDG) exemplifies such a substrate analog. Sokoloff et al had used initially C-14 labeled deoxyglucose to measure local cerebral glucose metabolism in rats by autoradiography. Substitution of the 2-deoxy group by an F-18 atom[3] permitted use of this analog for PCT imaging of the brain and heart[7,8,9]. FDG traces the transcapillary and transmembraneous exchange of exogeneous glucose and the initial, hexokinase mediated phosphorylation of glucose to glucose-6-phosphate. Since FDG-6-phosphate is not a substrate for glycolysis, the pentose shunt or for glycogen storage, it becomes metabolically trapped. The tissue concentrations can be quantified externally by PCT and are a measure of local glucose utilization rates. At near steady state conditions, FDG tissue concentrations reflect the amount of phosphorylated FDG which is related to the input function, the rate of phosphorylation, and the time after administration.

Physiologic modeling

Measurement of local metabolic rates requires physiologic modeling of the tracer kinetics. This entails mathematical description of the kinetics of a given tracer with the aid of a physiologic model. Two types of physiologic models are currently in use: The steady state, multicompartment model and the unidirectional transport model. In the latter model, the radioindicator is transported from the vascular compartment into the cell unidirectionally where it is subsequently fixed or metabolically trapped. In the former model, metabolic rates are either measured using labeled compounds which equilibrate

between physiologic compartments and accumulate in tissue in proportion to the rate of the metabolic process or which clear as metabolic breakdown products from the tissue. The rates of these processes are estimated from the arterial plasma concentration of the labeled substrate - the input function - and the tissue radioactivity concentration as a function of time. If the labeled product of metabolism is trapped in the tissue the model can be simplified and requires only a single measurement of the tissue radioactivity concentration if the average values of the rate constants of the model are known. If the metabolic products of the labeled substrate rapidly clear from tissue then the tissue concentrations must be measured as a function of time and the model becomes more complex. The latter approach applies to the study of myocardial FFA metabolism with C-11 palmitate whereas the simplified steady state model can be employed with FDG.

Sokoloff's original model[5] was adopted to FDG[7] and, subsequently modified[10] and validated in our laboratory[11]. The kinetics of FDG are expressed by a three compartmental model with a vascular, extravascular and metabolic compartment. Exchange between compartments is described by first order kinetic rate constants that characterize the forward and reverse transport of FDG across the capillary and cell membranes and the enzyme mediated rates of phosphorylation and dephosphorylation. The rate constants and the physiologic model are entered into the PCT system computer so that regional metabolic rates can be measured semiautomatically by trained technicians from the images of regional tissue FDG concentrations, serial arterial plasma FDG and plasma glucose.

Clinical Results

To date, systematic investigations with PCT have been performed mainly in the brain and heart. Initial experience with PCT of the brain has been very encouraging and suggests an important future role of PCT in the clinic. Kuhl et al[12] demonstrated local functional abnormalities with FDG and N-13 ammonia in patients with strokes. Abnormalities detected by PCT correlated far better with the clinical symptomatology than structural abnormalities seen on the X-ray CT images. Not only did PCT delineate metabolic alterations in brain segments affected directly by the ischemic event but also in structurally intact tissues that were affected secondarily by disruption of neuron tracts. In epilepsy, Kuhl et al[13] demonstrated reductions in glucose

metabolism in brain regions which marked degenerative changes on histologic exmination of surgical specimens. Seizure activity provoked in these segments striking increases in flow and glucose metabolism. Phelps et al[14] demonstrated the possibility to quantify regional metabolic responses to visual stimulation in man. The metabolic activity of the visual cortex was found to progressively increase as the visual scene became more complex with a maximum increase by a factor of two. These studies demonstrate the unique capability of PCT to develop a better understanding of local cerebral function in health and disease.

Similar progress has been made in the heart[15]. Unlike the brain which almost exclusively uses glucose as its energy substrate, the heart uses FFA, glucose, lactate, and ketone bodies to varying degrees depending upon the state of supply and demand. This complicates the noninvasive study of regional myocardial metabolism. Secondly, extensive neuroscientific research has provided a framework for metabolic studies with PCT which does not exist to the same degree for the heart. Nevertheless, we have demonstrated that despite the object size related loss in count recovery reported by Hoffman et al[16] true myocardial indicator tissue concentrations can be accurately measured once the thickness of the relatively thin myocardium is known[17]. This also permits measurements of myocardial wall thickening as an index of regional mechanical function. Similarly, the microsphere technique for myocardial blood flow (MBF) measurements in animals was adopted to the noninvasive measurement of regional MBF by PCT[17]. While Budinger et al[18] have used the generator produced Rubidium-82 as diffusible flow indicator, we have characterized N-13 ammonia as an indicator of MBF that is suitable for PCT[17].

PCT together with N-13 ammonia injected during pharmacologically induced coronary hyperemia has allowed detection of mild coronary stenoses in experimental animals[19]. These studies have been extended to man and suggest that coronary stenoses can be detected with a similar degree of accuracy[21]. Not only does this approach appear more sensitive than Tl-201 stress imaging but also superior for detecting multivessel involvement.

The kinetics of C-11 palmitate in myocardium have been extensively evaluated. This metabolic radioindicator has been used for the study of myocardial metabolic integrity in animals and patients with acute myocardial

infarction[22,23]. Hypothesizing that myocardial ischemia is associated with anaerobic glycolysis we evaluated the possibility of demonstrating noninvasively metabolic consequences of acute myocardial ischemia. In the experimental animal uptake of exogeneous glucose in the ischemic segment was either increased or in excess of flow and, hence, oxygen availability[24]. Similar observations were made in man and lead us to conclude that the acutely ischemic myocardial segment resorts to glucose as its energy substrate which probably is metabolized through residual oxidative capacity and/or anaerobic glycolysis. Similarly encouraging are observations in children with segmental myocardiopathies, where the initial defect appears localized to cellular metabolism rather than the vascular supply (SCHELBERT, unpublished data).

Future Trends

During the past years, PCT has developed into a powerful and unique means for the in vivo study of organ physiology. The observations in cerebral disorders strongly suggest a potentially important role for PCT. Current efforts focusing on the development or testing of labeled ligands for studying neuroreceptors will provide additional insights into the cerebral physiology and perhaps become useful in evaluating degenerative disorders and psychiatric problems.

PCT further appears promising for the study of each aspect of cardiac performance, i.e. mechanical function, MBF and metabolism. Because these measurements can be obtained in a single setting, it is conceiveable that the metabolic link between blood flow and mechanical function can be established. Moreover, if it becomes possible to identify regional derangements in metabolism as a consequence of ischemia and their significance regarding cell viability, then PCT may become useful for identifying ischemic and potentially salvageable myocardium, for testing the effectiveness of therapeutic interventions and perhaps to develop new treatment modalities. To date, only indicators of FFA and carbohydrate metabolism have been evaluated. Considering the complexities of metabolic derangements in acute myocardial ischemia, labeled metabolic intermediates or their analogs and amino acids may become useful in the future in defining more specific aspects of metabolic alterations.

Obviously, future developments will include improvement in current

instrumentation. One of the major limitations of PCT has been the need for on-site production of positron emitters. Significant progress is being made in developing small, inexpensive and reliable accelerators that can be used by technologists in a generator-like fashion. It also will be necessary to reduce indicator labeling to a state where it can be performed in a "kit like" manner. Improvements in imaging equipment are also under way. Design of more efficient, multislice tomographs with higher efficiencies and improved spatial resolution is in progress. This should provide statistically improved imaging with greater anatomical detail acquired at less patient and personnel time. It would seem to us that these improvements in instrumentation and radiopharmaceuticals will permit a wider, more convenient and less expensive applicability of PCT to clinical studies. Despite these improvements it appears that PCT will remain limited to major medical institutions. Yet it seems to us that techniques developed with PCT for the study of local organ metabolism may provide the framework and eventually be adopted to the less costly and widely available emission tomography with single photon emitters.

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