LABORATORY OF NUCLEAR MEDICINE AND RADIATION BIOLOGY

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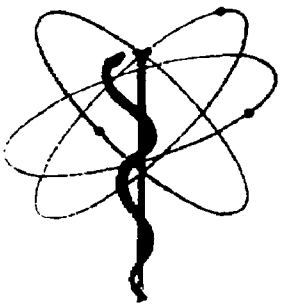

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NONINVASIVE MEASUREMENT OF REGIONAL MYOCARDIAL GLUCOSE METABOLISM BY POSITRON EMISSION COMPUTED TOMOGRAPHY

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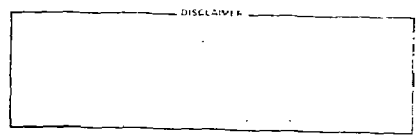

In addition to its quantitative capabilities, positron emission computed tomography (PCT) offers an additional advantage: the use of physiologic indicators. The positron emitting isotopes of oxygen, nitrogen, carbon and fluorine can be attached to substrates without significantly modifying their normal physiologic kinetics.

While it seems entirely possible to label glucose with Carbon-11, the use of this radioactive substrate exemplifies the difficulties encountered in external quantification of regional metabolic rates of the heart. Once administered intravenously it rapidly accumulates in myocardium. Yet its rapid turnover poses several limitations on its use for the external quantification of regional myocardial glucose metabolism by PCT imaging. Because the activity is retained in myocardium for only a short period statistically adequate images are difficult to obtain. More importantly, the myocardial Carbon-11 activity measured by PCT represents a complex distribution of metabolized substrates that constantly changes with time which however remains unknown to the PCT. Measurement of metabolic rates therefore requires substrate analogs that may identify only one specific yet representative segment of a metabolic pathway while its kinetics can be well characterized, formulated as a physiologic model and expressed in mathematical terms.

Several years ago, SOKOLOFF and coworkers employed 2-deoxyglucose labeled with Carbon-14 and developed such a physiologic model that permitted the in vivo determination of regional cerebral glucose utilization in rat brain[1]. In order to adopt this compound and the physiologic model for use with PCT, IDO and coworkers succeeded in labeling deoxyglucose with the positron emitter Fluorine-18 to Fluorine-18-2-deoxyglucose [FDG][2]. Subsequently, REIVICH and KUHL and their associates demonstrated the use of this analog for imaging regional glucose metabolism in brain in man[3-4]. HUANG et al[5] in our

laboratory modified the physiologic model originally proposed by SOKOLOFF and PHELPS and coworkers[6] validated its use for the measurement of local cerebral glucose metabolism in man.

PHYSIOLOGIC MODEL FOR FDG:

As glucose exchanges across the capillary wall and enters the interstitial and intracellular space, it is metabolized by the action of hexokinase to glucose-6 phosphate. It then can be stored in form of glycogen or enter the glycolytic pathway for subsequent oxidation in the citric acid cycle. The initial exchange of FDG from the intravascular into the extravascular space and phosphorylation to Fluorine-18 deoxyglucose-6 phosphate [FDG-6-Ph] occurs similar and in proportion to glucose. However, FDG becomes trapped as FDG-6-Phosphate in the cell and is neither converted to glycogen nor can it enter glycolysis or the pentose-fructose shunt. As shown in Figure 1 the kinetics of FDG can be described by a three compartmental model with a vascular, an extravascular and a metabolic compartment. The exchange between these compartments is determined by first order kinetic rate constants. K_1 and K_2 are the rate constants for the forward and reverse transport of FDG between the intra and extravascular compartment and K_3 and K_4 the rate constants for the exchange between the extravascular and the metabolic compartments or the rate constants for phosphorylation of FDG and dephosphorylation of FDG-6-Ph. Once these rate constants have been established they are together with the physiologic model implemented into the tomographs systems computer. Regional glucose utilization rates can then be calculated from regions-of-interest on the PCT images, the arterial input function for FDG (the area under the FDG plasma curve) and the plasma glucose levels (Figure 2). While the first order kinetic rate constants have been determined and validated in the brain, they remain to be established for myocardium. How-

ever, there is evidence that they are of similar magnitude as those in the brain(7). In preliminary animal studies we demonstrated that with this technique regional glucose utilization rates indeed can be determined with a high degree of accuracy. Uptake of exogeneous glucose by myocardium measured by the FDG technique closely correlated to measurements employing the Fick principle (PHELPS, unpublished data.)

ASSESSMENT OF METABOLIC CHANGES ASSOCIATED WITH ACUTE PACING INDUCED ISCHEMIA

Acute myocardial ischemia is known to be associated with severe derangements in myocardial metabolism. For example, the work by OPIE and coworkers(8) in open chest dogs suggested that in acute myocardial ischemia fatty acid utilization decreases while glucose uptake increases. The possibility of demonstrating this metabolic derangement noninvasively by PCT and FDG was examined in open chest dogs. In these animals, pacemaker electrodes were attached to the left atrium and systemic arterial blood pressure monitored through catheters advanced into the thoracic aorta. The anterior interventricular vein was cannulated for sampling venous effluent from the LAD distribution. An electromagnetic flow probe was fit snugly around the proximal left anterior descending coronary artery. Using a screw type constricter a stenosis was applied to the mid left anterior descending coronary artery until reactive hyperemia to a 10 sec occlusion was completely abolished. Following positioning of the animals to the positron emission tomograph, pacing was begun and perfusion during pacing induced ischemia assessed with intravenous N-13 ammonia and subsequent PCT imaging. Microspheres were injected together with N-13 ammonia into the left atrium for subsequent in vitro measurements of regional myocardial blood flow. During pacing, myocardial oxygen consumption, glucose, fatty acid and lactic uptake

or production in the ischemic segment were determined from flow and the AV difference across the LAD distiribution. After cross sectional images of the N-13 ammonia distribution in left ventricular myocardium had been obtained, pacing was resumed one hour later (after N-13 activity had decayed to near undetectable levels). At this time, FDG was injected into the left atrium together with gamma emitting microspheres, pacing continued for an additional ten minutes and PCT cross sectional images of the myocardial FDG distribution obtained 40 min later. Upon completion of PCT imaging, the animals were sacrificed with high concentrated KCl, the heart sliced into 1cm thick cross sections. Two of these cross sections corresponding to the imaging planes were then divided into multiple segments for subsequent in vitro tissue counting.

Typical examples of myocardial perfusion images with N-13 ammonia and images of glucose metabolism are shown in Figure 3. The panel to the left shows a set of contiguous cross sectional images of the regional myocardial perfusion obtained with N-13 ammonia. As indicated by the arrows the decrease in activity in the anterior wall or the LAD distribution is consistent with a marked perfusion defect. On the FDG images to the right and as indicated by the arrows, glucose uptake in the anterior wall is also decreased yet in comparison to the perfusion images the fall in FDG uptake in the anterior wall is disproportionately less than flow. These images indicate that glucose uptake in acute myocardial ischemia occurs in excess of blood flow.

The relationship between regional myocardial blood flow as assessed by the microsphere technique and in vitro counting and regional FDG concentrations is shown in Figure 4. Within the normal flow range there is a close correlation between regional FDG concentrations and myocardial blood flow. For example, as myocardial blood flow increases FDG concentrations increase in

proportion. On the other hand, in the low flow or ischemic range, where blood flow decreases towards zero, FDG concentrations remain unchanged or even increase. This mismatch between flow and regional FDG uptake is consistent with the observations on the cross-sectional images and again suggests that FDG uptake occurred in excess of flow. The most likely explanation for the linear relationship between myocardial blood flow and FDG concentrations as as seen in Figure 4 is that myocardial blood flow and consequently demand for glucose is a function of the mechanical demands of the myocardium. Within the normal flow range therefore the ratio between FDG concentrations of glucose uptake and myocardial blood flow is constant while this relationship appears altered in the low flow range. This is indicated in Figure 5 where the ratios of FDG concentrations to myocardial blood flow are plotted along one unrolled cross section of the left ventricular myocardium and compared to regional myocardial blood flow. While in the anterior wall myocardial blood flow had significantly decreased with pacing, the ratio of FDG over MBF markedly increases.

The findings in these animal experiments are in agreement with those previously reported by OPIE and coworkers(8). It would appear that despite a marked reduction in myocardial blood flow glucose utilization in the ischemic myocardium is impaired less and, if flow correlates to the availability of oxygen, may be used to produce high energy phosphates either through residual oxidative capacity and/or anaerobic glycolysis. The results further indicate that these changes associated with acute myocardial ischemia can indeed be visualized by external imaging with PET and physiologic indicators or their analogs.

SUMMARY AND CLINICAL INDICATIONS:

While these results are promising their utility and value remains to be determined in man. If this technique can be applied to patients with acute myocardial ischemia or infarction it may permit delineation of regional myocardial segments with altered , yet still active metabolism. Further, it may become possible to evaluate the effects of interventions designed to salvage reversibly injured myocardium by this technique.

ACKNOWLEDGEMENTS:

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LEGENDS:

Figure 1: Three compartmental model for F-18 2-deoxyglucose (see text).

Figure 2: Determination of regional myocardial glucose utilization from the cross-sectional PCT images of the myocardial FDG concentration. The rate of glucose uptake in the segment of interest (arrow) is indicated on the right and is 11.1mg/100gm/min.

Figure 3: Myocardial perfusion and glucose images obtained during pacing induced ischemia of the anterior wall.

Figure 4: Comparison between regional myocardial blood flow and FDG concentrations.

Figure 5: Regional myocardial blood flow and the ratio of FDG concentration to myocardial blood flow plotted along one unrolled left ventricular cross section.

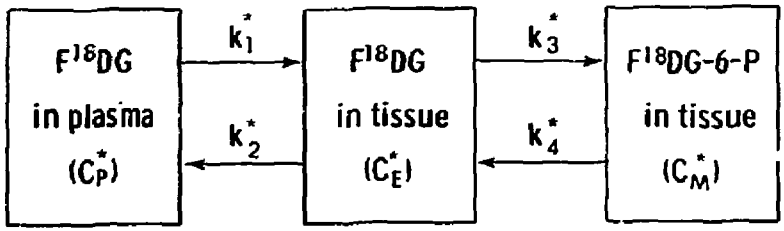

DIAGRAM OF THE THREE COMPARTMENTS IN FDG MODEL

Figure 1.

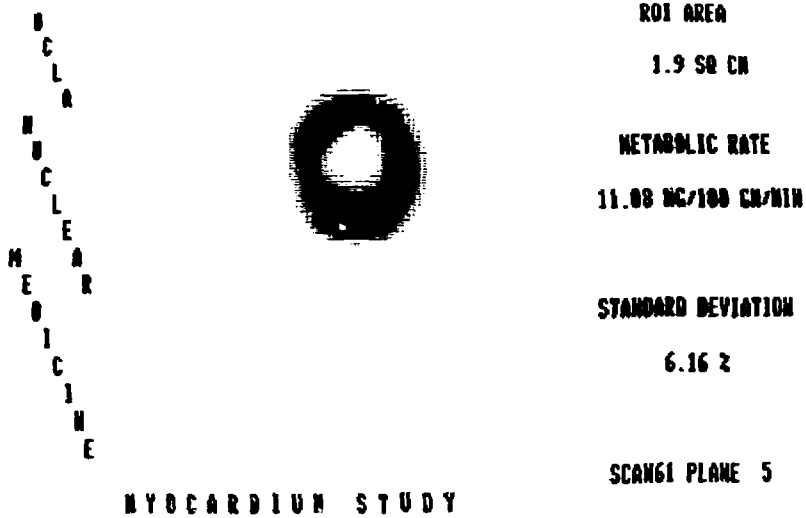

Figure 2.

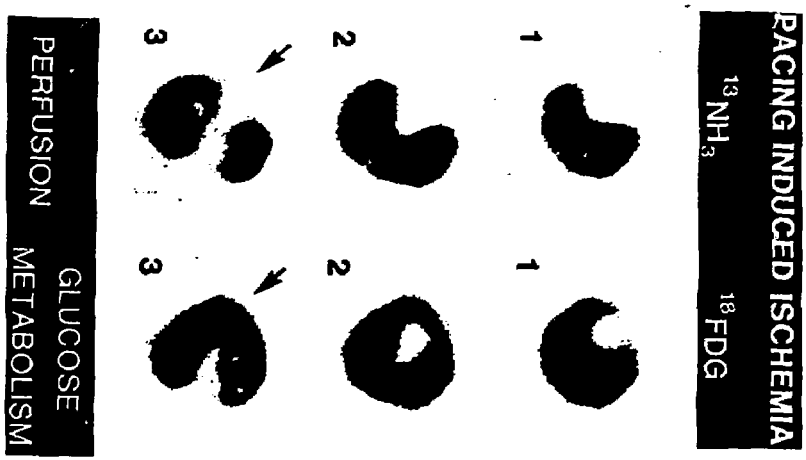

Figure 3.

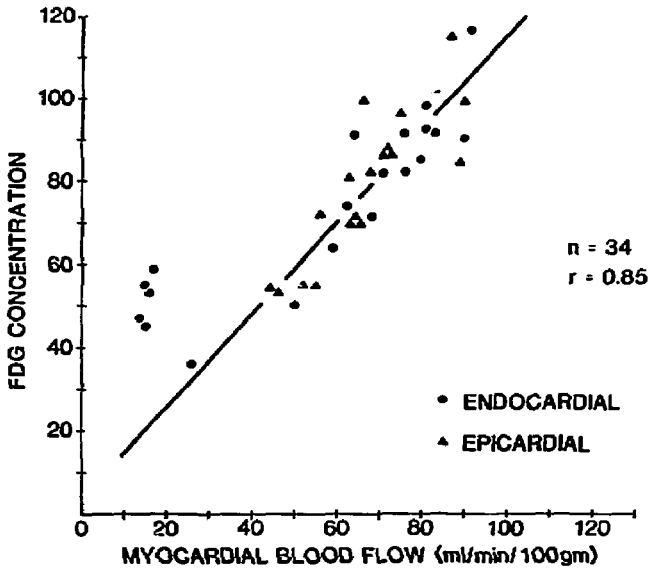

Figure 4.

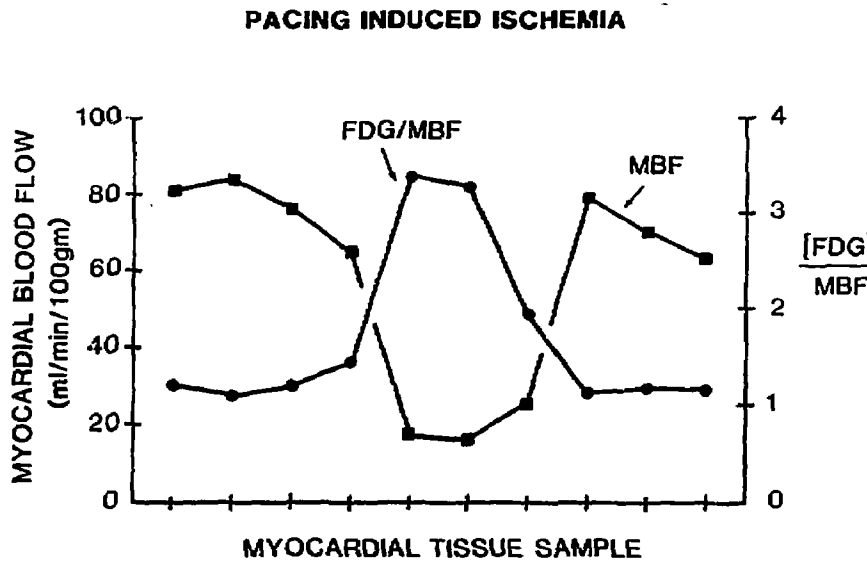
PACING INDUCED ISCHEMIA
MYOCARDIAL BLOOD FLOW
(ml/min/100gm)
100
80
60
40
20
0
FDG/MBF
MBF
4
3
2
1
0
[FDG]
MBF
MYOCARDIAL TISSUE SAMPLE

Figure 5.