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Imaging of Myocardial Metabolism by Positron Emission Tomography

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Summary. **Tracer techniques have provided new insight in cardiology by allowing noninvasive studies of myocardial perfusion, function, metabolism, and, more recently, ligand-receptor interaction. Positron emission tomography allows accurate quantification and the use of natural substrates labelled with ^{11}C, ^{13}N, or ^{15}O.**

Myocardial metabolism is complex and utilizes a number of substrates, primarily fatty acids. Fatty acids utilization can be studied with ^{11}C palmitate, while ^{11}C acetate more selectively traces TCA cycle activity and reflects myocardial oxygen utilization. Glucose uptake can be traced using ^{18}F deoxyglucose, a glucose analog that is a substrate for hexokinase but is not further metabolized. Flow and oxidative glucose metabolism are usually coupled, and thereby the uptake of FDG and perfusion tracers are usually similar. In myocardial ischemia, however, glucose utilization can persist due to anaerobic glycolysis, and its uptake is frequently enhanced. Clinical applications of the use of metabolic studies in patients with ischemic heart disease are presented.

Key Words. **metabolism, deoxyglucose, ischemia, positron emission tomography**

Positron emission tomography (PET) presents unique characteristics for the noninvasive assessment of regional myocardial metabolism in vivo [1]. Indeed, the only convenient isotopes of oxygen, nitrogen, and carbon for human imaging use are positron emitters, and they can be incorporated into natural substrates without the changes in chemical properties frequently induced by hetero-atom substitution. Furthermore, the physical characteristics of positrons allow quantitative determination of tissue radioactive concentration with good spatial and temporal resolution. PET can not only be of value for the study of myocardial metabolism, but also for the study of myocardial blood flow, myocardial viability, and for the imaging of myocardial neurotransmitter storage and receptor activity [2]. Frequently, studies are combined to use one tracer as a reference or to confront information from different tracers studying different functions.

Positron Emission Tomography

Positron emitters decay by emission of a positively charged electron. They rapidly loose their kinetic energy in the surrounding tissues, and within a range of a few mm annihilate with their antiparticle, a negative electron, giving rise to two 511 Kev photons emitted in opposite directions. These simultaneous photons are detected in coincidence by two opposite scintillation crystals of a polygonal or annular detector array placed around the body. Electronic collimation made possible by this coincidence circuit and by miniaturization of the individual detectors has enabled the development of machines with good sensitivity and high resolution (around 5 mm in all directions). Multiple plane acquisitions are also possible to encompass the whole organ (heart or brain). Coincidence detection of opposite photons is also easily amenable to attenuation correction, as the total distance travelled by both photons through the body is independent of their depth of origin along the line of detection. It is therefore possible to determine attenuation coefficients by use of a transmission scan using a ring source positioned around the body prior to the injection of the tracer.

These characteristics combine to make positron emission tomographs quantitative instruments of superior accuracy in nuclear medicine. In practice, the machine must operate in close proximity with a cyclotron to make effective use of the short-lived tracers ^{11}C (20 minutes), ^{15}O (2 minutes), ^{13}N (10 minutes), and ^{18}F (110 minutes), despite the time necessary for the synthesis of the labelled substrate.

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Strategy for the Evaluation of Myocardial Metabolism by PET

Myocardial energetic metabolism is complex and utilizes a number of substrates. The primary energy fuels in the normal oxidative state are the fatty acids, but glucose, lactate, ketonic bodies, and amino acids are other substrates. Their relative contribution to the energetic metabolism of the myocardium can be altered by substrate availability, among other factors. Indeed, the oxidative metabolism of these tracers is largely interrelated, as the tricarboxylic acid (TCA) cycle is their final common pathway. It should be pointed out, however, that while all the principal substrates can be effectively labelled using short-lived isotopes, it is not possible to follow the trace of these substrates while they are metabolized. Indeed, it is not possible with PET to determine with which chemical species the radiolabel is associated at a given moment.

The fate of the tracer follows a global process that has to be analyzed using *a-priori* knowledge of cardiac metabolism, tracer kinetics analysis, and modelling of part or whole of the kinetic data. Thus, information on substrate utilization can be derived from the determination of first-pass tracer extraction (for instance, by comparing the accumulation of substrate with that of a flow tracer or with a nondiffusible tracer). Determination of the rate of uptake of a nonmetabolized substrate analog (such as FDG for glucose or beta-methyl-heptadecanoic acid for palmitate) is also of value. Finally, tracer kinetic analysis of the uptake and clearance of the radiolabel from the myocardium can be assessed using a compartmental model when the fate of the radiolabel and substrate are well known.

Fatty acid metabolism

Fatty acids usually represent the main oxidative fuel of the myocardium, except in a few physiologic conditions (for instance, strenuous exercise, where lactate is mainly used, or after a glucose load, when glucose is mainly used).

Transfer of free fatty acids through the cellular membrane has long been thought to be a passive phenomenon, but remains incompletely understood. Extraction of the tracer is high. Within the cell, fatty acids are activated by esterification with coenzyme A to form fatty acyl coenzyme A. They are incorporated into the mitochondria by the carnitine shuttle, degraded by beta oxidation into two-carbon units, and then finally oxidized in $^{11}CO_2$ labelled and water in the TCA cycle.

^{11}C palmitate is usually used to trace fatty acids metabolism with PET [3]. Palmitate is a saturated 16-carbon fatty acid that is present in most natural fats. Its initial uptake is flow dependent, as its extraction is high (30–60% [4–6]. Activity clearance is biexponential, and the rapid clearance curve component is thought to represent palmitate oxidation, while the slow clearance phase corresponds to incorporation of the radiolabel into the phospholipid and triglyceride pools. The initial phase has been shown to parallel $^{11}CO_2$ production and can be modified by the factors that affect beta oxidation. ^{11}C palmitate, however, does not only trace beta oxidation and the TCA cycle activity, but also fatty acid transport and extraction, which could also be affected by ischemia or hypoxia. In particular, Fox et al. [7] have demonstrated that back diffusion of unaltered ^{11}C palmitate significantly contributes to myocardial activity clearance in ischemia or hypoxia, and has to be taken into account in attempts to assess oxidative metabolism from these curves.

^{11}C acetate that is highly extracted (40%) [8] and is metabolized only by the TCA cycle has been proposed as a more direct reflection of myocardial oxidative metabolism [9,10]. Experimentally, Brown et al. [4] and Buxton et al. [5] compared acetate clearance with MVO_2. K_1, the rate constant of the early rapid phase, correlates with MVO_2 and is only minimally influenced by myocardial substrate availability.

Glucose metabolism

To study myocardial glucose metabolism in humans, the use of ^{18}FDG, a glucose analog, is usually preferred [11]. Indeed, although glucose can be labelled with ^{11}C, its metabolic fate is too complex for modelling, as it can be transformed into glycogen and degraded into lactate, pyruvate, or acetyl coenzyme A and the ^{11}C label transferred to the TCA cycle intermediates, $^{11}CO_2$, or other metabolic pathways.

Fluorodeoxyglucose shares the same membrane transporter as glucose. It is also phosphorylated by hexokinase, but is no further metabolized, as FDG-6-phosphate is not a substrate for glycolysis. It remains trapped in the myocardium because of a low membrane permeability for back diffusion. Measurement of ^{18}FDG incorporation into the myocardium, together with the input function and use of a mathematical model, allow the estimation of glucose utilization.

Use of ^{18}FDG has demonstrated normal glucose utilization in non-ischemic myocardium, depending upon substrate availability: It is depressed in fasting conditions but is enhanced after carbohydrate administration. In myocardial necrosis resulting from coronary artery obstruction, a concordant marked diminution of all substrate utilization can be demonstrated in

some areas of flow deficit [12,13]. In myocardial ischemia, however, oxidative metabolism is depressed (fatty acids, lactate), but glucose can initially still undergo anaerobic glycolysis, and its uptake and utilization are frequently enhanced in conditions of moderate anaerobiosis and a reduction of blood flow [14,15]. This pattern of enhanced glucose utilization, concomitant with a moderate reduction of flow and typically of a more significant depression of oxidative metabolism, can be observed in patients with severe coronary artery disease and repetitive or chronic ischemia (frequently with a clinical presentation of unstable angina or postinfarction angina). It can also be seen in the border zone of myocardial infarction [13,16]. Finally, ^{18}FDG uptake can be observed in patients with exercise-induced ischemia if ^{18}FDG is injected during the recovery period [15]. In this case, it seems to represent reconstitution of glycogen stores rather than direct utilization, although the persistence of metabolic abnormalities (stunned myocardium) is an alternative explanation.

Amino acid metabolism

Amino acids are incorporated into proteins but they also participate in energy metabolism. They can be labelled with ^{13}N, but this label is easily transferred by transamination and the ^{11}C label is usually preferred for kinetic studies. Few tracers have been used in vivo in humans. Despite conflicting results, it seems that glutamate, due to its high extraction, is primarily a flow tracer [17,18]. Protein synthesis could probably be studied using ^{11}C methionine or ^{11}C l-leucine.

Myocardial oxygen metabolism

Myocardial oxygen consumption is the product of blood flow and oxygen extraction. The latter is difficult to measure in humans because of methodologic problems, and myocardial blood flow has generally been used as an index of oxygen supply. However, for the study of myocardial ischemia, knowledge of oxygen supply provides only one side of the coin, as we do not have precise methods to determine oxygen demand.

A method to study the balance of supply and demand experimentally is to measure oxygen tissue content. Recently, a new approach has been proposed, making use of ^{18}F misonidazole [19,20]. This labelled hypoxic radiosensitizer is known to accumulate in hypoxic cells. Recent experiments have shown persistent accumulation of ^{18}F misonidazole in the setting of experimental acute ischemia. The proposed mechanism of accumulation of this tracer involves enzymatic reduction of a nitro group to a reactive anion radical. In the presence of oxygen, it reacts with the radical anion, yielding superoxide and noncharged ^{18}F misonidazole, the parent compound, which is free to diffuse out of the cell. In hypoxia or ischemia, reduction of the ^{18}F misonidazole radical anion proceeds further, yielding compounds that bind to intracellular macromolecules, thereby becoming trapped in the cell. In necrotic tissue, enzyme activity is lacking and binding does not occur.

Clinical Applications

Fatty acid metabolism

In humans, ^{11}C palmitate has been used by Schelbert and Schwaiger [21], who have demonstrated the clearance of ^{11}C activity following a biexponential curve, as in experimental animals. The half-time of these curves are longer in humans. Peak activity occurs 3 minutes after injection. The rapid phase is frequently prolonged up to 20–25 minutes, while the half-life of the slow phase is often too long to be accurately measured. Back extrapolation of the slow-phase clearance curve indicates that, depending on metabolic conditions, approximately 50% of palmitate enters the rapid turnover pool. When MVO_2 increases, the clearance of the rapid phase also increases, as well as the proportion of palmitate metabolized by beta oxidation. Inversely, palmitate clearance diminishes in ischemic regions, despite increased back diffusion of nonmetabolized tracers and an increase in the proportion of palmitate incorporated in the phospholipid pool [7].

The group at St. Louis uses ^{11}C palmitate and determination of its initial uptake to define myocardial infarction and to size the ischemic defect [22,23]. They have demonstrated that the so-called subendocardial myocardial infarct can frequently affect the complete thickness of the myocardial wall. Furthermore, metabolic defects are generally present, even when ischemia remains reversible.

Selwyn et al. [24] have used ^{11}C acetate in humans as a metabolic marker of ischemia. They have demonstrated that the initial clearance rate of acetate is slower in ischemic than in normally perfused regions. On delayed images, activity persists as a hot spot in ischemic regions, while activity from the normal regions has disappeared.

Use of FDG to define anaerobic glucose metabolism

The ischemic myocardium remains frequently capable of anaerobic but not of aerobic glucose metabolism. In myocardial ischemia or infarction, myocardial blood flow data are probably a reasonable estimate of oxygen supply. After a glucose load, aerobic glucose utilization should be proportional to the oxygen supply

observed in normal tissue and in necrotic tissue. Glucose uptake in excess of flow is likely to represent anaerobic glucose utilization, although a shift from oxidation of free fatty acids to oxidation of glucose cannot as yet be ruled out. This observation was first published by Marshall in 15 post-MI patients [25]. They observed a correlation between "anaerobic glucose utilization" and residual angina, persisting ECG abnormalities, persisting regional asynergy, and severe coronary artery disease. The predictive value of "anaerobic glucose utilization" for reversibility after revascularization has been analyzed by Tillish [14]. These authors have studied 17 patients before and after aortocoronary bypass. Sixteen of these patients had a previous MI. Sixty-seven segments were adequately revascularized by the bypass intervention. Forty-one segments had an improved contractility postsurgery, while 26 segments did not. Preservation of glucose metabolism correctly classified 85% of the 41 segments that improved and 92% of the 26 segments that did not improve.

We have studied 82 patients classified in three groups and compared them with controls [26,28]. Perfusion studies were usually performed with ^{38}K (or ^{13}N ammonia in a few instances). ^{18}F deoxyglucose studies were performed after an enriched carbohydrate meal. Data were normalized to peak activity and the segment with the highest flow was considered as the reference (100%) for both tracers. The glucose to perfusion ratio was calculated after normalization. In patients with a chronic infarct and occlusion of the involved coronary artery, PET demonstrates low flow (39% of maximal reference) and FDG uptake with a glucose to perfusion ratio (G/P) of 1.02 ± 0.27.

In patients with unstable angina and ischemia in an area supplied by a severely stenosed coronary artery, perfusion was also depressed, but to a lesser extent (55 ± 10% of the maximal reference), while FDG uptake was increased above the reference value (value in an area of normal perfusion) and the glucose to perfusion ratio was 2.47 ± 1.36 (upper limit of normal, 1.42).

The third group of patients was composed of patients studied at the subacute stage of myocardial infarction (3–30 days; mean, 7 days). Eleven patients were treated by conventional therapy, 37 were submitted to intravenous streptokinase administered within 3 hours after the onset of symptoms, and 7 patients were treated by coronary angioplasty in addition to fibrinolysis.

Nine of 11 patients with conventional therapy demonstrated matched defects of perfusion and FDG uptake, while a persistence of enhanced glucose metabolism was observed in 30 of the other 44 patients. In patients treated with fibrinolysis alone, myocardial perfusion and FDG uptake correlated with the degree of residual stenosis. Indeed, in patients without residual stenosis, perfusion is partially restored (58.2 ± 19.6% of maximal reference; as compared with 81% ± 5% in normal subjects in the same anterior segments), while FDG uptake is matched. However, in patients with severe residual stenosis (90–99%), the uptake of perfusion tracer is low (38% ± 8%) and the glucose to perfusion ratio is 1.84 ± 0.96, reflecting the likely persistence of anaerobic glucose utilization in these regions. Patients with angioplasty had less improvement than expected from the angiographic results.

In summary, PET provides an exciting new means to analyze regional myocardial blood flow, substrate utilization, and regional metabolic alterations in patients with ischemic heart disease. The ability to noninvasively recognize anaerobic glucose utilization has important consequences, both as a means to directly identify ischemic myocardium and as a marker of persistent viability. This concept should be increasingly used as an end point to judge the success of these interventions.

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