Myocardial Metabolic Imaging: A New Diagnostic Era

The article in this issue of the *Journal* by Ratib et al. is an example of a newly emerging discipline: human intermediary metabolism (*1*). Until recently, studies of cardiac metabolism in man have been limited to arteriovenous differences of myocardial substrates using arterial and coronary-sinus sampling techniques (*2,3*). This procedure is invasive and can only determine global cardiac metabolism. Therefore, in diseases that are characterized by regional abnormalities of flow and metabolism (especially coronary disease) this information is inadequate. Our understanding of myocardial metabolism is based primarily on experimental studies in animals. One method that has been used extensively in animal preparations consists of administration of exogenous, labeled substrates to the heart (*4*). Analysis of tissue samples or venous effluent allows calculation of the rate of substrate metabolism. The effects of alternative substrates, hormones, work load, and perfusion rate can readily be determined. This method can now be directly applied to man using labeled substrates quantitatively imaged by positron emission tomography.

Positron emitters have been the most widely used radionuclides for metabolic imaging in man. Nuclides such as C-11, O-15, and N-13 can be substituted into the structure of physiologically important compounds without alteration of their biochemical properties (*5*). Fluorine-18 labeling of sugars and fatty acids provides analogs that are extracted like their unlabeled analogs, but once inside the cell, their metabolism is incomplete and they are trapped (*6*). In addition, positron emitters have physical properties especially suited for imaging metabolic processes in vivo. Positron annihilation produces two photons that are emitted in opposite directions, thereby permitting coincidence detection; collimation is therefore achieved electronically without the loss of efficiency characteristic of lead collimation. The high-energy photons emitted (511 keV) minimize tissue attenuation and improve depth resolution. Half-lives of these agents are short (C-11 = 20 min, O-15 = 2 min, N-13 = 10 min, and F-18 = 108 min), so that sequential studies of substrate kinetics can be obtained in rapidly changing disease processes, such as myocardial ischemia. The new time-of-flight generation of positron cameras such as the TOFPET are particularly good for dynamic studies because they allow collection of data at short intervals with improved counting statistics and resolution (*7*).

Intermediary metabolism of the heart involves a complex interplay between fatty acids, carbohydrates, and amino acids (*4*). Utilization of these substrates is significantly altered in various cardiac disorders, and it is likely that they can be assayed in living patients by metabolic imaging (*2,3*). In order to interpret metabolic studies in man, these pathways of intermediary metabolism must be understood.

Fatty-acid oxidation is the primary source of energy for the heart under aerobic conditions (*4*). Several investigators have demonstrated that fatty-acid utilization is augmented in response to increased myocardial oxygen demand, whereas metabolism of other substrates remains essentially constant (*8*). In the blood fatty acids are transported bound to albumin. After diffusion into the cell, they are activated to a fatty-acyl CoA at the outer mitochondrial membrane. The acyl unit is then transferred to carnitine, which transports the activated fatty acids into the mitochondrial matrix where it either undergoes beta oxidation or is utilized in the synthesis of phospholipids and triglycerides. Beta oxidation of fatty acids predominates during aerobic metabolism, whereas during anaerobic conditions, synthesis of lipids increases (*9*).

Weiss et al. administered [^{11}C]palmitate to the perfusate of isolated hearts and found that extraction of tracer decreased following prolonged reductions of flow (*10*). Subsequent studies in man have shown that infarct size determined by positron emission tomography correlates with infarct size determined from creatine kinase − MB blood curves (*11*). The study, however, did not prove whether the decrease in tracer uptake was the result of alterations of metabolism or de-

creased tracer delivery due to an inadequate blood supply. A recent study suggests that both factors are important (12). The fast sampling intervals available with newer positron cameras should clarify important questions since quantitative regional metabolic rates of fatty-acid oxidation can be measured to delineate infarct size rather than using simple regional mapping of count density. For example, Goldstein et al. have demonstrated that the cardiac global rate of fatty-acid oxidation can be determined by analysis of myocardial time-activity curves after intravenous injection of [11C]palmitate (13). After extraction from the blood, the rate of myocardial clearance of [11C]palmitate correlates linearly with myocardial oxygen demand. The relationship between oxygen demand and metabolic rate does not merely represent washout of tracer, since Klein et al. demonstrated that clearance of tracer was markedly decreased during potassium arrest in isolated hearts, despite high levels of flow (14). These observations of metabolic clearance have recently been confirmed in an in vivo preparation with constant flow (12). Lerch et al. have applied the same principles to obtain myocardial [11C]palmitate time-activity curves from the PET to determine the regional oxidative rate of fatty acid during ischemia (15). It is likely that regional rates of fatty-acid oxidation can be measured in man in a variety of normal and diseased states.

Another approach to the study of fatty-acid metabolism has been reported by Livni et al. (16). These investigators found that beta-methyl [1-11C]heptadecanoic acid is taken up by myocardial cells and is trapped metabolically by virtue of the methyl group on the β-carbon. This tracer should therefore be useful for measuring fatty-acid uptake. Correct interpretation of fatty-acid uptake requires simultaneous measurement of circulating free fatty acids, since uptake is directly related to available fatty acids (17).

Carbohydrate metabolism is less important than that of fatty acids to normally oxygenated myocardium, but predominates during ischemia (9). Uptake of labeled glucose has been proposed as a means of identifying ischemic myocardium since anaerobic metabolism is increased when the oxygen supply of the myocardium is limited (4,18). The study in this issue of the Journal by Ratib et al. uses 2-[18F]deoxyglucose (FDG) to determine the rate of myocardial glucose oxidation (1). Beginning with Gallagher in 1977, this glucose analog (FDG) has been well validated in numerous animal studies (11). FDG is extracted in competition with endogenous glucose. However, once it is phosphorylated in the cell, it does not progress in the glycolytic cycle. Thus the rate of accumulation provides a means of determining the myocardial metabolic rate of glucose. However, changes in regional blood flow must be taken into consideration in order to interpret these studies adequately. Phelps et al. found that the myocardial metabolic rate for glucose determined by FDG uptake was 2.8 times greater in dogs given glucose and insulin than during the fasting state (20). Schelbert et al. showed that uptake of FDG allowed positive identification of ischemic myocardium when appropriate corrections were made for regional flow by subsequent administration of N-13 ammonium ion (18). Use of [11C]glucose has been limited for myocardial studies because of a low rate of extraction that makes it difficult to image (10).

The rate of glycolysis is closely linked to cellular viability in ischemic myocardium. Jennings and Reimer have shown that the rate of glycolysis increased in reversibly injured myocardium, but as tissue changes became irreversible, glycolysis decreased markedly and then ceased (21). The imaging of regional rates of carbohydrate metabolism might therefore be useful in identifying reversibly injured myocardium and providing end points for assessment of myocardial salvage. However, independent determination of flow would be required to characterize this flow-dependent metabolic process. Hence, concomitant use of tracers with very short half-lives such as rubidium-82 might be advantageous for flow measurement. Another approach for assessing myocardial viability utilizes an injection of [11C]pyruvate, which is rapidly metabolized by normal myocardium but accumulates as lactate during ischemia. Thus, Goldstein et al. have shown that more labeled pyruvate accumulates in ischemic tissue than in normal tissue without the necessity of a correction for flow (22). Moreover, regional metabolic turnover rates of pyruvate may be measured by repetitive imaging because of the short half-life of C-11.

The balance between fatty-acid and carbohydrate metabolism is important in some diseases. For example, hearts from diabetic animals rely almost exclusively on fatty acids whereas glucose utilization is decreased (4). Our ability to diagnose abnormalities in glucose and fatty-acid uptake and fatty-acid oxidative metabolism may provide a more sensitive measure of the metabolic state of the diabetic heart, and the extent of cellular disease may be recognized thus rather than relying solely on the level of glucose and insulin.

Amino acids play a minor role in myocardial energy production under aerobic conditions but are primarily involved in protein synthesis (23). Amino acids labeled with N-13 are taken up rapidly by the myocardium (24). However, the metabolic fates of amino acids have not been studied extensively by imaging techniques. Recent information about the role of amino acids in providing carbon skeletons for anaerobic glycolysis suggests that amino acid imaging may provide another means toward an understanding of the derangements that occur during myocardial ischemia in man (13). Furthermore, the role of amino-acid incorporation into structural protein may improve our understanding of hypertrophic cardiomyopathies or mechanisms of compensatory hypertrophy following myocardial infarction and pressure overload.

Clinical imaging of metabolism is an important step toward our understanding, and therefore treating, of cardiac diseases because man is used as the experimental "clinical" model rather than relying on extrapolation from animals. It represents a new multidisciplinary science that requires a joint effort by investigators in biochemistry, radiochemistry, radiation physics, and functional disease. This area should herald a new way of thinking about clinical disorders where characterization of the metabolic disorders produces new modes of therapy designed to restore normal metabolism. A report prepared for the Department of Energy concluded that positron imaging will produce significant advances in basic biomedical knowledge (25). They recommend that an investment of financial resources for developing new centers would be cost effective. With the possibility of small, dedicated, less expensive cyclotrons and commercially available positron tomographic systems, the number of investigations in this area should increase dramatically over the next several years. Dr. Donald Fredrickson, a former director of the NIH, has been quoted as saying that the future of cardiology is at the molecular level. I have little doubt that he is correct.

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