THE MIKAMO LECTURE

PROBING THE HEART'S BIOCHEMISTRY WITH POSITRON EMISSION TOMOGRAPHY

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MYOCARDIAL metabolism has been intensively investigated for nearly a century. However, the metabolism of the human heart has remained largely inaccessible to study. Our knowledge of myocardial metabolism therefore is based on observations from in vitro experimental systems, but remains largely untested in the human myocardium. Techniques for probing the metabolism of the human heart in vivo would be of considerable merit. Findings from in-vitro experimental systems could be directly tested in humans with such techniques and would allow new insights into the human heart's physiology. They also could significantly contribute to detection and management of cardiac disease.

Disease is now most commonly detected in its endstage, when irreversible structural abnormalities have already developed. These are often the consequence of long standing processes either of biochemical origin or mediated through metabolic derangements. Identification of these biochemical alterations therefore not only would allow earlier recognition of disease but also aid in designing therapeutic interventions aimed at interfering more directly with the disease mechanism and thus halting the development of irreversible structural abnormalities.

Positron emission tomography (PET) has opened the human heart to the noninvasive study

of its biochemistry. Biochemical reaction rates, substrate fluxes and blood flow can now be measured in myocardial regions in micromoles substrate or ml blood per minute per gram myocardium. With this unique capability it is now possible to probe the human heart's biochemistry in vivo and to enter a still largely unexplored territory. The value of PET for investigational purposes has never been disputed. Yet, as this new imaging modality is applied to the study of human cardiac disease, PET also emerges as a technique that might add a new dimension to clinical cardiology.

Principles of Positron Emission Tomography

PET's capabilities derive from several features which are linked by specific properties of positrons! Positrons are particles with a mass equal to that of electrons but carry a positive charge. As they travel through tissue, positrons lose kinetic energy and combine with an electron. The combined mass then "annihilates". Mass is converted into energy in form of two photons which leave the site of annihilation in diametrically opposed directions (Fig. 1). An annihilation event is recorded when the two 511 keV photons simultaneously strike two scintillation detectors.

Why then do positrons make PET unique?

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Fig.1. Principles of "Positron-Annihilation" and Positron Emission Tomography. Left Panel: After the positively charged positron loses its kinetic energy, it combines with a negatively charged electron. The combined mass then "annihilates", that is, mass converts into energy which in form of two 511 keV photons leaves the site of annihilation in diametrically opposed directions. An annihilation event is registered when the two photons strike near simultaneously two scintillation detectors. Right Panel: A circular array of scintillation detectors with diametrically opposed detectors in coincidence permits detection and localization of annihilation events, that is the site of accumulation of positron emitting tracers in tissue. After sampling of statistically adequate numbers of events, cross-sectional images of the distribution of tracers in an organ are formed. The reconstruction process also corrects for photons that are absorbed by tissue or "photon attenuation", which is measured directly by placing a positron emitting source around the patient and acquiring a transmission image or an image of photon attenuation.

First, positron emitting isotopes of elements as for example of carbon, nitrogen, oxygen and fluorine are tagged to organic substances without altering their physiologic properties. Thus, they distinctly differ from radiopharmaceuticals used with conventional nuclear medicine techniques, including single photon emission tomography, where relatively large atoms like technetium-99m or iodine-123 are inserted into compounds which then may lose their specific physiologic properties. Positron emitting tracers are administered intravenously or by inhalation for PET studies in only minute quantities or tracer amounts. This avoids a "mass effect", which would perturb the very process under study. Tracers in PET distinctly differ in this regard from "contrast agents" used with nuclear magnetic resonance imaging which are administered in millimolar quantities in order to obtain adequate signals. Such large quantities may well interfere with the process to be studied. Uptake and turnover of positron emitting tracers in myocardial tissue therefore parallel closely the biochemical fate of their parent substrate as for example glucose, fatty acid or amino acid. Second, the use of "true tracers" with PET allows application of tracer kinetic principles, provided the substance traces a physiologic

process in a predictable manner and its uptake and turnover in tissue are amenable to tracer kinetic modeling. Regional tissue concentrations of tracers and their changes over time are measured *in vivo*. Thus, external quantification of regional tracer concentrations by PET is the third major feature of this imaging modality which again derives from physical properties of positrons. Different from SPECT, cross-sectional images acquired by PET are corrected adequately for photon attenuation. Cross-sectional images obtained with PET reflect quantitatively the regional distribution of tracer in tissue. One might therefore compare the tomographic PET images with autoradiograms with the important difference being that PET images can be acquired *in vivo*. Combination of the quantitative imaging capabilities with tracer kinetic models as the base for mathematical descriptions of the tracer behavior in tissue and its relation to the process under study, permits noninvasive measurements of regional myocardial blood flow and more importantly, of biochemical reaction rates and substrate fluxes (See also below).

The Study of Myocardial Metabolism with PET

Myocardial substrate metabolism links regional myocardial blood flow to regional mechanical

Fig.2. Myocardial substrate metabolism depicted schematically and in simplified form as related to PET studies. Free fatty acid (FFA), glucose and lactate serve as major fuels for myocardial substrate oxidation. Upon entering the cell, FFA is activated to FFA-CoA, which then is in part esterified to triacyl esters (glycerides) and phospholipids and deposited in the endogenous lipid pool, or is transported via the carnitine shuttle to the inner mitochondrial membrane. From the long carbon-chain FFA-CoA, β -oxidation cleaves off two carbon-fragments which then enter as acetyl-CoA the TCA (tricarboxylic acid or Krebs) cycle for complete oxidation to CO₂ and H₂O. The TCA cycle and the electron transport chain are the final pathway for oxidative metabolism common to all substrates. Energy liberated through this pathway is stored in high energy phosphate bonds of for example ATP which then is spent largely into mechanical work. Glucose enters the cell via a facilitated transport mechanism, is phosphorylated to glucose-6-phosphate which then is either synthesized to glycogen or catabolized through glycolysis to pyruvate. An intermediate of glycolysis, α -glycerolphosphate (α -GP) interacts with FFA-CoA for synthesis of triglycerides. A small fraction of the latter may leave myocardium after conversion to lactate while the major part is transferred into mitochondria, converted to acetyl-CoA and enters the TCA cycle. Depending on its concentrations in plasma, lactate enters the cell, is converted to pyruvate which then enters the mitochondria for further oxidation. FDG traces the transmembraneous exchange and the initial phosphorylation step while C-11 palmitate traces the entire metabolic pathway of palmitate including esterification and oxidation through β -oxidation and TCA cycle.

function. Blood flow carries oxygen and fuel substrates as for example, glucose, free fatty acid (FFA), lactate, amino acids and ketone bodies to myocardium where these substances are oxidized and energy rich phosphates like ATP are generated (Fig. 2). The chemical energy is spent largely for development of contractile force. Normally, several substrates are utilized simultaneously, although the contribution of each substrate to overall oxidative metabolism varies as a function of the dietary state, of physical activity and of endocrine regulation². For example, when FFA levels in plasma are high after moderate fasting, the heart primarily resorts to FFA.³ After carbohydrate intake, FFA levels fall and glucose concentrations rise in plasma so

that more glucose and less FFA is utilized.⁴ Prolonged starvation raises the concentration of circulating ketone bodies and hence, augments oxidation of ketone bodies by myocardium.⁵ Strenuous physical exercise on the other hand is associated with an increase in levels of lactate which then becomes a major contributor to oxidative metabolism.⁶

Studies of the heart's substrate metabolism with PET necessitate therefore several tracers, each suited for exploring one of the several metabolic pathways. Numerous positron emitting tracers of substrate metabolism have been synthesized, although the utility of many for noninvasive PET studies of cardiac metabolism awaits validation. Tracers that are best character-

Fig.3. Tracer kinetic model for measurements of exogenous glucose utilization by myocardium with FDG. The tracer kinetic model (Panel C) is compared to the tissue kinetics of FDG (Panel B) and the metabolism of glucose (Panel A). The asterisks indicate the tracer concentration in plasma (C_p^*), in tissue (C_e^*) and of phosphorylated FDG in tissue (C_m^*). Exchange between compartments is described by first order rate constants (k^*). (see text).

ized are F-18 2-fluoro 2-deoxyglucose (FDG) as a marker of exogenous glucose utilization and C-11 palmitate as a tracer of myocardial fatty acid metabolism.

FDG is a glucose analog which exchanges across the capillary and cellular membranes in proportion to glucose. It then competes with glucose for hexokinase which catalyzes the phosphorylation of glucose to glucose-6-phosphate (See also Fig. 2). Unlike the latter, FDG-6-phosphate is only a weak substrate for glycogen synthesis, glycolysis, the pentose-phosphate shunt or for dephosphorylation to FDG. It is also relatively impermeable to the cell membrane. FDG-6-phosphate becomes therefore virtually trapped in the cell. A tracer kinetic model, initially developed for measurements of glucose metabolism in the brain,⁷⁻⁹ has been adopted to the heart and allows measurements of regional myocardial rates of exogenous glucose

Fig.4. Noninvasive measurement of exogenous glucose utilization in dog myocardium with the PET/FDG technique. Note the close agreement of the noninvasive measurements with simultaneously performed measurements of myocardial glucose uptake by the Fick technique. (Reproduced with permission; Ratib et al., J Nucl Med 23: 577, 1982).

TABLE I KEY FEATURES OF POSITRON EMISSION TOMOGRAPHY

A. Physiologic Tracers of Blood Flow and Metabolism

Natural compounds labeled with ^{15}O , ^{13}N , ^{11}C or ^{18}F without loss or modification of their physiologic properties

Administered in "true" tracer amounts (nanomolar or picomolar quantities)

B. Quantitative Imaging Capability

Cross-sectional images are quantitative representations of regional tracer concentrations in tissue; "in vivo" recorded "autoradiograms"

Serial imaging permits tracking of tracer uptake and turnover in tissue

C. Application of Tracer Kinetic Principles

Tracer kinetic model, mathematical description of tracer kinetics in tissue and their relation to metabolic processes; allows formulation of operational equation for calculating rates of physiologic processes

utilization (Fig. 3 and 4).¹⁰⁻¹² Differences in glucose metabolism between brain and heart limit the FDG technique to measurements of the

Fig. 5. Serial PET images obtained in a human subject after intravenous injection of C-11 palmitate. On the early images, most of the C-11 activity is still contained in blood with visualization of the cardiac chambers. As C-11 palmitate clears from blood into myocardium, homogeneous uptake of tracer in myocardium is noted. A blood flow image obtained after intravenous injection of N-13 ammonia is shown in the left upper panel for comparison. As indicated by the color code, C-11 activity subsequently clears homogeneously from myocardium in this normal volunteer.

rate of exogenous glucose utilization in myocardium which synthesizes glucose-6-phosphate to glycogen or catabolizes glucose to pyruvate. Therefore, FDG fails to trace glucose metabolism beyond this branch point. Conversely, synthesis of glycogen in brain is negligible. Hence, the flux of glucose through the initial phosphorylation step equals the flux of glucose through glycolysis and the FDG technique provides estimates of glycolytic rates in brain.^{8,9}

C-11 palmitate has also been extensively evaluated as a tracer of myocardial FFA metabolism. An appropriate tracer kinetic model awaits validation. Therefore, use of C-11 palmitate has been confined to qualitative studies of regional myocardial fatty acid metabolism. Regional myocardial uptake and turnover of C-11 palmitate in tissue is evaluated by serial PET imaging which commences at the time of tracer injection and continues for about 45 to 60 minutes (Fig. 5). Uptake and turnover of tracer in myocardium is evaluated from myocardial tracer time activity curves which are derived from serial

PET images (Fig. 6). Tracer concentrations in tissue reach a maximum about 3 to 6 minutes after injection and subsequently decline. Clearance from tissue is characteristically biexponential, indicating distribution of tracer in myocardial tissue between at least two metabolic pools which turnover at different rates.

The fractional tissue distribution appears to reflect the metabolic fate of FFA. After activation to acyl-CoA, FFA is either deposited in the endogenous lipid pool (mainly in form of triacylglycerols) or immediately proceeds to oxidation, initially through the β -oxidation spiral and then through the TCA cycle (See also Fig. 1). That the biexponential clearance and fractional distribution does in fact correspond to the metabolic fate of FFA is supported by substantial experimental evidence. Amounts and rates of release of C-11 CO_2 as the end product of oxidation of C-11 palmitate are directly related to the tracer fraction that enters the rapid clearance curve component and its clearance rate.¹³⁻¹⁵ Size and clearance rate increase in

Fig.6. Myocardial C-11 palmitate time activity curve (derived from serial PET images) in a dog experiment in order to illustrate the relationship between C-11 palmitate clearance from myocardium and release of the end product of oxidation C-11 CO₂ from myocardium. The upper panel shows the initial uptake of C-11 palmitate into myocardium and its subsequent biexponential clearance from myocardium as the lower panel shows the coronary sinus-arterial differences (CS-A) of ¹¹CO₂. The early rapid clearance phase is associated with release of C-11 CO₂ as the end product of oxidation of C-11 palmitate from myocardium and indicates the relationship of this particular curve component to the fraction of C-11 palmitate that immediately enters oxidation and the rate of oxidation. (Reproduced with permission; Schelbert et al., "C-11 palmitate for the Non-invasive Evaluation of Regional Myocardial Fatty Acid Metabolism With Positron Computed Tomography. III. In Vivo Demonstration of the Effects of Substrate Availability in Myocardial Metabolism. Am Heart J 105: 492, 1983)

proportion to cardiac work and MVO_2 ,¹⁴ when substrate levels are maintained constant in plasma, but decline with falling FFA and rising glucose levels as the heart shifts from FFA to glucose oxidation while cardiac work remains the same (Fig. 7 and 8).¹⁶

PET studies are performed after carefully

positioning the patient in the positron emission tomograph in order to assure that the imaging planes traverse the heart, in particular the left ventricle. Tilting of the imaging gantry allows cross-sectional imaging perpendicular to the long axis of the left ventricle. Acquisition of transmission images follows (see also Fig. 9). These

Fig.7. Effect of increased cardiac work on the myocardial tissue kinetics of C-11 palmitate in human myocardium. A control study, including intravenous injection of C-11 palmitate and serial PET imaging, was performed first while the heart rate was only 49 beats/min. Cardiac work was then increased by raising the heart rate two times control by atrial pacing and the C-11 palmitate/PET study was repeated. Plasma concentrations of glucose, lactate and FFA were similar during both studies. Analysis of the tissue time activity curve for the fractional distribution clearance rate of C-11 palmitate in tissue reveals that at control, 31% of the tracer enters the early rapid phase and clears with a half-time of 24.1 min. During pacing, the tracer fraction entering the early rapid phase has increased to 62% and its clearance half-time decreased to 11.5 minutes. Higher workload as induced in this study by rapid atrial pacing causes an increase in the rate of oxidative metabolism. Because substrate concentrations in plasma and, therefore plasma availability remain constant between the two studies, myocardium oxidized mainly FFA for production of ATP. The myocardial tissue time activity curve reflects this increase, as a greater fraction of C-11 palmitate entered the rapid turnover (oxidation phase) and cleared more rapidly from tissue. The observed effects of cardiac work on the tissue kinetics of C-11 palmitate support the utility of the early rapid phase as an index of oxidation of FFA.

Fig.8. Effect of substrate availability on myocardial substrate utilization, demonstrated with FDG (upper panel) and C-11 palmitate (lower panel). The studies on the right (A) were performed in two normal volunteers after an overnight fast when FFA levels in plasma were high and glucose levels low. The lack of FDG accumulation in the heart (arrow) indicates little if any glucose utilization (top panel) while the C-11 palmitate tissue time activity curve indicates oxidation of FFA. Sixty-four percent of the C-11 palmitate is immediately oxidized. The remainder enters the endogenous lipid pool. The same volunteer was restudied after glucose levels in plasma were raised by oral glucose administration which also caused a fall in FFA levels. As less FFA and more glucose became available, the heart's substrate selection shifted to glucose. This is reflected on the C-11 palmitate tissue time activity curve on the left (B) by the lesser fraction of tracer entering the oxidation phase and the intense FDG uptake as seen on the upper right panel. Because the brain almost exclusively utilizes glucose, it depends less on the composition of substratum levels in blood. Therefore, FDG uptake is similarly intense under both study conditions.

POSITRON EMISSION TOMOGRAPHY

Fig.9. Noninvasive measurement of regional myocardial rates of metabolism with PET. After positioning the patient in the tomograph (imaging gantry), transmission images are acquired (1). They serve for correction of photon attenuation on the emission images, recorded after intravenous tracer administration (2) and constructed by the imaging system central computer. Only one (as in the case of FDG) or serial images are recorded (as in the case of C-11 palmitate). Tissue tracer concentrations are measured from regions of interest (ROI) assigned to the corrected emission images. From the myocardial tracer concentrations or their changes over time, the arterial input function (obtained through serial arterial blood sampling or from ROI's assigned on the serial PET images directly to the left ventricular blood pool) and the arterial plasma substrate concentration (e.g., of glucose for FDG studies), the operational equation, implemented into the system's computer, calculates the metabolic rate in mmol/substrate per minute per gram myocardium.

BLOOD FLOW $\longleftrightarrow$ **OXYGEN SUPPLY** $\longleftrightarrow$ $\longrightarrow$ **FUNCTION**

Fig.10. Expenditure of chemical energy (high energy phosphate, for example ATP), in the resting heart for various cell functions. Blood flow as the carrier of oxygen is closely inter-related to mechanical function. Both are linked by substrate metabolism which generates chemical energy (high energy phosphate like ATP) which is utilized for various cell functions. The largest fraction is spent for development of contractile force, a fraction that changes in proportion to cardiac work.

images are comparable to x-ray computer tomographic images and serve for correction of photon attenuation of the emission images, which are recorded serially after tracer administration. Either one set of images, for example for FDG, recorded 45 to 60 min after tracer injection suffices or serial images are acquired over a 45 to 60 min period as for example for C-11 palmitate. Regional myocardial tracer concentrations are measured from the attenuation corrected emission images after assigning regions of interest to myocardium and blood pools. Arterial plasma substrate concentrations are determined from samples withdrawn directly from an artery or after arterialization of venous blood by hand warming.⁹ The operational equation derived from the corresponding tracer kinetic model and implemented into the tomograph's system computer, then calculates rates of metabolism from the tissue tracer concentrations or their changes over time, the arterial input function derived through a region of interest assigned on the rapid dynamic images to the left ventricular blood pool, and the concentration of substrate in plasma.¹⁶ As shown below, images can be acquired in a gated fashion, which minimizes motion artifacts and improves the accuracy of measurements of tracer tissue concentrations. It also permits evaluation of regional and global myocardial function which then can be related to blood flow and metabolism.

Evaluation of Regional Myocardial Ischemia with PET

Extent and severity of regional myocardial ischemia are usually described in terms of regional abnormalities of blood flow and function. However, changes in substrate metabolism may hold the key for more accurately assessing the severity of myocardial ischemia. The conventional approach assumes a general interrelation between function and blood flow on the one hand and substrate metabolism on the other. For example, greater development of contractile force requires higher rates of substrate oxidation which in turn increases demands for oxygen. The latter is accomplished by an increase in blood flow which then can be measured non-invasively. Conversely, if regional blood flow declines as for example in ischemia, supply of oxygen to tissue becomes inadequate and regional function deteriorates or even ceases altogether.

The conventional approach equates the absence of appreciable blood flow and function in regional myocardial ischemia with complete cessation of substrate metabolism. If these assumptions were correct, they would be difficult to reconcile with the fact that regional function recovers completely if for example blood flow is restored in time. Therefore, despite absent blood flow and lack of oxygen, metabolic processes persist, at least for some time after the onset of ischemia, and maintain the cell viable so that the injury is initially reversible. In the same line of argument, assessment of regional myocardial function is of limited value in distinguishing reversible from irreversible tissue injury. Again, indices of metabolism may hold the key here.

Thus, while inferences from functional parameters on substrate metabolism may be valid over a wide physiologic range, they are constrained or even invalid in ischemia. An examination of the heart's energy expenditures illustrates this limitation (Fig. 10). The major fraction of high energy phosphate is spent for development of contractile force and relaxation.¹⁷ This fraction increases with higher cardiac workload. About 3 to 5% is used for maintaining electrical activity and another 20% for "wear and tear". Survival or repair is the cells' highest priority and outranks other more specialized tasks as for example mechanical work. In ischemia therefore, the cell reduces the amount of energy spent for mechanical work and utilizes all residual production of high energy phosphate for maintenance of cellular integrity or for repair. Indices of blood flow and mechanical function alone are therefore unlikely to provide information on the degree of residual metabolic activity that will be critical for cell survival.

The heart's ability to derive high energy phosphate from a variety of substrates or to generate high energy phosphate even without oxygen complicates the study of residual metabolic activity in myocardial ischemia. Reduction of blood flow and, thus, of oxygen supply leads to an immediate reduction or loss of regional function and triggers a sequence of metabolic events that will decide the ultimate fate of the cell. The rate of oxidation of fatty acid declines while glycolytic flux increases.^{18,19} Glucose metabolism may remain largely aerobic, or, when oxygen availability becomes more severely limited, largely anaerobic. Persistence of

Fig.11. Acute myocardial ischemia in humans and uptake and turnover of C-11 palmitate. Ischemia was induced in this patient with disease of the left anterior descending coronary artery by rapid atrial pacing. C-11 palmitate was administered intravenously and serial PET images recorded while pacing continued throughout the image acquisition period. Serial PET images are depicted. Most of the C-11 activity on the early images is still contained in blood; therefore, the early images (1.5 min) show mainly the left and right ventricular cavities. The myocardium is fully visualized at 4.5 minutes. As the color scale indicates (red reflects highest and blue lowest tissue tracer concentrations) the subsequent images reveal clearance of C-11 palmitate from myocardium. Unlike in Fig. 5, where C-11 palmitate clears from myocardium homogeneously, clearance of tracer in this study is more rapid in the antero-lateral wall (arrow) than in the septum. Hence, more tracer is retained in the acutely ischemic septum. This is seen best on the late images (18 to 24 min).

residual flow may then become critical for removal of lactate and maintenance of glycolysis. If flow deteriorates further, rising lactate and hydrogen ion concentrations in cytosol inhibit residual glycolysis and deprive the cell of one of the residual mechanisms for anaerobic production of ATP. This downward course of biochemical events may progress to complete cessation of energy production and thus, to irreversible cell injury, or halt at a level that allows production of energy in amounts adequate for cell survival. The various metabolic events occur all the time that segmental blood flow and function is impaired. Hence, the evaluation of the latter two indices is unlikely to be of use for assessing the severity of an ischemic injury, while direct assessment of the degree of residual metabolic activity could identify persistence of metabolic activity that may be critical for cell

survival.

How then can FDG and C-11 palmitate be used with PET for evaluating noninvasively ischemia induced alterations in regional myocardial metabolism? Both Liedtke and Neely refer to β -oxidation as the locus most sensitive to inadequate tissue oxygenation^{2,18}. If mild ischemia impairs β -oxidation, this then could be demonstrated with C-11 palmitate. Acute myocardial ischemia in dog experiments reduces regional uptake of C-11 palmitate and alters the subsequent clearance of C-11 activity from ischemic tissue. Relative to control myocardium, the size of the early rapid clearance curve component declines in ischemic myocardium and C-11 activity clears from tissue less rapidly²⁰⁻²². Both changes are consistent with a segmental impairment of β -oxidation. Rapid atrial pacing in patients with angiographically documented

Fig.12. C-11 palmitate kinetics in acute human myocardial ischemia. The time activity curves were obtained from regions of interest assigned to the interventricular septum and the antero-lateral wall on the serial PET images shown in Fig. 11. As compared to the normal antero-lateral wall, the time activity curve for the septum reveals that in acute myocardial ischemia a smaller fraction of tracer enters the rapid oxidation turnover pool and clears from myocardium less rapidly. Clearance halftimes ($T_{1/2}$) are given in minutes. The altered kinetics of C-11 palmitate in the ischemic segment are consistent with an impairment of β -oxidation in mild myocardial ischemia and a greater deposition of tracer in the endogenous lipid pool as expressed by the greater amount of tracer retained in the septum (see also Fig. 2 and text).

coronary artery disease induced similar changes of segmental C-11 palmitate uptake and turnover (Fig. 11 and 12).²³ Importantly, regional abnormalities of C-11 palmitate kinetics occurred even in the absence of angina, electrocardiographic changes or segmental wall motion abnormalities observed on echocardiography.²³

The latter observation raises the question whether compensatory changes in substrate metabolism occur, for example a regional shift of FFA to glucose oxidation, in order to maintain segmental function. If such mechanism does indeed exist, separation of normal from ischemic myocardium may become even more difficult. Indeed, a regional shift in substrate utilization may then become indicative of "mild ischemia" that could be elicited only by techniques that evaluate regional myocardial metabolism.

The "compensatory" increase in glycolytic flux has been demonstrated in animal experiments.²⁴ In mildly ischemic canine myocardium, it persisted for several hours and was largely aerobic. Only 15% of exogenously used glucose was metabolized through glycolysis to pyruvate and released from ischemic myocardium in form of lactate.²⁴ The degree of anaerobic glucose metabolism may largely depend upon how much pyruvate can be transferred into mitochondria for oxidation through the TCA cycle. Whether

anaerobic glycolysis with moderate though critical ATP production can be maintained depends largely upon the rate of lactate production and the rate of lactate removal through residual blood flow. If lactate cannot be removed, rising cytosolic concentrations of lactate and of hydrogen ions inhibit glycolysis,¹⁸ and thus deprive the cell of one of the remaining mechanisms of high energy phosphate production.

Augmented glycolytic flux can indeed be demonstrated noninvasively with PET and FDG. In acute experimental regional myocardial ischemia, FDG in the ischemic segment is increased relative to blood flow, indicating exogenous glucose utilization in excess of oxygen availability or blood flow which suggests, as demonstrated by net lactate production, the occurrence of anaerobic glucose utilization.^{25,26} Such mismatches, where FDG uptake is increased relative to blood flow, can also be demonstrated in human myocardium (Fig. 13).²⁷

Blood flow and glucose utilization are relatively homogeneous in normal myocardium (Fig. 13). In ischemic heart disease, segmental blood flow at rest can be decreased and be associated with a proportionate decline in exogenous glucose utilization. This pattern observed with PET in ischemic heart disease is subsequently referred to

Fig.13 A and B. Relationship between blood flow and exogenous glucose utilization in normal and ischemic myocardium. Blood flow was evaluated in these four patient examples with N-13 ammonia and exogenous glucose utilization with FDG. Images of blood flow are compared with images of regional myocardial glucose uptake at corresponding cross sections through the heart. Patient A had no evidence of cardiovascular disease. Myocardial blood flow and glucose utilization are therefore homogeneous. By contrast, patient B with ischemic heart disease reveals a large segment of reduced blood flow involving the anterior and anterolateral wall which is associated with a proportionate decline in glucose utilization. This pattern is defined as "match". By contrast, in patient C, glucose utilization is preserved in the segment with reduced blood flow, whereas in patient D, glucose utilization in the underperfused segment is enhanced relative to control myocardium. The latter patient was fasted and caused normal myocardium to utilize primarily FFA and little if any glucose. Patient C however was studied after a light breakfast which resulted in glucose utilization by normal myocardium (see also Fig. 8). This is indicated by FDG uptake in apparently normal myocardium. The pattern of preserved or even enhanced glucose utilization in segments with reduced blood flow is referred to as "mismatches".

Fig.14. Effects of surgical revascularization on regional myocardial blood flow and glucose utilization. Prior to surgery (PRE-OP), left ventricular function was depressed as indicated by a left ventricular ejection fraction of 42%. Blood flow was reduced in the anterior wall and septum. Note the residual glucose metabolism in the underperfused segment (arrows). As seen on the right (POST-OP), surgical revascularization improved blood flow to the ischemic segment and enhanced segmental glucose utilization. Global left ventricular function improved as indicated by an increase in the left ventricular ejection fraction to 60%. The example illustrates the value of residual or preserved glucose metabolism in myocardium with reduced blood flow and absent wall motion for predicting the benefits of surgical revascularization on segmental and global function despite the presence of Q-waves in the affected segment (as shown in Fig. 15) that had suggested the presence of irreversibly ischemic tissue injury. It should be noted that this example does not represent "a mismatch" by previously established criteria. These criteria were derived from patients studied under standardized dietary conditions. The patient shown in this example were studied after a carbohydrate meal which substantially augmented glucose utilization and with it FDG uptake in normal myocardium relative to the ischemic segment (see also Figs. 8 and 13). Of importance is however the persistence of glucose utilization in the ischemic dysfunctional and antero-septal myocardium.

as "match". In other patients with ischemic heart disease, segmental blood flow is reduced but uptake of FDG in the same segment is increased relative either to blood flow or in absolute terms (i.e., higher than in control myocardium).

Assessment of Tissue Viability in Ischemia:

The pattern of relative or absolute increases of exogenous glucose utilization in segments with reduced blood flow has been most extensively studied in patients. "Mismatches" are frequently

observed in patients who are asymptomatic prior to or at the time of the PET study. This raises questions as to the underlying mechanisms and the significance of this pattern. Does it reflect only acute myocardial ischemia, is it an expression of metabolically "stunned" myocardium or of an adaptation of regional myocardial metabolism to chronically low tissue oxygenation states? Acute ischemia is one cause of this pattern, as demonstrated in animal experiments^{25,26} It also can be induced by physical exercise in patients with coronary artery disease

Fig.15. Electrocardiograms obtained prior (PRE-OP) and six weeks (POST-OP) after bypass surgery in the patient shown in Fig. 14. Note the Q-waves in leads V_1 and V_2 prior to surgery, consistent with a previous infarction and indicating irreversibly tissue injury. After surgery, however, R-waves reappear in V_2 together with an improvement in segmental blood flow, metabolism and function.

where it persists for some time after the ischemic episode and may reflect in addition to persistent impairment of FFA oxidation replenishment of glycogen stores.^{28,29} Metabolic "stunning" is another cause.³⁰ "Mismatches" occurred in animal experiments after 24 hours of reperfusion following a 3 hour balloon occlusion of the left anterior descending coronary artery.³¹ They predicted early after reperfusion late recovery of segmental function and therefore indicated the presence of viable tissue or of reversible ischemic injury, regardless of the course of segmental function during the early reperfusion phase. In some experiments, function early during reperfusion deteriorated in segments with viable tissue by PET. However, function subsequently improved over a period of several weeks. Whether the pattern of "mismatch" reflects a metabolic adaptation to a chronically low tissue oxygenation state remains uncertain. This possibility would depend on a delicate balance between supply and demand.¹⁸ Whether such balance can indeed be maintained in humans seems unlikely. Given a fixed anatomic stenosis, demand and supply would be required to be constant, which is unlikely. Not only does physical activity change demand but even mild mental stress could severely affect this balance as recently shown by serial studies with PET and rubidium-82 in patients with coronary artery disease.³² Thus, it seems more likely that this pattern is

	FDG UPTAKE	NO FDG UPTAKE
MBF	15	0
NO MBF	7	12

$p < 0.005$

Fig.16. Comparison between blood flow (MBF) and exogenous glucose utilization (FDG uptake) in myocardial segments with Q-waves. As the table indicates, blood flow (MBF) in Q-wave segments was generally associated with preserved glucose utilization or, conversely, in 63% of segments without flow or no FDG uptake on PET. This association was statistically significant by chi square analysis ($p < 0.005$). However, seven segments despite apparent lack of blood flow (no MBF) exhibit residual glucose metabolism.

caused by repetitive transient ischemic insults and then reflects "chronically" or "repeatedly stunned myocardium".

In patients with ischemic heart disease, function in segments with PET "mismatches" is usually impaired. The central question to the cardiologist is therefore whether this pattern

Fig.17. Metabolic activity in acutely "infarcted" myocardium. Two contiguous cross-sectional images of regional myocardial blood flow (NH_3) and of glucose utilization (FDG) are shown in a patient studied with PET 48 hours after onset of acute symptoms. Infarction was confirmed by history, electrocardiographic changes and elevated serum enzymes. Note the reduced blood flow in the anterior wall with preserved or even augmented glucose utilization in this same segment.

identifies viable tissue or myocardium that is functionally impaired but might benefit from restoration of blood flow. Investigations in patients undergoing bypass surgery addressed this issue.³³ Only patients with regional wall motion abnormalities were included. Abnormally moving segments were examined with PET and defined as "irreversibly injured" and PET disclosed segmental "matches". They were defined as "reversibly injured" when PET showed segmental "mismatches". Evaluation of regional myocardial function after coronary artery bypass surgery confirmed that prediction of tissue viability by PET prior to revascularization was highly accurate. Indeed, function in 92% of segments with "matches" failed to improve after surgical revascularization as compared to an improvement of regional function in 85% of segments with "mismatches". (See also Fig. 14 and 15).

These observations provided first evidence that metabolic indices can indeed be clinically useful. Because "mismatches" accurately predicted functional improvement after surgical

restoration of blood flow, findings by PET in patients with ischemic heart disease enter into the clinical decision making process. For example, PET can now identify patients who are likely to benefit from surgical revascularization or conversely, patients who are unlikely to gain from surgery. The functional improvement after surgical restoration of blood flow in segments with "mismatches" provided proof for this pattern as an indicator of tissue viability. It subsequently will be referred to as "PET ischemia". On the other hand, a concordant decrease in glucose utilization in segments with perfusion defects correctly identified irreversibly injured tissue and this pattern is subsequently referred to as "PET infarction".

Does PET then exceed the accuracy of conventional techniques for separating reversible from irreversible ischemic injury? This question was pursued along several lines. For example, chronic Q-waves are conventionally considered as markers of transmural infarction or irreversible tissue injury. Nevertheless, in segments with chronic Q-wave infarctions, studies with N-13

Fig.18. FFA metabolism in acute myocardial infarction. Selected serial images after C-11 palmitate administration are shown for the patient displayed in Fig. 17. The study was performed two days after the FDG/N-13 ammonia study. Note the reduced tracer uptake on the early images (9.9 min). However, the tracer clears rapidly from control myocardium but is retained in the "infarcted" anterior wall, indicating preserved although impaired fatty acid metabolism. Notably, oxidation of C-11 palmitate was impaired and deposition of C-11 palmitate into the endogenous lipid pool enhanced (see also Fig. 11 and metabolic scheme in Fig. 2).

ammonia, FDG and PET revealed "PET infarction" in only about 35%, whereas the others exhibited "PET ischemia" or even were "normal" by previously established PET criteria.³⁴ The latter does not imply the absence of ischemic injury, yet the magnitude of segmental reductions in blood flow or FDG uptake was insufficient to meet PET criteria for either ischemia or infarction. These findings indicate a limited value of Q-waves as an index of true transmural irreversible injury and point to the presence of viable in addition to necrotic cells in previously infarcted segments as well as considerable variations in the transmural extent of tissue necrosis in regions with Q-waves.

These observations are not surprising. They support earlier observations that questioned the value of Q-waves as an index of irreversible transmural injury. For example, histology of biopsy material removed from anterior left ventricular myocardium with Q-waves revealed cell degeneration.³⁵ The same study further reported disappearance of Q-waves after surgical revascu-

larization. Moreover, Q-waves may occur only transiently during ischemic episodes,^{36,37} again pointing to Q-waves as an unreliable index of irreversible transmural tissue injury. It would seem that PET studies in this context might hold the key for clarifying the significance of Q-waves and separating reversible from irreversible injury as well as for identifying the extent of transmural involvement.

Compared to "PET ischemia" and "PET infarction" segments, wall motion was significantly better in "PET normal" Q-waves regions, possibly because of a lesser degree of transmural involvement of ischemic injury.³⁴ However, wall motion was similarly reduced in "PET ischemia" as compared to "PET infarction" Q-wave regions. The absence of a significant difference might be attributed to the earlier mentioned loss of function regardless of residual metabolic activity or tissue necrosis. From a clinical standpoint however, these observations emphasize limitations of wall motion studies for separation of reversible from irreversible ischemic injury.

PRECORDIAL LEADS - SERIAL ELECTROCARDIOGRAMS

Fig.19. Serial electrocardiographic changes after acute myocardial infarction in the patient shown in Figs. 17 and 18 with sustained metabolic activity on PET in the "infarcted" antero-septal myocardium. The initial ECG (office ECG) was recorded at the time of an office visit because of anginal episodes. Three days later, the patient developed severe prolonged chest pain, the ECG reveals evolving and antero-septal myocardial infarction and is admitted (acute MI and pre-PTCA). PET at the time of these ECG's reveals residual metabolic activity as shown in Figs. 17 and 18. Angiography revealed a long 80% stenosis of the left anterior descending coronary artery which involved the origin of a large first diagonal branch. Percutaneous transluminal coronary angioplasty was performed seven days later and reduced the angiographic stenosis from 80% to a 10% diameter narrowing. Three days later the patient experienced sudden onset of severe substernal chest pain. ECG and serum enzymes were diagnostic of recurrent infarction in the antero-septal region of the ventricle, to have resulted from plaque dissection and acute occlusion of the anterior descending artery. In this study, PET predicted a significant amount of viable myocardium in the "initial" infarct region which subsequently became necrotic during recurrent infarction after PTCA.

Similar limitations apply to the evaluation of regional myocardial blood flow. In all instances of "PET infarction", the cross-sectional PET images of N-13 ammonia failed to demonstrate appreciable residual tissue perfusion (See

Fig. 16).³⁸ The reverse however was not true. For example, regions where residual tissue perfusion could be appreciated on the cross-sectional images, revealed enhanced FDG uptake. However, there were also Q-wave regions with

Fig.20. Dilated cardiomyopathy and C-11 palmitate uptake. Note the characteristic heterogeneous tracer uptake throughout the entire left ventricular myocardium.

enhanced FDG uptake but without appreciable uptake of N-13 ammonia or, in other words, without appreciable blood flow. Further evidence for the limited value of blood flow studies for assessing tissue viability came from comparative studies with conventional Tl-201 scintigraphy (Brunken et al, unpublished data). Partial or complete resolution of exercise induced perfusion abnormalities is considered as an index of tissue viability. Myocardial segments with stress induced perfusion defects that resolved over a 4 hour period revealed consistently by positron tomography regional "PET ischemia". Hence, both techniques identify tissue viability. However, in about one third of segments that failed to redistribute on Tl-201 scintigrams, PET disclosed the presence of viable tissue. These findings agree with recent observations in patients submitted to transluminal angioplasty.³⁹ Although pre-intervention stress Tl-201 scintigraphy had indicated irreversible tissue injury because defects failed to redistribute, regional function improved in about 30% of such segments following the intervention. Thus, viable or only reversibly injured tissue can be identified with conventional approaches like Tl-201 scintigraphy. However, PET substantially exceeds these techniques with a markedly higher sensitivity.

As an incidental finding in these studies, PET

uncovered also "ischemia" or "infarction" segments in myocardium that did not reveal Q-waves.³⁰ Wall motion in such segments was impaired to the same extent as in Q-wave segments with "PET ischemia" or "infarction". The latter indicates that these incidental findings did indeed reflect segmental ischemia. On the other hand, these findings suggest that infarction or ischemia may exist without electrocardiographic correlates of ischemic injury.

Thus, evaluation of residual or preserved glucose metabolism in segments with reduced blood flow with PET appears to be an accurate technique for identifying the presence of ischemic but viable tissue. As discussed earlier, documentation of such tissue viability by other conventional techniques is limited. Thus, direct evaluation of metabolism as the critical link between blood flow and function is now possible with PET. Conventional approaches for evaluating regional myocardial ischemia by means of regional blood flow and function assume a proportional and uniform response in metabolism. This response may however be modulated by factors such as oxygen demand and supply, residual tissue perfusion through residual antegrade flow through the stenosed vessel or through collateral vessels, factors that often escape adequate assessment by conventional techniques.

Fig.21. Effects of oral administration of glucose on uptake and clearance of C-11 palmitate in patients with dilated cardiomyopathy. The time activity curves were derived from serial PET images after an overnight fast (control study) and again two hours after 50 grams of oral glucose (post-glucose). Note the characteristic biexponential clearance pattern. In the study shown in the upper panel (normal response) glucose administration reduces the relative size and clearance rate of the early rapid curve component. An opposite or paradoxical pattern is observed in the lower panel (abnormal response) where a fall in FFA and a rise in glucose plasma levels (induced by oral glucose) caused an increase in the size of the early rapid clearance curve component and increase in its clearance rate.

More recent investigations addressed the question of residual viable tissue in patients with acute myocardial infarction.⁴⁰ In about half of the Q-wave regions studied, PET revealed the presence of ischemically injured yet viable myocardium as identified by "PET ischemia" (Figs. 17, 18, 19). The other segments exhibited "PET infarction". Over a two month period, function failed to improve or deteriorated in "PET infarction" regions, but improved spontaneously in half of the "PET ischemia" segments. Function remained unchanged or worsened in the other half of "PET ischemia" segments. These observations could have important clinical implications. For example, would aggressive treatment

strategies have improved function in "PET ischemic" segments that failed to improve spontaneously? Or, which segments will improve function spontaneously? How much viable tissue is left in a given myocardial segment and how much is necrotic? While residual tissue perfusion may in fact be one of the major factors, analysis of residual blood flow in the cross-sectional images failed to disclose differences between segments that recovered spontaneously and those which did not. The latter also poses questions in regards to the underlying causes of the "PET ischemia" pattern in acute myocardial infarction. "Stunned" myocardium in territories with recanalization or collateral blood flow as com-

pared to persistent low level perfusion with continued ischemia are possibilities but await confirmation. Clinically important will be the development of criteria that reliably predict spontaneous recovery versus failure to improve and possibly the need for acute interventions.

PET Studies in Mycardiopathies

Earlier findings in experimental in vitro systems provided much of the rationale along which metabolic aspects of myocardial ischemia could be explored with PET. With cardiomyopathies, by contrast, information on biochemical derangements is far more limited. Deficiencies of specific enzymes or certain metabolic faults have been identified as origins of some types of mycardiopathies. Examples are carnitine or carnitine palmityl transferase deficiencies.^{41,42} Yet, these particular disease entities are rare. Biochemical abnormalities as the cause of other types of cardiomyopathies are likely, though they await identification. Moreover, other types of cardiomyopathies may be unrelated to an initial causative metabolic derangement or defect. In these cases, invasion of myocardium by for example viruses or toxic substances may induce metabolic alterations which then mediate the disease process and possibly accelerate its progression. Hence, characterization of causative or secondary metabolic alterations may allow insights into disease mechanisms and, further, design of interventions to correct the disease process, to slow its rate of progression or to ameliorate pathologic expressions of disease.

Early investigations, performed more than 20 years ago with the coronary sinus catheter techniques failed to uncover abnormalities in substrate metabolism in patients with dilated or congestive cardiomyopathies.⁴³ These observations differed from an earlier described augmented myocardial glucose utilization in dogs with experimentally induced congestive heart failure.⁴⁴ Postmortem assays of myocardial tissue samples from patients who succumbed to congestive heart failure did however disclose abnormal enzyme activities in the glycolytic pathway and the TCA cycle.⁴⁵ Other more recent studies have advanced the hypothesis that a mechanism similar to that in ischemia may also account for mycardiopathies. One such hypothesis postulates the occurrence of microvascular events in myocardial hypertrophy leading to focal necrosis and scar formation and

progression of hypertrophy to dilated cardiomyopathy. Such mechanisms remain however in the realm of speculation. Quantitative studies with PET on tissue perfusion, metabolism and membrane exchange conceivably could allow testing of such hypotheses directly in humans. Such studies will be more important because an experimental model that adequately describes human mycardiopathy is still lacking.

Dilated cardiomyopathies were first evaluated with PET and C-11 palmitate.⁴⁷ Despite homogeneous perfusion on Tl-201 scintigraphy, uptake of C-11 palmitate in myocardium was highly heterogeneous (Fig. 20).⁴⁷ While the mechanism underlying these findings await further elucidation, the authors concluded that these findings might indicate the existence of spatially and temporally disparate cellular processes that will ultimately lead to necrosis and scar formation.

Subsequent investigations with PET and C-11 palmitate went beyond examining only the initial uptake of tracer and evaluated the subsequent regional clearance of C-11 palmitate from myocardium.⁴⁸ The hypotheses underlying these studies were based on previous observations in dog experiments as well as in humans.^{20,49} In these, changes in substrate concentrations in plasma were induced by glucose administration and produced concomitant changes in the heart's selection of oxidizable substrates (See also Fig. 8). For example, as plasma FFA concentrations fell and glucose concentrations rose, substrate selection shifted from FFA to glucose, changes that were clearly demonstrated by serial imaging of the uptake and clearance of C-11 palmitate in myocardium. This then raised the question whether such normal responses of the heart's substrate selection to changes in substrate availability were unique to normal myocardium and, consequently, were impaired in myocardial disease.

In a group of 16 patients with ventricular dysfunction of varying degrees and etiologies, this hypothesis was tested by studying each patient initially after an overnight fast and then again after raising plasma glucose levels with oral glucose administration.⁴⁸ About half of the patients responded to the interventional test in a normal fashion, that is, as the heart shifted from FFA to glucose utilization, the fractional distribution of C-11 palmitate and tissue clearance rates changed accordingly (Fig. 21). Less C-11 palmitate entered the rapid turnover oxidation

Fig. 22. Regional myocardial C-11 palmitate tissue kinetics in response to altered substrate availability in dilated cardiomyopathies. The patient was studied after an overnight fast (upper panel) and then again two hours later after oral administration of 50 grams of glucose. Only an early and a late image of the serial cross-sectional images are selected. Corresponding regional time activity curves are shown on the right. In the fasted state, C-11 activity clears uniformly from myocardium as the 6 and 17 min images and the corresponding tissue clearance curves illustrate. (EP % = Relative size of the early rapid phase in percent; T 1/2 = clearance half-time in minutes). The size of the early rapid clearance phase and its clearance half-time are virtually identical between these two regions. Glucose administration (lower panel) elicited regional differences in the response of C-11 palmitate tissue kinetics to changes in substrate availability induced by glucose administration. The intraventricular septum (solid line) reveals a normal response with a decline in the size of the early rapid phase and a slower clearance rate. However, the response in the lateral wall is "paradoxical". The size of the early rapid phase increases and the clearance half-time declines. Thus, in addition to heterogeneous tracer uptake in dilated cardiomyopathies, there are also regional differences in tissue kinetics of C-11 palmitate as well as regional dissimilar responses to changes in substrate availability.

pool and cleared from tissue more slowly. These changes corresponded to a decline in oxidation of FFA in favor of greater oxidation of glucose and cardiac work and, hence, oxygen consumption remained similar for both studies. However, the other half of patients responded "paradoxically", that is, glucose administration raised the fraction of tracer that entered the rapid turnover pool and accelerated clearance of tracer from myocardium. The difference in response was unaccounted for by differences in plasma substrate levels or heart rate and blood pressure between normal and paradoxical responders. Only left ventricular function differed between the two types of responders. Left

ventricular ejection fraction was frequently lower in the "paradoxical" than in the normal responders.

Of further interest and also consistent with earlier described findings, was that not only was the initial uptake of C-11 palmitate heterogeneous throughout the diseased myocardium but also the fractional distribution of tracer in tissue and its clearance rate from tissue. The "provocative test" of glucose administration after overnight fasting enhanced these differences even further (Fig. 22).⁵⁰ For example, within a given a ventricle, some segments responded in a normal and others in a paradoxical fashion to glucose administration. Again, these findings would

Fig.23. Myocardial perfusion and regional exogenous glucose utilization in Duchenne's muscular dystrophy. Three contiguous cross-sectional PET images after intravenous N-13 ammonia (upper panel) and of FDG (lower panel) are shown from left to right. The center images the mid-left ventricle. Note the decrease in N-13 ammonia uptake in the postero-lateral and antero-lateral wall of the left ventricle. An opposite pattern of FDG uptake is noted on the corresponding myocardial glucose uptake image. Note the enhanced glucose utilization in the segments with decreased N-13 ammonia uptake.

favor the existence of temporally and spatially disparate disease processes. As to the mechanism underlying these observations, they remain speculative at best. Because the patients consisted of a highly heterogeneous group, a variety of mechanisms may account for these observations. On the other hand, different disease mechanisms may converge into a common metabolic expression of the disease process. Possible explanations are replenishment of TCA cycle intermediates after glucose administration which then facilitates oxidation of FFA. Additional inhibition of transfer of FFA into mitochondria through augmented glycolysis and greater back diffusion of tracer from tissue into blood is another possibility. The present findings do not delineate or enhance our understanding of the pathophysiology of congestive cardiomyopathy. They lend however support to our hypothesis of an impairment in substrate utilization in diseased myocardium, which now can be demonstrated noninvasively with PET. Moreover, these observations allow formulation of hypotheses on mechanism of disease that can be tested in human myocardial pathologies and offer an

opportunity for clarifying disease mechanisms and for deriving more efficacious and selective therapeutic interventions.

At the outset, we had postulated that probing the heart's biochemistry may allow identification of disease processes still confined to the biochemical level and prior to the development of structural abnormalities or prior to clinical manifestations. Initial findings with PET support such possibility. We studied a group of adolescents with Duchenne's muscular dystrophy, a disease with a high prevalence of a "regional myocardial pathology".⁵¹ Obviously, the disease occurs rarely and its exploration by PET is therefore of limited clinical significance. Nevertheless, nature offers the disease as a "model of cardiomyopathy". This unique disease genetically targets specific regions of the myocardium. Postmortem examinations have revealed regional fibrotic degeneration in the posterobasal and adjacent lateral segments of the free left ventricular wall while the coronary artery supplying these regions have been found to be normal. A pre-dystrophic metabolic fault has been postulated for this region.^{52,53}

Fig.24. Gated PET images obtained in a normal volunteer after intravenous FDG acquired with a high temporal and spatial resolution whole body tomograph (ECAT III, CTI Inc., Knoxville, TN). Three contiguous cross sections through the mid-heart are shown in systole and diastole. Images are presented as seen from the subject's feet. Note the homogeneous tracer distribution throughout the left ventricular (LV) myocardium with excellent visualization of anatomical detail. The free right ventricular wall (RV) is clearly defined as well as the posterior and anterior papillary muscles (APM and PPM). Also, note the difference in LV cavity size and LV wall thickness between systole and diastole.

To test this hypothesis we used PET with N-13 ammonia and FDG in 15 adolescents with Duchenne's muscular dystrophy. Ninety-three percent of the 15 patients had distinctive though non-specific electrocardiograms. In only 25% of the patients did conventional Tl-201 scintigraphy and/or gated radionuclide ventriculography demonstrate regional perfusion or visually detectable regional wall motion abnormalities. However, PET revealed segmental reductions in N-13 ammonia uptake in 86% of the patients. In eleven of 12 patients studied in addition with FDG, the decreased N-13 ammonia uptake was associated with increased FDG uptake in the same region (Fig. 23). This study identified regional involvement in patients with Duchenne's muscular dystrophy and established the sensitivity of PET compared with that of conventional noninvasive scintigraphy. These findings need further confirmation and clarification, yet they

have several potentially important implications. The absence of appreciable regional wall motion abnormalities might suggest the possibility of compensatory mechanisms in substrate metabolism in affected regions. Also, the findings indicate that PET can identify abnormalities that remained inaccessible to other study techniques. Lastly, it may well be possible that PET detected abnormalities at a pre-dystrophic stage, or at a time prior to clinical disease manifestation. Thus, PET may indeed offer an opportunity for detecting disease early, still in its developmental stage, and thus allow early intervention.

Conclusions and Future Developments

In reviewing PET's ability for probing the biochemistry of the heart, it is important to remember that use of this new technology for clinical investigations is still in its infancy. Compared to the complexities and intricacies of

Fig.25 A and B. Multiple gated myocardial (FDG; Panel A) and blood pool (C-11 CO; Panel B) images with PET. The image plane was positioned through the mid-left ventricle and the RR interval divided into 16 frames, each of 50 millisecond duration. The sequence of images is presented from left to right and proceeds from enddiastole to endsystole and back to enddiastole. Note the corresponding changes in left ventricular size on both image sets. On the blood pool images the right and left ventricular cavities (RV and LV), the interventricular septum, the right atrium (RA) and vena cava (VC) and aorta (A) are well delineated. Again, note the changes in interventricular septal thickness and the changes in ventricular cavity size which are out of phase with the changes in right atrial size. Multi-gated image acquisition with high temporal resolution tomographs affords assessment of global and regional myocardial function.

Fig.26. Dynamic image acquisition after a bolus injection of N-13 ammonia (10 mCi) in a human volunteer. The initial 6 frames depict 3-sec images, illustrating the transit of the radioactivity through the right ventricle (RVC), both lungs and then the left ventricle (LVC). The last 6 frames represent 60-sec images and depict uptake of N-13 ammonia by left and right ventricular myocardium (LV and RV). Note also residual activity throughout the lungs as well as the intense uptake of N-13 activity by the liver. Such rapid dynamic images which can be performed with high temporal resolution tomographs at 1-sec intervals allow determination of the arterial input function by assigning regions directly to the left ventricular blood pool as well as determination of the myocardial tissue response by assigning regions of interest to the left ventricular myocardium. This will facilitate noninvasive studies of regional myocardial metabolism with positron emission tomography and avoid determination of the arterial input function from arterial blood samples and by well counting.

myocardial substrate metabolism, PET studies to date have focused on only two aspects of substrate metabolism. Among these, use of FDG affords evaluation of only one specific though important step within a chain of reactions or for substrate flux. Conversely, C-11 palmitate traces the fate of FFA through an entire and highly complex and diversified metabolic pathway. Neither tracer allows evaluation of a specific metabolic derangement nor its location within the pathway but rather provides estimates or measurements of flux of substrate through a given metabolic pathway. Therefore, additional and more specific tracers are needed to localize a particular metabolic defect. For example, abnormalities in the tissue kinetics of C-11 palmitate related to the early rapid turnover curve component may be caused by alterations in the initial activation steps, transfer into mitochondria, passage through the β -oxidation

spiral or reside in the TCA cycle. Use of more specific tracers, for example for TCA cycle activity, will then allow distinction between defects in the β -oxidation part or the TCA cycle. Such tracers are available but need to be tested. Other tracers will allow studies of intermediate amino acid metabolism and its contribution to energy metabolism in aerobic and anaerobic states. Measurements of rates of protein synthesis are likely. Also, testing membrane function with specific tracers appears possible in the future. Examples are initial studies with C-11 labeled cholinergic and adrenergic receptor binding agents.

These developments are on the horizon. Yet, even use of a small number of tracers of blood flow and of the main components of substrate metabolism illustrate the potential of PET for not only probing the heart's biochemistry but for its potentially important role in clinical cardiol-

gy. This latter role is likely to grow rapidly and expand as new technology improves. High spatial and temporal resolution tomographs are now available and afford monitoring of rapid dynamic events (Figs. 24–26). High spatial resolution is likely to improve the accuracy of noninvasive measurements of regional physiologic processes and the spatial distribution of alterations induced by physiologic interventions and disease processes. New dedicated medical minicyclotrons with largely automated radio-pharmaceutical synthesis will allow access to this new technique to a larger group of users and introduction of this new technology as a new dimension to the detection, characterization and treatment of cardiovascular disease.

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