Several approaches have become available for cardiac diagnosis, including two-dimensional echocardiography, pulsed Doppler echocardiography, gated bloodpool imaging, thallium 201 scintigraphy, and computer-assisted tomography (CT scanning). Each exhibits strengths and limitations dependent in part on the physical nature of the image forming variable. Thus, CT scanning, which employs x-rays as the image forming variable, provides excellent delineation of cardiac structure. Pulsed Doppler echocardiography, which employs high-frequency sound waves as the image forming variable, permits assessment of flow dynamics. Despite their utility, however, none of these approaches characterizes regional myocardial metabolism or perfusion quantitatively.

**Comparative Aspects of Positron and Gamma Emission Imaging**

Conventional nuclear medicine techniques such as technetium ($^{99m}$Tc) pyrophosphate imaging, radionuclide ventriculography, and thallium 201 ($^{201}$Tl) scintigraphy employ gamma-emitting radionuclides. The tracers used emit radiation in the form of single gamma photons. They are not normal physiologic substrates or metabolites, and their biologic behavior differs markedly from that of their physiologic counterparts. Detection of their emitted radiation is dependent on the energy of the emitted photon, the nature of the tissue, and the square of the distance between the source and detector. As much as 80 percent of emitted radioactivity may be attenuated (absorbed or scattered) between the heart and the detector. Furthermore, the amount of radiation detected is highly variable from region to region.

Detection of photons from single photon emitters with a standard gamma camera provides a two-dimen-

sional representation of three-dimensional events. Superimposition of events from multiple depths with different degrees of attenuation leads to additional variability. Although "single photon tomography" has been attempted with several detector systems, none obviates quantitative limitations due to variable attenuation as a function of depth.

Tracers employed in positron emission tomography (PET) such as carbon-11 ($^{11}$C), nitrogen-13 ($^{13}$N), oxygen-15 ($^{15}$O), fluorine-18 ($^{18}$F), and gallium-68 ($^{68}$Ga) decay by emitting positrons, subatomic particles with the mass of an electron and with a positive charge. Positrons traverse only a short distance in tissue (approximately 1 to 2 mm) before encountering a negatively charged electron. Interaction between the two results in annihilation and emission of energy (annihilation radiation) in the form of two high-energy (511 keV) gamma photons directed approximately 180° apart. Each pair of emitted photons can be detected readily by an appropriately aligned pair of detectors sensing the nearly simultaneous arrival of the two photons at opposite detectors (Fig 1). Thus, electronic coincidence detection provides collimation and compensation for attenuation, since total attenuation is not dependent on the position of the emitting radionuclides between the two detectors composing a pair. This advantage accrues from the generally inverse relation between attenuation and distance of the source from either detector and the constant algebraic sum of attenuation with respect to both regardless of the position of the source within their colinear fields of view.

Available detector systems include paired planar wire chambers or multicrystal cameras which parallel faces rotated around the patient during data acquisition; and single or multiple hexagonal arrays of detectors which undergo programmed translational and rotational motion, or circular rings with programmed rotation and wobble. Improved spatial resolution and sensitivity result from detection of the minute, temporal difference between the arrival times of the paired photons from a single disintegration event at opposite detectors (time of flight tomography).
Assessment of Myocardial Metabolism With Fatty Acids

Accumulation of labeled metabolites within the heart is complex. It depends on the following: the rate of delivery of the metabolite to the tissue (a function of regional perfusion); the interval during which extraction of the metabolite into the myocardium is possible (residence time); the percentage of the metabolite extracted by myocardium during a single pass through the coronary vascular tree (extraction fraction); rates of metabolism and washout; dilution of the tracer in the nonradioactive, chemically similar precursor pool.

Since long-chain fatty acids are the primary energy source of myocardium in vivo, factors influencing extraction, intracellular distribution, and metabolic fate have been characterized extensively. In perfused, isovolumically beating rabbit hearts and in hearts of intact rabbits, myocardial time-activity curves after bolus injection of $^{13}$C-palmitate exhibit several distinct phases. The last one represents extraction of $^{13}$C-palmitate into the neutral lipid pool. Its slope is a measure of myocardial oxygen consumption. When myocardial work is held constant, extraction of fatty acid is constant over a wide range of flow. However, when ischemia or hypoxia without hypoperfusion results in decreased work and altered metabolism, extraction and turnover decrease.

Analogous results have been obtained with the use of a $\beta$-probe. In normal, closed-chest dogs, the regional disappearance of $^{13}$C-palmitate is spatially homogeneous. However, distal to subcritical coronary stenosis, decreased regional turnover is evident under conditions of physiologic stress compared with turnover in normal myocardium. These findings have been confirmed by Schon et al with scintillation detectors in open-chest dogs.

Positron Emission Tomography With $^{13}$C-Palmitate

Initial tomographic studies in dogs given $^{13}$C-palmitate intravenously (IV) demonstrated homogeneous distribution of tracer in normal myocardium. When transient regional ischemia was induced, the ischemic region exhibited depression of $^{13}$C-palmitate accumulation, reversible after reperfusion. With persistent ischemia, regionally depressed accumulation of $^{13}$C-palmitate correlated closely with morphologically and enzymatically delineated infarction.

Paired tomographic studies after the IV injection of $^{13}$C-palmitate have been used recently to assess salvage of jeopardized myocardium. Thus, after coronary thrombosis in closed-chest anesthetized dogs, tomographic imaging with IV $^{13}$C-palmitate, clot lysis induced by intracoronary streptokinase after selected intervals, and repeated tomography, metabolic salvage was evident only when thrombolysis induced by streptokinase was initiated within six hours of the onset of infarction.

Studies on Patients

The distribution of $^{13}$C-palmitate throughout left ventricular myocardium is homogeneous in normal subjects studied tomographically. Discrete regions of depressed accumulation occur in patients with infarction and correlate with the ECG locus of infarction.
The role of altered myocardial metabolism in the pathophysiology of cardiomyopathies has been explored to a limited extent with endomyocardial biop-
sies, postmortem analysis of myocardial enzymatic activities, and vital staining. However, elucidation of cardiac metabolism in vivo in patients with cardiomyopathy has been difficult. PET with \(^{13}C\)-palmitate demonstrates marked spatial heterogeneity of palmitate accumulation in patients with congestive cardiomyopathy, which is not attributable to dyskinesia, wall thinning, or patchy perfusion abnormalities judging from concomitant radioventriculography, echocardiography, and thallium scintigraphy.\(^{12}\)

**Carbohydrate Metabolism**

Although aerobic myocardial metabolism utilizes primarily long-chain fatty acids, hypoxic or ischemic myocardium catalyzes glucose almost exclusively. Accordingly, \(^{13}C\)-glucose and \(^{18}F\)-labeled 2-deoxy-2-fluoro-D-glucose (\(^{18}FDG\)) and 3-deoxy-3-fluoro-D-glucose have been utilized in some studies. Unfortunately, \(^{13}C\)-glucose extraction fraction is relatively low (3 percent and 17 percent under normoxic and ischemic conditions, respectively), making imaging difficult. Although transient ischemia increases glucose uptake, prolonged ischemia inhibits glycolytic flux. Thus, changes in glucose accumulation with ischemia are variable. The kinetics of \(^{18}FDG\) differ markedly from those of \(^{13}C\)-glucose, since \(^{18}FDG\) is phosphorylated and trapped within the cell. Phosphorylated \(^{18}FDG\) is neither transported back to the interstitium nor metabolized further. Thus, imaging with \(^{18}FDG\) provides high target to background ratios with \(^{18}FDG\) accumulating in ischemic zones.\(^{13}\) However, interpretation of results is clouded by the anomalous metabolism of the tracer and can not be defined directly in terms of metabolism of a physiologic metabolite.

Other metabolites, such as pyruvate and acetate, have been evaluated for cardiac PET. In isolated, isovolumically beating rabbit hearts, myocardial pyruvate extraction decreases immediately after the onset of ischemia. However, the pyruvate concentration in ischemic hearts soon surpasses that in normal zones (by more than sixfold) because the pyruvate is trapped as lactate. Thus, ischemic but still viable zones may be detectable tomographically with a carbon-11 labeled glycolytic intermediate.\(^{14}\)

**Amino Acid Metabolism**

With the availability of \(^{13}C\), \(^{35}N\), and \(^{18}F\) labeled amino acids, assessment of the myocardial protein metabolism may be possible tomographically. However, incorporation of amino acids is tissue and amino acid specific. For example, valine is extracted and concentrated avidly in the pancreas, with accumulation more than ninefold that in the liver; and liver accumulation is more than fivefold that in muscle. In contrast, \(^{15}N\) glutamate and \(^{15}N\)-asparagine accumulate

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**Figure 2.** PET IV reconstructions obtained at midventricular level after IV injection of \(^{13}C\)-palmitate in normal subject, patients with transmural and nontransmural infarction, and patient with congestive cardiomyopathy. Horseshoe-shaped region, left ventricular (LV) myocardium. Accumulation of palmitate is homogeneous throughout left ventricle in normal subject. Region of nontransmural infarction (arrow) involves only a portion of thickness of anterolateral LV wall. Homogeneous, intense depression of accumulation of palmitate (arrow) is found in subject with anterior transmural infarction. Subject with cardiomyopathy demonstrates marked LV enlargement with marked spatial heterogeneity of accumulation of palmitate within LV myocardium. A = anterior, P = posterior, L = left, R = right.

1. With the use of 14 indigitated slices reconstructed from two data collection intervals alter a single injection of \(^{13}C\)-palmitate and with the use of sagittal and coronal reconstructions, delineation of infarction is facilitated, particularly when the bloodpool is visualized after the patient inhales tracer amounts of \(^{14}CO\) which binds to hemoglobin. With this technique, PET detects infarction in 96 percent of patients with nontransmural injury.\(^{19}\) The concordance between the tomographically and the enzymatically estimated extent of infarction is close (r = 0.92).\(^{19}\)

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more avidly in the heart. PET images of the heart obtained after IV injection of L-13N-alanine in animals and normal human subjects may offer particular promise for improved understanding of the role of altered protein metabolism in the genesis of cardiomyopathic states.15

**Evaluation of Myocardial Perfusion**

Coronary angiography is the most widely utilized approach for assessment of coronary functional reserve. Despite its inestimable value, limitations include its invasive nature, interobserver-variability, and lack of correspondence between visualized epicardial vessel diameter, cross-sectional area as well, and nutritional blood flow. Scintigraphic techniques with I-123 or analysis of washout of diffusible tracers, such as xenon-133 (xe133), administered as a bolus into the coronary arteries, entails the physical constraints inherent with the use of gamma emitters noted earlier. In addition, conventional scintigraphy with diffusible tracers does not satisfy several assumptions implicit in measurement of regional myocardial blood flow including: (1) constant extraction fraction of the tracer into the tissue (ideally 100 percent) independent of flow; (2) absence of recirculation; (3) extraction fraction independent of the metabolic status of the tissue; (4) an aqueous lipid partition coefficient near unity so that the lipid content of the tissue does not induce variability of measurement; (5) complete trapping of the tracer within the tissue during the imaging interval.

To obviate some of these difficulties several approaches have been employed with positron emitting isotopes. 15N-labeled ammonia (NH3) has been considered by some to behave as a potassium analog, similar to I-123. However, its accumulation is dependent on myocardial metabolism, since ammonia is incorporated into glutamine by glutamine synthetase. Thus, retention of 15NH3 is depressed when glutamine synthetase is inhibited. In addition, extraction is dependent on pH. In isolated, perfused rabbit hearts, the extraction fraction is increased (sic) with low flow due to prolonged residence time. Thus, 15NH3 accumulation does not correlate directly with coronary blood flow. Nevertheless, a nonlinear relationship exists between regional accumulation of 15NH3 and flow measured at selected intervals after 15NH3 administration in dogs. Regional differences reflecting coronary stenosis can be augmented by pharmacologically induced vasodilatation, providing a qualitative estimate of coronary obstruction.17

Rubidium (Rb) is a positron emitting potassium analog of particular interest, since it can be obtained, on line, from a chemical generator obviating a requirement for an on-site cyclotron. In open-chest dogs, myocardial extraction fraction is inversely related to flow. However, net extraction correlates with flow because of the dominant effect of flow-dependent delivery of the tracer. Preliminary studies in patients indicate that decreased myocardial accumulation of 82Rb detectable by PET, correlates with the ECG locus of ischemia and the distribution of lesions detectable by coronary arteriography.18

Other approaches employ positron emitting, 18O-labeled water. In one, equilibrium levels of radioactivity in tissue are measured after inhalation of C02, which is converted to H218O by carbonic anhydrase. In another, the regional disappearance rates of H218O are characterized in a fashion analogous to that employed with xenon washout curves. Unfortunately, neither approach fulfills all of the assumptions required.

An alternative approach to the assessment of myocardial perfusion with H218O relies on administration of the tracer at an exponentially increasing rate and calculation of a mathematical parameter (Q*) which rapidly reaches a constant value as a function of isotope decay rate, tracer delivery rate, and the observed changes in tissue radioactivity. The parameter (Q*) is proportional to tissue perfusion. With flow varied from 1.2 to 5 ml/g/min in isolated, perfused hearts, measured flow correlates closely with flow estimated based on tracer kinetics (r = 0.95).19

Radioactive microspheres meet the criteria for a flow marker. Accordingly, microspheres of human serum albumin labeled with 67Ga have been evaluated with positron emission tomography in experimental animals after injection of the microspheres into either the coronary artery or the left atrium. Accumulation of radioactivity is depressed in regions distal to coronary occlusions, and antemortem estimates of myocardial blood flow obtained by PET correlate well with post-mortem estimates based on well counting of myocardial samples after injection of cerium 141-labeled microspheres (r = 0.98).20

**Future Directions**

Major efforts are currently in progress to improve instrument design facilitating more rapid data acquisition and improved spatial resolution. "Time of flight" reconstruction is particularly promising. It requires temporal resolution of the order of nanoseconds, possible with recently developed detectors and electronics. Rapid scanning instruments which incorporate time of flight technology should permit the acquisition of sufficient data for image reconstruction under conditions of breath-holding and ECG gating, thereby reducing motion artifacts due to the respiratory and cardiac cycles. Rapidly scanning instruments should permit more ready implementation of studies with short-lived isotopes, such as oxygen-15 and rubidium-82, and improved assessment of dynamic metabolic events.

Within the past five years, positron emitting amino
acids, carbohydrates, fatty acids, and fatty acid analogs have been labeled with several radionuclides, widening the scope of potential characterization of abnormalities of myocardial metabolism in cardiomyopathic states. The recent availability of generator-produced isotopes may decrease the dependence of PET on close proximity to a cyclotron.

Quantitative analysis of the regional myocardial blood flow is of potentially great importance in the screening of patients for coronary artery disease, perhaps permitting the noninvasive localization of functionally significant coronary occlusions and left main coronary disease. Realization of these and other potentials of positron emission tomography will undoubtedly require the continued efforts of physicists, radiation chemists, computer scientists, and clinicians. Results already available appear to justify the investment required.

REFERENCES