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Rationale for the rational development of new cardiac imaging agents

D. Douglas MILLER

St. Louis University Medical Center, Department of Internal Medicine, Division of Cardiology, St. Louis, Missouri, USA

There are several prerequisites for the development of new diagnostic cardiovascular radiopharmaceuticals. Agents which are proposed for clinical use must offer significant advantages in one or more of the following categories: I) Radiopharmacy [dosimetry, dose preparation, dose availability]; II) Imaging characteristics [spatial and temporal resolution, radiotracer biokinetics, patient throughput and acquisition protocols]; and III) Measurement of a previously unmeasurable physiologic or pharmacologic event [metabolic pathways, receptors, neural pathways, preclinical disease]. Technetium-99m-based radiopharmaceuticals are particularly attractive, in view of their excellent characteristics for imaging with the Anger gamma camera. In addition, the increasing use of tomographic imaging and reconstruction techniques has magnified the importance of developing radiotracers with minimal soft tissue attenuation effects. Technetium-99m and positron emitting radioisotopes offer this advantage. A wide choice of biologically and pharmacologically relevant ligands are available for complexing with these radiotracers. The clinical studies are underway in order to validate these new agents, and to determine their value in the modern practice of nuclear medicine. Technetium-99m sestamibi is just one example of a novel radiotracer with improved imaging characteristics that has undergone careful pre-clinical and clinical testing, and which has emerged as a useful diagnostic imaging agent. Future studies should be directed towards the development of tracers with well-defined biokinetic characteristics, which are advantageous for tomographic imaging. The future applications of tracer imaging techniques for the pre-clinical diagnosis of cardiovascular, oncologic and other medical conditions are significant and are expanding. Combined diagnostic and therapeutic approaches may eventually be possible with a single injection of a pharmacologically active radiotracer.

Key words: myocardial perfusion, radionuclide imaging, positron emission tomography, receptors, atherosclerosis.

INTRODUCTION

AS WITH OTHER PHARMACEUTICALS, diagnostic radiopharmaceutical research and development is proceeding at a rapid pace.[1] A wide range of radiopharmaceuticals have been developed for evaluation of myocardial perfusion, ventricular function, myocardial viability and substrate metabolism.[2] The first era of cardiovascular nuclear medicine has witnessed the experimental and clinical validation of thallium-201 myocardial perfusion imaging and technetium-99m radionuclide angiography, two techniques which are widely applied in medical practice for detection and prognostication of cardiac diseases. Planar and tomographic single photon nuclear medicine camera-computer systems have been configured to accommodate the physical characteristics and biologic behavior of these two isotopes. Applica-

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For reprints contact: D. Douglas Miller, M.D., Director, Nuclear Cardiology, Associate Professor of Medicine, Division of Cardiology, 14th floor, Post Office Box 15250, St. Louis, Missouri 63110-0250, USA.

tion of comparable image acquisition protocols, implementation of radiopharmacy preparation for dose preparation and quality control, and dissemination of validated quantitation software and standardized normal files have significantly enhanced the diagnostic utility of these radionuclide procedures.

Despite changing patient referral bases and laboratory utilization profiles, these radionuclide studies have persistently demonstrated high sensitivity for disease detection and significant positive predictive accuracy for adverse cardiac events. Specificity values vary widely between 50 and 90%, principally due to post-test referral bias, which directs positive test responders to diagnostic cardiac catheterization. Collaboration between industry and investigators has led to the development of quantitative image analytic techniques which demonstrate excellent transportability between medical centers, and high reproducibility between studies. In this setting, novel cardiovascular radiopharmaceuticals must offer improved dosimetry or image resolution [temporal or spatial], or provide diagnostic information on a previously unmeasurable but relevant biologic parameter.

State-of-the-art

The proceedings of the 38th Annual Meeting of the Society of Nuclear Medicine[3] produced an interesting survey of the current international trends in cardiovascular radiopharmaceutical development. Despite the significant numbers of papers on the use of thallium-201 for coronary disease diagnosis, prognosis and viability assessment [7%], and of PET studies of cardiac flow and metabolism with rubidium-82, nitrogen-13 ammonia and fluorine-18 deoxyglucose [5%], 107 of the 843 general and cardiovascular papers accepted for this meeting [13%] provided information on the radiochemistry and applications of new tracers for cardiovascular imaging. Of these papers, 77% evaluated single photon emitting radionuclides, while 23% presented data on position emitting radiotracers.

Studies of then approved myocardial perfusion tracers, Tc-99m sestamibi [24%] and Tc-99m teboroxime [20%], were most numerous among these new radiopharmaceuticals. Single photon and positron emitting isotope labeled radioligands for receptor binding [alpha and beta adrenergic, cholinergic/muscarinic] also constituted a significant percentage [17%] of "new agent" papers (i.e. iodine-125 labeled hydroxy-phenyl-ethyl-amino-methyl-tetralone [HEAT] for studies of the alpha-I receptor, carbon-11 [S] CGP-12177, iodine-125 iodocyanopindolol and carbon-11 carazolol [for beta-adrenergic receptor studies], carbon-11 epinine [a dobutamine derivative], and 6-[F-18]fluorodopamine [for dopaminergic receptors], carbon-11 benzovesamicols [for acetylcholine receptors], and iodine-123 3-quinuclidinyl benzilate [QNB] analogs [for muscarinic receptors]). More established adrenergic neuronal tracers including iodine-123 meta-iodobenzyl-guanidine [MIBG], and carbon-11 [meta] hydroxyephedrine [MHED] were the subject of further studies.

Useful clinical applications for antimyosin antibody imaging of myocardial necrosis were presented [9%], including molecular modifications of antimyosin to produce sFv fragments for rapid blood pool clearance, fluorine-18 labeling for PET studies and indium-111 liposomes for antimyosin delivery. For detection of thrombosis and early atherosclerosis, technetium-99m labeled antifibrin [T_2G_2] and antiplatelet monoclonal antibodies [S12] were represented. Additional studies of radiolabeled low density lipoprotein [LDL], indium-111 Z_2D_3 [IgM] antibody directed against atheromatous ground substance, and a placental anticoagulant protein I ligand for platelet imaging were reported. Overall, single photon agents for plaque and thrombus imaging totalled 8% of new studies.

Single photon labeled modified fatty acid analogs for studies of cardiac metabolism made up 4% of studies, including papers on iodine-123 beta-methyl IPPA and technetium-99m N_2S_2 derivatized analogs. Fluorine-18 FTHA [fluoro-6-thia-hepadecanoic acid] studies of a modified long chain fatty acid designed to undergo beta-oxidation and subsequently be metabolically "trapped" in the myocardium were also reported [2%].

Positron-emitting copper-62 PTSM [pyruvaldehyde-bis-N_4-methyl thiosemicarbozone]. A generator-produced PET imaging agent which may be an alternative to cyclotron-produced carbon-11 acetate, was the subject of 5% of papers presented.

New single photon emitting myocardial flow markers [3%] and potential positron emitting perfusion tracers [4%] were represented. Including technetium-94, gallium-68 BAT-TECH [a lipid soluble agent], Tc-99m [III] cationic diphosphines [Q12, P53] and Fluorine-18 fluoromisonidazole [FMISO], which concentrates in ischemic tissue.

Each of these novel radiotracers fulfills one or more of the specifications for cardiovascular radiopharmaceutical development. A range of pre-clinical to post-release studies were represented. While a significant percentage of these agents may never achieve widespread clinical utilization, others have already become significant elements of modern cardiovascular nuclear medicine practice.

Published studies: 1990–1991

Between August 1990 and July 1991, a total of 30

manuscripts were published in the *Journal of Nuclear Medicine* dealing with the experimental and clinical validation of novel cardiovascular radioisotopes. Nineteen of these articles (63%) reported studies on single photon radiotracers, while the remaining 11 manuscripts (37%) dealt with new positron emitting radiotracers. Significant numbers of both single photon and positron emitting myocardial perfusion imaging radiotracers were studied. In addition to further studies of the technetium-99m perfusion agents sestamibi[4–7] and teboroxime,[8] iodine-123 9-methyl PPA,[9–13] C-11 acetate,[14–18] and Ga-68 BAT TECH[19,20] were evaluated as myocardial perfusion radiotracers. Fluorine-18 misonidazole uptake was reported to be increased in studies of acute reversible myocardial ischemia associated with changes in glycolytic metabolism.[52] Several studies examined the myocardial uptake of indium-111 antimyosin antibody in previously untested clinical subgroups,[21–24] including patients with dilated hypertrophic cardiomyopathy, doxorubicin cardiac toxicity, and non-Q wave myocardial infarction. A new technetium-99m based carbohydrate ligand, Tc-99m glucaric acid, demonstrated increased uptake in experimental zones of infarctions, reflecting alternative cardiac metabolism.[53]

I. Perfusion imaging agents

A new generator produced positron emitting myocardial perfusion agent, copper-62 pyruvaldehyde bis (N^4-methythiosemicorbazone) [PTSM] has been extensively studies.[25–27] The production of this compound from a zinc-62/copper-62 generator provides a more convenient source of positron radiopharmaceutical for regional blood flow determinations in both the heart and brain. The half life the parent compound (9 hours) and daughter (9 minutes) may limit the clinical utility due to a generator life span of 2 days. Radiochemical complexing of Cu-62 with PTSM produces a neutral, lipid soluble compound which passes rapidly through cell membranes and is subsequently trapped intracellularly after interacting with sulfhydril groups. The short physical half life of the Cu-62 daughter permits repeat imaging studies over short time intervals as well as "kit" chemical synthesis of radiopharmaceuticals. Intravenous, Cu-62 PTSM is highly extracted by myocardial tissues, with good myocardial retention and no recognized toxicity.

Additional copper-62 based radiotracers produced from this generator include Cu-62 benzyl TETA-human serum albumin (HSA) for intravascular blood pool imaging.[27] As such, a zinc-62/copper-62 positron generator can produce radionuclide for both blood pool imaging with Cu-62 benzyl TETA-HSA and perfusion studies with Cu-62 PTSM. Subtraction imaging of blood pool and myocardial perfusion phases is possible with Cu-62 benzyl TETA-HSA at laboratories that do not possess an on site cyclotron. PET blood pool images obtained with this agent are comparable to those generated with $C^{15}O$. Gated right and left ventricular blood pool function studies can be acquired with this agent in combination with traditional PET perfusion agents (i.e. rubidium-82, nitrogen-13 ammonia, etc.).

Another potentially useful positron generator system is the germanium-68/gallium-68 generator.[20,27] The parent compound has a half life of 287 days and is useful for approximately 1 year, while the daughter has a half life of 68 minutes, making it suitale for complex radiochemical labeling studies. Lipid soluble Ga-68 complexes of potential utility for myocardial perfusion imaging have been investigated, but have significant limitations for this application.

Other neutral lipid soluble Ga-68 complexes have been studied for cerebral perfusion imaging. Ga-68 BAT TECH is a complex of Ga^{3+} with bis-amino-ethanethiol-tetra-ethyl-cyclohexyl (BAT TECH) ligand. PET myocardial perfusion imaging studies with this agent have been reported. The percent of the initial dose retained by the rat myocardium 2 minutes following injection of Ga-68 BAT TECH is 1.68%. Rapid myocardial clearance of BAT TECH and other agents limits late image quality, since the rate of radiotracer clearance is likely to be greater in hyperemic than ischemic myocardial regions. Tracer clearance enforces the need for abbreviated imaging acquisition times to assure a constant relationship between tissue counts and relative regional myocardial perfusion, potentially reducing clinical applications. Heart to blood activity ratios obtained 2 minutes following injection of Ga-68 BAT TECH are 3.5, decreasing to 3.1 at 30 minutes and 1.2 at 60 minutes in a rat model. Comparable heart to blood activity ratios for Cu-62 PTSM at 1 minute, 5 minutes and 120 minutes are 5.9, 9.8 and 9. Thus, Cu-62 PTSM myocardial activity appears better suited to cardiac imaging PET studies.

II. Metabolic imaging

Iodinated fatty acid molecules have been evaluated over the last decade for detection of myocardial metabolism rates and viability with single photon imaging systems.[9–13] Analogs of phenyl pentadecanoic acid (PPA) have demonstrated the capacity for perfusion assessment based on initial uptake, and fatty acid metabolism based on differential myocardial clearance. Limited iodine-123 availability for labeling to this moiety have reduced its clinical application. The desire to provide cardiac metabolic information without the need for expensive PET detector systems and cyclotrons has fueled con-

Table 1 Prerequisites for Development of New Diagnostic Cardiovascular Radiopharmaceuticals

I. Radiopharmacy Advances
1. Dosimetry:
   a. total body
   b. critical organ
2. Dose Preparation:
   a. labeling method (*in vitro*, *in vivo*, "kit", etc)
   b. quality control (labeling efficiency, detecting contaminants)
3. Dose Availability:
   a. radiochemistry
   b. source (cyclotron, generator, etc.)
   c. physical half-life (ultrashort, short, long)

II. Imaging Advantages
1. Resolution:
   a. spatial
      i. biodistribution (target-to-background, tissue "crosstalk", etc.)
      ii. gating (possible?)
   b. temporal
      i. dynamic vs. static acquisition
      ii. tissue clearance ("washout") kinetics
2. Radiotracer Properties:
   a. tissue extraction (from blood pool, low-flow to hyperemia)
   b. tissue retention (vs. clearance)
   c. isotope (positron vs. single photon emitter, photopeak, etc.)
3. Patient "Throughput":
   a. single vs. multiple doses (reinjection nec.?)
   b. rest vs. stress (vs. both) studies
   c. minimum interstudy "window" (physical and biologic clearance rates)
   d. post-injection "window" for acquisition
   e. "delayed" study (4 hr, 24 hr, <24 hr)
   f. counts statistics (activity/dose, acquisition time/study)
   g. "dual purpose" study (i.e. flow, function)

III. Physiology/Pharmacologic-Driven
1. Metabolic Pathways (*de novo*, response to anaerobic stress, etc.)
2. Neuro-adrenergic/cholinergic Pathways:
   a. receptor (binding, processing, up- and down-regulation)
   b. en/denervation (response to injury)
   c. humoral effects
   d. drug effects
3. "Pre-clinical" Diagnosis (occult disease, early recovery, early dysfunction, etc.):
   a. atherosclerosis (platelets, thrombosis, plaque components)
   b. "silent" myocardial ischemia
   c. tissue viability (pre-infarction/pre-necrotic injury phase)

tinued investigation. Recently, iodine-131 ortho-PPA has demonstrated a reasonable correlation with FDG data (r=0.51) for detection of viability in "fixed" thallium-201 defects.[13] Additional studies have correlated modified 9-methyl iodine-123 PPA with thallium-201 uptake in patients with coronary artery disease induced myocardial ischemia.[12] Ortho-PPA is another compound which binds to co-enzyme A and remains principally within the free fatty acid pool, while para-PPA enters mitochondrial beta oxidation.[9] The implications of these metabolic pathways for detection of myocardial viability, and the relationship to myocardial ATP content have been evaluated in further basic studies.[10] The search for a single photon emitting fatty acid metabolic tracer for the detection of viability continues.

PET imaging studies utilizing carbon-11 acetate as a marker of aerobic metabolism via the tricarboxylic acid (TCA) cycle metabolism have increased.[14–18] The myocardial uptake of this agent at steady state is proportional to the cellular generation of carbon dioxide. The agent is avidly extracted by the myocardium in response to increased myocardial oxygen consumption; mitochondria convert it to carbon-11 acetyl-CO-A prior to entering the TCA cycle. As compared to carbon-11 palmitate, C-11 acetate is rapidly and completely oxidatively metabolized. Its experimental myocardial clearance

is closely related to myocardial oxygen consumption over a range of physiologic conditions and cardiac workloads. The metabolism of carbon-11 acetate is not significantly affected by circulating levels of other competitive substrates, as opposed to carbon-11 palmitate and fluorine-18 FDG. Modeling of C-11 acetate clearance kinetics should permit absolute quantification of myocardial oxygen consumption using PET imaging. In addition to the value of clearance data following injection of this agent, preliminary studies indicate a direct proportionality between initial uptake and myocardial blood flow in coronary artery disease patients. Despite its relatively complex radiochemistry, carbon-11 acetate is being widely evaluated as a clinical diagnostic tool.

III. Neuro-humoral imaging agents

Cardiac adrenergic and muscarinic receptor radiotracers continue to be the focus of new studies.[30–34] The myocardial beta adrenergic receptor can be characterized by PET imaging with C-11 CGP 12177 and C-11 metahydroxyephedrine (MHED). Fluorine-18 labeling of the norepinephrine analog, metaraminol, provides an indirect approximation of tissue NE levels from PET images. C-11 CGP 12177 is a potent high affinity hydrophilic beta adrenergic receptor ligand which couples to adenylate cyclase,[33] and has significant image advantages over C-11 propranolol, which is confounded by excessive background lung uptake. C-11 MHED can detect myocardial denervation in response to a variety of insults including myocardial infarction, congestive heart failure and chronic hypoxia.[30,34] This sympathetic nervous system probe provides for competitive uptake between the radiolabeled drug (carbon-11 MHED) and the endogenous neurotransmitter, norepinephrine (NE). Mathematical modeling has been developed for quantification of the uptake of this agent.

Another radiolabeled catecholamine analog, fluorine-18 metaraminol (FMR), is used to assess the sympathetic nervous system responses to regional myocardial ischemia.[31] Transient disturbances of sympathetic neuronal function may occur in response to ischemia, and may be dynamically assessed by FMR imaging. Experimental studies have demonstrated significantly reduced F-18 metaraminol activity in post occlusive zones with 87% flow reduction and 18% reduction of tissue NE concentration. Pharmacologic blocking studies of this agent *in vivo* confirm neuronal localization by the uptake I carrier system and subsequent vesicular storage. The relationship between regionally depressed postischemic FMR concentrations derived by PET imaging and electrophysiologic instability and arrhythmogenesis remains unconfirmed.

Muscarinic receptor binding agents including 4-iodine-125-iododexetimide[32] and carbon-11 MQNB have been studied. The potential for single photon or PET imaging of muscarinic cholinergic (ACH) receptors may be valuable in the assessment of cardiac dysfunction due to diabetes, aging, congestive heart failure and anti-arrhythmic therapy. Fluorine-18 flurodopamine can experimentally assess cardiac sympathetic innervation in animals.[51] Cardiac uptake of this positron emitting neuronal radiotracer is significantly diminished by pre-treatment with the competitive antagonist, desipramine. Clinical studies with these and other radioisotope markers of neuronal function are proceeding with the goal of defining the cardiac response to pharmacologic interventions and diseases.

IV. Myocardial perfusion imaging with technetium based radionuclides

The relative advantages and disadvantages of thallium-201 and technetium-99m sestamibi (Cardiolite®) and Tc-99m teboroxime (Cardiotec®) have been extensively reviewed.[35] Prior approval of the technetium-based perfusion compounds by licensing bodies in Europe and Canada was followed by approval in the United States. Insufficient time has elapsed to determine what impact these novel perfusion agents will have on the day-to-day practice of clinical nuclear cardiology. Whether these agents will completely replace thallium-201 for the detection and assessment of patients with known or suspected coronary artery disease is unclear.

Tc-99m sestamibi (Cardiolite®) offers significant advantages for SPECT imaging over results achieved with thallium-201, with improved diagnostic accuracy in most clinical validation trials. Thallium-201 activity distribution over time, in particular detection of defect "redistribution" by thallium-201 reinjection or delayed (18–24 hour) imaging, is highly correlated with myocardial viability. The relationship between technetium-99m perfusion agent distribution and perfusion is better validated than is the distribution of these agents to tissue viability.[36] PET imaging and dual isotope imaging studies with indium-111 antimyosin and thallium-201 may clarify this unresolved aspect of technetium-99m perfusion agent imaging. Software for reconstruction and quantitative analysis of Tc-99m sestamibi images have been developed by extrapolation from techniques of thallium-201 image analysis.[4]

Despite the rapid myocardial clearance of technetium-99m teboroxime, it appears that planar and tomographic images can be generated with this perfusion agent. Differential clearance from ischemic and normal myocardial zones may permit detection of early perfusion defect "redistribution" within

10 minutes of stress injection.[37,38]

The evolution of thallium-201 myocardial perfusion imaging from its inception in 1977[39] to the tomographic description of persistent fluorine-18 deoxyglucose uptake in persistent thallium perfusion defects[40] and delayed (8–24 hour) tomographic defect redistribution[41] required a decade of intensive experimental and clinical evaluation. Despite tremendous interest and enthusiasm, a full understanding of the scope and importance of myocardial perfusion imaging with technetium-99m isonitrile[42] and teboroxime[43] may not be achieved without a similar duration of intensive investigation and validation.

V. Indicators of atherosclerotic plaque instability

A significant future challenge for cardiovascular radionuclide imaging is the detection of insipient subclinical atherosclerotic plaque instability. The local metabolic activity of atheroma and activated platelets can now be assessed *in vivo* using radiolabeled plaque components and monoclonal antibodies. For example, monoclonal antibodies specific for the platelet surface membrane glycoprotein IIB–IIIA, indium-111 P256 antibody, has been utilized to image canine vascular thrombi. Another monoclonal antibody within this cluster of differentiation with specificity for translocated α-granule membrane proteins, iodine-123 anti-PADGEM, has been utilized to detect baboon deep venous thrombi.[44] A novel technetium-99m monoclonal antibody with specificity for the α-granule GMP-140 membrane glycoprotein expressed on the surface of activated platelets, Tc-99m S12, has been successfully imaged in animals and man following arterial angioplasty injury.[45,46] These highly specific radiolabeled monoclonal antibodies demonstrate favorable biodistribution and imaging characteristics with minimal contamination of blood pool usually associated with autologous platelet imaging studies.

Other components of atherosclerotic lesions[47] and local thrombi[48] can be directly imaged following technetium-99m labeling of low density lipoproteins and thrombus-specific monoclonal antibodies. Thrombus components including recombinant tissue plasminogen activator (t-PA) and factor-XIII have also been radiolabeled for non-invasive *in vivo* imaging studies of experimental thrombi.[49,50] The incorporation of various thrombus components has been studied *in vivo* with radiotracers including indium-111 antifibrin monoclonal antibody (for deep venous thrombosis)[28] and indium-111 "inhibited" recombinant tissue plasminogen activator (rt-PA).[29] The role of cardiovascular nuclear medicine studies of thrombotic and thrombolytic proteins is being evaluated during the pre-clinical and therapeutic phases of thrombogenesis and fibrinolysis.

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REFERENCES

1. Miller DD, Gill JB, Fischman AJ, et al: New radionuclides for cardiac imaging. *Prog Cardiovasc Dis* 28: 419–434, 1986
2. Miller DD, Elmaleh DR, McKusick KA, et al: Radiopharmaceuticals for cardiac imaging. *Radiol Clinics of N Am* 23: 765–781, 1985
3. Proceedings of the 38th Annual Meeting, Society of Nuclear Medicine. *J Nucl Med* 32 (5): 909–1108, 1991
4. Koster K, Wackers FJ Th, Mattera JA, et al: Quantitative analysis of planar technetium-99m sestamibi myocardial perfusion images using modified background subtraction. *J Nucl Med* 31: 1400–1408, 1990
5. Pellikka PA, Behrenbeck T, Verani MS, et al: Serial changes in myocardial perfusion using tomographic technetium-99m-hexakis-2-methoxy-2-methylpropyl-isonitrile imaging following reperfusion therapy of myocardial infarction. *J Nucl Med* 31: 1269–1275, 1990
6. Tartagni F, Dondi M, Limonetii P, et al: Dipyridamole technetium-99m-methoxy isobutyl isonitrile tomoscintigraphic imaging for identifying diseased coronary vessels: comparison with thallium-201 stress-rest study vessels: comparison with thallium-201 stress-rest study. *J Nucl Med* 32: 369–376, 1991
7. De Puey EG, Jones ME, Garcia EV: Evaluation of right ventricular regional perfusion with a technetium-99m-sestamibi SPECT.
8. Nakajima K, Taki J, Bunko H, et al: Dynamic acquisition with a three-headed SPECT system: application to technetium-99m-SQ30217 myocardial imaging. *J Nucl Med* 32: 1273–1277, 1991
9. Kaiser KP, Geuting B, Großmann, et al: Tracer kinetics of 15-(ortho-$^{123/131}$I-phenyl)-pentadecanoic acid (oPPA) and 15-(para-$^{123/131}$I-phenyl)-pentadecanoic acid (pPPA) in animals and man. *J Nucl Med* 3: 1608–1616, 1990
10. Fujibayashi Y, Yonekura Y, Takemura Y, et al: Myocardial accumulation of iodinated beta-methyl branched fatty acid analogue, iodine-125-15-(p-iodophynyl)-3-(R,S)methylpentadecanoic acid (BMIPP), in relation to ATP concentration. *J Nucl Med* 31: 1818–1822, 1990
11. Fink GD, Montgomery, David F, et al: Metabolism β-methyl-heptadecanoic acid in the perfused rat heart and liver. *J Nucl Med* 31: 1823–1830, 1990
12. Chouraqui P, Maddahi J, Henkin R, et al: Comparison of myocardial imaging with iodine-123-iodophenyl-9-methyl pentadecanoic acid and thallium-201-chloride for assessment of patients with exercise-induced myocardial ischemia. *J Nucl Med* 32: 447–452, 1991
13. Heinrich MM, Vester E, von der Lohe E, et al: The comparison of a 2-^{18}F-2-deoxyglucose and 15-(ortho-^{131}I-phenyl)-pentadecanoic acid uptake in per-

sisting defects on thallium-201 tomography in myocardial infarction. *J Nucl Med* 32: 1353–1357, 1991
14. Hicks RJ, Herman WH, Kalff V, et al: Quantitative evaluation of regional 41 substrate metabolism in the human heart by positron emission tomography. *J Am Coll Cardiol* 18: 101–111, 1991
15. Kotzerke J, Hicks RJ, Wolfe E, et al: Three-dimensional assessment of myocardial oxidative metabolism: a new approach for regional determination of PET-dervied C-11 acetate kinetics.
16. Gropler RJ, Siegel BA, Geltman EM: Myocardial uptake of carbon-11 acetate as an indirect estimate of regional myocardial blood flow. *J Nucl Med* 32: 245–251, 1991
17. Schwaiger M, Hicks R: The clinical role of metabolic imaging of the heart by positron emission tomography. *J Nucl Med* 32: 565–578, 1991
18. Chan SY, Brunken RC, Phelps ME, et al: Use of the metabolic tracer carbon-11-acetate for evaluation of regional myocardial perfusion. *J Nucl Med* 32: 665–672, 1991
19. Kung HF, Liu BL, Mankoff D, et al: A new myocardial imaging agent: synthesis, characterization, and biodistribution of gallium-68-BAT-TECH. *J Nucl Med* 31: 1635–1640, 1990
20. Green MA. Editorial: The potential for generator-based PET perfusion tracers. *J Nucl Med* 31: 1641–1645, 1990
21. Hendel RC, McSherry BA, Leppo JA: Myocardial uptake of indium-111-labeled antimyosin in acute subendocardial and autoradiographic correlation of myocardial necrosis. *J Nucl Med* 31: 1851–1853, 1990
22. Estorch M, Carrio I, Berna L, et al: Indium-111-antimyosin scintigraphy after doxorubicin therapy in patients with advanced breast cancer. *J Nucl Med* 31: 1965–1969, 1990
23. Nakata T, Sakakibara T, Noto T, et al: Myocardial distribution of indium-111-antimyosin fab in acute inferior and right ventricular infarction: comparison with technetium-99m-pyrophosphate imaging and histologic examination. *J Nucl Med* 32: 865–866, 1991
24. Nishimura T, Nagata S, Uehara T, et al: Assessment of myocardial damage in dilated-phase hypertrophic cardiomyopathy by using indium-111-antimyosin fab myocardial scintigraphy. *J Nucl Med* 32: 1333–1337, 1991
25. Green MA, Mathias CJ, Welch MJ, et al: Copper-62-labeled pyruvaldehyde *Bis* (N^4-methylthio-semicarbazonato) copper (II): synthesis and evaluation as a positron emission tomography tracer for cerebral and myocardial perfusion. *J Nucl Med* 31: 1989–1996, 1990
26. Mathias CJ, Welch MJ, Green MA, et al: *In vivo* comparison of copper blood-pool agents: potential radiopharmaceuticals for use with copper-62. *J Nucl Med* 32: 475–479, 1991
27. Subramanian KM. Editorial: Cardiac blood-pool tracers. *J Nucl Med* 32: 480–482, 1991
28. DeFaucal P, Peltier P, Planchon B, et al: Evaluation of indium-111-labeled antifibrin monoclonal antibody for the diagnosis of venous thrombotic disease. *J Nucl Med* 32: 785–790, 1991
29. Butler SP, Kadar KL, Owen J, et al: Rapid localization of indium-111-labeled inhibited recombinant tissue plasminogen activator in a rabbit thombosis model. *J Nucl Med* 32: 461–467, 1991
30. Rosenspire KC, Haka MS, Van Dort ME, et al: Synthesis and preliminary evaluation of carbon-11-meta-hydroxyephedrine: a false transmitter agent for heart neuronal imaging. *J Nucl Med* 31: 1328–1334, 1990
31. Schwaiger M, Guibourg H, Rosenspire K, et al: Effect of regional myocardial ischemia on sympathetic nervous system as assessed by fluorine-18-metaraminol. *J Nucl Med* 31: 1352–1357, 1990
32. Matsumura K, Uno Y, Scheffel U, et al: *In vitro* and *in vivo* characteristics of 4-[^{125}I]Iododexetimide binding to muscarinic cholinergic receptors in the rat heart. *J Nucl Med* 32: 76–80, 1991
33. Delforge J, Syrota A, Lamcon JP, et al: Cardiac beta-adrenergic receptor density measured *in vivo* using PET, CGP 12177, and a graphical method. *J Nucl Med* 32: 739–748, 1991
34. Schwaiger M, Kalff V, Rosenspire K, et al: Noninvasive evaluation of sympathetic nervous system in human heart by positron emission tomography. *Circ* 82: 457–464, 1990
35. Berman DS (Ed.) A symposium: Technetium-99m myocardial perfusion imaging agents and their relationship to thallium-201. *Am J Cardiol* 66: 1E–96E, 1990
36. DeCoster PM, Wijns W, Cauwe F, et al: Area-at-risk determination by technetium-99m-Hexakis-2-methoxyisobutyl isonitrile in experimental reperfused myocardial infarction. *Circ* 82: 2152–2162, 1990
37. Hendel RC, McSherry B, Karimeddini M, et al: Diagnostic value of a new myocardial perfusion agent, teboroxime (SQ30,217), utilizing a rapid planar imaging protocol: Preliminary results. *J Am Coll Cardiol* 16: 855–861, 1990
38. Stewart RE, Heyl B, O'Rourke RA, et al: Demonstration of differential post-teboroxime clearance kinetics after experimental ischemia and hyperemic stress. *J Nucl Med* 1991 (in press)
39. Strauss HW, Pitt B: Thallium-201 as a myocardial imaging agent. *Semin Nucl Med* 7: 49–58, 1977
40. Brunken R, Schwaiger M, Grover-McKay M, et al: Positron emission tomography detects tissue metabolic activity in myocardial segments with persistent thallium perfusion defects. *J Am Coll Cardiol* 10: 557–567, 1987
41. Cloninger KG, DePuey EG, Garcia EV, et al: Incomplete redistribution in delayed thallium-201 SPECT images: An overestimation of myocardial scarring. *J Am Coll Cardiol* 12: 955–963, 1987
42. Jones AG, Davison A, Abrams MJ, et al: Biological studies of a new class of technetium complexes: The hexakis (alkyl/isonitrile) technetium (I) cations. *Int J Nucl Biol* 11: 225–234, 1984
43. Treher EN, Gougoutas J, Malley M, et al: New technetium radiopharmaceuticals: boronic acid ad-

ducts of vicinal dioxime complexes. *J Label Comp Radiopharm* 23: 118–120, 1986
44. Palabrica TM, Furie BC, Konstam MA, et al: Thrombus imaging in a primate model with antibodies specific for an external membrane protein of activated platelets. *Proc Natl Acad Sci USA* 86: 1036–1040, 1989
45. Miller DD, Boulet AJ, Tio FO, et al: *In vivo* technetium-99m S12 antibody imaging of platelets ??-granules in rabbit endothelial neointimal proliferation after angioplasty. *Circ* 83: 224–236, 1991
46. Miller DD, Palmaz JC, Garcia OJ, et al: Platelet activation at human angioplasty sites: Noninvasive detection by specific S12 monoclonal antibody imaging. *Circ* 82 (Suppl III): III-650, 1990
47. Lees AM, Lees RS, Schoen FJ, et al: Imaging human atherosclerosis with Tc-99m labelled low-density lipoproteins. *Arteriosclerosis* 8: 461–470, 1988
48. Rosebrough SF, McAfee JG, Grossman ZD, et al: Thrombus imaging: a comparison of radiolabeled GC4 and T2G1s fibrin-specific monoclonal antibodies. *J Nucl Med* 31: 1048–1054, 1990
49. Ord JM, Daugherty A, Thorpe SR, et al: Detection of thrombi with modified t-PA coupled to a residualizing radiolabeled. *Cir* 82 (Suppl III): III-320, 1990
50. Cergueira MD, Edwards M, Bishop P, et al: *In vivo* arterial thrombus labeling with recombinant factor-XIII. *Circ* 82 (Suppl III): III-650, 1990
51. Goldstein DS, Chang PC, Eisenhofer G, et al: Positron emission tomographic imaging of cardiac sympathetic innervation and function. *Circ* 81: 1606–1621, 1990
52. Shelton ME, Dence CS, Hwang DR, et al: *In vivo* delineation of myocardial hypoxia during coronary occlusion using F-18 misonidazole and positron emission tomography: a potential approach for identification of jeopardized myocardium. *J Am Coll Cardiol* 16: 477–485, 1990
53. Orlandi C, Crane PD, Edwards S, et al: Early scintigraphic detection of experimental myocardial infarction in dogs with technetium-99m-glucaric acid. *J Nucl Med* 32: 263–268, 1991