TECHNOLOGISTS' SECTION

An overview of radiotracers in nuclear cardiology

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Coronary blood flow is regulated by anatomical, hydraulic, mechanical, and metabolic factors.[1] Myocardial perfusion depends on both the driving pressure gradient and the resistance of the vascular bed. Through autoregulation, the coronary bed maintains myocardial perfusion within a narrow range, despite wide fluctuations in coronary perfusion pressure.[2] Autoregulation of coronary blood flow is driven by changes in regional myocardial metabolism and oxygen consumption. Coronary artery stenosis may induce different alterations of the autoregulation of coronary blood flow, resulting in impairment in myocardial function such as myocardial ischemia, myocardial stunning, myocardial hibernation, and myocardial infarction.

Different radiotracers may be used as means of assessing the impairment of myocardial function; the choice of which tracer must be used as a means of identifying this dysfunction should depend primarily on the clinical questions to be answered. Myocardial perfusion single-photon emission computed tomography (SPECT) with thallium-201– and technetium-99m–labeled agents is a well-established modality for the evaluation of patients with suspected or known coronary artery disease (CAD).[3-7] Furthermore, different positron emission tomography (PET) perfusion tracers may be used for the quantitative measurement of absolute or relative myocardial blood flow, such as nitrogen-13 ammonia, rubidium-82 chloride, and oxygen-15 water. Moreover, considering that myocardial ischemia is associated with alterations in myocardial metabolism, the use of metabolic tracers has emerged as a useful approach in investigating the effects of CAD on myocardial metabolism. The tracers used as a means of assessing cardiac metabolism in patients with heart diseases are labeled fatty acids and fluorine-18 fluorodeoxyglucose (FDG).

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PERFUSION IMAGING AGENTS WITH SPECT

Thallium-201

For the last 2 decades, Tl-201 has been a clinically important tracer in assessing both regional blood flow and myocardial viability. Although thallium myocardial perfusion imaging has been one of the most used procedures in nuclear cardiology, the physical characteristics of this isotope are suboptimal. Thallium emits predominantly mercury x-rays at 69 to 83 KeV, an energy level that is marginally suitable for imaging with conventional gamma cameras. This relatively low energy causes some problems because of attenuation within the body. Additionally, because of the relatively long physical half-life (73 hours) and biological half-life (10 days) that lead to a radiation dose to the kidneys of 1 rad/mCi, only a small amount (74 to 111 MBq) of thallium can be administered. The initial myocardial accumulation of thallium is proportional to regional myocardial blood flow with a high first-pass extraction in the range of 85%. The relationship between regional blood flow and myocardial uptake is almost linear at low and moderate flow levels, to at least 3 mL/min/g. Beyond this level, there appears to be a decrease in the uptake of thallium in relation to blood flow. However, at approximately 3 mL/min/g, there is a plateau effect such that, despite increases in blood flow, thallium activity does not change.[8] Thallium presents biological similarities to potassium, the principal cation in human myocardial cells. Potassium is concentrated in the myocardium by the adenosine triphosphate (ATP)-dependent sodium-potassium pump. The ATP-dependent sodium-potassium pump does not differentiate between potassium and thallium, providing a determining role in the myocardial handling of thallium. The accumulation and retention of thallium within the myocardium depend on both coronary blood flow and cellular viability. Intracellular uptake of thallium across the sarcolemmal membrane is maintained as long as sufficient blood flow is present to deliver thallium to the myocardial cell. Once thallium has entered myocardial cells, a continuous exchange (washing in and washing out) takes place across the cell membrane. After the initial extraction of thallium by the myocardium, an equilibrium process between the myocardium and the blood pool determines the subsequent myocardial concentra-

tion of thallium. The washout of thallium from the myocardium and the new myocardial uptake of thallium from the blood pool characterize this equilibrium process. Thus, thallium in myocardial tissue is in equilibrium with the tracer amount that remains in the blood, which is in equilibrium with the pool of activity that is sequestered in other tissues, such as the liver and the skeletal muscle. In conditions of myocardial ischemia resulting from reduced myocardial blood flow, the intrinsic myocardial washout rate for thallium is reduced. This contributes to the equalization of late tracer activity between initially ischemic and initially normally perfused myocardial regions and is referred to as tracer redistribution. Therefore, decreased myocardial uptake early after thallium injection could be caused either by reduced regional blood flow or by myocardial infarction. After thallium injection, the early images obtained reflect the regional distribution of myocardial blood flow, whereas the delayed images (redistribution), acquired 2 to 4 hours after injection or 24 hours later, indicate myocardial viability. Furthermore, approximately one-third of the defects containing viable myocardium appears to be unchanged after 3 to 4 hours, but shows uptake after tracer reinjection at rest. In a limited number of studies, defects that fill in with reinjection have shown good concordance with segments that accumulate FDG, suggesting that such segments remain viable. Thus, many thallium protocols are currently used as means of evaluating patients with CAD. The advantages and disadvantages of these different protocols reflect the complex kinetic characteristics of thallium, and their use is related to clinical indications in such patients.

Sestamibi

Hexakis-2-methoxy-2-isobutil isonitrile (sestamibi) has the most favorable myocardial-to-background ratios for myocardial images of any of the isonitriles. It is a lipophilic cation labeled with Tc-99m, which emits gamma rays at 140 KeV, an energy level ideal for imaging with conventional gamma cameras. The emission of higher energy photons than Tl-201 decreases the problems of soft tissue attenuation. In contrast with the kinetics of thallium, Tc-99m sestamibi has a shorter half-life (6 hours). Therefore, larger doses of sestamibi can be administered. The initial myocardial accumulation of sestamibi, like thallium, is proportional to regional myocardial blood flow, with a first-pass extraction fraction lower than that of thallium.[9] However, the much higher dose of sestamibi used more than compensates for lower extraction, as compared with thallium. The linear relationship between regional blood flow and myocardial uptake is maintained to approximately 2 mL/min/g. Above this level, sestamibi myocardial uptake is not linear with increasing flow.[10] The myocardial handling of sestamibi is related to its lipophilicity, which makes it able to partition across biological membranes. In contrast with thallium, once sestamibi accumulates within the myocardial cell, it is bound in a relatively stable fashion. Earlier studies examined the myocardial transmicrovascular transport of sestamibi in a perfused isolated rabbit heart model.[11] The parenchimal cell permeability and volume of distribution of sestamibi are much greater than those of thallium, resulting in a longer residence time within myocardium cells. Therefore, at the time of clinical imaging after tracer injection, net myocardial tracer content is similar for thallium and sestamibi, although there is higher and more rapid tracer extraction for thallium. The distribution of sestamibi in myocytes has been demonstrated to be strongly dependent on plasma membrane and mitochondrial membrane potentials.[12] Moreover, approximately 90% of intracellular sestamibi is associated with mitochondria as a free cationic complex. Sestamibi has no definite evidence of differential washout from ischemic and normal tissue. Therefore, images obtained at 1 hour reflect perfusion at the time of injection. Unlike thallium, sestamibi demonstrated a nonrelevant degree of redistribution.[13] Thus, to be a means of evaluating the presence of myocardial ischemia, sestamibi imaging requires 2 separate injections: after stress and under resting condition. Considering that the entry of sestamibi into the myocardial cells cannot be explained by means of passive diffusion across the myocyte, but requires cellular integrity to create membrane potentials, sestamibi cannot be considered a pure flow tracer. It is not retained in necrotic areas. Thus, sestamibi uptake, like thallium, is considered to be a marker of myocardial viability. Because activity in the hepatobiliary system is initially high and redistribution is negligible, imaging after exercise is performed 30 minutes after injection. After the injection of sestamibi with the patient at rest, clearance from the liver is considerably slower. Thus, optimal images cannot be obtained before a period of 1 hour has passed.

Tetrofosmin

Tetrofosmin is a lipophilic diphosphine labeled with Tc-99m. Thus, compared with thallium, it presents the same advantages as sestamibi for energy level, half-life, and the larger doses that can be administered. The initial myocardial accumulation of tetrofosmin, like thallium, is proportional to regional myocardial blood flow, with a first-pass extraction fraction lower than that of thallium. Myocardial uptake is proportional to blood flow over the physiological range of flow in an experimental model.

Blood flow and tetrofosmin myocardial activity show a linear relationship to approximately 2 mL/min/g. Above this level, like sestamibi, tetrofosmin uptake is not linear with increasing blood flow. Furthermore, tetrofosmin demonstrates a plateau during stress at a blood flow level lower than that of sestamibi.[14] After intravenous injection, tetrofosmin clears rapidly from the blood. Myocardial extraction from blood into myocardium is less efficient than for thallium. Although thallium is more avidly extracted into myocardium than tetrofosmin initially, tetrofosmin myocardial content approaches that of thallium because of the progressive loss of thallium through washout. Myocardial uptake of tetrofosmin is similar to that of sestamibi. Uptake of the tracer in vivo is related to the metabolic status of the myocytes, in particular plasma membrane and mitochondrial membrane potentials. Tetrofosmin, like sestamibi, is characterized by rapid heart uptake and stable retention, without evidence of redistribution for as long as 3 hours after injection, even in reversible ischemic segments.[6,7] Therefore, to be a means of evaluating the presence of myocardial ischemia, tetrofosmin imaging also requires 2 separate injections of the tracer: at peak exercise and at rest. Clearance of tetrofosmin from the lungs and the liver is faster than that of sestamibi, improving the resolution of early cardiac images. Early imaging can be performed within 15 to 30 minutes, reducing the waiting time for patients and the total study time. Moreover, tetrofosmin, like sestamibi, is reconstituted with Tc-99m; however, it is allowed to stand at room temperature, unlike sestamibi, which requires boiling. Although these methodological observations are less important than biological characteristics, they may be important in clinical practice, especially in patients with acute ischemic syndromes.

PERFUSION IMAGING AGENTS WITH POSITRON EMISSION TOMOGRAPHY

Rubidium-82

Rubidium-82 is a cation, the uptake of which depends on myocardial perfusion. Rubidium has a short half-life (75 seconds), which makes it possible to carry out multiple examinations of the same patient within an acceptable period. Experimental studies suggest that myocardial uptake of rubidium is proportional to blood flow as high as 2 to 3 mL/g/min.[15] The single-pass extraction of rubidium by the heart is inversely and nonlinearly related to myocardial blood flow. Although the extraction fraction of rubidium may decrease during periods of myocardial ischemia, the qualitative assessment of relative rubidium perfusion defects has correlated well with those obtained from microspheres. Like potassium and thallium, rubidium is concentrated in the myocardium by the Na/K ATPase pump. Furthermore, because of the short half-life of rubidium-82 (75 seconds), imaging protocols and pharmacokinetics are dominated by the physical characteristics of the nuclide. Myocardial imaging with this generator-produced isotope requires rapid acquisition of data, because of its short physical half-life, which might make it very attractive for use in rapid repeat studies, such as stress/rest protocols and preintervention/postintervention studies. The quality of myocardial images obtained after intravenous administration of rubidium depends on the tracer infusion duration and imaging protocol. Although the disappearance of tracer from arterial blood is rapid, an infusion system with prolonged administration times results in high cardiac blood-pool activity.

Nitrogen-13 Ammonia

Nitrogen-13 (N-13) ammonia is the most commonly used extractable perfusion tracer with PET.[16] When injected, ammonia is extracted by myocardial tissue with a very high extraction fraction, at which point it is converted to N-13 glutamine. The clearance half time of ammonia activity from the myocardium is slow enough that one can wait until blood-pool activity is significantly lower than myocardial activity. Like that of rubidium, myocardial extraction of ammonia is nonlinear and inversely related to blood flow. The myocardial uptake of ammonia reflects absolute blood flows as high as 2 to 2.5 mL/g/min, and it plateaus in the hyperemic range.[17] With increasing flow rates, the metabolic trapping involving a carrier-mediated transport becomes rate limiting, reducing the net tissue retention fraction. Like rubidium, the Na/K ATPase pump takes up ammonia, because it exists in solution as cationic NH_4. Ammonia provides excellent quality images of the myocardium, because of the high single-pass extraction (approximately 70% to 80% at physiologic flow rates), the relatively prolonged retention of tracer by the heart (biological half-life of 80 to 400 minutes) after intravenous administration, and the rapid blood-pool clearance.

Oxygen-15 Water

Oxygen-15 (O-15) water is a freely diffusible tracer with a short physical half-life (2.1 minutes). To be an effective means of obtaining myocardial images, O-15 (because of its short half-life) requires administration of 80 to 100 mCi/injection, with rapid data acquisition. Quantitative assessment of regional O-15 water perfusion correlates closely with perfusion assessed by means of microspheres in a wide range of flow.[18] Because water is

distributed in both the vascular space and myocardium, visualization of myocardial activity with this tracer requires correction for activity in the vascular compartments, which makes the images difficult to interpret visually. This is accomplished by acquiring a separate scan that identifies either the intravascular or myocardial compartments.

CARDIAC METABOLISM IMAGING AGENTS

Fatty Acid Metabolism

Radioiodinated fatty acids were initially used as a means of determining regional myocardial perfusion. The terminally iodinated compounds had excellent myocardial extraction, comparable with that of potassium, but their residence time in the myocardium was extremely short because of rapid metabolism and the subsequent release of free iodine.[19] The shorter retention time was prohibitive, and the advent of thallium imaging reduced the value of these perfusion agents. It was recognized that methods for preventing deiodination and/or slowing down β-oxidation were needed to maintain the radioactivity in the myocardium and that, with these improvements, it might be possible to assess myocardial metabolism rather than myocardial flow. Fatty acids are the principal source of energy for the heart under resting conditions, and their metabolism is greatly influenced by ischemia and other pathological states. The problem of deiodination of fatty acids was solved with the modification of paraisomer to the orthoisomer. The orthoisomer bounding to coenzyme A is retained in the cytosolic pool, whereas the paraisomer progresses further to be metabolized by mitochondrial β-oxidation and release the myocardium. Despite orthoisomer containing the attributes necessary for metabolic imaging of the myocardium, it has not been widely investigated. The prevention of β-oxidation has been addressed by placement of stearic blocks in the fatty acid chain, in particular the methyl groups. Any branching of the fatty acid chain should lead to a reduction in metabolism (the position and the degree of substitution in the fatty acid chain produce different effects) to produce higher quality images. Because of the high cost of iodine-123 and the lack of a Tc-99m based fatty acid, the clinical use of these tracers is still limited.

BMIPP

The 3-methyl derivative 15-(p-I-123 iodophenyl-)-3-R,S-methylpentadecanoic acid (BMIPP), obtained with the placement of methyl group in the fatty acid chain, was approved for clinical use and has been tested as a means of evaluating cardiac metabolic activity and assessing myocardial viability by using SPECT. Its normal injected dose is about 3 mCi (111 MBq), which contains about 0.5 mg of stable fatty acid. There is rapid uptake of radioactivity by the myocardium, which contains about 5% of the injected dose within 1.5 hours. Imaging of the myocardium can commence immediately after tracer injection. The liver takes up radioactivity, but there is little hepatobiliary excretion. There is little washout of radioactivity from the myocardium, so after 24 hours, the myocardium still contains about 4% of the injected dose.

Carbon-11 Palmitate

Palmitate comprises approximately 25% to 30% of circulating fatty acid in blood. After administration, single-pass extraction averages 30% to 60%. The myocardial time-activity curve of the PET tracer carbon-11 (C-11) palmitate exhibits several components. The initial uptake of this tracer by the myocardium reflects blood flow, because of its high extraction fraction. The clearance of activity from the myocardium reflects the metabolic fate of this tracer. Clearance from the heart occurs in 3 identifiable phases. The first reflects vascular washout of nonextracted or back-diffused tracer. The second (biological half-life, 20 minutes) reflects primarily β-oxidation. The third phase (with biological half-life of hours) reflects predominately the incorporation of tracer into triglyceride and phospholipid pools and subsequent turnovers of these pools. The palmitate extracted by the myocardium is metabolized to C-11-labeled CO_2 that then egresses from the myocardium. The rate of clearance of the second phase has been demonstrated by experimental studies to directly couple to β-oxidation in aerobic condition.[20]

GLUCOSE METABOLISM

Fluorine-18 FDG

Fluorine-18 2-fluoro-2-deoxyglucose is transported across the sarcolemma and can either back diffuse or be phosphorylated. F-18 FDG-6-phosphate is not available for further metabolism to either glycogen or to pyruvate. The phosphorylated compound is thought to remain trapped intracellularly because of the relative impermeability of the sarcolemma to this intermediate phase, and because dephosphorylation is thought to be modest in the heart and cannot be metabolized further. After intravenous administration, F-18 FDG accumulates only slowly in the myocardium, but remains trapped for several hours. Myocardial accumulation of the tracer is markedly dependent on the nutritional status of the

patient. In fasting conditions, arterial fatty-acid content is high, and uptake of F-18 FDG is markedly suppressed. After a patient consumes a carbohydrate meal or glucose load, however, myocardial F-18 FDG accumulation is augmented. Early after ischemia, when aerobic metabolism becomes limited, energy supplies from glucose increase. F-18 FDG is administered intravenously, and myocardium is scanned 45 to 60 minutes after tracer administration, a time sufficient for accumulation of tracer in the heart and clearance of tracer from blood.[21]

CLINICAL APPLICATIONS OF IMAGING AGENTS IN NUCLEAR CARDIOLOGY

All tracers available for myocardial perfusion imaging have different kinetic characteristics that must be considered to maximize their clinical applications in nuclear cardiology. Currently, thallium and Tc-99m–labeled agents represent the most-used imaging agents in nuclear cardiology. Despite the differences in tracer kinetics, comparative studies involving thallium and Tc-99m labeled agents have failed to show significant differences in some of their clinical applications.

Coronary Artery Disease

The clinical impact of thallium imaging in the detection of CAD has been documented by means of several studies.[22,23] In particular, the sensitivity rate of SPECT thallium imaging has been reported to be approximately 90%, with a relatively low specificity rate (range, 60% to 70%).[24] In different trials since their introduction, sestamibi and tetrofosmin have been compared with thallium as the gold standard in the identification of patients with CAD.[25,26] The reported average sensitivity and specificity rates of sestamibi and tetrofosmin in the identification of CAD were very similar to those obtained with thallium imaging. Furthermore, some data revealed that sestamibi and tetrofosmin might underestimate the total extent of myocardial ischemia, as compared with thallium imaging, in patients with CAD.[27] However, significant differences in the image quality has been reported in all comparative studies performed. In particular, images obtained by using sestamibi or tetrofosmin were of superior quality than those obtained with thallium, and they tended to show fewer artifactual defects caused by soft tissue attenuation. Better definition of the myocardium, endocardial and epicardial borders, and perfusion defects has been observed. In general, there was much less statistical noise with these Tc-99m–labeled tracers, and the myocardial-to-background ratios were similar to those obtained with thallium imaging. Moreover, the permissible administered dose is much larger than that of thallium. It resulted in an increase in pixel count densities for Tc-99m–labeled tomographic projection images, and it permits the use of higher resolution filters during study reconstruction. In the detection of CAD, there are only few studies comparing the diagnostic accuracy of rubidium-82 or N-13 ammonia with that of thallium SPECT imaging in the same patient population. It is suggested by means of clinical data, combining the results of different studies in approximately 300 patients, that PET imaging improves the diagnostic accuracy of SPECT by approximately 10%.

Myocardial Viability

It has been demonstrated that one third of patients with chronic CAD and left ventricular (LV) dysfunction have the potential for significant improvement in ventricular function after myocardial revascularization procedures. These findings have several implications. First, there is an important relationship between LV function and patient survival. Numerous studies have demonstrated that nuclear cardiology techniques involving SPECT and PET are a means of providing important viability information in patients with CAD and impaired ventricular function.[28,29] Although PET remains the most accurate technique for the detection of viable myocardium, by demonstrating a mismatch between reduced myocardial blood flow and preserved glucose use, its availability remains limited. Different thallium protocols have been used in earlier studies as a means of assessing myocardial viability in patients with an earlier myocardial infarction and chronic LV dysfunction. In particular, if the clinical issue to be addressed is the viability of one or more ventricular regions with systolic dysfunction and not whether there is also inducible ischemia, rest-redistribution thallium imaging can be a means of yielding useful viability data. In particular, quantitative analysis of rest-redistribution images has been demonstrated to be a means of predicting recovery of regional LV function and to compare favorably to the results of both thallium reinjection imaging and metabolic PET imaging.[29]

Optimal interpretation of thallium imaging for the detection of myocardial viability can be accomplished by measuring regional tracer uptake and by selecting the most appropriate cutoff to differentiate reversible from irreversible LV dysfunction.[30-32] Furthermore, sestamibi and tetrofosmin show similar results to those of thallium scintigraphy in the identification of viable myocardium.[30] Quantitative analysis of tracer content and the administration of nitroglycerin before tracer injection increase the overall accuracy of Tc-99m–labeled agents for identifying viable myocardium. Recent data indicate that in patients with chronic myocardial infarction and impaired

LV function who are receiving nitrate treatment, quantitative analysis of resting thallium and sestamibi regional activities is a means of comparably predicting recovery of regional and global ventricular function after revascularization procedures.[33]

Acute Ischemic Syndromes

The detection of CAD is only one aspect of the clinical usefulness of myocardial perfusion imaging. In patients with acute chest pain that is suspected to be myocardial ischemia, it may be helpful to image objectively the presence of regional myocardial hypoperfusion. Rest/delayed thallium imaging may be useful in such patients for assessing myocardial hypoperfusion and redistribution in viable tissue. In acute ischemic syndromes, both sestamibi and tetrofosmin have been demonstrated to be particularly convenient agents, as compared with thallium. In particular, these Tc-99m–labeled tracers have characteristics that are well-suited for application in patients undergoing thrombolytic therapy for acute myocardial infarction.[34] Because of slow myocardial clearance, it is feasible to administer either agent immediately before the thrombolytic therapy in the emergency department. Imaging can be performed later, at a convenient time. By using thallium as a radiotracer in this condition, we must consider the interplay between initial myocardium uptake and redistribution. Moreover, the changes in the territory of the infarction-related artery are complex and variable in individual patients, and the interpretation of serial thallium images after a single intravenous injection may be uncertain.

Prognosis and Risk-stratification

Another key role of myocardial perfusion imaging has been its ability as a means of providing prognostic information in patients after acute myocardial infarction, in patients with chronic CAD, and in patients scheduled for major surgery. The usefulness of thallium scintigraphy associated with exercise or pharmacological stress testing for this purpose has been widely documented. In particular, in patients without an earlier myocardial infarction, the number of reversible thallium defects was demonstrated to be the most important statistically significant predictor of future cardiac events.[35] Moreover, the extent and severity of thallium defects correlated with the occurrence of cardiac event.[36] Several studies have reported similar results on the prognostic value of thallium stress imaging after myocardial infarction and in patients with suspected or known CAD. The extent of perfusion abnormality on SPECT imaging has also been demonstrated to be the single most important prognostic predictor.[37-39] More recently, the prognostic value of Tc-99m–labeled myocardial perfusion agents has been demonstrated with concordant data, as compared with thallium imaging.[40]

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