Recent advances in nuclear cardiology in the study of coronary artery disease

Nagara Tamaki,* Eiji Tadamura,** Takashi Kudoh,** Naoya Hattori,** Masayuki Inubushi** and Junji Konishi**

*Department of Nuclear Medicine, Hokkaido University School of Medicine
**Department of Nuclear Medicine, Kyoto University Faculty of Medicine

A variety of new radiopharmaceutical agents have been introduced to probe myocardial function in vivo. This review will introduce these new techniques which have recently been available in Japan. Tc-99m perfusion imaging agents provide excellent myocardial perfusion images which may enhance diagnostic accuracy in the study of coronary artery disease. In addition, greater photon flux from the tracer permits simultaneous assessment of regional perfusion and function with use of first-pass angiography or ECG-gated acquisition. Positron emission tomography enables metabolic assessment in vivo. Preserved FDG uptake indicates ischemic but viable myocardium which is likely to improve regional dysfunction after revascularization. In addition, FDG-PET seems to be valuable for selecting a high risk subgroup. Recently I-123 BMIPP, a branched fatty acid analog, has been clinically available in Japan. Less uptake of BMIPP than thallium is often observed in the ischemic myocardium. Such perfusion metabolic mismatch which seems to be similarly observed in FDG-PET is identified in the stunned or hibernating myocardium with regional dysfunction. Both of them are likely to recover afterwards. Severe ischemia is identified as reduced BMIPP uptake at rest, suggesting its role as an ischemic memory imaging. I-123 MIBG uptake in the myocardium reflects adrenergic neuronal function in vivo. In the study of coronary artery disease, neuronal denervation is often observed around the infarcted myocardium and post ischemic region as well. More importantly, reduced MIBG uptake in these patients can identify high risk for ventricular arrhythmias and assess severity of congestive heart failure. These new techniques will provide insights into new pathological states in the ischemic heart disease and enable to select optimal treatment in these patients.

Key words: emission computed tomography, ischemic heart disease, myocardial perfusion, BMIPP, MIBG

INTRODUCTION

Ischemic heart disease is quite common caused by reduced coronary artery blood flow to the myocardium and is the most frequent cause of death in the USA and second cause of death in Japan as well. Coronary angiography has been widely used for final diagnosis and management of patients with coronary artery disease. However, radionuclide studies can noninvasively demonstrate regional myocardial perfusion at rest and during stress and this may provide important information for the accurate diagnosis and management of patients with coronary artery disease.

Recently, a variety of radiopharmaceutical agents have been introduced to probe myocardial function in vivo. These new techniques will provide new insights into myocardial pathophysiology in ischemic heart disease. This review will introduce the new techniques which have recently become available in Japan.
I. Evaluation of myocardial perfusion

Evaluation of myocardial perfusion during exercise is of clinical importance for the diagnosis of ischemic heart disease. Thallium-201 chloride has been widely used for the detection and viability assessment of coronary artery disease. However, the long physical half life of the tracer and the low-energy photons emitted from thallium-201 may limit its value as a tracer for myocardial perfusion analysis.

To minimize these physical limitations of thallium-201, a group of technetium-99m labeled compounds have been developed. Among them, Tc-99m methoxy isobutyl isonitrile (sestamibi) provided the best biologic properties for clinical applications. However, it requires heating for the preparation of the tracer and it is necessary to wait for 40–60 minutes before imaging after injection due to the clearance of liver activity.

Recently, Tc-99m-1,2-[bis(2-ethoxyethyl)phosphino] ethane (tetrofosmin) has been introduced. This compound showed favorable characteristics, including high myocardial uptake and retention, and more rapid clearance from the liver. In addition, this agent can be labeled with Tc-99m at room temperature and without heating. The phase I clinical study confirmed the safety of this radiopharmaceutical and provided excellent myocardial images with rapid clearance from the blood.

These Tc-99m labeled perfusion agents have provided excellent myocardial images which provided better diagnostic accuracy for the detection of coronary artery disease with lower false positive rate than thallium-201. In addition, greater photon flux obtained with these agents permits first-pass study at the time of administration or ECG-gated acquisition for the imaging. These techniques permit simultaneous analysis of regional myocardial perfusion and function, which is of clinical importance for the evaluation of coronary artery disease.

Figure 1 shows a series of short-axis slices of myocardial perfusion images at stress and rest obtained with Tc-99m tetrofosmin and radionuclide ventriculograms both at rest and during stress in a patient with severe coronary artery disease. A medium-sized perfusion defect is seen in the inferior region at rest with stress-induced ischemia is noted in anterior and septal region on these perfusion images. The regional wall motion is normal with LVEF of 51% at rest. However, severe regional asynergy is seen with reduction in LVEF to 38% during stress, indicating poor ventricular function during stress despite normal function at rest. Such combined assessment of perfusion and function at the time of tracer administration can be obtained. This technique provides clinically important indices for the assessment of severity of myocardial ischemia.
ischemia and prognosis in these patients.

Figure 2 shows a series of short-axis slices in end-diastolic and end-systolic phases in a patient with inferior wall myocardial infarction which was obtained by ECG-gated SPECT images 60 minutes after Tc-99m sestamibi administration at rest. A large perfusion defect is observed in the inferoposterior region in the end-diastolic and end-systolic phases. However, regional wall thickening is well demonstrated in the remaining myocardium despite no regional wall thickening in the inferior region, indicating normal ventricular function at rest. This type of analysis permits assessment of regional function such as wall thickening and global function as well such as volume and ejection fraction calculation. Recently, change in wall thickening caused by low-dose dobutamine is also quantitatively measured by gated myocardial perfusion SPECT in order to assess inotropic functional reserve, and thus, tissue viability.36

The prognosis for patients with coronary artery disease is related to the degree of impairment of resting and exercise ventricular function30,37 and the severity of reversible perfusion abnormality.28,29 The combined assessment of regional perfusion and function should therefore, have a prognostic value as well as a diagnostic value in the evaluation of these patients.30,31

Our preliminary comparative study of regional perfusion and wall motion at stress in the segments showed concordant score in 42–50% of them.30 On the other hand, the remaining 50% of segments showed discordant findings for stress perfusion and wall motion. Interestingly, many segments showed greater severity in wall motion abnormality than in regional perfusion at rest, but a smaller number of segments showed similar findings at stress. This may be partly due to stunned myocardium where perfusion recovered but ventricular dysfunction persisted.31 These data indicate that regional wall motion and perfusion may provide rather independent parameters of regional function. Thus, the first-pass radionuclide ventriculography may provide important and valuable information in the regional myocardial condition, which seems to be rather independent of regional perfusion.

Another important aspect of Tc-99m perfusion agent is to freeze myocardial perfusion at the time of tracer administration. This advantage permits evaluation of the area at risk in patients with acute myocardial infarction on admission. When the tracer is administered on admission, the perfusion images obtained after emergency revascularization therapy may reflect myocardial perfusion on admission. When another perfusion study is done several days after revascularization therapy, the location and amount of salvaged myocardium can be accurately analyzed.31–35

Some reported that the residual uptake of Tc-99m perfusion tracer may reflect tissue viability.36–39 Udelson et al.39 reported that the Tc-99m sestamibi uptake correlated well with redistribution thallium activity and can differentiate reversible ischemia from irreversible myocardial scar. It is, however, controversial whether the residual uptake of Tc-99m perfusion tracer may accurately reflect tissue viability, compared to thallium redistribution or positron emission tomography.40–42

Because of superior physical characteristics, myocardial perfusion studies with Tc-99m perfusion agents have become more popular recently all over the world. Similarly, these new agents are expected to be more widely used in Japan. However, since the chemical characters of these agents are slightly different from those of thallium, a more careful comparisons may be warranted for deciding the optimum perfusion tracer for a variety of conditions in the assessment of coronary artery disease.

II. Evaluation of myocardial metabolism

The advantage of tracer techniques is to use a radiolabeled compound for in vivo quantification of specific biological processes. With introduction of positron emission tomography (PET), the spectrum of in vivo tissue characterization has been widened with use of physiological tracers labeled with C-11, N-13, O-15 and F-18 which allow the synthesis of naturally occurring and biologically active compounds. In parallel with advances in imaging technologies, cardiovascular research has extended beyond the evaluation of myocardial perfusion and function in various cardiac diseases. For example, the importance of energy metabolism in maintaining the integrity of cardiac performance has been increasingly recognized with PET.

Table 1 summarizes positron labeled compounds which
Table 1  Positron emitting tracers commonly used in the study of cardiac PET

<table>
<thead>
<tr>
<th>Category / Compounds</th>
<th>Function (Mechanism)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tracers of blood flow</strong></td>
<td></td>
</tr>
<tr>
<td>N-13 ammonia</td>
<td>(Metabolic trapping)</td>
</tr>
<tr>
<td>Rb-82</td>
<td>(Sodium-potassium pump)</td>
</tr>
<tr>
<td>O-15 water</td>
<td>(Diffusion)</td>
</tr>
<tr>
<td>Cu-62 PTSN</td>
<td>(Lipophilicity)</td>
</tr>
<tr>
<td>C-11 (Ga-68) albumin microspheres</td>
<td>(Capillary blockage)</td>
</tr>
<tr>
<td><strong>Tracers of metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>C-11 palmitate</td>
<td>Fatty acid metabolism</td>
</tr>
<tr>
<td>F-18 2-fluoro 2-deoxyglucose (FDG)</td>
<td>Exogenous glucose utilization</td>
</tr>
<tr>
<td>C-11 acetate</td>
<td>Oxidative metabolism</td>
</tr>
<tr>
<td>O-15 oxygen</td>
<td>Oxygen consumption</td>
</tr>
<tr>
<td>C-11 (N-13) amino acids</td>
<td>Amino acid metabolism &amp; protein synthesis</td>
</tr>
<tr>
<td><strong>Tracers of innervations</strong></td>
<td></td>
</tr>
<tr>
<td>F-18 metaraminol</td>
<td>Adrenergic neuron density</td>
</tr>
<tr>
<td>C-11 hydroxyephedrine</td>
<td>Adrenergic neuron density</td>
</tr>
<tr>
<td><strong>Tracers of receptors</strong></td>
<td></td>
</tr>
<tr>
<td>C-11 methyl QNB</td>
<td>Muscarinic receptor function</td>
</tr>
<tr>
<td>C-11 CGP-12177</td>
<td>Beta-adrenergic receptor function</td>
</tr>
<tr>
<td>C-11 practorol</td>
<td>Beta-adrenergic receptor function</td>
</tr>
<tr>
<td>C-11 PK-11195</td>
<td>Benzodiazepine receptor function</td>
</tr>
<tr>
<td><strong>Other tracers</strong></td>
<td></td>
</tr>
<tr>
<td>F-18 misonidazole</td>
<td>Hypoxic and ischemic tissue</td>
</tr>
<tr>
<td>O-15 (C-11) carbon monoxide</td>
<td>Blood pool</td>
</tr>
</tbody>
</table>

Fig. 3  Representative short-axis (left) and vertical long-axis slices of N-13 ammonia perfusion images (top) and F-18 FDG glucose metabolic images (bottom) of a patient with coronary artery disease. Preserved FDG uptake relative to perfusion (so-called perfusion-metabolism mismatch) is observed in inferolateral regions, indicating presence of myocardial ischemia.

are commonly employed in the study of cardiac PET. Among them, N-13 ammonia as a marker of myocardial perfusion and FDG as a marker of exogenous glucose utilization are commonly used in the clinical cardiac PET studies.

FDG, the most important radiopharmaceutical for the clinical application of cardiac PET, is transported across membranes and phosphorylated to FDG-6-phosphate in the myocyte. Because FDG-6-phosphate does not enter glycolysis or participate in glycogen synthesis, the radioactivity in the tissue may represent the integral of glucose phosphorylation. Thus, imaging of tissue FDG uptake permits the assessment of exogenous glucose utilization.43 The myocardium can use various substrates for its energy metabolism. The major energy source for high energy phosphate (ATP) production is oxidation of long-chain fatty acids. Carbohydrates play a rather minor role in the myocardial substrate metabolism in the fasting state. After carbohydrate exposure, on the other hand, glucose becomes an important source for oxidative metabolism, so that the relative contribution of each substrate to myocardial metabolism depends on the substrate availability in plasma, the hormonal milieu, and the cardiac workload.44–46

Early laboratory studies indicated that utilization of exogenous glucose is accelerated in acutely ischemic myocardium and fatty acid oxidation is rapidly reduced.44–46 These data imply that the use of FDG can be used for identifying ischemic myocardium. In the hypoperfused regions on the N-13 ammonia perfusion studies, accelerated glucose utilization was identified by the relative increase in FDG uptake in the ischemic areas. The areas with such perfusion-metabolism mismatch may represent ischemic myocardium (Fig. 3), and those with concordant decrease in perfusion and glucose metabolism may represent scar tissue.47
FDG-PET has been considered as a gold standard for tissue viability in noninvasive clinical studies to predict the recovery of cardiac function after revascularization. A number of reports showed that FDG uptake in the presence of reduced flow was highly predictive for recovery, while the absence of metabolic activity in the segments with perfusion defect was associated with lack of recovery in contractile function. 48-52

Redistribution thallium imaging has been widely used for identifying ischemic and viable myocardium. Preserved glucose metabolism was observed in the areas with redistribution on stress thallium scan.53 However, preserved glucose metabolism was also observed in the areas of persistent thallium defect, 54-56 supporting the underestimation of tissue viability on stress-redistribution thallium scan. On the other hand, when FDG findings were compared to the stress-reinjection thallium findings, a closer correlation was expected.57 However, FDG-PET seems to be slightly more sensitive for detecting ischemic myocardium.58 These data indicate that identification of residual metabolic activity has advantages over thallium perfusion imaging, since metabolic imaging provides a better quality positive signal in the viable myocardium, and perhaps more accurate information regarding reversibility than the residual perfusion or membrane potential on thallium imaging.

Another clinical importance of FDG-PET is that it may select a high risk subgroup in patients with coronary artery disease. Eitzman et al.,59 and our group60 both showed a high incidence of cardiac complications in patients with decreased perfusion and enhanced glucose utilization. Our preliminary results in the follow-up study of patients with myocardial infarction showed a slightly higher predictive value for future cardiac events obtained by FDG-PET than that by the routine stress thallium scan. More importantly, the incidence of cardiac events in patients with a perfusion-metabolism mismatch can be reduced by revascularization.61 These results also support that those with reduced perfusion and enhanced glucose metabolism are good candidate for revascularization predicted on the concept of improving regional cardiac function and reducing future cardiac events.

Based on the hypothesis that viable tissue requires oxygen to maintain cell survival, C-11 acetate has been proposed as a marker of tissue viability. Following administration of C-11 acetate, this is activated to acetyl CoA, oxidized in mitochondria by the TCA cycle, and washed out of the myocardium as C-11 CO₂ and H₂O. The early clearance rate in the myocardium measured by serial dynamic PET study corresponds closely to release of C-11 CO₂ from the myocardium, and it may therefore represent oxidative metabolism.62,63 The major advantage of this tracer is that, unlike glucose metabolism, the clearance rate constant was not influenced by plasma substrate levels.64

Gropler et al.65 showed the preliminary results indicating the areas with preserved oxidative metabolism as reversible ischemic tissue which is likely to improve regional asynery after revascularization. The predictive value of C-11 acetate PET was slightly better than that of FDG-PET. The experimental study also supports the idea that the functional recovery after reperfusion was associated with the recovery of oxidative metabolism.66 We have recently reported that oxidative metabolic reserve after low-dose dobutamine infusion was a better marker of the recovery of regional function than resting oxidative metabolism.67 Such an intervention study may play a more important role in assessing tissue viability.

Long chain fatty acids are the most important energy-yielding substrate for oxidative metabolism in the normal myocardium. Approximately 60-80% of ATP produced in aerobic myocardium derives from fatty acid oxidation. In ischemic myocardium, on the other hand, oxidation of free fatty acids is greatly suppressed and glucose metabolism plays a major role in residual oxidative metabolism.68,69 In myocardial necrosis, since there will be no further metabolism, preserved glucose metabolism is considered to be an important marker of ischemic but viable myocardium, while alteration of fatty acid oxidation is considered to be a sensitive marker of ischemia or myocardial damage.

In the study of fatty acid metabolism, a variety of radionuclide tracers have been focused on evaluating fatty acid metabolism in vivo by using positron tracers. Among them, C-11 palmitate has long been used to probe fatty acid metabolism by PET.68-73 However, there have been only a few reports with this technique partly due to the limited availability of PET and the complicated kinetic model. On the other hand, a variety of I-123 labeled fatty acid compounds have been introduced to probe myocardial energy metabolism in vivo in the routine clinical nuclear medicine facilities. Among them, I-123 labeled 15-(p-iodophenyl)-3R,S-methyl pentadecanoic acid (BMIPP) has been most extensively applied in clinical studies, particularly in Japan.

BMIPP is a branched fatty acids which goes into the myocardium and is long retained in the cells with metabolic trapping, since methyl branching of the fatty acid chain may protect against metabolism via beta-oxidation.74-77 Therefore, excellent myocardial image can be obtained with long residence time, which permits SPECT acquisition with the conventional rotatable camera.

Experimental studies show slow clearance of approximately 25% of BMIPP in 2 hours.78 The fractional distribution of these compounds at 30 minutes after tracer injection in rats indicated that 65 to 80% of the total activity resided in the triglyceride pool.79 Our experimental studies indicated that BMIPP uptake correlated with the ATP concentration in acutely damaged myocardium treated with occlusion-reperfusion model80 or dinitrophenol, an electron transport uncoupler.81 In addition, the occlusion-reperfusion canine models showed abnormal BMIPP
In the study of myocardial infarction, less BMIPP uptake than thallium perfusion in the areas of myocardial infarction was often observed. Such discordant BMIPP uptake was often seen in recent onset of infarction, the areas with recanalized arteries, and those with severe wall motion abnormalities in comparison with thallium perfusion abnormality, indicating mostly metabolically stunned myocardium. Recent preliminary results showed that such discordant BMIPP uptake was observed in the areas associated with redistribution on stress thallium scan, indicating that such discordant areas may represent ischemic but viable myocardium. The areas with discordant BMIPP uptake which is often observed in acute myocardial infarction may likely to improve perfusion and function in the subacute stage of infarction. Such improvement is also observed after PTCA. Most of them are associated with partial improvement in BMIPP uptake (Fig. 4). The difference between the defect scores for BMIPP and thallium correlates well with improvement in wall motion on the follow-up study. Similar findings have been reported by European groups using BMIPP and Te-99m sestamibi. These data indicate that the discordant BMIPP uptake in the acute stage of myocardial infarction may represent stunned myocardium where perfusion is almost normalized after reperfusion therapy on admission but regional wall motion abnormalities persist in association with sustained metabolic abnormalities.

This concept has been extended to the study of ischemic heart disease without prior myocardial infarction. Abnormal BMIPP uptake at rest is often observed in the ischemic regions (Fig. 4). Such BMIPP findings are seen in severe myocardial ischemia and associated with regional wall motion abnormalities. In addition, exercise BMIPP study has also been attempted to detect stress-induced metabolic abnormality. Resting perfusion is often reduced but some cases there is normal perfusion at rest. These data indicate that BMIPP can reflect repetitive and/or severe prior ischemia, and thus, this may represent “ischemic memory imaging.” It is quite controversial whether the areas with such discordant BMIPP uptake represent hibernating myocardium, and it may improve regional dysfunction after revascularization. However, since stunned myocardium is often mixed with myocardial hibernation in the clinical setting, areas of discordant BMIPP uptake may be likely to improve regional function after revascularization therapy.

On the basis of the concept that areas with discordant BMIPP uptake reflect severe ischemic myocardium associated with thallium redistribution and increase in FDG uptake, we hypothesized that this finding may have prognostic significance. In the follow-up of patients with prior myocardial infarction, those with discordant BMIPP uptake may be more likely to have future cardiac events than those without such findings. Although these data remain quite preliminary, perfusion-metabolism mismatch
identified with SPECT tracers may play an important role for assessing ischemic but viable myocardium and risk stratification with a similar concept to FDG-PET.

III. Evaluation of adrenergic neuron function

With advance in biochemical imaging in vivo by the radionuclide technique, the modulation of the functional and electrophysiological properties of the heart by the autonomic nervous system has become the focus of intense research. The pathophysiologic role of the autonomic nervous system in patients with congestive heart failure has recently been emphasized. For instance, the presence of heterogeneous sympathetic innervation is considered to be associated with fatal arrhythmias. Tracer approaches are considered uniquely suited for in vivo characterization of neuronal structures and function in the myocardium by radionuclide imaging.

The autonomic nervous system consists of two main parts: sympathetic and parasympathetic innervation. Their major transmitters are norepinephrine and acetylcholine, respectively, which define the stimulatory and inhibitory physiological effect of each system. Sympathetic nerve fibers are characterized by multiple nerve endings which are filled with vesicles containing norepinephrine. Sympathetic nerve fibers travel parallel to the vascular structures on the epicardial surface of the heart and penetrate in to underlying myocardium in a similar fashion to the coronary vessels. On the basis of the tissue norepinephrine concentration, mammalian heart is characterized by dense adrenergic innervation with a norepinephrine concentration gradient from the atria to the base of the heart and from the base to the apex of the left ventricle. These autonomic nervous systems involve the synthesis and storage of neurotransmitters, their release, reuptake, metabolism, and interaction with presynaptic and postsynaptic receptor sites. Such a complicated system cannot be characterized by a single radiopharmaceutical.

There are a number of radiotracers probing each step of autonomic neuronal functions. Of particular, norepinephrine analog has been widely used for experimental and clinical studies. In the early 1980s, I-131 labeled metadobenzylguanidine (MIBG), one of norepinephrine analogs was developed by a group in University of Michigan for selective mapping of sympathetic nerve ending in the heart. This compound is an analog of the antihypertensive drug guanethidine, which is taken up and stored by the neurons followed by release along with endogenous norepinephrine on nerve stimulation, but this has low affinity for postsynaptic adrenergic receptors. I-123 labeled MIBG has been used in many clinical studies instead of the I-131 labeled one and yielded high quality images of myocardial neuron function images. In recent experience in the human studies, the normal distribution of MIBG in the myocardium may not be quite homogeneous with a slight reduction in the inferior region. This heterogeneity seems to be more enhanced with age. The interpretation of the MIBG images should be cautious with this physiological heterogeneity of the tracer distribution in the myocardium.

Different patterns of abnormal MIBG distribution in the myocardium indicating abnormalities in the cardiac sympathetic activity have been demonstrated after myocardial infarction, dilated and hypertrophic cardiomyopathy, diabetic cardiomyopathy and patients with idiopathic long QT syndrome or arrhythmogenic right ventricular cardiomyopathy.

Following myocardial infarction, decreased MIBG relative to thallium perfusion is observed as a evidence of denervation to varying degrees. The transmural lesions showed denervation primarily distal and adjacent to the site of infarction. Transmural infarction produces necrosis of nerves coursing in the epicardium leading to viable but denervated myocardium. This partial denervation may produce imbalanced sympathetic innervation, which may predispose the heart to arrhythmia. Interestingly, nontransmural infarction is associated with myocardial denervation as an area of reduced MIBG uptake both in experimental and clinical studies. Nontransmural infarction largely involves the subendocardium with the preserved subepicardial layer where the sympathetic nerve trunks are located. However, neuronal damage is often associated with severe myocardial ischemia despite the absence of myocardial necrosis. In this areas MIBG defect is usually larger than the thallium perfusion defect. Such denervation but viable myocardium is often observed in nontransmural infarction and some transmural infarction which is often reduced in size on the follow-up study.

Although the sympathetic nerves are considered to be rather resistant to the effects of anoxia, some studies show histochemical evidence of nerve damage with diffusion of catecholamines after 30 min to 4 hour of ischemia. Our experimental study showed the reduction of MIBG in the repetitive occlusion and reperfusion model. In this model, the reduction of MIBG is associated with reduction of wall motion in the stunned myocardium. These experimental results can expand the clinical application of the detection of severe myocardial ischemia by MIBG. Actually the reduction in MIBG uptake in the myocardium is well demonstrated in patients with vasospastic angina and unstable angina (Fig. 4).

MIBG imaging may play additional important roles besides the detection of myocardial infarction and ischemia in the study of patients with coronary artery disease. One is the identification of sympathetic denervation in patients with tachyarrhythmia with underlying coronary artery disease. In addition, regional sympathetic denervation showing MIBG defect was also demonstrated in structurally normal hearts in patients with ventricular arrhythmia. The other is evaluation of the severity of heart failure, as a consequence of severe coronary artery disease. It is well
known that adrenergic dysfunction plays a key role in heart failure, and plasma catecholamine levels, for example, have been recognized as valuable prognostic tools. In patients with congestive heart failure, decreased retention and increased washout of MIBG from the myocardium is noted.\textsuperscript{112-114} This may be due to increased plasma catecholamine concentration. In addition, increased sympathetic function together with a decrease in the number of uptake sites may play a key role in heart failure. More importantly, reduced MIBG uptake is considered to be a single and independent prognostic parameter among a variety of clinical parameters in the study of congestive heart failure.\textsuperscript{115} Besides, recent experimental study showed the improvement of MIBG uptake in the failing heart after administration of renin-angiotensin converting enzyme inhibitor.\textsuperscript{116} These data indicate that adrenergic neuronal function analysis with MIBG is of clinical importance in the evaluation of coronary artery disease and associated conditions.

CONCLUSION

New techniques in nuclear cardiology have provided better accuracy in the detection of coronary artery disease on the basis of regional perfusion and function, but more importantly, they will permit precise tissue characterization, including metabolic alteration and neuronal function. This important information will play a key role in estimating severity and prognosis, and in planning the best strategy for managing these patients. Nevertheless, we are now entering a new era in nuclear cardiology. More clinical experience with the new techniques is required to confirm these exciting results.

REFERENCES

19. Villanueva-Meyer J, Menà J, Narahara KA. Simultaneous assessment of left ventricular wall motion and myocardial

62 Nagara Tamaki, Eiji Tadamura, Takashi Kudoh, et al

Annals of Nuclear Medicine


76. Ambrose KR, Owen BA, Goodman MM, Knapp FF Jr. Evaluation of the metabolism in rat heart of two new radiodinated 3-methyl-branched fatty acid myocardial...


