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REVIEW

Clinical use of nuclear cardiology in the assessment of heart failure

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Abstract

A nuclear cardiology test is the most commonly performed non-invasive cardiac imaging test in patients with heart failure, and it plays a pivotal role in their assessment and management. Quantitative gated single positron emission computed tomography (QGS) is used to assess quantitatively cardiac volume, left ventricular ejection fraction (LVEF), stroke volume, and cardiac diastolic function. Resting and stress myocardial perfusion imaging, with exercise or pharmacologic stress, plays a fundamental role in distinguishing ischemic from non-ischemic etiology of heart failure, and in demonstrating myocardial viability. Diastolic heart failure also termed as heart failure with a preserved LVEF is readily identified by nuclear cardiology techniques and can accurately be estimated by peak filling rate (PFR) and time to PFR. Movement of the left ventricle can also be readily assessed by QGS, with newer techniques such as three-dimensional, wall thickening evaluation aiding its assessment. Myocardial perfusion imaging is also commonly used to identify candidates for implantable cardiac defibrillator and cardiac resynchronization therapies. Neurotransmitter imaging using ^{123}I-metaiodobenzylguanidine offers prognostic information in patients with heart failure. Metabolism and function in the heart are closely related, and energy substrate metabolism is a potential target of medical therapies to improve cardiac function in patients with heart failure. Cardiac metabolic imaging using ^{123}I-15-(p-iodophenyl)3-R, S-methylpentadecacoic acid is a commonly used tracer in clinical studies to diagnose metabolic heart failure. Nuclear cardiology tests, including neurotransmitter imaging and metabolic imaging, are now easily preformed with new tracers to refine heart failure diagnosis. Nuclear cardiology studies contribute significantly to guiding management decisions for identifying cardiac risk in patients with heart failure.

Key words: Quantitative gated single photon emission computed tomography; Metaiodobenzylguanidine; β-methyl-p-iodophenyl-pentadecanoic acid; Diastolic function; Prognosis

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INTRODUCTION

Congestive heart failure is a specific term that is used to define the clinical syndrome that describes the situation when the heart is unable to pump enough blood for the metabolic needs of the body. Systolic and diastolic heart failure have been commonly used in clinical settings to describe a category of congestive heart failure[1]. There are several conditions that can lead to heart failure, including coronary artery disease and cardiomyopathy. It is helpful for the clinician to identify non-invasively the underlying cause of heart failure by means of nuclear cardiology studies. A substantial proportion of patients with symptomatic heart failure have been known to have relatively normal or preserved left ventricular ejection fraction (LVEF)[1,2]. Diastolic heart failure has been found to play an important role in cardiac morbidity and mortality in patients with preserved systolic function. Diastolic function is influenced by myocardial relaxation, ventricular filling and ventricular elastic properties. Moreover, in cases of ischemic heart disease, hypertension, and cardiomyopathy, myocardial involvement has been detected early by evaluation of diastolic abnormalities by means of a nuclear technique. Recently, electrocardiography (ECG)-gated single photon emission computed tomography (SPECT) has become a common procedure in patients with ischemic heart disease. A nuclear cardiology test, including the quantitative ECG-gated SPECT (QGS), sympathetic and metabolic imaging, is well suited for serial follow-up of changes in the myocardium[3]. The aim of the present review is to describe the measurement of cardiac function and the evaluation of patients' risk, including diastolic properties, by means of a nuclear technique, and to provide an overview of the state of the art of nuclear cardiology and physiology of the heart.

CLINICAL APPLICATION

Diagnosis of coronary artery disease

Myocardial perfusion imaging is an established method for the primary detection of coronary artery disease[4-10]. The development of ischemia or coronary flow heterogeneities is then used to represent physiological coronary stenosis as shown in Figure 1. The myocardium can increase coronary flow from its basal levels to a maximal flow in response to physiological or pharmacological stress. Nitric oxide and other metabolic mediators increase blood flow[11,12]. Coronary arteries without focal stenosis are generally considered non-flow-limiting. However, the levels of coronary flow reserve in non-obstructive coronary arteries vary in each subject[13,14]. Diffuse coronary atherosclerosis also accounts for persistently abnormal myocardial perfusion imaging studies without obstructive coronary artery segments. Physiological information from nuclear cardiology tests is essential for the assessment and management of heart disease, which might not otherwise be obtained by anatomical imaging such as CT.

Left ventricular function analysis

A number of studies have shown that ECG-gated SPECT can provide accurate and reproducible values for ejection fraction, regional wall motion, and wall thickening[15-17], and dyssynchrony[18]. Left ventricular function can be quantitatively analyzed with QGS software. QGS software has often been used to evaluate wall ejection fraction and left ventricular volume[19]. For data analysis, the QGS program has been applied to process short-axis tomograms to determine LVEF, end-systolic volume (ESV), and end-diastolic volume (EDV)[5]. The reproducibility in LVEF and volumes within each work station has been validated[20,21], even although the gated SPECT preferences have varied. Normal limits for gated SPECT and QGS software have been determined based on a Japanese database, including the Japanese Assessment of a Cardiac Event Survival Study (J-ACCESS)[8]. The study defined ESV in a normal range when it was ≥ 60 mL in male subjects, or when it was ≥ 40 mL in female subjects. The study therefore defined gated SPECT images as normal when LVEF in men was ≥ 49%, or when LVEF in women was ≥ 55%[8].

To evaluate left ventricular regional wall motion, wall thickening seems to be more appropriate for the evaluation in many cases, including evaluation of patients with left bundle branch block or coronary artery bypass graft. Normal standard values of myocardial wall thickening were created by the database of the Japanese Society of Nuclear Medicine (JSNM). Myocardial wall thickening in the apex was higher than that in the mid and basal regions. The wall thickening of the left ventricle was higher in women than in men[17].

Post-stress dysfunction

Post-ischemic stunning has been well documented in animal models and in humans[4,21,22]. In detecting multi-vessel coronary artery disease, post-stress dysfunction using SPECT imaging provides critical diagnostic information as shown in Figure 2. Transient ischemic dilatation (TID) of the left ventricle refers to an imaging pattern in which the left ventricle cavity appears to be larger on the stress image than on the rest image. The phenomenon of TID is considered to be a sensitive marker of extensive ischemia and prolonged post-ischemic systolic dysfunction, which results in a dilated, dysfunctional left ventricle during stress acquisition relative to rest acquisition. Patients with TID are considered to be high risk for future cardiac events. Patients with multi-vessel or left main coronary artery disease have reduced left ventricular systolic and diastolic function, especially in stressed conditions. The phenomenon of post-ischemic stunning consists of the presence of abnormal regional function in the absence of necrosis. Therefore, functional information after stress might be associated with severe and extensive ischemia in the myocardium. Persistence of functional abnormalities is certainly proportional to the degree of ischemia induced by exercise or pharmacological stress. An exercise stress perfusion thallium-201 (^{201}Tl) study can identify patients at high risk[4]. In previous studies using ^{99m}Tc-sestamibi (MIBI) gated SPECT, LVEF after stress was depressed in patients with reversible myocardial ischemia compared to those at rest[18,19]. Assessment of post-stress left ventricular function by gated SPECT provides incremental prognostic information and is useful in predicting cardiac events in patients with coronary artery disease[23,24].

Risk stratification using myocardial perfusion imaging

Assessment of prognosis by a nuclear cardiology study contributes significantly to guiding management decisions

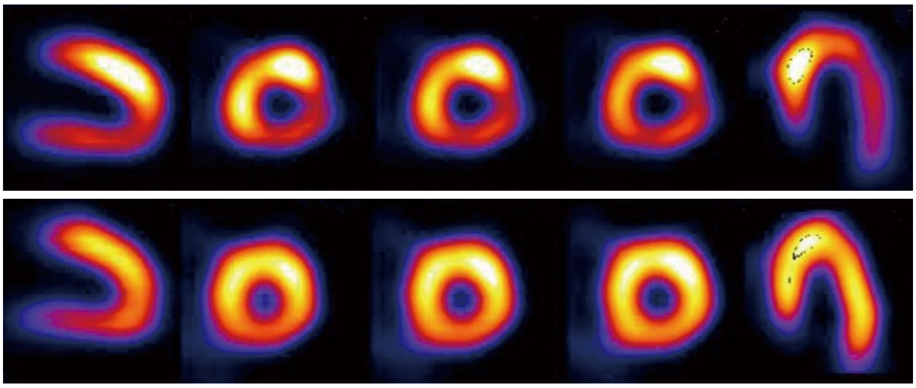

Figure 1 Single photon emission computed tomography image of exercise ^{201}Tl scintigraphy in a 70-year-old man. The stress image (upper panel) shows decreased perfusion in the infero-lateral region. There is a redistribution of the tracer in the rest image (lower panel), which indicates exercise-induced myocardial ischemia in the infero-lateral region of the left ventricle.

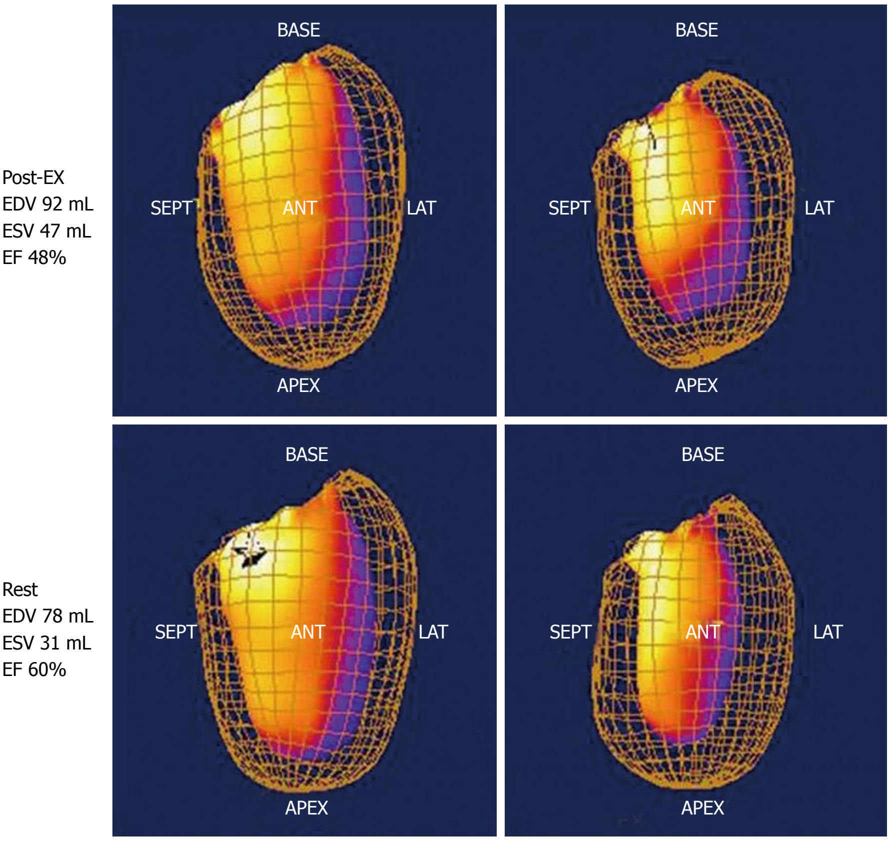

Figure 2 Post-stress left ventricular dysfunction detected by quantitative gated single positron emission computed tomography analysis. Transient ischemic dilatation was observed in a patient with multi-vessel disease. ESV: End-systolic volume; EDV: End-diastolic volume; EF: Ejection fraction.

for identifying patients with suspected or documented coronary artery disease. A multicenter nuclear cardiology study of > 45000 subjects was conducted in Japan. J-ACCESS has demonstrated the low risk associated with normal SPECT images[4,8,25]. Many studies have revealed important findings that have demonstrated that stress SPECT images alone have incremental information[25-28]. Moreover, cardiac function analysis by QGS adds incremental prognostic information[4,25]. It has been found that patients with normal SPECT have a low major cardiac event rate (< 1% per year)[8,26]. These findings have important clinical implications because these patients can be exempted from further invasive procedures. A policy of proceeding directly with coronary angiography in suspected coronary artery disease without performing stress nuclear cardiology tests would result in subjecting patients to expensive and invasive procedures, with an expected good prognosis without interventions. The use of normal SPECT images needs no further invasive procedure. This type of management strategy results in cost efficiency and substantial cost savings compared with a more aggressive, invasive diagnostic workup strategy that includes diagnostic cardiac catheterization[29]. The patients undergo no further testing after a normal SPECT image, although studies of long-term outcome after a normal stress radionuclide study are scarce[8,26]. As a result of greater frequency in atypical presentation, physicians rely more often on imaging results to guide management decisions. Thus, in clinical practice, SPECT imaging is frequently being employed as a first-line test. Risk stratification is essential to the development of evidence-based strategies for improved patient care in medicine[30-35]. For patients with normal SPECT images, no additional testing is required because of the projected benign course. J-ACCESS has shown that patients with normal perfusion imaging require a watchful waiting approach to care[8]. These results indicate that using stress myocardial SPECT images can be used as a gate-keeper for selective catheterization. Patients with type 2 diabetes mellitus have a higher risk of cardiovascular events and death than those without. Moreover, coronary artery disease in diabetic patients is frequently silent. It is important to identify coronary artery disease objectively in asymptomatic diabetic patients in a noninvasive way as early as possible. A risk-based approach is also essential in the management of diabetic patients with atherosclerosis[26]. Screening coronary artery disease in diabetic patients using SPECT has been proven to be beneficial to determine the therapeutic strategy. Focusing on cardiovascular disease in diabetes, J-ACCESS-2 study is the first large-scale prospective study in diabetic patients to evaluate the prognostic value of ECG-gated SPECT imaging in Asia[26,30]. Cardiac event rates associated with normal or low-risk myocardial perfusion SPECT imaging with ^{99m}Tc-tetrofosmin have been shown by the study. Results from J-ACCESS-2 provide further supportive evidence that the excellent prognosis associated with a normal SPECT scan does not require invasive therapy[26]. In patients with documented coronary stenosis, the extent of stress myocardial perfusion imaging perfusion defects is reportedly related to increased risk of cardiac death[33]. Myocardial perfusion imaging can be a significant predictor of sudden cardiac death[35]. Summed stress scores provide incremental prognostic power to clinical history, and the LVEF can be the current gold standard for the risk stratification of sudden cardiac death[35].

Assessment of myocardial viability and prediction of functional recovery

The aim of assessing myocardial viability is to optimize selection of patients with heart failure, whose symptoms and natural history might improve following revascularization. The presence of ^{201}Tl after redistribution indicates preserved cellular viability. However, the absence of ^{201}Tl uptake on the redistribution image is not sufficient to assert no viability[27]. Myocardial uptake of ^{99m}Tc- MIBI is associated with regional perfusion and provides adequate information for the detection of coronary artery disease[33]. The uptake and retention of ^{99m}Tc-MIBI is also dependent on cell membrane integrity and mitochondrial function (membrane potential), therefore, the uptake of ^{99m}Tc-MIBI in the myocardium might reflect cellular viability. Many studies have compared ^{99m}Tc-MIBI imaging with other scintigraphic modalities, including ^{201}Tl stress-redistribution-reinjection, ^{201}Tl rest, ^{201}Tl rest-redistribution and ^{18}F-2-furoro-2-deoxy-D-glucose positron emission tomography (FDG PET), and ^{123}I-β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP)[32]. In patients with chronic total occlusion and viable myocardium, successful revascularization of chronic total occlusion can have a favorable outcome for left ventricular perfusion and function. Viable myocardium should be identified, particularly in such patients before percutaneous coronary intervention. Gated SPECT myocardial perfusion imaging with ^{99m}Tc-MIBI might be useful for monitoring long-term functional outcome of percutaneous coronary intervention in patients with chronic total occlusion[36].

Assessment of myocardial viability with PET also improves the potential benefit of revascularization. A previous study has shown that patients with preserved myocardial viability who underwent revascularization had a significant reduction in the risk of cardiac death during follow-up[37]. The mismatch pattern (enhanced FDG uptake relative to blood flow) can be related to the magnitude of improvement in left ventricular function after revascularization in patients with heart failure. On the other hand, the matched pattern (severe FDG uptake reduction and severely decreased myocardial perfusion) can be a sign of unfavorable outcome of revascularization and will unlikely lead to functional recovery.

Assessment of diastolic function with nuclear techniques

Systolic and diastolic heart failure have been commonly used in clinical settings to describe a category of congestive heart failure[1]. There are several conditions that can lead to heart failure, including coronary artery disease and cardiomyopathy. It is helpful for the clinician to identify non-invasively the underlying cause of heart failure by means of a nuclear cardiology study. A substantial portion of patients with symptomatic heart failure are known to have relatively normal or preserved LVEF. In patients with symptomatic or suspected heart failure, determination of the presence and severity of diastolic dysfunction becomes increasingly important. Diastolic function analysis is often made by echocardiography, including tissue Doppler imaging and tracking techniques. Recent cardiac magnetic resonance techniques like strain-encoded cardiac magnetic resonance might provide accurate information of inducible ischemia and cardiac diastolic function[38]. Diastolic heart failure, also termed as heart failure with preserved LVEF, is readily identified by nuclear cardiology techniques, and it can accurately estimate LV filling velocity rate and one third filling fraction. The reliability of diastolic function has been established in gated blood-pool studies but not in gated myocardial SPECT, especially in a ^{201}Tl study[16]. The diastolic function determined for the Japanese population using a 16-frame format is summarized in Table 1, using the JSNM database[10]. Although a 32-frame division of

Table 1 Normal values of diastolic parameter using ^{99m}Tc tracers

	JSNM WG
No. of subjects	60
Age (yr)	58 ± 15
Heart rate (beats/min)	66 ± 12
PFR (/s)	2.69 ± 0.57
1/3 mean filling rate (per s)	1.60 ± 0.39
TTPF (ms)	167 ± 38
TTPF/RR interval	0.18 ± 0.03
EF (%)	68 ± 6

JSNM WG: Japanese Society of Nuclear Medicine Working group; PFR: Peak filling rate; TTPF: Time to PFR; EF: Ejection fraction.

a cardiac cycle can provide better correlation with those determined by radionuclide ventriculography[39], diastolic functional parameters can be analyzed in a more practical way by using a 16-frame acquisition per RR interval[16,40-42]. Using the QGS software algorithm, abnormal thresholds in an American population have included peak filling rate (PFR) < 1.70/s and time to PFR (TTPF) > 208 ms[41]. Multivariable analysis has shown that age, sex, LVEF and heart rate are strong predictors for PFR, whereas TTPF is not influenced by any clinical or systolic function variables. The Japanese population also has shown comparable normal values (Table 1). When patients were classified into two age groups of < 60 and ≥ 60 years, standard deviations of peak filling rate, one third mean filling rate, TTPF and TTPF/RR were larger in the older group than in the younger group. Because age-related differences were observed, it should be kept in mind that diastolic dysfunction in elderly patients and in those with LVEF < 50% are more common. Quantitative measurement depends on the tracers used, therefore, diastolic function analysis using ^{201}Tl requires further investigation[16].

Evaluation of severity in patients with non-ischemic cardiomyopathy

Determination of left ventricular dysfunction due to non-ischemic cardiomyopathy is crucial in the management of heart failure. Cardiomyopathy constitutes a group of disorders in which the dominant feature is direct involvement of the cardiac myocardium itself. Hypertrophic cardiomyopathy and dilated cardiomyopathy are characterized by the presence of many alterations of adrenergic nerve function, such as decreased cardiac norepinephrine uptake, increased norepinephrine release, and decreased norepinephrine cardiac content and partial denervation. Myocardial damage or dysfunction leads to symptomatic heart failure[43-46]. Non-ischemic cardiomyopathy can be evaluated also by metabolic imaging. The evaluation of metabolic status in addition to perfusion can offer clues to the underlying pathophysiology of the disease.

^{123}I-MIBG scintigraphy

^{123}I-MIBG scintigraphy is now used as an important technique for studying cardiac neuronal function[43-49]. ^{123}I-MIBG, an analog of guanethidine, is taken up and stored similarly to norepinephrine. It is taken up by sympathetic efferent nerve terminals, which are most abundant in the left ventricle. Distribution of ^{123}I-MIBG uptake is heterogeneous in normal subjects, with a relatively low uptake in the inferior and apical regions[44]. ^{123}I-MIBG shares the same uptake and storage mechanisms as norepinephrine. It is reported that the uptake-1 system is mediated by the norepinephrine transporter, and the uptake-2 system is an extra-neuronal system. Planar imaging of the heart-mediastinum count ratio (H/M) of ^{123}I-MIBG is a simple method that allows comparison of inter-individual and institutional results by correcting for differences in body geometry and attenuation between individual subjects. In MIBG SPECT, a regional heterogeneity of ^{123}I-MIBG uptake exists, especially in the inferior and apical lesion in normal subjects[9,44]. ^{123}I-MIBG uptake can vary depending on age or sex[9]. Diabetes can affect the less inferior uptake of ^{123}I-MIBG.

^{123}I-MIBG scintigraphy has been accepted for routine use in many countries, and the standardization of ^{123}I-MIBG parameters among various collimators has been crucial. It has been shown that the H/M ratios obtained with low-energy high-resolution (LEHR) collimators with the ^{123}I dual energy (IDW) method are similar to those obtained with a medium-energy collimator[50]. The scatter-correction IDW method could make it possible to standardize planar imaging of the H/M ratio among various collimators in clinical settings[50].

Assessment of severity and prognosis of patients with heart failure, using MIBG imaging

Cardiomyopathy is a myocardial disease that often manifests as cardiac dysfunction and reduced ^{123}I-MIBG uptake, which could reflect associated abnormalities in sympathetic nerve function. This results in decreases in ^{123}I-MIBG uptake in patients with hypertrophic cardiomyopathy[43,45]. The early and delayed images of ^{123}I-MIBG provide information about the ^{123}I-MIBG washout rate. The delayed image in patients with hypertrophic cardiomyopathy is significantly lower than that in control subjects, and the washout rate of ^{123}I-MIBG is significantly higher[43]. ^{123}I-MIBG imaging shows that the cardiac sympathetic nerve function is impaired in hypertrophic cardiomyopathy, and the impairment might reflect progression of myocardial damage or dysfunction[43]. The increased wall thickness of the left ventricle in hypertrophic cardiomyopathy is closely related to the perfusion defect based on a ^{201}Tl study, which is suggestive of myocardial damage, including myocardial hypertrophy, disarray or fibrosis[43]. Furthermore, in patients with left ventricular dysfunction, decreased uptake-1 function has been found to be related to both myocardial overexposure to norepinephrine and decreased myocardial β-receptors[46]. The norepinephrine levels that are required to inhibit ^{123}I-MIBG uptake in these conditions seem to be much higher than those in patients with hypertrophic cardiomyopathy. Cardiac sympathetic abnormalities are observed in hypertrophic cardiomyopathy patients with coronary

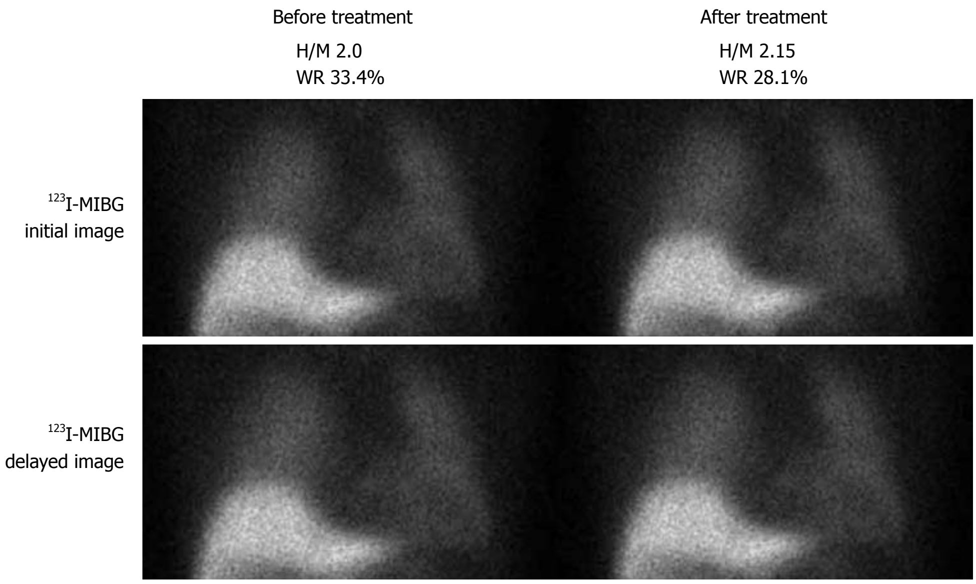

Figure 3 A patient with heart failure had ^{123}I-MIBG imaging and was treated with β-blockers. After treatment, ^{123}I-MIBG H/M ratio and washout rate (WR) were improved.

vasospasm, which suggests that the impaired sympathetic nerve function is associated with coronary vasospasm and diminished coronary blood flow reserve in hypertrophic cardiomyopathy[43].

Dilated cardiomyopathy is also characterized by the presence of many alterations of adrenergic nerve dysfunction[46]. The myocardial responsiveness of β-adrenergic agonists is blunted because of the increase in circulating catecholamines. A study of dilated cardiomyopathy has shown that ^{123}I-MIBG uptake is a predictor of life duration, and that impaired cardiac sympathetic nerve innervation, as assessed by ^{123}I-MIBG images, is strongly related to mortality in patients with heart failure[49]. The delayed H/M ratio might reflect the myocardial contractile reserve in dilated cardiomyopathy patients[51,52]. Cardiac resynchronization therapy has proven beneficial in dilated cardiomyopathy patients with advanced chronic heart failure or bundle branch block[53,54]. Baseline cardiac sympathetic activity evaluated by ^{123}I-MIBG scintigraphy offers additional information for patients with dyssynchrony[53], as well as both systolic and diastolic function[54].

Merlet *et al*[47] have documented that there is a strong relationship between sympathetic nerve dysfunction and prognosis. Patients with the lowest uptake of ^{123}I-MIBG have the poorest prognosis[48]. Sympathetic activity is enhanced with increasing severity of heart failure, therefore, the severity and prognosis of congestive heart failure can be evaluated based on two parameters that are determined by ^{123}I-MIBG scintigraphy. Previous studies have shown that delayed H/M ratio is the best predictor of survival in patients with heart failure with reduced cardiac function[47,48]. Others have reported that the washout rate of ^{123}I-MIBG seems to be the most powerful predictor of subsequent mortality and morbidity in patients with heart failure. ^{123}I-MIBG imaging can be a useful tool in the evaluation of response to pharmacological treatment[46,49]. On the basis of the parameters of ^{123}I-MIBG such as H/M and washout rate, treatment for congestive heart failure with angiotensin-converting enzyme inhibitors, angiotensin Ⅱ receptor blockers, β-blockers, spironolactone, or torasemide can be monitored and evaluated for its efficacy in improving cardiac sympathetic nerve activity (Figure 3)[56,57]. In ischemic patients with heart failure, an ^{123}I-MIBG study can also be predictive of improvements. Medical therapy can be effective when the H/M ratio on the initial image is maintained and the washout rate is increased on MIBG myocardial scintigraphy[57-60]. Patients with heart failure can be good candidates for β-blocker treatment. The evaluation of severity and prognosis of heart failure is considered as class Ⅰ evidence for nuclear cardiology based on the Japanese Circulation Society guidelines. Parameters obtained with delayed ^{123}I-MIBG scintigraphy images such as delayed H/M ratio and washout rate can be used as indicators of sympathetic activity[59].

Following studies in Japan and European countries, the use of ^{123}I-MIBG imaging has also been validated by a large prognostic multicenter trial in patients with heart failure of NYHA functional class Ⅱ/Ⅲ and LVEF of ≤ 35%. The 2-year event rate in this trial was 15% for H/M > 1.60 and 37% for H/M < 1.60. The authors found that ^{123}I-MIBG provided additional discrimination in analyses of interactions between B-type natriuretic peptide, LVEF and H/M ratio[61].

A previous study has reported that there is no accumulation in the heart within 1 year after heart transplantation, and that the accumulation begins to recover in the anterobasal site during the subsequent course[48,58]. An ^{123}I-MIBG study can be used to monitor the course of sympathetic re-innervation in the transplanted heart.

Cardiac metabolic imaging with ^{123}I-BMIPP

Glucose and fatty acids are the major energy sources in the myocardium. Under normal conditions, approximately two-thirds or more of the total energy produced by the myocardium is derived from fatty acid oxidation. Fatty acid oxidation is the most efficient method of energy production[62-64]. This process requires a large amount of oxygen. Therefore, under hypoxic or ischemic conditions, oxidation of long-chain fatty acids is greatly suppressed, and glucose metabolism, which requires less oxygen consumption, plays a major role in residual oxidative metabolism. Thus the evaluation of fatty acid metabolism is considered to be a sensitive marker of ischemia and myocardial damage. ^{123}I-BMIPP distribution in normal subjects is homogeneous[9]. Initial myocardial ^{123}I-BMIPP uptake depends heavily on regional perfusion. Therefore, accurate reading of a ^{123}I-BMIPP image in comparison with a perfusion image is very important. In interpreting ^{123}I-BMIPP regional images, we should take into consideration the fact that ^{123}I-BMIPP uptake in the septal wall is higher than that of ^{99m}Tc tracer, and apical inferior uptake is higher in women than in men[9].

Heart failure with metabolic imaging

In heart failure derived from cardiomyopathy, myocardial substrates can change significantly. Therefore, evaluation of metabolic status in addition to perfusion can offer clues to the underlying pathophysiology of cardiomyopathy. Currently available tracers for metabolic imaging comprise several fatty acid tracers[64-67], ^{18}F-FDG for the evaluation of glucose metabolism and ^{11}C-acetate for the assessment of oxygen consumption. Animal experiments with autoradiography using methyl-branched fatty acids in cardiomyopathic hamsters and hypertensive rats have demonstrated that fatty acid uptake is heterogeneous and lower than thallium uptake in the endocardium. ^{123}I-labelled 15-(p-iodophenyl)3-R, S-methylpentadecanoic acid (BMIPP) is the most commonly used tracer in clinical studies. It has been reported that less ^{123}I-BMIPP than ^{201}Tl uptake (disparity) is occasionally observed in patients with myocardial infarction, and such disparity segments tend to show redistribution in a stress ^{201}Tl study and increased FDG uptake in a PET study[68]. In patients with cardiomyopathy, discordant ^{123}I-BMIPP uptake less than thallium uptake is a general finding, especially in patients with hypertrophic cardiomyopathy[64]. Several studies using ^{201}Tl scintigraphy in patients with hypertrophic cardiomyopathy have revealed that, despite a normal epicardial coronary artery, a reversible perfusion defect on stress-distribution is often observed[64]. A recent study has demonstrated that decreased myocardial ^{123}I-BMIPP uptake is observed in the area of stress-induced ischemia on ^{201}Tl imaging, which indicates the exercised-induced metabolic changes that occur even in a resting state[64]. Similarly, exercise-induced abnormal blood pressure response is related to subendocardial ischemia in hypertrophic cardiomyopathy[69]. Disparity of two tracers has frequently been observed in hypertrophic regions[70,71]. This discrepancy could have been due to the multifactorial etiology of hypertrophic cardiomyopathy. It has been reported that patients with hypertrophic cardiomyopathy show substantial heterogeneity in the distribution of ^{123}I-BMIPP, and accelerated washout of ^{123}I-BMIPP. Nishimura[72] have suggested that impairment of myocardial fatty acid metabolism precedes a decrease in myocardial perfusion in hypertrophic cardiomyopathy because decreased ^{123}I-BMIPP uptake and normal ^{201}Tl perfusion are frequently observed. An ^{18}F-FDG study has shown that the reduction in ^{123}I-BMIPP uptake is followed by oxidative metabolism and ^{18}F-FDG uptake. Although most patients with hypertrophic cardiomyopathy have an excellent prognosis, some might progress to dilated cardiomyopathy or a poor prognostic course[73]. ^{123}I-BMIPP imaging might be a tool to identify a subgroup of patients at risk of future cardiac events. Ishida *et al*[70], however, have failed to reveal abnormal distribution on ^{123}I-BMIPP images from patients with dilated cardiomyopathy despite severe left ventricular dysfunction. Myocardial fatty acid metabolism is impaired in heart failure patients with cardiomyopathy. In patients with congestive heart failure, myocardial metabolic abnormality evaluated by ^{123}I-BMIPP scintigraphy is related to the severity of congestive heart failure. Furthermore, it might be useful as a predictor of cardiac events[62].

Metabolic abnormality observed as decreased ^{123}I-BMIPP uptake is related to myocardial creatine depletion by means of magnetic resonance spectroscopy[74]. The detection of myocardial damage and prediction of prognosis can be achieved by metabolic imaging[75,76], which might precede myocardial scarring that is detected by gadolinium-enhanced cardiovascular magnetic resonance imaging in patients with hypertrophic cardiomyopathy[77].

An important feature of metabolic imaging is to provide a treatment strategy for patients with dilated cardiomyopathy. The decrease in ^{123}I-BMIPP uptake in patients with dilated cardiomyopathy might be a poor indicator for β-blocker therapy, whereas patients with relatively preserved ^{123}I-BMIPP uptake might respond well to therapy.

Metabolism and function of the heart are closely related, therefore, energy substrate metabolism is a potential target of medical therapy to improve cardiac systolic and diastolic function in patients with heart failure[78]. PET imaging with recent advanced techniques offers good potential to evaluate cardiac stem-cell therapy by means of ^{18}F-FDG-labeled bone marrow cells[79]. Metabolic imaging with PET, including ^{11}C-acetate, ^{18}F-FDG and new tracers, can be a tool to evaluate the efficacy of new therapies to improve cardiac function in heart failure.

Mitochondrial function imaging

^{99m}Tc-sestamibi (MIBI) is a lipophilic cation. Myocardial uptake and retention of ^{99m}Tc-MIBI involve passive diffusion across the plasma and mitochondrial membranes[3]. Cellular influx of the tracer is driven by the inside negative plasma membrane and mitochondrial inner membrane potentials, which concentrates on the tracer within the cytosol and mitochondria[3]. The retention of ^{99m}Tc-MIBI in the mitochondria is related to mitochondrial function. In the analysis of the ^{99m}Tc-MIBI images, the regions of interest are placed on planar images to quantify cardiac ^{99m}Tc-MIBI uptake and calculate the H/M count ratio. The washout rate of ^{99m}Tc-MIBI is calculated from the segmental counts in the early and delayed images. Ischemia reportedly causes increased clearance of ^{99m}Tc-MIBI[76]. In patients with heart failure, recent human studies have shown that the myocardial washout rate of ^{99m}Tc-MIBI is thought to be a novel marker for the diagnosis of myocardial damage or dysfunction, which provides prognostic information in patients with congestive heart failure[3]. ^{99m}Tc-MIBI washout is increased in patients with anthracycline-induced cardiomyopathy. ^{99m}Tc-MIBI washout can be a marker of mitochondrial dysfunction[3].

Restrictive cardiomyopathy can be idiopathic or secondary to heart muscle disease that manifests itself as restrictive physiology[55]. The most common hemodynamic disturbance is impairment of ventricular filling due to the thickening and increased rigidity of the endocardium and myocardium secondary to infiltration by amyloid tissue or fibrosis. One study has shown the case of restrictive cardiomyopathy in which sympathetic and metabolic abnormalities and normal perfusion imaging were demonstrated[55]. These findings of scintigraphic studies have shown us that restrictive physiology seems to cause metabolic and sympathetic abnormality with normal perfusion. Alcoholic cardiomyopathy, as a result of chronic alcohol abuse, results in heart failure. Up to 45% of all dilated cardiomyopathy appears to be due to alcohol abuse[76]. The first sign of myocardial dysfunction is decreased diastolic function. Systolic dysfunction can appear later in these patients. Thereafter, cardiac enlargement is seen as a part of a compensatory mechanism. In our previous study, cardiac metabolic abnormalities were demonstrated in a patient with alcoholic cardiomyopathy[76]. ^{123}I-MIBG identified myocardial damage in the inferior wall of the left ventricle, and mild heterogeneity of ^{123}I-MIBG uptake was observed in the myocardium. ^{123}I-BMIPP showed low uptake in the inferior wall of the myocardium, concordant with perfusion. These scintigraphic findings suggest that chronic alcoholism can cause myocardial damage, which results in metabolic and sympathetic neuronal abnormalities[76]. Mitochondrial disorders are a heterogeneous group of diseases that result from abnormalities in mitochondrial DNA and function. In mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), cardiac involvement manifested as hypertrophic (symmetrical or asymmetrical) or dilated cardiomyopathy is frequently observed[77]. In a patient with MELAS, decreased ^{99m}Tc-MIBI uptake and increased ^{99m}Tc-MIBI washout, which correlate inversely with LVEF, is observed. In addition, increased ^{123}I-BMIPP uptake is observed in the region of decreased ^{99m}Tc-MIBI uptake. ^{123}I-BMIPP is an analog of free fatty acid, which enters the intracellular triglyceride pool. In mitochondrial respiratory chain failure, energy production shifts from aerobic to the anaerobic pathway (glycolytic pathway), which results in increased lactic acid formation and increased ^{123}I-BMIPP uptake[77].

Various etiologies of heart failure

Less common forms of cardiomyopathy are recognized: arrhythmogenic right ventricular cardiomyopathy (ARVC) and unclassified; the latter includes fibroelastosis, systolic dysfunction with minimal dilation, and isolated ventricular non-compaction; an unusual disease marked by prominent endocardial thickening with prominent trabeculations and deep recesses. ARVC is a condition in which the right ventricle is partially or totally replaced by adipose tissue[80,81]. The involved myocardium provokes ventricular arrhythmias of a right ventricular origin that might lead to sudden death. Pathological abnormalities mostly affect the right ventricle, particularly the epimyocardium, but left ventricular involvement has been reported in up to 76% of patients with ARVC. The origin of ventricular tachycardia is related to the decreased accumulation of ^{123}I-MIBG[82,83].

There are unusual types of cardiomyopathy that are recognized by nuclear techniques. Takotsubo cardiomyopathy is a newly defined syndrome that was first described in Japanese patients in 1991, and is characterized by transient, left ventricular apical ballooning. This name is related to the peculiar shape of the left ventricle, which can be visualized by end-systolic left ventriculograms, and it resembles an octopus-trapping pot, which is referred to as "Takotsubo" in Japanese[84,85]. It is also referred to as stress cardiomyopathy, ampulla cardiomyopathy, apical ballooning syndrome, or broken heart syndrome. The mental stress due to earthquakes or train accidents could be one of the causes of the disease. This cardiomyopathy is now becoming recognized around the world and needs to be included in the differential diagnosis of acute coronary syndrome. It is recognized as a reversible left ventricular dysfunction with symptoms similar to those of acute myocardial infarction, but without coronary artery lesions, even during the acute phase of ST segment elevation. ^{123}I-MIBG and ^{123}I-BMIPP show reduced uptake in the apical segment of the myocardium in the acute phase, which indicates impairment of fatty acid metabolism and sympathetic nerve abnormalities. ^{99m}Tc-tetrofosmin uptake abnormality and apical wall motion dysfunction in the acute phase rapidly recover at the sub-acute stage, however, ^{123}I-BMIPP abnormalities persist for a longer period. These findings suggest that transient ventricular dysfunction might essentially be in stunned myocardium. ^{123}I-MIBG seems to be a specific diagnostic modality which is useful in the diagnosis of neurogenic myocardial stunning in Takotsubo cardiomyopathy, as shown in Figure 4.

Other forms of cardiomyopathy include sarcoidosis[86], cardiomyopathy related to inflammatory disease[87], and cardiac sympathetic dysfunction in the hearts of athletes[88]; all of which can be diagnosed by ^{123}I-MIBG imaging. Athlete's hearts are commonly characterized by an increase in left ventricular mass because of an increase in the left ventricular diastolic cavity dimension and/or wall thickness. Endurance exercise also increases numerous cardiovascular adaptations, such as increased vagal tone. Prolonged exercise training can alter cardiac sympathetic function, which can be detected by ^{123}I-MIBG imaging[88].

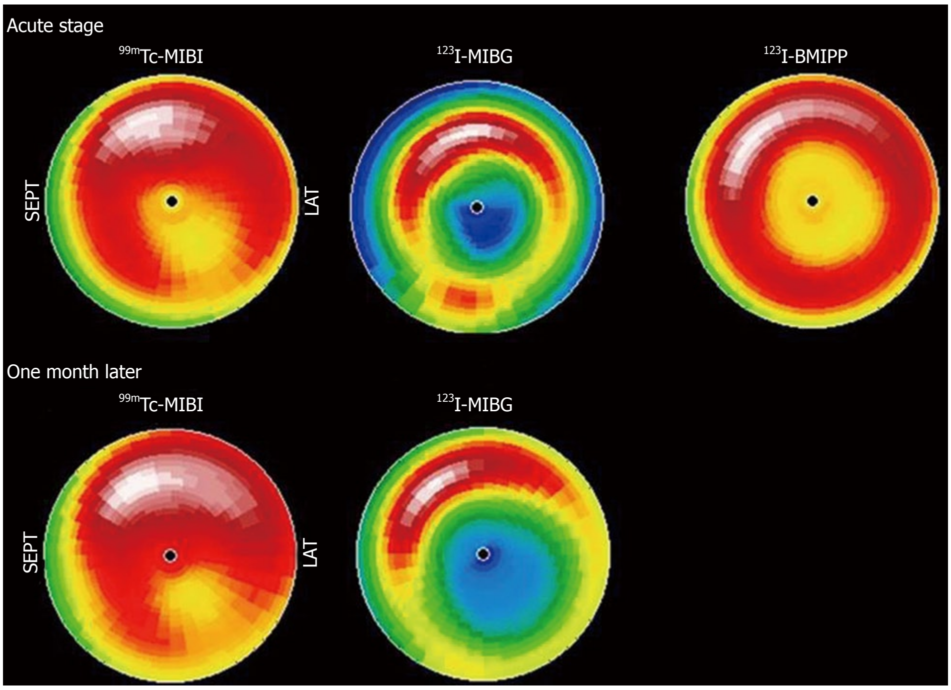

Figure 4 Scintigraphic features of Takotsubo cardiomyopathy are depicted. Bull's eye maps of ^{99m}Tc-sestamibi (MIBI), ^{123}I-MIBG and ^{123}I-β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) are shown. Both ^{123}I-MIBG and ^{123}I-BMIPP images show reduced uptake in the apical segment of the myocardium, which are typical features of the disease.

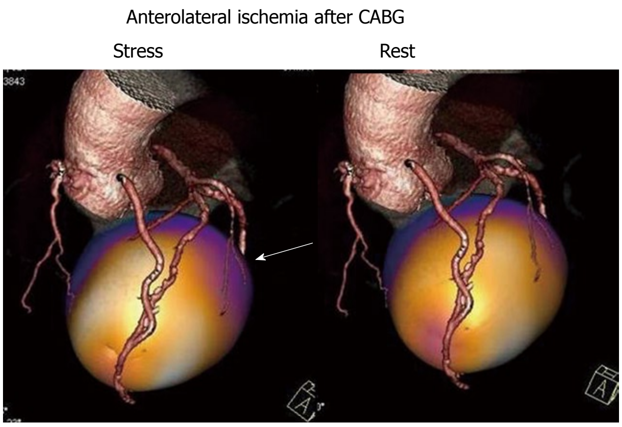

Figure 5 Fusion image reveals that the ischemic area in the basal anterolateral region shown by single photon emission computed tomography image is perfused by small vessels or has no corresponding artery assessed as imaging artifacts. Thus, the fusion image has increased diagnostic confidence for the detection of the culprit lesion in patients with coronary artery bypass grafting.

Advancement of technology with SPECT/CT

In the recent advances of fusion technology using X-ray CT angiography and myocardial perfusion imaging, SPECT/CT fusion imaging provides additional information about hemodynamic relevance and exact allocation of perfusion abnormalities to the subtending coronary artery. Software-based fusion imaging between SPECT and CT coronary angiography can offer better diagnostic information even if the culprit lesion is not identified by SPECT alone. The creation of the SPECT/CT fusion imaging by different manufacturers has made these techniques more available to clinicians[89,90]. In patients with coronary bypass graft surgery, the culprit lesion is difficult to determine, as shown in Figure 5. Fusion imaging has made it possible to diagnose more confidently the culprit region of ischemia using SPECT/CT imaging. Quantitative accuracy could be further improved by anatomical and functional correlation using fusion imaging.

Radiation exposure could be an issue with nuclear medicine imaging and CT. A number of techniques can be used to minimize the dose from CT[91]. Also, the protocol to obtain CT images should be performed in a way in which the dose can be minimized. In terms of radiation dose reduction, ^{99m}Tc agents are more favorably used than ^{201}Tl.

Future perspective on nuclear imaging

The most important area of application of nuclear cardiology is risk stratification in the management of patients. A risk-based approach in patients with heart failure is clinically more important than simple diagnosis. The basic concept in the use of a nuclear cardiology test in myocardial perfusion imaging is that it can be applied to patients with an intermediate risk of death. With the use of sympathetic nerve imaging, prognostic evaluation of heart failure might be possible. Metabolic imaging also has prognostic information, including ischemic, myocardial damage and fibrosis. These nuclear techniques contribute significantly to guiding management decisions for identifying patients with heart failure.

CONCLUSION

There are several conditions that can lead to heart failure, including coronary artery disease and cardiomyopathy. It would be helpful for the clinician to identify non-invasively the underlying cause of heart failure. Physicians should rely more often on myocardial perfusion imaging to evaluate non-invasively cardiac function and ischemic conditions in patients with heart failure. Nuclear cardiology tests, including neurotransmitter imaging and metabolic imaging, are now easily performed with new tracers to refine heart failure diagnosis. Nuclear cardiology studies contribute significantly to guiding management decisions for identifying patients with heart failure.

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