—Review—

Clinical Applications of ECG-gated Myocardial Perfusion SPECT

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Abstract

Erectrocardiogram (ECG)-gated myocardial perfusion single photon emission computed tomography (SPECT) can be used to assess myocardial perfusion and left ventricular function simultaneously. Various clinical applications of gated SPECT and their usefulness have been reported. The functional variables that can be determined with gated SPECT have been limited to systolic indices. Therefore, we evaluated left ventricular diastolic function with gated SPECT using data obtained from various frames per cardiac cycle and found that date generated from 32-frames are suitable for clinical use. Serial assessment of left ventricular function was also performed during bicycle exercise and dobutamine stress by means of gated SPECT using short-time data collection. These techniques, therefore, have the potential to provide useful information for evaluating myocardial conditions, such as hibernation and residual ischemia in infarct areas. Recently, we have developed a new technique for three-dimensional registration of CT coronary angiography (CTCA) and ECG-gated myocardial perfusion SPECT. This technique of registration may assist the integration of information from gated SPECT and CTCA and may have clinical application for the diagnosis of ischemic heart disease. These various applications would contribute to the development of nuclear cardiology.
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Key words: myocardial perfusion SPECT, gated SPECT, ischemic heart disease, myocardial infarction, exercise, dobutamine stress

Introduction

Nuclear cardiology continues to contribute substantially to the diagnosis of cardiovascular disease, especially coronary artery disease, to the assessment of its risk, and to its management. Recently, technetium labeled myocardial perfusion tracers, such as ^{99m}Tc-1,2-bis [bis (2-ethoxyethyl) phosphino] ethane (^{99m}Tc-tetrofosmin) and ^{99m}Tc-methoxy-isobutyl isonitrile (^{99m}Tc-sestamibi), have allowed simultaneous assessment of myocardial perfusion and left ventricular (LV) function using electrocardiogram (ECG)-gated single-photon emission computed tomography (SPECT). With the QGS program™ (Cedars-Sinai Medical Center), gated SPECT provides high-quality data regarding LV function which are operator-independent and, therefore, reproducible[1,2]. These measurements have proven more advantageous than the conventionally used cardiac blood pool scintigraphy in recent studies. There are a variety of unique and clinically

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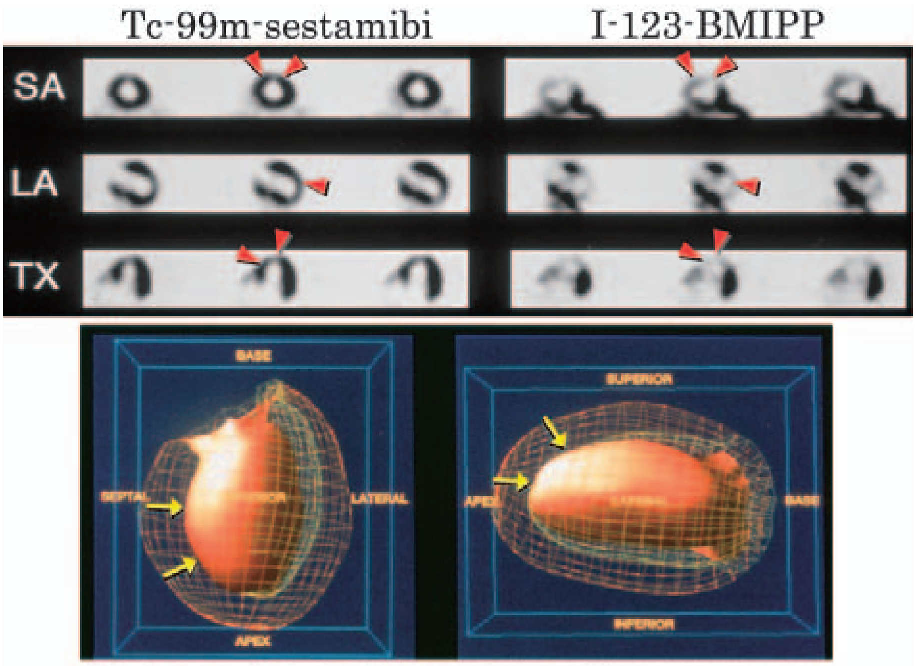

Fig. 1 ECG-gated dual-isotope SPECT with ^{99m}Tc-sestamibi and ^{123}I-BMIPP of a patient with acute anterior myocardial infarction who received PTCA therapy on admission. The SPECT images reveal perfusion/ metabolism mismatch **(arrowheads)** and function images demonstrate akinesis **(arrows)** in the infarct area. In the function images, the inner wire cage and the solid surface represent the endocardial surfaces at end-diastole and end-systole, respectively. (Kumita S, Cho K, Nakajo H, et al. Ann Nucl Med 2000; 14: 453)

relevant applications of gated SPECT. These clinical applications and their usefulness in our laboratory are described in this review.

Simultaneous Assessment of Myocardial Perfusion and Fatty Acid Metabolism Using Dual-isotope ECG-gated SPECT

Under aerobic conditions, 60% to 70% of the energy for myocardial metabolism is dependent on the β oxidation of fatty acids. However, in ischemic myocardium, fatty acid oxidation is suppressed and glucose becomes the major substrate for the production of high-energy phosphates. ^{123}I-labeled 15-(p-iodophenyl)-3R, S-methy pentadecanoic acid (BMIPP) is a branched-chain free fatty acid that is well suited to SPECT because of its very long myocardial retention[3,4]. A perfusion/metabolism mismatch, defined as lower BMIPP activity relative to perfusion, is more frequently observed in areas of acute myocardial infarction and in regions supplied by a revascularized vessel compared with non-revascularized areas[5]. In addition, discordant BMIPP decreases are frequent in areas with wall motion abnormalities and relatively preserved perfusion.

In our previous study, ^{99m}Tc-sestamibi (555 MBq) and ^{123}I-BMIPP (148 MBq) were injected simultaneously during rest after a fast of at least 6 hours[6]. ECG-gated dual-isotope myocardial SPECT data acquisition was started 40 to 60 min after injection using a three-head gamma camera. Sixteen frames per R-R interval were acquired in a 64 × 64 matrix. To separate the distribution of the isotopes, ^{99m}Tc data were obtained in a symmetrical 140 keV with 10% width (133 to 147 keV) and ^{123}I were obtained in an asymmetrical 159 keV (using the upper half of the photopeak) with 10% width (159 to 175 keV)[6,7].

In an acute myocardial infarct area after revascularization, reperfused viable myocardium often displays a prolonged wall motion abnormality, referred to as "stunned myocardium". Clinical studies have suggested that an area-at-risk, showing a distribution mismatch between BMIPP and flow

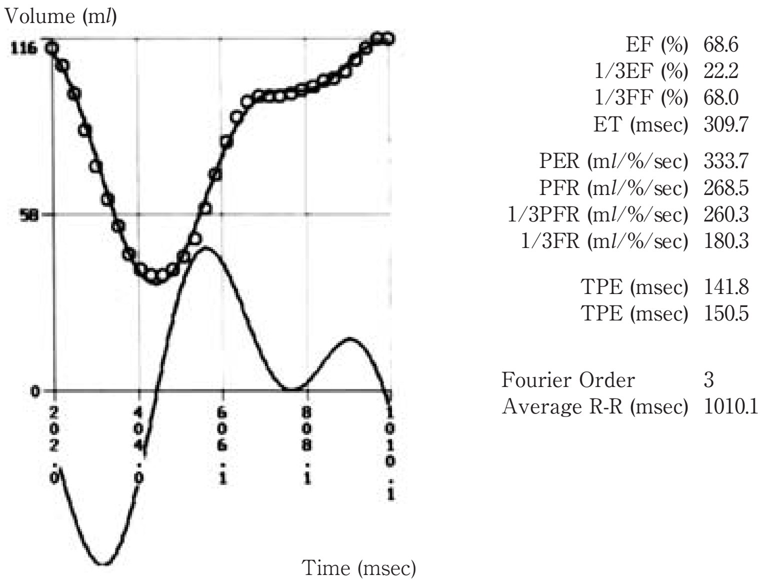

Fig. 2 Time-volume curve obtained from 32-frame gated SPECT data acquired from a 44-year-old male with effort angina pectoris. (Kumita S, Cho K, Nakajo H, et al. J Nucl Cardiol 2001; 8: 568)

tracers, may reflect reversible conditions, such as myocardial stunning or hibernation. Gated dual-isotope SPECT offers the advantage of simultaneous assessment of myocardial perfusion, fatty acid metabolism, and regional wall motion (**Fig. 1**). This technique, therefore, has the potential to provide useful information for evaluating myocardial conditions, such as stunning or hibernation.

Assessment of LV Diastolic Function

The functional variables that can be calculated with gated SPECT have been limited to systolic indices. Therefore, we evaluated LV systolic and diastolic function with gated myocardial perfusion SPECT using data obtained from 32 frames per cardiac cycle. To validate the method, results were compared with LV functional variables determined from conventional planar equilibrium radionuclide angiography (ERNA)[8].

After receiving an injection of ^{99m}Tc-tetrofosmin, 48 patients with cardiac diseases were examined with gated SPECT. During gated data collection, 32 frames per cardiac cycle were acquired over 360° in 60 steps, each of which consisted of 60 beats. Immediately thereafter, the 32 frames taken at each projection angle were combined into 16- and 8-frame datasets. LV end-diastolic volume (LVEDV, ml), LV end-systolic volume (LVESV, ml) and LV ejection fraction (LVEF, %) were automatically calculated from the 32-, 16- and 8-frame gated datasets. The LV time-volume curves were generated from the three datasets by means of Fourier curve-fitting analysis with 3 harmonics, after which peak filling rate (PFR, sec^{-1}) was measured (**Fig. 2**). Twenty-nine patients also underwent ERNA to determine the LVEF and PFR.

The LVEFs determined with ERNA correlated closely with those obtained from the three gated SPECT datasets (**Fig. 3**). The PFRs determined with ERNA correlated with those obtained from the 32- ($r=0.75$, $p<0.0001$), 16-($r=0.61$, $p<0.001$), and 8-frame gated SPECT data ($r=0.51$, $p<0.005$), as in **Figure 4**. Data generated from 32-frame gated SPECT closely correlated with ERNA data with respect to the PFR calculation[8].

ECG-gated SPECT using 32-frame data can provide comprehensive information with which to evaluate many types of cardiac diseases, such as hypertrophic cardiomyopathy, hypertensive heart disease, and valvular disease.

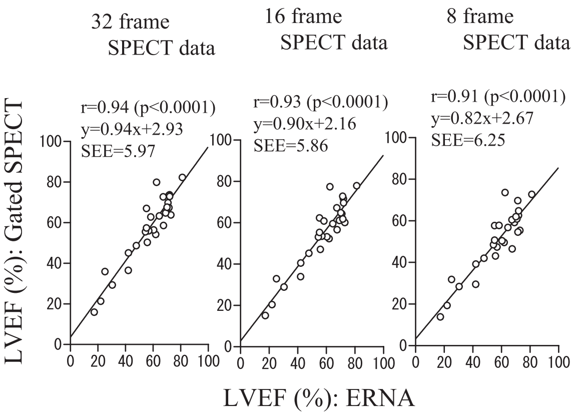

Fig. 3 Comparison of LVEF obtained from gated SPECT and from equilibrium radionuclide angiography (ERNA). (Kumita S, Cho K, Nakajo H, et al. J Nucl Cardiol 2001; 8: 568)

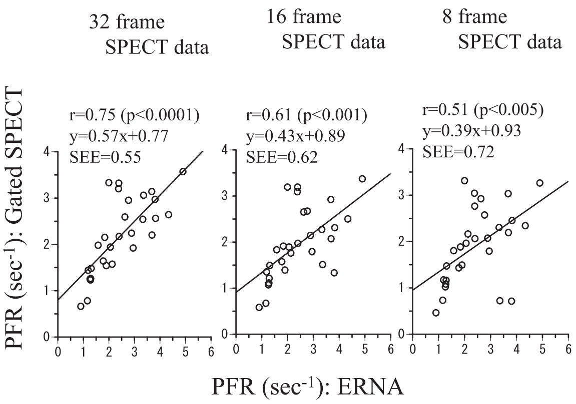

Fig. 4 Comparison of peak filling rate (PFR) obtained from gated SPECT and ERNA studies. (Kumita S, Cho K, Nakajo H, et al. J Nucl Cardiol 2001; 8: 568)

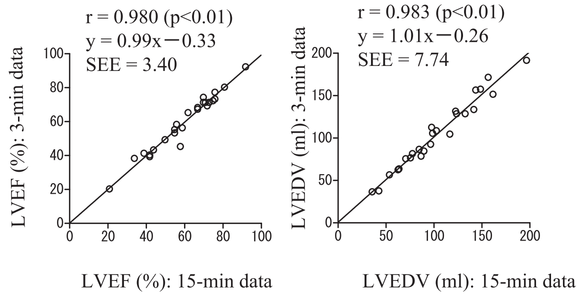

Fig. 5 Correlations of LV function and volume between standard and rapid gated SPECT. (Kumita S, Kumazaki T, Cho K, et al. Ann Nucl Med 1998; 12: 71)

Rapid Data Acquisition Protocol in ECG-gated Myocardial Perfusion SPECT

Myocardial perfusion data with a technetium-labeled tracer is usually acquired 30 to 60 minutes after the intravenous injection taking account of washout through the hepatobiliary system. Since this agent does not show a significant redistribution phenomenon clinically, SPECT images reflect myocardial perfusion at injection, but LV function based on the ECG-gated data is estimated at nearly the resting state in spite of the actual situation at injection[9]. For assessment of LV function during exercise or in drug loading, we need to contract the data collection time as soon as possible. We therefore tried rapid ECG-gated SPECT acquisition in patients with heart disease, and examined the reliability of the LV functional data[10].

Twenty-five patients with ischemic heart disease underwent gated SPECT with standard data collection (acquisition time, 15 min) and with rapid data collection (acquisition time, 3 min). The LVEF (%) and LVEDV (m*l*) determined automatically with the QGS program showed excellent correlations between the two protocols (**Fig. 5**). Subsequently visual assessment of regional wall motion based on a four-point grading system was carried out with a cine LV display. High complete agreement was obtained in 158 (90.3%) of 175 segments, so assessment of the global and regional LV function with the rapid data acquisition protocol demonstrated high reliability and feasibility[10].

Serial Assessment of LV Performance during Bicycle Exercise in Healthy Subjects

Radionuclide ventriculography (RNV) has gained wide popularity as a noninvasive method for determining LV performance. The clinical RNV can be categorized into two major techniques of ECG-gated equilibrium and first-pass method. In both techniques, LVEF is calculated from changes in radioactivity those are assumed to be proportional to changes in LV volume. Measurements of LVEF using the two methods correlated closely, but data acquisition time is markedly shorter for first-pass studies. First-pass RNV offers the unique ability to record and analyze the transit of radionuclide bolus

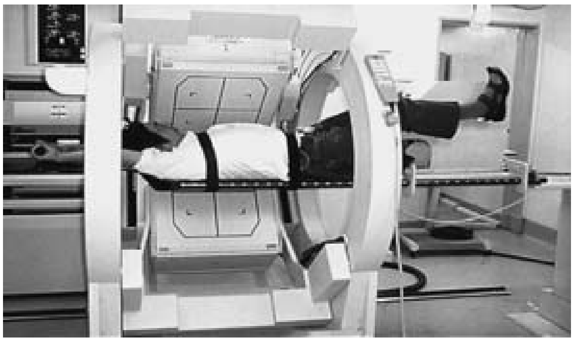

Fig. 6 Gated SPECT data acquisition during exercise using a detachable bicycle ergometer.

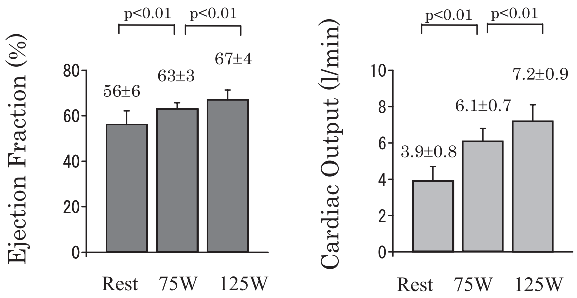

Fig. 7 Ejection fraction and cardiac output responses during exercise using gated SPECT data in 8 healthy subjects. (Kumita S, Cho K, Mizumura S, et al. Nucl Med Commum 1999; 20: 427)

through the central circulation, and one of its benefits is the suitability for the evaluation of ventricular function at peak stress[11,12]. However, conventional acquired first-pass RNV can only analyze planar wall motion.

On the other hand, ECG-gated myocardial SPECT can assess the myocardial perfusion and LV function simultaneously as a pair of tomographic data sets. For assessment of LV function during exercise by means of gated SPECT, data acquisition time must be contracted to approximately 3 min at the longest. In our laboratory, LV function during exercise was evaluated using gated SPECT[13] on the basis of our previous report in relation to the feasibility of short time (3 min) gated data collection as mentioned earlier[10]. And each exercise level lasted 5 min in order to reach the steady state for that level and to allow sufficient time for isotopic data acquisition. The exercise protocol involved a detachable bicycle ergometer (Exometer™, ADAC, Milpitas, CA) installed on a table **(Fig. 6)**, and the use of a motion correction program (AMC program).

After administration of ^{99m}Tc-tetrofosmin, eight healthy volunteers aged from 27 to 49 years were examined gated SPECT at rest and during supine submaximal exercise of 75 and 125 watts. Each of gated data collection time was 3 min. With the use of gated SPECT data, LVEDV demonstrated a biphasic response during exercise (from 106.4 ± 17.5 to 119.9 ± 19.9, 108.1 ± 19.2 m*l*). In contrast, LVESV decreased gradually and significantly during exercise (from 47.1 ± 11.9 to 41.5 ± 8.9, 36.1 ± 10.1 m*l*, $p<0.05$), and LVEF continued to increase at higher work loads despite a fall in LVEDV. There was a progressive increase in cardiac output during exercise which reached a peak of 7.2 ± 0.9 *l*/min **(Fig. 7)**.

An increase was noted in ejection fraction and cardiac output during supine bicycle exercise, which was similar to that found in almost all of previous studies[14]. Thus, this technique can assess the LV function during exercise and has a possibility to offer useful informations for the evaluation of patients with ischemic heart disease.

Serial Assessment of LV Performance during Bicycle Exercise in Patients with Ischemic Heart Disease

As the next step, we have evaluated LV performance during exercise by ECG-gated SPECT in patients with ischemic heart disease[15]. The study population consisted of 10 healthy volunteers (Group N) and 9 patients with ischemic heart disease (Group I). Seven patients in Group I had a history of prior myocardial infarction. Rest gated SPECT was performed 40 min after an injection of ^{99m}Tc-tetrofosmin. After resting data acquisition, Group N underwent up to two 5-min stages of exercise (75 and 125 watts) using a detachable bicycle ergometer. Group I patients all underwent symptom-limited, maximal testing using the ergometer. ECG-gated SPECT data were acquired from both groups for 3 min at rest and during the last 3 min of each exercise stage. Significant increases occurred in LVEF from rest to peak stress in both groups (from

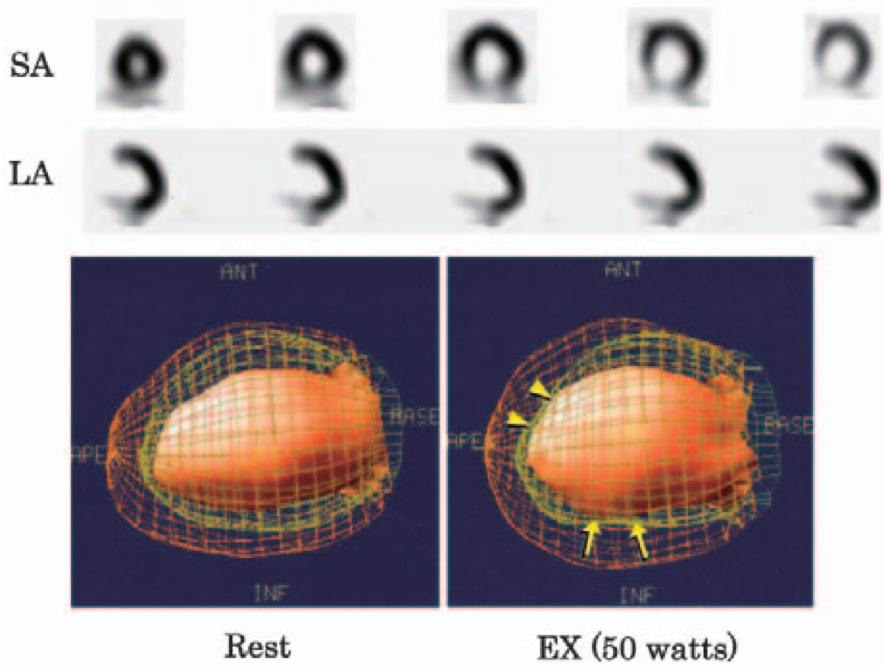

Fig. 8 Resting myocardial perfusion SPECT image and LV functional images at rest and during bicycle exercise in a 69-year-old male with inferior myocardial infarction. The function image at rest demonstrates moderate hypokinesis in the inferior wall. Whereas, the function image during exercise shows severe hypokinesis in the infarct area **(arrows)**. In addition, anterior wall motion abnormality is depicted **(arrowheads)** on the stress image. Coronary angiography revealed three-vessel disease. (Kumita S, Cho K, Nakajo H, et al. Ann Nucl Med 2002; 16: 329)

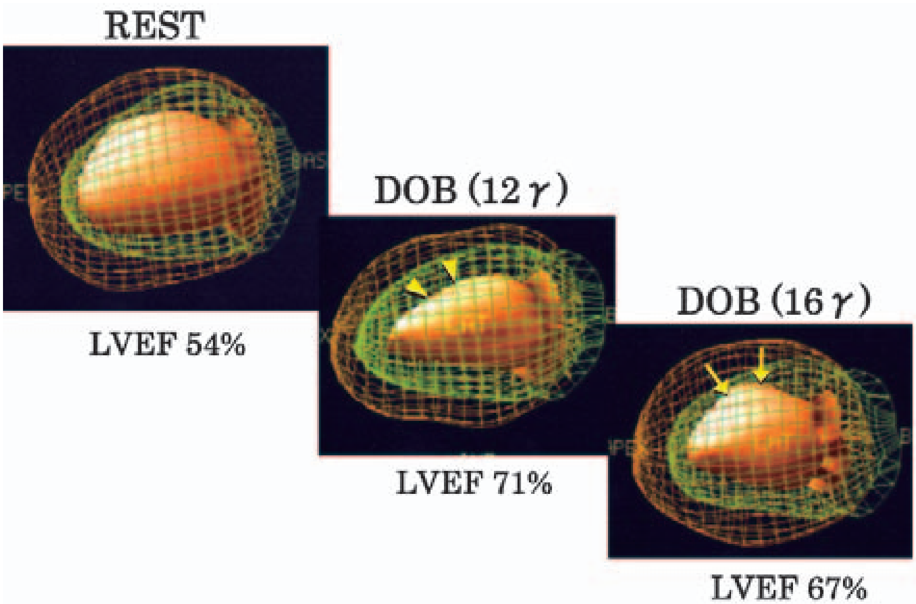

Fig. 9 ECG-gated SPECT in a 71-year-old male with anterior myocardial infarction. Coronary angiography revealed 99% stenosis of the proximal left anterior descending branch. Regional wall motion abnormality in the infarct lesion fit a biphasic response, which disappears at 12 μg/kg per min stress **(arrowheads)**, and reappears at 16 μg/kg per min stress **(arrows)**. (Kumita S, Cho K, Nakajo H, et al. J Nucl Cardiol 2001; 8: 152)

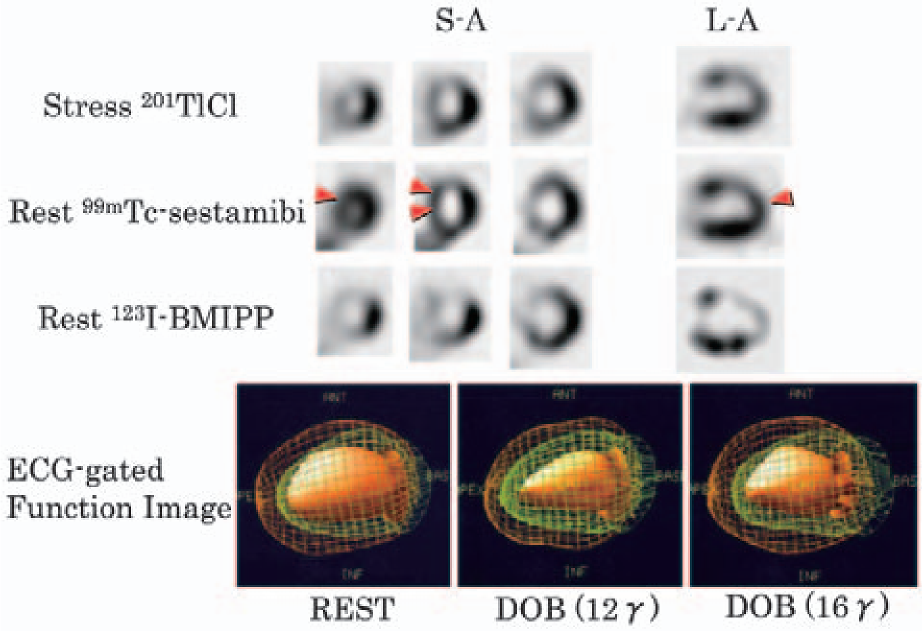

Fig. 10 Myocardial SPECT and LV function images obtained from gated SPECT at rest and during dobutamine stress (biphasic response) in a patient with anterior myocardial infarction. There is a large area of perfusion abnormality involving the anterior and anteroseptal wall on the stress ^{201}TlCl images, which is partially reversible on rest ^{99m}Tc-sestamibi images (**arrowheads**). The intensity and size of accumulation abnormality are greater on ^{123}I-BMIPP SPECT compared with the perfusion images. (Kumita S, Cho K, Nakajo H, et al. Ann Nucl Med 2005; 19: 379)

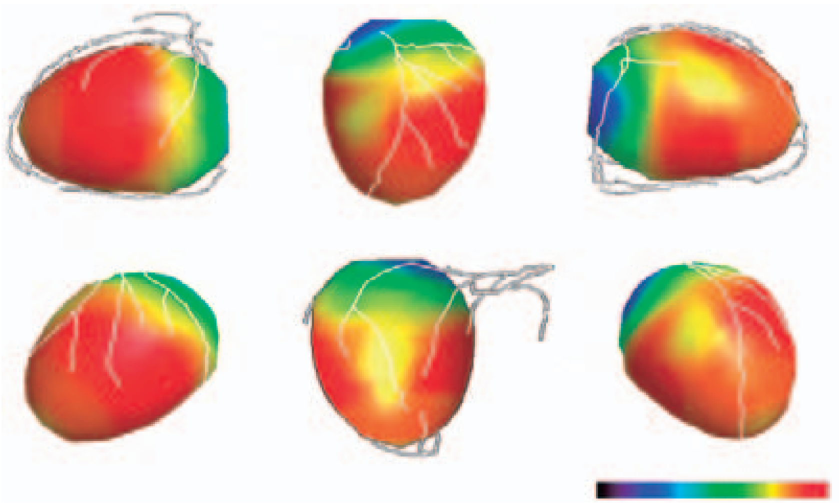

Fig. 11 An example of the 3D registration and fusion images of SPECT and CT coronary artery. (Nakajo H, Kumita S, Cho K, et al. Ann Nucl Med 2005; 19: 207)

55.4 ± 5.8 to 66.6 ± 4.1% in group N, $p<0.0001$; from 49.0 ± 12.8 to 56.7 ± 13.8% in Group I, $p<0.001$). The LVESV value significantly decreased to peak stress in Group N (from 49.9 ± 13.1 to 37.8 ± 10.0 m*l*, $p<0.0001$), whereas LVEDV did not change (from 110.6 ± 18.9 to 112.0 ± 19.0 m*l*). In contrast, the LVESV values at rest and under peak stress were similar in Group I (from 52.6 ± 23.9 to 51.7 ± 31.4 m*l*) and LVEDV in Group I at peak exercise tended to increase (from 102.8 ± 36.7 to 111.3 ± 39.0 m*l*). Changes in LVESV from rest to peak stress were significantly different between Groups N and I (−12.1

± 6.3 vs. −0.9 ± 11.6 m*l*, $p<0.02$).

ECG-gated SPECT revealed regional wall motion abnormalities in 8 (42.1%) of 19 segments with significant coronary arterial stenosis in 9 patients (27 segments) with ischemic heart disease (Group I). In contrast, the wall motion response of the remaining 8 segments without coronary stenosis was normal (improvement or no change) during exercise. These results indicated that assessment of regional wall motion in the present study could be considered as a specific marker for detection of affected coronary arterial stenosis.

ECG-gated SPECT using short-time data collection can assess LV function during exercise (**Fig. 8**) and may offer useful information with which to evaluate patients with ischemic heart disease.

Serial Assessment of LV Performance during Dobutamine Stress in Patients with Ischemic Heart Disease

Dobutamine increases myocardial oxygen consumption by increasing heart rate, contractility and arterial blood pressure. In addition, it causes myocardial blood flow heterogeneity, and thus may be a useful stress for noninvasive detection of coronary artery disease. Two-dimensional echocardiography[16], radionuclide ventriculography[17], magnetic resonance imaging[18], SPECT[19] and various combinations of these methods[20] have been used in conjunction with dobutamine to detect ischemia. In a previous study of ours, we evaluated LV performance during dobutamine stress by means of ECG-gated myocardial perfusion SPECT[21] using short-time data collection. In this study, there was no need to consider motion artifacts during dobutamine infusion, unlike the bicycle exercise.

After administration of ^{99m}Tc-sestamibi or tetrofosmin, 67 patients with ischemic heart disease (including 35 patients with prior myocardial infarction) were examined by gated SPECT at rest and during dobutamine stress (4, 8, 12, 16, 20 μg/kg per min, or until limited by symptoms, with increments every 8 min). The criteria for early termination of the dobutamine infusion were a systolic blood pressure≧210 mmHg, ST segment depression≧2 mm, supraventricular or ventricular arrhythmias, severe angina or other intolerable symptoms. The gated data collection time was 5 min for each. After acquisition of gated SPECT data at the highest dose, ^{201}TlCl was injected and dual-isotope SPECT was also performed to assess the myocardial ischemia. In 32 patients without prior myocardial infarction, based on coronary angiography, the sensitivity of individual stenosed vessel detection with dual-isotope perfusion SPECT, wall motion abnormality obtained from gated SPECT, and the combined method were 55.9, 52.9 and 73.5%, respectively. Out of 33 infarct areas with culprit coronary arterial stenosis, gated SPECT during dobutamine infusion revealed regional wall motion abnormalities (worsening or biphasic response) in 57.6% (**Fig. 9**). The prevalence of reversible perfusion defects on dual-isotope SPECT was higher in the segments with wall motion abnormalities than in the segments with normal wall motion response (89.5% vs. 42.9%, $p<0.02$).

Myocardial perfusion and LV function during dobutamine infusion were analyzed in a single examination by means of the combined method. This procedure has the potential to provide comprehensive information with which to evaluate hibernating myocardium in patients with myocardial infarction.

Assessment of Contractile Response to Dobutamine Stress

Myocardial hibernation is a condition of chronic LV dysfunction that is associated with severe coronary artery disease. Significant recovery of function, however, can be obtained with revascularization. Dobutamine stress echocardiography is a widely available, relatively cheap method for detecting myocardial ischemia, which is thought to be capable of discerning viable myocardium in myocardial infarct areas.

As mentioned above, serial assessment of regional LV function during low- and high-dose dobutamine stress was performed using short-time gated SPECT data collection. One of our previous studies was to characterize the patterns of dysfunctional myocardium by dobutamine infusion assessed by gated SPECT in relation to rest-stress perfusion, and fatty acid metabolism with ^{123}I-BMIPP SPECT[22].

Thirty-six patients with myocardial infarction given ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin were examined by gated SPECT at rest and during dobutamine stress (4 to 20 μg/kg per min). After acquisition data at the highest dose, ^{201}TlCl was injected and dual-isotope SPECT was performed to assess myocardial ischemia. Thirty of 36 patients also underwent myocardial SPECT with ^{123}I-BMIPP. Regional wall motion changes during dobutamine infusion were determined from the gated SPECT data and classified as: (1) Sustained improvement, (2) Worsening, (3) No change, and (4) Biphasic response[23,24]. For myocardial segments of each infarct area, stress ^{201}Tl, rest ^{99m}Tc and ^{123}I-BMIPP uptakes were graded on a five-point scoring system. Rest ^{99m}Tc defect score index (DSI) in No change area was significantly higher than that in Biphasic area. ΔDSI (stress ^{201}Tl-rest ^{99m}Tc) in Biphasic area was significantly higher than those in Improvement and No change areas. The ΔDSI (BMIPP-^{99m}Tc) in Worsening area tended to be higher than that in No Change area.

In summary, the present results were as follows: Biphasic areas showed mildly reduced rest myocardial perfusion, severe ischemia, and moderately reduced BMIPP uptake (**Fig. 10**); Sustained improvement areas showed moderately reduced rest myocardial perfusion, mild ischemia, and moderately reduced BMIPP uptake; Worsening areas showed moderately reduced rest myocardial perfusion, severe ischemia, and severely reduced BMIPP uptake; and No change areas showed severely reduced rest myocardial perfusion, almost no trace of ischemia, and severely reduced BMIPP uptake.

Regional contractile response to dobutamine stress analyzed by gated SPECT showed that the response in myocardial infarct areas could be classified by rest and stress myocardial perfusion and BMIPP accumulation.

Future Possibilities

In our previous study, a new technique for three-dimensional registration of CT coronary angiography (CTCA) and ECG-gated myocardial perfusion SPECT was developed (**Fig. 11**)[25]. Coronary arteries and their branches were traced using CTCA data manually and reconstructed three-dimensions. Gated SPECT data were registered and mapped to a LV binary model extracted from CTCA data using manual, nonrigid registration method. This technique of registration may assist the integration of information from gated SPECT and CTCA, and may have clinical application for the diagnosis of ischemic heart disease.

In addition, we hope for the achievement of attenuation correction of myocardial perfusion image using the myocardial CT data. The use of attenuation correction in conjunction with gating may lead to an increase in the use of stress-only (single-injection) protocol. If a stress perfusion defect demonstrated normal wall motion, we could conclude that myocardial ischemia is present (not myocardial infarction). There would be enormous radiopharmaceutical, instrumentation, and cost saving. Consequently, it may lead to the spread of nuclear cardiology.

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