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Assessment of myocardial washout of Tc-99m-sestamibi in patients with chronic heart failure: Comparison with normal control

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Background: In contrast to ^{201}TlCl, ^{99m}Tc-sestamibi shows very slow myocardial clearance after its initial myocardial uptake. In the present study, myocardial washout of ^{99m}Tc-sestamibi was calculated in patients with non-ischemic chronic heart failure (CHF) and compared with biventricular parameters obtained from first-pass and ECG-gated myocardial perfusion SPECT data. ***Methods and Results:*** After administration of ^{99m}Tc-sestamibi, 25 patients with CHF and 8 normal controls (NC) were examined by ECG-gated myocardial perfusion SPECT and planar data acquisition in the early and delayed (interval of 3 hours) phase. Left ventricular ejection fraction (LVEF, %), peak filling rate (PFR, sec^{-1}), end-diastolic volume (LVEDV, m*l*) and end-systolic volume (LVESV, m*l*) were automatically calculated from the ECG-gated SPECT data. Myocardial washout rates over 3 hours were calculated from the early and delayed planar images. Myocardial washout rates in the CHF group (39.6 ± 5.2%) were significantly higher than those in the NC group (31.2 ± 5.5%, $p < 0.01$). The myocardial washout rates for the 33 subjects showed significant correlations with LVEF ($r = -0.61$, $p < 0.001$), PFR ($r = -0.47$, $p < 0.01$), LVEDV ($r = 0.45$, $p < 0.01$) and LVESV ($r = 0.48$, $p < 0.01$). ***Conclusion:*** The myocardial washout rate of ^{99m}Tc-sestamibi is considered to be a novel marker for the diagnosis of myocardial damage in patients with chronic heart failure.

Key words: ^{99m}Tc-sestamibi, myocardial washout, chronic heart failure

INTRODUCTION

^{99m}Tc-methoxyisobutyl isonitrile (^{99m}Tc-sestamibi) is a synthetic lipophilic, cationic, myocardial perfusion tracer. ^{99m}Tc-sestamibi accumulates linearly in the myocardium according to blood flow in much the same manner as microspheres. In contrast to ^{201}TlCl, ^{99m}Tc-sestamibi shows very slow myocardial clearance after its initial myocardial uptake.[1,2] On the other hand, ^{99m}Tc-sestamibi imaging allows first-pass[3,4] and ECG-gated single-photon emission computed tomography (SPECT) data acquisition,[5–9] permitting the simultaneous evaluation of biventricular function and myocardial perfusion. In the present study, myocardial washout of ^{99m}Tc-sestamibi was calculated in patients with non-ischemic chronic heart failure and compared with biventricular parameters obtained from first-pass and ECG-gated myocardial perfusion SPECT data.

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MATERIALS AND METHODS

Study Population

Twenty-five patients with chronic heart failure (*CHF group*; 13 men and 12 women; mean age of 59 ± 17 yr, range from 21 to 87 yr; New York Heart Association [NYHA] functional class II or III) and 8 normal controls (*NC group*; 7 men and one woman; mean age of 51 ± 9 yr, range from 38 to 66 yr) were included in this study. The etiology of chronic heart failure was dilated cardiomyopathy in 10 patients, hypertrophic cardiomyopathy

in 3, hypertensive heart disease in 3, cardiac sarcoidosis in 3, valvular disease in 2, and other etiologies in 4 patients. At the start of the trial, patients were receiving optimal treatment with any drug for heart failure. Patients who had a history of previous myocardial infarction or diabetes mellitus were excluded from the study. The diagnosis of heart failure was based on clinical criteria: a history of heart disease with symptoms of dyspnea or fatigue or both. On the basis of history and physical examination, there was no evidence of cardiorespiratory disease in normal controls. Informed consent was obtained from each participant before the study.

Study Protocol

First-pass radionuclide angiography was acquired, in the 30-degree right anterior oblique projection with the participant supine, by means of a single-head gamma camera (GCA 602A, Toshiba) equipped with a low-energy all-purpose collimator. A 20% window was centered at the 140-keV photopeak of ^{99m}Tc. ^{99m}Tc-sestamibi 815.9 ± 46.2 MBq (717–909 MBq) was injected into an antecubital vein in the right arm for the first-pass study. The tracer bolus was then injected and flushed with 20 m*l* 0.9% (wt/vol) saline solution. The study was acquired in the non-frame mode, set at the sampling intervals of 50 msec for 50 seconds.

Thirty minutes after the injection of ^{99m}Tc-sestamibi, ECG-gated myocardial perfusion SPECT data acquisition was started with a triple-head gamma camera (PRISM 3000, Marconi/Shimadzu), equipped with low-energy, general purpose collimators. The ECG-gated SPECT data were acquired over 360° in 20 (× 3) steps, each of which was 50 seconds. Thirty-two frames per R-R interval were acquired in a 64 × 64 matrix and a 20% window centered on the 140-keV photopeak of ^{99m}Tc. The acceptance window was set at 20% during beat collection. Immediately after SPECT data acquisition, initial planar imaging was performed in a 256 × 256 matrix for 3 min in the anterior view of the thorax. Three hours after the termination of the first planar imaging (early image), delayed planar acquisition was performed in the same anterior view for 3 min. The subjects were kept in a resting state during the 3 hour interval.

Assessment of Myocardial Distribution

Summed (non-gated) myocardial perfusion SPECT data with ^{99m}Tc-sestamibi were processed by filtered back projection (Butterworth filter, with cutoff frequency at 0.28 cycles/pixel; order, 5; and slice thickness, 3.9 mm). Data were reconstructed in the transaxial, short-axial and vertical long-axial planes with an OdysseyFX^{TM} processing computer (Marconi/Shimadzu). The myocardial images were normalized to the maximal activity they contained and presented for analysis at a 20% threshold. Visual assessment of myocardial distribution was then done by two experienced observers after consultation to define whether distribution was normal or not.

Assessment of Ventricular Function and Volume

From among the data on first-pass radionuclide angiography, a set of images in which the right ventricle was most clearly seen were chosen, and regions of interest were manually traced on the right ventricle and background. The right ventricular volume curve was then obtained, and the right ventricular ejection fraction (RVEF, %) was automatically calculated with commercially available software (NEW GMS; Toshiba, Tokyo, Japan).

The left ventricular ejection fraction (LVEF, %), end-diastolic volume (LVEDV, m*l*) and end-systolic volume (LVESV, m*l*) were automatically calculated from the ECG-gated SPECT data with ^{99m}Tc-sestamibi in the OdysseyFX^{TM} processing computer and the function analysis software QGS program^{TM} (Cedars-Sinai Medical Center).[10,11] The left ventricular endocardial surface and volume were determined for all gating intervals in the cardiac cycle by means of the QGS program. Left ventricular time-volume curves from gated data were generated by Fourier curve fitting analysis with three harmonics. In addition to ejection fraction determination, the peak filling rate (PFR, sec^{-1}) was calculated with original

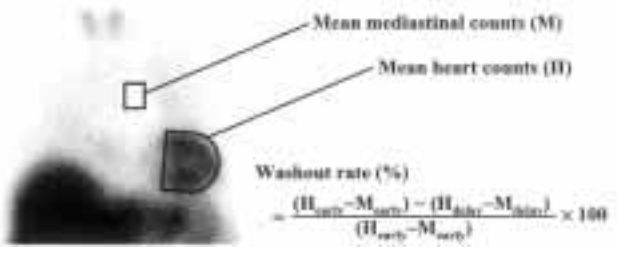

Fig. 1 Calculation of myocardial washout rate with ^{99m}Tc-sestamibi.

Table 1 Clinical data and biventricular parameters of studied subjects

	Normal control	Chronic heart failure	p value
	n = 8	n = 25	
Age (yr)	51 ± 9	59 ± 17	NS
Sex (M : F)	7 : 1	13 : 12	NS
NYHA (I/II/III/IV)	8/0/0/0	0/19/6/0	< 0.001
Gated SPECT			
LVEF (%)	67.0 ± 11.8	43.2 ± 15.7	< 0.001
LVEDV (m*l*)	84.0 ± 24.9	161.0 ± 70.9	< 0.001
LVESV (m*l*)	29.5 ± 16.4	99.0 ± 65.5	< 0.001
PFR (/sec)	2.28 ± 0.69	1.47 ± 0.71	< 0.05
First-pass RNA			
RVEF (%)	50.0 ± 9.4	42.9 ± 9.6	NS

NYHA, New York Heart Association functional class; RNA, radionuclide angiography

software (Shimadzu, Kyoto, Japan) as previously reported.[12]

Assessment of Myocardial Uptake and Washout Rate

^{99m}Tc-sestamibi uptakes were quantified by calculating the heart-to-mediastinum (H/M) ratio, after drawing regions of interest over the myocardium and the mediastinum in the anterior planar images. Without correction of ^{99m}Tc decay time, average counts per pixel in the myocardium were divided by average counts per pixel in the mediastinum. As shown in Figure 1, the myocardial washout rate of ^{99m}Tc-sestamibi was defined as:

$$\frac{(H_{early} - M_{early}) - (H_{delayed} - M_{delayed})}{H_{early} - M_{early}} \times 100\ (\%)$$

Statistical Analysis

All data are expressed as means ± one standard deviation. Unpaired Student's t-tests, as well as the Chi-squared analysis determined differences between proportions. Linear regression analysis determined correlations between proportions. A p-value of <0.05 was considered significant.

RESULTS

All subjects completed the study, and no untoward symptoms were observed in any of them during data acquisition.

In the visual assessment of myocardial distribution on non-gated (summed) SPECT images, 10 of 25 patients

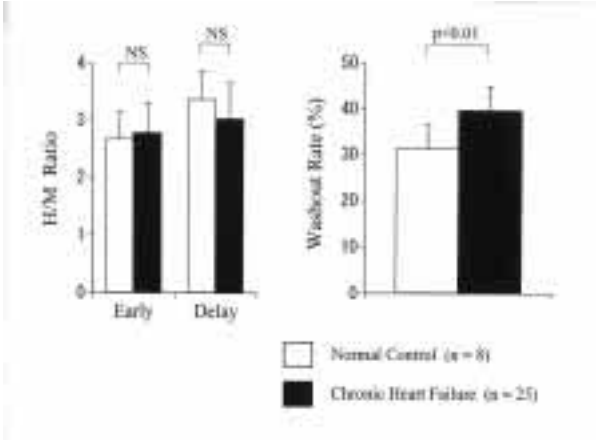

Fig. 2 Heart-to-mediastinum (H/M) ratio and myocardial washout rate obtained from ^{99m}Tc-sestamibi planar data.

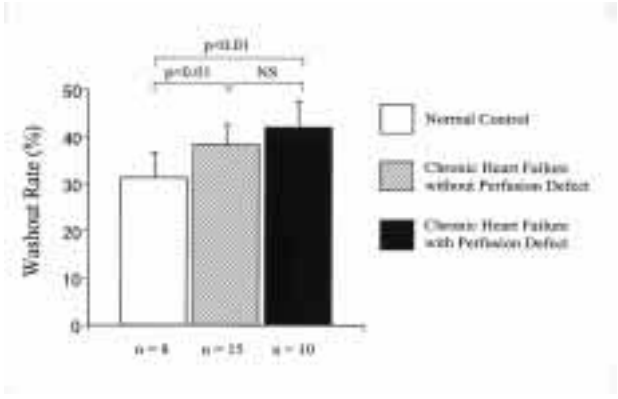

Fig. 3 Comparison of myocardial washout rates grouped by clinical classification and myocardial SPECT images.

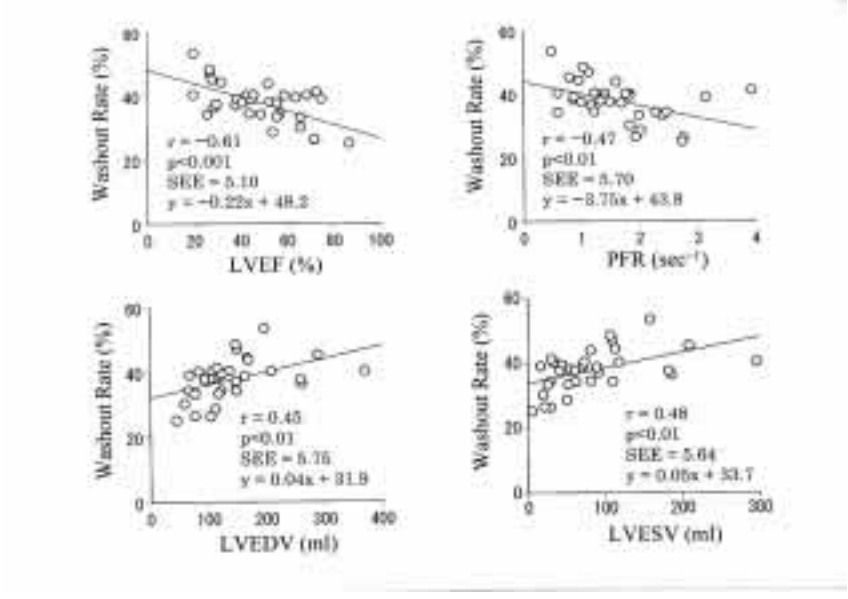

Fig. 4 Myocardial washout rate of ^{99m}Tc-sestamibi compared with left ventricular functions and volumes.

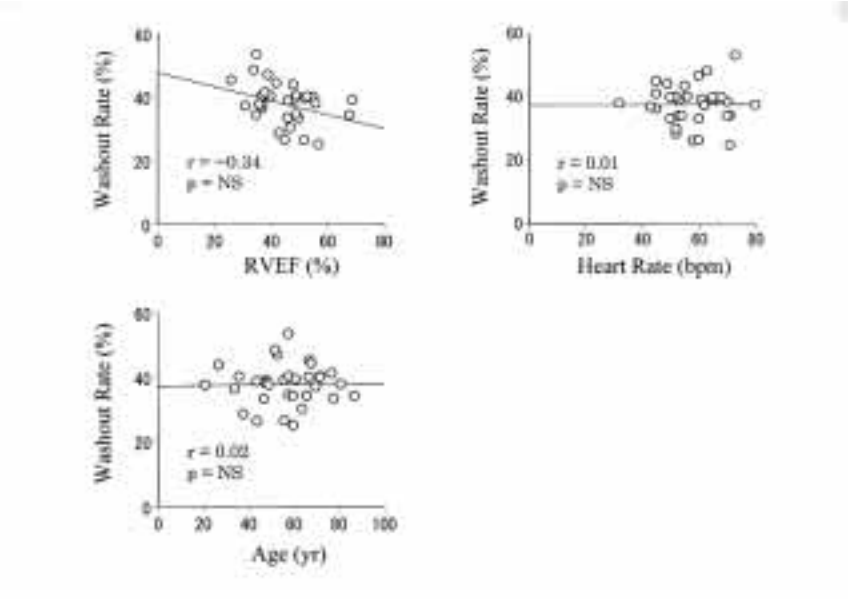

Fig. 5 Myocardial washout rate of ^{99m}Tc-sestamibi compared with right ventricular ejection fraction (RVEF), heart rate and age.

(40.0%) in the CHF group revealed segmental hypoperfused lesions in the myocardium, whereas no significant defect was observed in the NC group.

Biventricular parameters in both groups are shown in Table 1. Left ventricular volumes obtained from gated SPECT in the CHF group were significantly higher than those in the NC group (both $p < 0.001$). And LVEF values in the CHF group were significantly lower than those in the NC group ($p < 0.001$). RVEF values in the CHF group also tended to be lower than those in the NC group, although the difference was not statistically significant ($p = 0.09$).

H/M ratios obtained from planar images in the CHF group (Early, 2.77 ± 0.54; Delayed, 3.02 ± 0.64) showed no statistical difference from those in the NC group (Early, 2.66 ± 0.48; Delayed, 3.36 ± 0.51). Myocardial washout rates obtained from planar images in the CHF group ($39.6 \pm 5.2\%$) were significantly higher than those in the NC group ($31.2 \pm 5.5\%$, $p < 0.01$; Fig. 2). As shown in Figure 3, myocardial washout rates showed no statistical difference between patients with and without hypoperfused areas on myocardial perfusion SPECT in the CHF group ($41.9 \pm 5.7\%$, $n = 10$ vs. $38.2 \pm 4.4\%$, $n = 15$; $p = NS$).

As shown in Figure 4, the myocardial washout rates showed significant correlations with LVEF ($r = -0.61$, $p < 0.001$), PFR ($r = -0.47$, $p < 0.01$), LVEDV ($r = 0.45$, $p < 0.01$) and LVESV ($r = 0.48$, $p < 0.01$). Nevertheless, the myocardial washout rates did not correlate with RVEF ($r = -0.34$, $p = NS$), age ($r = 0.02$, $p = NS$) and heart rate ($r = 0.01$, $p = NS$), where heart rate was defined as the number of cycles/min during gated SPECT data acquisition (Fig. 5).

DISCUSSION

In the study presented here, we have demonstrated increased myocardial washout of ^{99m}Tc-sestamibi in the CHF group. And a significant inverse correlation between the myocardial washout rates and left ventricular function was shown. The increased washout of ^{99m}Tc-sestamibi may influence myocardial damage including left ventricular dysfunction.

Myocardial Uptake and Washout of ^{99m}Tc-sestamibi

Myocardial uptake of ^{99m}Tc-sestamibi is known to be dependent on passive distribution across sarcolemmal and mitochondrial membranes, driven by the transmembrane electrochemical gradient.[13,14] ^{99m}Tc-sestamibi uptake is diminished in the setting of irreversible injury to the myocardial cell membrane, suggesting that an intact cell membrane is an important component of uptake and retention.[15] Carvalho et al.[16] studied the subcellular distribution of ^{99m}Tc-sestamibi in isolated perfused rat heart, and showed that approximately 90% of the tracer was associated with mitochondria in an energy-dependent manner as a free cationic complex. Crane et al.[17] also have shown that more than 90% of myocardial sestamibi is localized within the mitochondrial fraction, and retention of sestamibi in the myocardium relates to mitochondrial function.

Wackers et al.[18] reported the results of multicenter phase I and phase II studies on blood clearance, biodistribution, dosimetry and the safety of ^{99m}Tc-sestamibi. As for the rest study, by 3 hours after injection, $27 \pm 4\%$ of initial cardiac activity had cleared. In the study presented here, the myocardial washout rate of ^{99m}Tc-

sestamibi (interval of 3 hours) in the NC group was 31.2 ± 5.5%, which was similar to the results for the multicenter phase I and II studies and the physical half-life of ^{99m}Tc (6 hours).

^{99m}Tc-sestamibi Washout in Damaged Myocardium

Piwnica-Worms et al.[14] studied the myocardial uptake and retention of ^{99m}Tc-sestamibi in a cultured chick embryo ventricular myocytes model. They showed that when mitochondrial and plasma membrane potentials are hyperpolarized, there is an increase in cellular uptake and retention of ^{99m}Tc-sestamibi. In contrast, when mitochondrial and plasma potentials are depolarized, there is inhibition of myocardial uptake and retention of the tracer. Beanlands et al.[15] showed that irreversible cellular injury, with cytochrome *c* oxidase inhibitor sodium cyanide and sarcolemmal membrane detergent Triton X-100, resulted in an increase in the ^{99m}Tc-sestamibi clearance.

Recently, reverse redistribution of ^{99m}Tc-sestamibi has been noted in patients with coronary artery disease.[19–21] Takeishi et al.[20] demonstrated that ^{99m}Tc-sestamibi reverse redistribution is evident after direct percutaneous transluminal coronary angioplasty (PTCA) in patients with acute myocardial infarction and is associated with the patent infarct-related artery and the preserved left ventricular function.

^{99m}Tc-sestamibi Washout in Patients with Chronic Heart Failure

Cardiac troponins T and I (cTnT and cTnI) are the sensitive markers for the diagnosis of myocardial injury.[22] Besides the myocardial infarction, other causes of cardiac injury can increase the biomarker. Missiv et al.[23] reported increased levels of cTnI in patients with advanced heart failure. Setsuta et al.[24] showed the correlations between the cTnT level and the severity of chronic heart failure and patient outcome, and suggested that increased levels of cTnT reflected the continuing myocardial damage.

In the present study, myocardial washout rates of ^{99m}Tc-sestamibi in the CHF group (39.6 ± 5.2%) were significantly higher than those in the NC group ($p < 0.01$). Continuing myocardial damage in the CHF group may accelerate the ^{99m}Tc-sestamibi clearance from the myocardium. The myocardial washout rates out of all subjects correlated with left ventricular function (LVEF and PFR values). From these results, insufficient ATP production caused by mitochondrial dysfunction in damaged myocardium may be related to concordant findings of ^{99m}Tc-sestamibi rapid washout and left ventricular dysfunction.

In the CHF group, myocardial washout rates showed no statistical difference between patients with and without hypoperfused areas on myocardial perfusion SPECT. This result suggested that washout of the hypoperfused areas did not necessarily contribute to the rapid washout in the CHF group. In other words, normoperfused myocardium was considered to be involved in the rapid washout in the CHF group. This phenomenon is attractive, as continuing myocardial damage with normal myocardial perfusion can be understood by means of the washout rates.

In the next step, it is necessary to compare the myocardial washout rates with several biomarkers (e.g., cTnT) to prove the continuing myocardial damage in the CHF group. Further follow-up studies are also required to clarify the relationship between the ^{99m}Tc-sestamibi myocardial washout and patient outcome, including left ventricular functional outcome and prognosis, in CHF group.

CONCLUSION

The myocardial washout rate of ^{99m}Tc-sestamibi was calculated in patients with non-ischemic CHF and compared with biventricular parameters obtained from first-pass and ECG-gated myocardial perfusion SPECT data. The myocardial washout rates in CHF patients were significantly higher than those in normal controls. The myocardial washout rate of ^{99m}Tc-sestamibi was thought to be a novel marker for the diagnosis of myocardial damage.

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REFERENCES

1. Li Q-S, Frank TL, Franceschi D, Wagner HN, Becker LC. Technetium-99m methoxyisobutyl isonitrile (RP30) for quantification of myocardial ischemia and reperfusion in dogs. *J Nucl Med* 1988; 29: 1539–1548.
2. Sinusas AJ, Bergin JD, Edwards NC, Watson DD, Ruiz M, Makch RW, et al. Redistribution of ^{99m}Tc-sestamibi and ^{201}Tl in the presence of a severe coronary artery stenosis. *Circulation* 1994; 89: 2332.
3. Meyer JV, Mena I, Narahara K. Simultaneous assessment of left ventricular wall motion and myocardial perfusion with Technetium-99m-methoxy isobutyl isonitrile at stress and rest in patients with angina: comparison with Thallium-201 SPECT. *J Nucl Med* 1990; 31: 457–463.
4. Jones RH, Borges-Neto S, Potts JM. Simultaneous measurement of myocardial perfusion and ventricular function during exercise from a single injection of technetium-99m sestamibi in coronary artery disease. *Am J Cardiol* 1990; 66: 68E–71E.
5. Grucker D, Florentz P, Ozwald T, Chambron J. Myocardial gated tomoscintigraphy with ^{99m}Tc-methoxy isobutyl isonitrile (MIBI): regional and temporal activity curve analysis. *Nucl Med Commun* 1989; 10: 723–732.
6. Marcassa C, Marzullo P, Parodi O, Sambuceti G, L'Abbate A. A new method for noninvasive quantitation of segmental

myocardial wall thickening using ^{99m}Tc-2-methoxy- isobutyl-isonitrile scintigraphy: results in normal subjects. *J Nucl Med* 1990; 31: 173–177.
7. Faber TL, Akers MS, Peshock RM, Corbett JR. Three-dimensional motion and perfusion quantification in gated single-photon emission computed tomograms. *J Nucl Med* 1991; 32: 2311–2317.
8. DePuey EG, Nichols K, Dobrinsky C. Left ventricular ejection fraction assessed from gated technetium-99m-sestamibi SPECT. *J Nucl Med* 1993; 34: 1871–1876.
9. Williams KA, Taillon LA. Left ventricular function in patients with coronary artery disease assessed by gated tomographic myocardial perfusion images. *J Am Coll Cardiol* 1996; 27: 173–181.
10. Germano G, Kavanagh P, Su HT, Mazzanti M, Kiat H, Hachamoritch R, et al. Automatic reorientation of three-dimensional transaxial myocardial perfusion SPECT images. *J Nucl Med* 1995; 36: 1107–1114.
11. Germano G, Kiat H, Kavanagh P, Moriei M, Mazzanti M, Su HT, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; 36: 2138–2147.
12. Kumita S, Cho K, Nakajo H, Toba M, Uwamori M, Mizumura S, et al. Assessment of left ventricular diastolic function using ECG-gated myocardial perfusion SPECT: comparison with multigated equilibrium radionuclide angiography. *J Nucl Cardiol* 2001; 8: 568–574.
13. Chiu ML, Kronauge JF, Piwnica-Worms D. Effect of mitochondrial and plasma membrane potentials on accumulation of hexakis (2-methoxyisobutylisonitrile) technetium (I) in cultured mouse fibroblasts. *J Nucl Med* 1990; 31: 1646–1653.
14. Piwnica-Worms D, Kronauge JF, Chiu ML. Uptake and retention of hexakis (2-methoxyisobutyl isonitrile) technetium (I) in cultured chick myocardial cells. Mitochondrial and plasma membrane potential dependence. *Circulation* 1990; 82: 1826–1838.
15. Beanlands RS, Dawood F, Wen WH, McLaughlin PR, Butany J, D'Amati G, et al. Are the kinetics of technetium-99m methoxyisobutyl isonitrile affected by cell metabolism and viability? *Circulation* 1990; 82: 1802–1814.
16. Carvalho PA, Chiu ML, Kronauge JF, Kawamura M, Jones AG, Holman BL, et al. Subcellular distribution and analysis of technetium-99m-MIBI in isolated perfused rat hearts. *J Nucl Med* 1992; 33: 1516–1521.
17. Crane P, Laiberte R, Heminway S, Thoolen M, Orlandi C. Effect of mitochondrial viability and metabolism on technetium-99m sestamibi myocardial retention. *Eur J Nucl Med* 1993; 20: 20–25.
18. Wackers FJ Th, Berman DS, Maddahi J, Watson DD, Beller GA, Strauss W, et al. Technetium-99m hexakis 2-methoxy-isobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. *J Nucl Med* 1989; 30: 301–311.
19. Shin WJ, Miller K, Stipp V, Mazour S. Reverse redistribution on dynamic exercise and dipyridamole stress technetium-99m-MIBI myocardial SPECT. *J Nucl Med* 1995; 36: 2053–2055.
20. Takeishi Y, Sukekawa H, Fujiwara S, Ikeno E, Sasaki Y, Tomoike H, et al. Reverse redistribution of technetium-99m-sestamibi following direct PTCA in acute myocardial infarction. *J Nucl Med* 1996; 37: 1289–1294.
21. Fujiwara S, Takeishi Y, Atsumi H, Yamaki M, Takahashi N, Yamaoka M, et al. Prediction of functional recovery in acute myocardial infarction: comparison between sestamibi reverse redistribution and sestamibi/BMIPP mismatch. *J Nucl Cardiol* 1998; 5: 119–127.
22. Jaffe AS, Ravkilde J, Roberts R, Naslund U, Apple FS, Galvani M, et al. It's time for a change to a troponin standard. *Circulation* 2000; 102: 1216–1220.
23. Missiv E, Calzolari C, Pau B. Circulating cardiac troponin I in severe congestive heart failure. *Circulation* 1997; 96: 2953–2958.
24. Setsuta K, Seino Y, Takahashi N, Ogawa T, Sasaki K, Harada A, et al. Clinical significance of elevated levels of cardiac troponin T in patients with chronic heart failure. *Am J Cardiol* 1999; 84: 608–611.