Incremental Prognostic Value of Cardiac Function Assessed by ECG-Gated Myocardial Perfusion SPECT for the Prediction of Future Acute Coronary Syndrome

Naoya Matsumoto, MD; Yuichi Sato, MD; Yasuyuki Suzuki, MD; Shu Kasama, MD*; Yoshimochi Nakano, MD; Masahiko Kato, MD; Shunichi Yoda, MD; Takaaki Miki, MD; Jun Iida, MD; Taeko Kunimasa, MD; Futoshi Tadehara, MD**;
Ken Nagao, MD; Atsushi Hirayama, MD

Background The prognostic value of ECG-gated rest ^{201}Tl /stress $^{99\text{m}}\text{Tc}$ -tetrofosmin myocardial perfusion single-photon emission computed tomography for the prediction of acute coronary syndrome (ACS: myocardial infarction (MI) and unstable angina (UA)) and the implications of ejection fraction (EF) has not yet been defined in Japanese.

Methods and Results The 1,895 patients were followed up for the occurrence ACS. The mean follow-up interval was 26.9 ± 15.5 months. The 142 patients with revascularization within 60 days were censored. Summed stress score (SSS) and summed difference score (SDS) were calculated. The 19 MI and 29 UA occurred (1.1% and 1.6%, respectively). Univariate Cox analysis showed that hypertension (Wald 5.09, $p < 0.05$), poststress EF (Wald 10.9, $p < 0.01$), SSS (Wald 12.4, $p < 0.001$) and SDS (Wald 18.7, $p < 0.001$) were significant predictors of ACS. Multivariate Cox analysis showed that hypertension (Wald 4.27, $p < 0.05$) and SDS (Wald 8.59, $p < 0.01$) were independent predictors. When multiple clinical risk factors (number of coronary risk factors ≥ 2), significant ischemia (SDS ≥ 4) and low EF (EF $< 45\%$) were applied to multivariate Cox analysis, the combination of significant ischemia and low EF showed the highest predictive value (Wald 11.9; $p < 0.001$) for future ACS.

Conclusion Poststress EF added incremental prognostic value for the prediction of ACS. (Circ J 2008; 72: 2035–2039)

Key Words: Acute coronary syndrome; Coronary artery disease; Gated SPECT; Prognosis; Single-photon emission computed tomography

Myocardial perfusion single-photon emission computed tomography (SPECT) has been shown to provide incremental prognostic value over clinical data and improves stratification of patients into different levels of risk in American populations^{1–3} as well as in Japanese patient populations.⁴ However, the predictive value of poststress ejection fraction (EF) provided by electrocardiogram (ECG)-gated rest ^{201}Tl /stress $^{99\text{m}}\text{Tc}$ -tetrofosmin dual-isotope myocardial perfusion SPECT for future acute coronary syndrome (ACS) events has not yet been reported in a large Japanese population. Furthermore, the incremental prognostic value of poststress EF to myocardial perfusion parameters is unclear. The goal of this study was to define the prognostic value of ECG-gated myocardial perfusion SPECT for the prediction of ACS.

Methods

Study Population

We prospectively identified 2,170 consecutive patients with known or suspected coronary artery disease who underwent dual isotope SPECT with either exercise or pharmacological stress between November 2001 and December 2005, at Nihon University Surugadai Hospital. Exclusion criteria were as follows: unstable angina (UA) or acute myocardial infarction (AMI) within 2 weeks from onset; hypertrophic or dilated cardiomyopathies, age less than 20 years; refusal to participate in the study. From the 1,988 patients without exclusion criterion, those with atrial fibrillation or atrial flutter (total 93 patients) were also excluded because arrhythmia might have affected the ECG-gated parameters. The total follow-up group consisted of 1,895 patients (follow-up rate 92.5%). Of this initial population, 142 patients revascularized in the first 60 days after nuclear testing were excluded from the prognostic portion of the analyses, and the prognostic data presented here are based on a subset of 1,753 patients.

Stress Myocardial Perfusion SPECT Protocol

All patients underwent stress dual-isotope myocardial perfusion SPECT as previously described.^{2–5} Initially, ^{201}Tl (111 MBq) was injected intravenously and rest ^{201}Tl imaging was initiated 5 min after injection of the isotope. Patients then performed bicycle ergometer stress or had

(Received May 19, 2008; revised manuscript received July 1, 2008; accepted July 23, 2008; released online October 24, 2008)

Department of Cardiology, Nihon University School of Medicine, Tokyo, *Department of Cardiovascular Medicine, Gunma University School of Medicine, Maebashi and **Department of Cardiovascular Medicine, Hiroshima University Hospital, Hiroshima, Japan
Mailing address: Yuichi Sato, MD, Department of Cardiology, Nihon University School of Medicine, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8309, Japan. E-mail: yuichis@med.nihon-u.ac.jp
All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Fig 1. The 20-segment model for the assessment of myocardial perfusion images.

pharmacological (adenosine triphosphate) stress induced. Exercise was stopped when the patient's heart rate reached more than 85% of the maximum predictive heart rate (220–age). When a patient's heart rate did not reach 85% of the maximum predictive heart rate, or there was severe chest pain on ergometer stress, pharmacological stress by adenosine triphosphate took over as the mode of stress. Low level (25 W) ergometer exercise was added during adenosine triphosphate stress whenever possible to minimize the side-effects related to adenosine triphosphate. ^{99m}Tc -tetrofosmin was injected 1 min prior to the end of exercise stress. ^{99m}Tc -tetrofosmin was also injected 3 min after the start of adenosine triphosphate stress whenever possible to minimize the side-effects related to adenosine triphosphate. Stress acquisition was started within 30 min after stress ^{99m}Tc -tetrofosmin injection (740 MBq). Patients were asked to discontinue β -blockers for 48 h, and nitrates and caffeine for 24 h prior to the study.

Acquisition Protocol and Image Reconstruction

Rest and stress scans were acquired on a dual detector gamma camera in the 90° detector configuration (E-CAM, Siemens Medical Solutions, Erlangen, Germany), using a high-resolution, low-energy collimator, pseudo-continuous detector rotation, 64 projections over an 180° arc from the right anterior oblique (RAO) to the left posterior oblique (LPO), and a non-circular orbit. Poststress images were acquired in the supine and prone positions. ECG-gated rest ^{201}Tl images were acquired for 23 s/projection for 64 stops (32 stops/head), giving an acquisition time of 16 min. ECG-gated ^{99m}Tc -tetrofosmin poststress images in the supine position were acquired for 20 s/projection (14 min) and non-ECG-gated ^{99m}Tc -tetrofosmin prone poststress images were acquired for 18 s/projection (9 min). For prone-position imaging, patients lay prone on the table and the detectors rotated underneath the table from the RAO to the LPO. ^{201}Tl images at rest were acquired with 30% of symmetrical window over 80 keV ^{201}Tl photopeak. All ^{99m}Tc -tetrofosmin images were acquired with a 15% of symmetrical window over the 140 keV ^{99m}Tc photopeak. The raw projection datasets were filtered with a Butterworth filter (order 10 and cutoff frequency 0.38 cycles/cm for rest images, order 5 and cutoff frequency 0.5 cycles/cm for stress supine images, and order 5 and cutoff frequency 0.42 cycles/cm for stress prone images). Scatter or attenuation correction was not applied. Filtered raw projection images were automatically reconstructed into transverse datasets. The 3-dimensional location of the long axis of the left ventricle was determined automatically, and the short-, vertical long- and horizontal long-axis images were generated.⁶

Image Interpretation

SPECT images were scored semiquantitatively by an experienced nuclear cardiologist (N.M) using a 20-segment model of the left ventricle with a 5-point scale (0=normal

uptake, 1=mild hypoperfusion, 2=moderate hypoperfusion, 3=severe hypoperfusion and 4=no uptake)^{4,5,7}. The inter-observer reproducibility of scoring in our laboratory, determined by Cohen's kappa analysis, has been reported to be excellent (kappa=0.92)⁵. In this model, the left anterior descending artery distribution territory comprised 10 segments (segments 1–3, 7–9, 13, 14, 19 and 20), the left circumflex artery comprised 5 segments (segments 5, 6, 11, 12, 17 and 18) and the right coronary artery comprised 4 segments (segments 4, 10, 15 and 16) (Fig 1). Summed stress score (SSS) and summed rest score were calculated by adding the scores of 20 segments in the stress and rest images, respectively. Summed difference score (SDS) was derived as the difference between the stress and rest scores. Non-reversible segments (stress-rest score combinations of 4–4, 4–3, 3–3, 3–2, or 2–2) were judged as infarcted myocardium^{4,8}.

ECG-Gated Parameters

Poststress EF using 8-frame ECG-gating was automatically calculated by QGSTM software (Cedars-Sinai Medical Center, Los Angeles, CA, USA)⁹. When the mitral valve plane or left ventricle contour was inappropriate for visual interpretation, manual fitting was applied. As previously described, poststress EF <45% was recognized as low left ventricular (LV) function^{10,11}.

Patient Follow-up

Patient follow-up was performed by checking the medical records or by mail interview by individuals who were unaware of the patients' test results. Cardiac events were defined as follows: (1) nonfatal AMI as evidenced by an elevation of creatine kinase and creatine kinase-MB more than twice the normal values, (2) UA defined as Braunwald severity class II and III (acute and subacute angina at rest), and clinical circumstance B (primary UA) angina.¹² All patients included in this report were followed for at least 1 year. The mean follow-up interval was 26.9±15.5 months.

The protocol was approved by the hospital's ethical committee, and written informed consent was given by all patients.

Statistical Analysis

Continuous variables are expressed as the means±standard deviation. A p-value <0.05 was considered statistically significant. The Cox proportional hazard regression model (Dr SPSS II, ver.11) was applied in a forward stepwise fashion to define models with ACS (AMI and UA) as separate endpoints. The threshold for entry of variables into all models was p<0.05. A statistically significant increase in the Wald value of the model after the addition of the nuclear variables defined incremental prognostic value. The probability of survival without ACS was estimated using the Kaplan-Meier method.

Table 1 Patient Characteristics

	Total (n=1,753)	Exercise (n=837)	Pharmacological stress (n=916)	p value
Male	1,218 (69.4%)	585 (69.8%)	633 (69.1%)	NS
Age	64±10	62±9.0	65±11	<0.001
Hypertension	954 (54.4%)	429 (51.2%)	525 (57.3%)	<0.05
Diabetes	545 (31.0%)	224 (26.7%)	321 (35.0%)	<0.001
HLP	955 (54.4%)	452 (54.0%)	503 (54.9%)	NS
Smoking	511 (29.1%)	216 (25.8%)	295 (32.2%)	<0.01
Previous MI	476 (27.1%)	186 (22.2%)	290 (31.6%)	<0.001
CAD family history	125 (7.13%)	63 (7.52%)	62 (6.76%)	NS
SSS	5.78±10.2	4.27±8.85	7.17±11.2	<0.001
SDS	1.84±4.07	1.58±4.02	2.08±4.10	<0.05
Poststress EF	60.8±14.5	63.7±12.4	58.4±15.5	<0.001

Hypertension, blood pressure $\geq 140/90$ mmHg or receiving antihypertensive treatment; Diabetes, hemoglobin A_{1c} $\geq 6.5\%$; HLP, hyperlipidemia (TC > 220 mg/dl); TC, total cholesterol; MI, myocardial infarction; CAD, coronary artery disease; SSS, summed stress score; SDS, summed difference score; EF, ejection fraction.

Table 2 Predictors of Acute MI and Unstable Angina by Univariate Cox Proportional Hazard Regression Analysis

	Wald	p value	95%CI	Hazard ratio
Age	3.46	0.06	0.99–1.05	1.02
Male	0.02	0.86	0.52–1.72	0.95
Previous MI	1.47	0.22	0.79–2.63	1.44
Diabetes	2.25	0.13	0.87–2.78	1.55
Hyperlipidemia	1.30	0.25	0.40–1.27	0.71
Hypertension	5.09	<0.05	1.11–4.56	2.25
Smoking	3.25	0.07	0.95–2.99	1.69
CAD family history	0.01	0.90	0.28–3.00	0.92
SSS	12.4	<0.001	1.01–1.05	1.03
SDS	18.7	<0.001	1.05–1.14	1.09
Poststress EF	10.9	<0.01	0.95–0.98	0.97

CI, confidence interval. See Table 1 for other abbreviations.

Table 3 Predictors of Acute MI and Unstable Angina by Multivariate Cox Proportional Hazard Regression Analysis

	Wald	p value	95%CI	Hazard ratio
Hypertension	4.27	<0.05	1.04–4.35	2.12
SSS	0.12	0.72	0.95–1.03	0.99
SDS	8.59	<0.01	1.02–1.15	1.09
Poststress EF	3.11	0.07	0.95–1.003	0.97

See Tables 1, 2 for abbreviations.

Results

Patient Population

Patients' characteristics are listed in Table 1; 837 patients were designated to exercise stress alone, 916 patients to pharmacological stress or a combination of low-grade exercise and pharmacological stress. Comparison of the patients undergoing exercise to those who underwent pharmacological stress revealed that the patients undergoing pharmacologic stress more frequently had hypertension, diabetes mellitus, smoking and previous myocardial infarction (MI). The pharmacological stress group also had advanced age and higher SSS and SDS than the exercise group. Patients who underwent pharmacological stress also showed lower post-stress EF than patients who underwent exercise (Table 1).

Outcome Events

Revascularization cases within the first 60 days after nuclear testing numbered 142 (7.5%). Among 1,753 patients,

Fig 2. Comparison of annual ACS event rates of SDS <4 and SDS ≥ 4 groups (Upper panel), and in EF $\geq 45\%$ and EF <45% groups (Lower panel). ACS, acute coronary syndrome; EF, ejection fraction; SDS, summed difference score.

19 cases of AMI (1.1%) and 29 (1.6%) of UA occurred.

Prediction of Cardiac Events

Univariate Cox proportional hazard regression analysis of age, gender, history of prior MI, cardiac risk factors, SSS, SDS and poststress EF showed that the predictors of ACS were history of hypertension (Wald 5.09; $p < 0.05$), SSS (Wald 12.4; $p < 0.001$), SDS (Wald 18.7; $p < 0.001$) and post-stress EF (Wald 10.9; $p < 0.01$) (Table 2). Multivariate Cox proportional hazard regression analysis showed that SDS (Wald 8.59; $p < 0.01$) and hypertension (Wald 4.27; $p < 0.05$) were the independent predictors of ACS (Table 3).

Fig 3. Kaplan-Meier curves for survival without ACS in SDS <4 and SDS ≥4 groups (Upper panel), and in EF (≥45%) and low EF (<45%) groups (Lower panel). See Fig 2 for abbreviations.

Fig 4. Predictive value for acute coronary syndrome among clinical risk factors, significant myocardial ischemia, low poststress EF and the combination of significant myocardial ischemia and low poststress EF. See Fig 2 for abbreviations.

Annual Event Rates and Event Survival Rates in Subgroups

Annual event rates of ACS in subgroups are depicted in Fig 2. There was statistical significance ($p<0.05$) of the annual ACS rate between the group with SDS <4 (0.9%/year) and the group with SDS ≥4 (2.6%/year). There was also statistical significance ($p<0.05$) of the annual ACS rate between the group with EF ≥45% (0.9%/year) and the group with EF <45% (2.9%/year).

Fig 3 shows the probability of survival without ACS in patients with SDS <4 and those with SDS ≥4. These groups were separated significantly (log rank <0.01). The probability of survival without ACS in the group with a normal EF (≥45%) and the group with low poststress EF (<45%) is shown in Fig 3, and these groups were also separated significantly (log rank <0.001).

Combined Assessment of Myocardial Perfusion and EF for Predicting ACS

The predictive value of the cumulative clinical risk factors (number of coronary risk factors ≥2), significant myocardial ischemia (SDS ≥4), low poststress EF (<45%) and the combination of significant myocardial ischemia and low poststress EF for predicting ACS are shown in Fig 4. The cumulative clinical risk factors alone was not a significant predictor (Wald 0.66; $p=0.41$), but significant myocardial ischemia (Wald 9.0; $p<0.01$) and low poststress EF (Wald 7.4; $p<0.01$) were significant predictors of ACS. However, the combined assessment of significant myocardial ischemia and low poststress EF was the best predictor (Wald 11.9; $p<0.001$) than myocardial ischemia alone or low EF alone.

Discussion

We previously described the prognostic value of myocardial perfusion SPECT for the prediction of nonfatal AMI, UA and cardiac death in a Japanese population.⁴ However, the prognostic significance and incremental value of poststress EF by ECG-gated myocardial perfusion SPECT for the prediction of ACS, which includes nonfatal MI and UA, has not been investigated in the Japanese population. Sharir et al showed in 1,680 patients that poststress EF is a strong and independent predictor of cardiac death and cardiac death or nonfatal MI in an American population.¹⁰ They further analyzed the data in which cardiac death and nonfatal MI were separated, and demonstrated that poststress EF was the best predictor of cardiac death, whereas SDS was the best predictor of nonfatal MI. However, poststress EF was not an independent predictor of nonfatal MI.¹³ On the other hand, our data from a univariate Cox proportional hazard regression analysis suggested that SDS and low poststress EF were significant predictors of not only AMI, but also UA. Similar to the results of Sharir et al,¹² our data from the multivariate Cox proportional hazard regression analysis indicated that independent predictors for predicting ACS were SDS (Wald 8.59, $p<0.01$) and hypertension (Wald 4.27, $p<0.05$), whereas poststress EF was not.

We previously documented that a normal SSS group (SSS, 0–3) had a low annual ACS event rate (0.9%/year).⁴ The present study showed that the probability of future ACS events defined by SDS and annual ACS rates in a group of patients with a minimum amount of stress-induced ischemia (SDS <4) was significantly lower than that in the patients with significant myocardial ischemia (Fig 2). This finding suggests that the indication for revascularization for eliminating future ACS events would be defined by the SDS. For patients who show a minimum amount of ischemia (SDS <4), medical therapy would be recommended because their annual ACS event rate is less than 1%. Conversely, patients who have a large amount of ischemia (SDS ≥8) may benefit from revascularization.¹¹

Multivariate Cox proportional hazard regression analysis showed that the addition of functional data (poststress EF <45%) to significant myocardial ischemia (SDS ≥4) re-

sulted in a significant increase in the Wald value in predicting ACS. These findings were also in good agreement with previous reports in American populations.^{13,14}

Previous prognostic research in a multicenter study in Japan (J-ACCESS)^{15–18} which combined cardiac death, non-fatal MI and severe heart failure requiring hospitalization as major cardiac events, demonstrated that the combination of rest EF and SSS is a strong predictor of major cardiac events. However, this combination failed to predict hard cardiac events such as ACS and cardiac death. The discrepancy between the J-ACCESS study and ours might be the difference in the study design used. The J-ACCESS study did not gather the images to a core center, instead they were interpreted at 117 participating hospitals, and this may have resulted in non-uniformity of image interpretation.

Study Limitations

First, we used an 8-frame ECG-gating method for calculating poststress EF by QGSTM, but this method has been found to underestimate LVEF by 3.7–4.0% because of undersampling of the time–volume curve.¹⁹ The 16-frame gating method should provide more accurate poststress EF and prognostic value in comparison to the 8-frame gating method. Second, our SPECT protocol used rest ²⁰¹Tl/stress ^{99m}Tc-tetrofosmin separate acquisition, and so the results of our study may not be applicable to other laboratories that use a single isotope protocol where myocardial perfusion parameters are concerned. Third, although the diagnoses of nonfatal MI and UA were firmly established in most of the patients, the exact cause of sudden death could not be known in each patient. However, previous clinical trials that concern prospective analysis of patients' prognoses have included these endpoints as separate outcomes.^{1–3,13} Fourth, the prolonged time between stress and poststress image acquisition (30–50 min) might have resulted in an overestimation of poststress EF,^{20,21} and the poststress EF might not represent the amount of stress-induced ischemia because of the inclusion of 476 (27.1%) patients with prior MI, in whom the difference between rest and poststress EF is not as much as in those without MI.

Conclusions

Our data indicate that SDS is a strong and independent predictor of the future occurrence of ACS, whereas poststress EF alone is not. However, when low poststress EF (<45%) is combined with significant myocardial ischemia (SDS ≥ 4), it provides valuable prognostic information for predicting future ACS events.

Acknowledgments

Authors thank Mr Yoshitaka Hori, Mr Satoshi Horie and Ms Miki Nakazawa for their assistance. Authors have indicated they have no financial conflicts of interest.

References

- Berman DS, Hachamovitch R, Kiat H, Cohen I, Cabico JA, Wang FP, et al. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: A basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. *J Am Coll Cardiol* 1995; **26**: 639–647.
- Hachamovitch R, Berman DS, Kiat H, Merz CNB, Cohen I, Friedman JD, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease. *Circulation* 1996; **93**: 905–914.
- Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: Differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998; **97**: 535–543.
- Matsumoto N, Sato Y, Suzuki Y, Kunimasa T, Yoda S, Iida J, et al. Prognostic value of myocardial perfusion single-photon emission computed tomography for the prediction of future cardiac events in a Japanese population: A middle-term follow-up study. *Circ J* 2007; **71**: 1580–1585.
- Yoda S, Sato Y, Matsumoto N, Tani S, Takayama T, Nishina H, et al. Incremental value of regional wall motion analysis immediately after exercise for the detection of single-vessel coronary artery disease: Study by separate acquisition, dual-isotope ECG-gated single-photon emission computed tomography. *Circ J* 2005; **69**: 301–305.
- Germano G, Kavanagh PB, Su HT, Mazzanti M, Kiat H, Hachamovitch R, et al. Automatic reorientation of three-dimensional, transaxial myocardial perfusion SPECT images. *J Nucl Med* 1995; **36**: 1107–1114.
- Matsumoto N, Sato Y, Suzuki Y, Yoda S, Kunimasa T, Kato M, et al. Usefulness of rapid low-dose/high-dose 1-day ^{99m}Tc-sestamibi ECG-gated myocardial perfusion single-photon emission computed tomography. *Circ J* 2006; **70**: 1585–1589.
- Zellweger MJ, Dubois EA, Lai S, Shaw LJ, Amanullah AM, Lewin HC, et al. Risk stratification in patients with remote prior myocardial infarction using rest-stress myocardial perfusion SPECT: Prognostic value and impact on referral to early catheterization. *J Nucl Cardiol* 2002; **9**: 23–32.
- Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; **36**: 2138–2147.
- Sharir T, Germano G, Kavanagh PB, Lai S, Cohen I, Lewin HC, et al. Incremental prognostic value of poststress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. *Circulation* 1999; **100**: 1035–1042.
- Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; **107**: 2900–2907.
- Braunwald E. Unstable angina: A classification. *Circulation* 1989; **80**: 410–414.
- Sharir T, Germano G, Kang X, Lewin HC, Miranda R, Cohen I, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: Risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. *J Nucl Med* 2001; **42**: 831–837.
- Hachamovitch R, Rozanski A, Hayes SW, Thomson LEJ, Germano G, Friedman JD, et al. Predicting therapeutic benefit from myocardial revascularization procedures: Are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? *J Nucl Cardiol* 2006; **13**: 768–778.
- Kusuoka H, Nishimura S, Yamashina A, Nakajima K, Nishimura T. Surveillance study for creating the national clinical database related to ECG-gated myocardial perfusion SPECT of ischemic heart disease: J-ACCESS study design. *Ann Nucl Med* 2006; **20**: 195–202.
- Nakajima K, Kusuoka H, Nishimura S, Yamashina A, Nishimura T. Normal limits of ejection fraction and volumes determined by gated SPECT in clinically normal patients without cardiac events: A study based on the J-ACCESS database. *Eur J Nucl Med Mol Imaging* 2007; **34**: 1088–1096.
- Nishimura T, Nakajima K, Kusuoka H, Yamashina A, Nishimura S. Prognostic study of risk stratification among Japanese patients with ischemic heart disease using gated myocardial perfusion SPECT: J-ACCESS study. *Eur J Nucl Med Mol Imaging* 2008; **35**: 319–328.
- Nakajima K, Nishimura T. Inter-institution preference-based variability of ejection fraction and volumes using quantitative gated SPECT with ^{99m}Tc-tetrofosmin: A multicentre study involving 106 hospitals. *Eur J Nucl Med Mol Imaging* 2006; **33**: 127–133.
- Manrique A, Koning R, Cribier A, Véra P. Effect of temporal sampling on evaluation of left ventricular ejection fraction by means of thallium-201 gated SPET: Comparison of 16- and 8-interval gating, with reference to equilibrium radionuclide angiography. *Eur J Nucl Med* 2000; **27**: 694–699.
- Sharir T. Role of regional myocardial dysfunction by gated myocardial perfusion SPECT in the prognostic evaluation of patients with coronary artery disease. *J Nucl Cardiol* 2005; **12**: 5–8.
- Johnson LL, Verdesca SA, Aude WY, Xavier RC, Nott LT, Campanella MW, et al. Postischemic stunning can affect left ventricular ejection fraction and regional wall motion on post-stress gated sestamibi tomograms. *J Am Coll Cardiol* 1997; **30**: 1641–1648.