主論文

Prognostic Value of Normal Stress-Only Technetium-99m Myocardial Perfusion Imaging Protocol

– Comparison With Standard Stress-Rest Protocol –

Takanao Ueyama, MD; Kazuya Takehana, MD, PhD;
Hirofumi Maeba, MD, PhD; Toshiji Iwasaka, MD, PhD

Circulation Journal
Vol. 76 No. 10 October 2012
(Pages 2386–2391)

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Imaging

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Background: Patients with a normal stress image on technetium-99 m (Tc-99 m) single-photon emission computed tomography (SPECT) have a good prognosis for diagnosing coronary artery disease. However, current guidelines recommend stress and rest imaging to confirm that a stress image is normal.

Methods and Results: We determined all-cause of cardiac events (acute coronary syndrome and sudden death) in 1,939 patients undergoing stress myocardial perfusion SPECT with Tc-99 m radiotracers. Patients with an abnormal stress image were excluded, so we focused on 1,125 patients in whom the stress SPECT study was interpreted as normal. A stress-only protocol was used in 726 patients (adenosine=339; exercise=387), whereas 399 had both stress and rest imaging (adenosine=294; exercise=105). Mean follow-up was 1,252 days. At the end of follow-up, there were 39 cardiac events in the stress-only cohort and 19 in the stress-rest cohort. Kaplan-Meier analysis revealed that there were no differences for the entire cohort of cardiac events not only between the stress-only and stress-rest protocols but also for stressor modality, despite the fact that the stress-rest cohort showed higher coronary risk factors.

Conclusions: Patients determined as having a normal SPECT on the basis of stress imaging alone have a similar cardiac event rate as those who have a normal SPECT on the basis of evaluation of both stress and rest images. This imaging strategy will significantly reduce radiation exposure in a substantial number of patients. (*Circ J* 2012; **76:** 2386–2391)

Key Words: Diagnostic and prognostic application; Myocardial perfusion imaging; Outcome research; SPECT

Stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) with technetium-99 m (Tc-99 m) based tracers was introduced into clinical practise in Japan during the past 2 decades. This method is the most robust and reliable noninvasive test for diagnosing obstructive epicardial coronary artery disease (CAD) and assessing patient risk.[1] With an aging population and the increasing number of individuals at risk for CAD, such as those with diabetes mellitus (DM) or hypertension, the necessity for SPECT studies is likely to increase.

Current SPECT imaging guidelines with Tc-99 m tracers recommend acquiring images after stress and again at rest,[2–4] which typically requires a patient to spend 4–5 h in the laboratory for 2 imaging sessions or return the following day for rest imaging. In spite of technological advances, such as electrocardiographic (ECG) gating or attenuation correction, the test procedure has remained unchanged. The advent of competing noninvasive imaging modalities (stress echocardiography and CT angiography) exposed the weakness of the original concept; that is, the test burdens the patients with a relatively high radiation exposure.[5,6]

We started using a 2-day stress-rest imaging protocol routinely in 2003 for patients with a low to intermediate CAD risk, and if the patient had have a normal stress image, the reader then interpreted the subsequent rest image. The advantages of such an approach are to reduce radiation exposure, lower costs by eliminating unnecessary imaging time and radiopharmacologic doses, and improve laboratory efficiency by freeing up camera time to study additional patients. Thus, the current study was conducted to further explore the feasibility of a stress-only MPI protocol in routine clinical practice, review accumulated experience, and propose a prospective protocol that appears more suitable for the current need for more efficient use of modern technology. The goal was to determine the prognosis of a normal stress-only MPI compared to a normal stress-rest MPI to establish the effectiveness of the protocol in a retro-

Received January 18, 2012; revised manuscript received May 6, 2012; accepted June 1, 2012; released online July 20, 2012 Time for primary review: 25 days
Division of Cardiology, Department of Medicine II, Kansai Medical University, Hirakata, Japan
Mailing address: Kazuya Takehana, MD, PhD, Division of Cardiology, Department of Medicine II, Kansai Medical University, 2-3-1 Shinmachi, Hirakata 573-1191, Japan. E-mail: takehana@hirakata.kmu.ac.jp
ISSN-1346-9843 doi:10.1253/circj.CJ-12-0081

Table 1. Baseline Demographic and Stress Information

	Total (n=1,125)	Stress-only (n=726)	Stress-rest (n=399)
Age (years)	68±10	67±10	69±11*
Female sex	599 (53%)	415 (57%)	184 (46%)*
Mean no. of risk factors	1.66±1.04	1.59±1.02	1.81±1.08*
DM	475 (42%)	297 (41%)	178 (45%)
Hypertension	766 (68%)	469 (65%)	297 (74%)*
Hyperlipidemia	637 (57%)	391 (54%)	246 (62%)*
Known CAD	199 (18%)	111 (15%)	88 (22%)*
Indications for stress MPI			
Chest pain	744 (66%)	507 (70%)	237 (59%)*
Exertional dyspnea	47 (4%)	20 (3%)	27 (7%)*
Preoperative clearance	76 (7%)	55 (8%)	21 (5%)*
Stressor used			
Exercise	492 (44%)	387 (53%)	105 (26%)*
Adenosine	633 (56%)	339 (47%)	294 (74%)*
^{99m}Tc tracer used			
Tetrofosmin	848 (75%)	517 (71%)	331 (83%)*
Sestamibi	277 (25%)	209 (29%)	68 (17%)*
LVEF (%)	66±13	68±12	64±14*
LVEDV (ml)	67±27	65±24	70±32*

*P<0.05 vs. stress-only protocol.
DM, diabetes mellitus; CAD, coronary artery disease; MPI, myocardial perfusion imaging; Tc, technetium; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume.

spective manner.

Methods

Study Population

From April 2003 to July 2008, 2,949 patients underwent stress myocardial perfusion SPECT with Tc-99m radiotracers for clinically indicated reasons. Reasons for choosing the SPECT protocol (exercise or adenosine stress, stress-only or stress-rest) was determined by the attending cardiologist. 1,010 patients were not contactable and were excluded from this retrospective study. The percentage of normal SPECT images of those patients without the 2-year follow-up was 59%, which was identical to the studied patients. 814 patients with an abnormal stress image, such as myocardial perfusion defect, hyper lung uptake or abnormal QGS data, were also excluded. Therefore, we focused on 1,125 patients (58% of study population) in whom the stress SPECT study was interpreted as normal, and who were followed clinically for at least 2 years. This percentage of patients with normal study results is similar to those reported in other large trials.[7–9]

Gated Stress SPECT Protocol

The routine protocol for gated SPECT with Tc-99m tracer in our laboratory is to perform stress imaging first in either a same-day low-dose stress (240MBq)/high-dose rest (500MBq) procedure or a 2-day high-dose stress/high-dose rest (600MBq, respectively) procedure. In the stress-only cohort, the 2-day high-dose stress/high-dose rest protocol was ceased when the stress image showed normal results.

Ergometer exercise was used as a stressor in 492 patients (44%), and 633 (56%) received adenosine with a standard weight-based infusion protocol. All exercise ECGs were interpreted in conjunction with the SPECT images. An ischemic ECG response was defined as a ≥1 mm ST-segment depression occurring >80 ms after the J point. When ischemic ECG changes were not revealed, exercise stress was ceased when the rate-pressure product was >25,000 or heart rate was >85% of the age-predicted maximum heart rate. In this study, 88.7% of patients in the stress-only group and 88.6% of patients in the stress-rest group achieved their maximum heart rates at peak exercise.

After the tracer injection, subjects ate a light meal to reduce the subdiaphragmatic activity of the tracer. ECG-gated SPECT data were obtained 1 h after the injection using a dual-head rotating gamma camera equipped with a low to medium energy, general-purpose collimator (E-CAM+; Siemens, Düsseldorf, Germany). The ECG-gated data were obtained from 60 projections over an 180° arc from the right anterior oblique (RAO) to the left posterior oblique (LPO) and an energy window of 10% centered over the 140keV Tc-99m photopeak. Eight frames (each 64×64 pixels) were acquired per R-R interval of the ECG. Non-gated SPECT data were processed by filtered back projection (Butterworth order=8, cutoff frequency 0.44 cycle). The uptake of the tracer was quantified with processing equipment (GMS 5500A/DI, Toshiba, Tokyo, Japan). Immediately after SPECT acquisition, a planar chest image (512×512 pixels) in the anterior view was acquired. After study acquisition, stress SPECT images were reconstructed and reoriented according to the American Society of Nuclear Cardiology guidelines and then visually reviewed in all 3 standard projections along with the gated SPECT data.[10] Attenuation correction was performed in all studies with either a transmission source or a computed tomography image. Quantitative perfusion SPECT was also performed with commercially available software.

Study Interpretation Procedure

After study acquisition, all stress images were interpreted on the basis of integration of the rotating raw projection data, the reoriented tomographic perfusion images, the gated SPECT information, and the quantitative perfusion SPECT results. A study was interpreted as normal if perfusion was assessed to

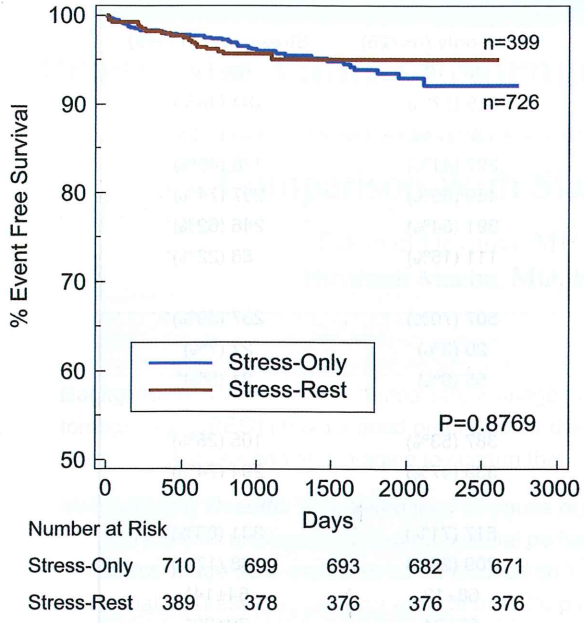

Figure 1. Event-free survival for the entire cohort. Survival curves for the entire cohort according to SPECT protocol on the basis of whether patients with normal stress SPECT underwent stress-only vs. additional rest imaging.

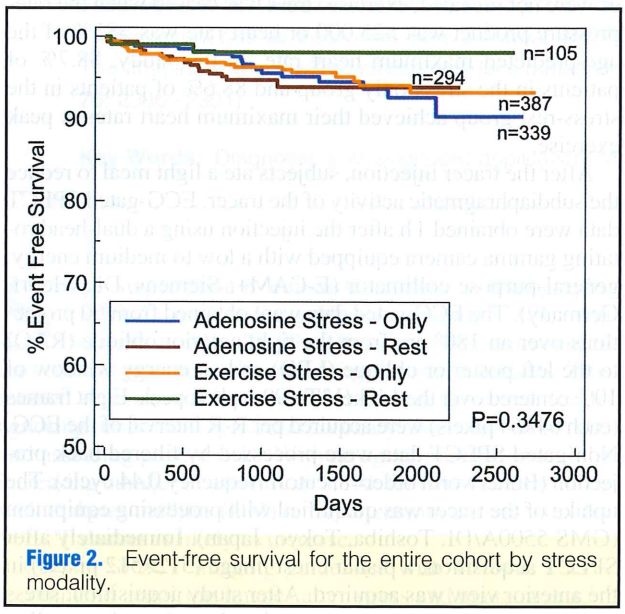

Figure 2. Event-free survival for the entire cohort by stress modality.

be homogeneous throughout the myocardium, the LV cavity size was normal (LV end-diastolic volume <80 ml in men; <60 ml in women), the left ventricular ejection fraction (LVEF) was ≥50% with normal regional wall motion, and the quantitative perfusion SPECT defect size was <5%. In the patients who could not achieve 5 METS exercise, adenosine stress was performed. Subsequent rest imaging was performed if the stress images did not fulfill the criteria and were therefore deemed to be abnormal or equivocal. Attenuation correction images were reviewed only to confirm that a study was normal, and were not otherwise used in diagnosis. The stress ECG results were not used to determine whether a patient with a normal stress perfusion study needed rest imaging.

Table 2. Univariate Analysis for Detecting Cardiac Events

	HR	95% CI	P value
Age	1.008	0.982–1.035	0.551
Sex (Female)	3.363	0.380–1.078	0.095
Pharmacologic stress	1.423	0.835–2.431	0.198
Hyperlipidemia	3.562	1.806–7.027	<0.001
DM	3.488	1.962–6.200	<0.001
Hypertension	3.363	1.530–7.390	0.003
Known CAD	9.743	5.685–15.692	<0.001

HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

Table 3. Multivariate Analysis for Detecting Coronary Events

	HR	95% CI	P value
DM	2.702	1.514–4.823	0.008
Known CAD	8.590	4.985–14.802	<0.001

Abbreviations as in Tables 1,2.

Follow-up and Outcomes

In August 2010, all of the study patients had their status assessed through our institutional medical records. Mean follow-up was 4.1±1.0 years and minimal follow-up duration was 25 months for those without cardiac events. The primary endpoint in this study was the total cardiac hard events, which included acute coronary syndrome (ACS) and sudden death. Deaths were categorized in etiology if thought to be from an ischemic coronary disease origin. Deaths were classified by consensus of 2 senior authors (K.T. and T.I.) based on all the available information and they were blinded to the subject's imaging protocol.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation, and categorical variables are expressed as frequency (percentage). Baseline patient characteristics were examined according to SPECT protocol. Student's t-test was used to identify mean differences for continuous variables according to SPECT protocol. Contingency table analysis was performed with chi-square tests. Kaplan-Meier analysis of all-cause mortality was performed. Time 0 was defined as the date of SPECT study. 2-sided log-rank tests were used to determine significance. Univariate and multivariate analyses were used to identify the association between time-to-event and baseline characteristics between the 2 SPECT protocols. Clinical characteristics included in this study were: age, sex, history of CAD, DM, hypertension, hyperlipidemia; and the stress modality used in conjunction with SPECT. All data were statistically analyzed using MedCalc Software (Version 9.4.2.0, Medcalc software, Mariakerke, Belgium). P<0.05 was considered statistically significant in all tests.

Results

Baseline Characteristics

For entire cohort of 1,125 patients with a normal SPECT, the mean age was 68 years, approximately one-half were female, 42% were diabetic, and one-half had hypertension and/or hyperlipidemia (Table 1). The major indications for SPECT were

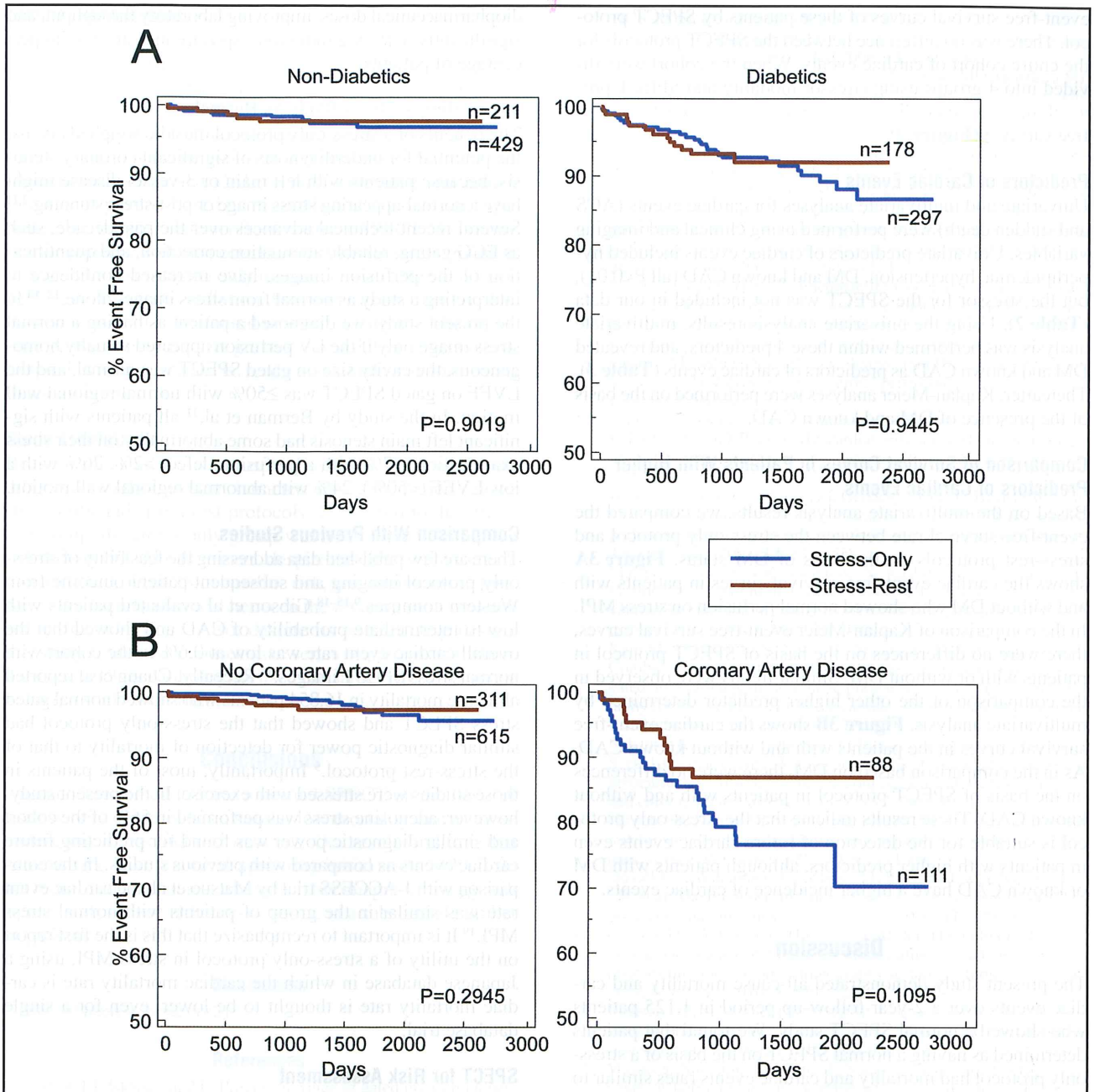

Figure 3. Event-free survival on the basis of higher predictors of cardiac events. Survival curves for the patients with and without diabetes mellitus (**A**) and for the patients with and without known coronary artery disease (**B**). These predictors were selected after multivariate analysis (**Table 3**).

evaluation of chest pain or exertional dyspnea and preoperative clearance. Other indications were evaluation of ECG (3.8%), new onset of tachyarrhythmia (1.0%) and syncope (0.4%). Almost one-half of the patients underwent pharmacological stress testing and the mean LVEF by gated SPECT was 66%.

There were significant differences in the baseline characteristics of patients who underwent stress-only imaging vs. those who had additional rest imaging. The stress-only group was younger, more commonly female, less likely to have the mean number of coronary risk factors or history of CAD compared with the stress-rest protocol group. There was no difference in stressor modality.

All-Cause Mortality Rate on the Basis of SPECT Protocol in All Patients

Over an average of 4.1±1.0 years of follow-up, 51 ACS (4.5%) and 7 sudden death (0.6%) events occurred. For the entire cohort of 1,125 patients, there were 51 ACS (4.5%) and 7 sudden death (0.6%) cases over a mean follow-up of 4.02 years. During follow-up, 39 cardiac events in the stress-only cohort (ACS 36, sudden death 3) and 19 in the stress-rest cohort (ACS 15, sudden death 4) were recorded. **Figure 1** shows the Kaplan-Meier

event-free survival curves of these patients by SPECT protocol. There was no difference between the SPECT protocols for the entire cohort of cardiac events. When the cohort were divided into 4 groups using stressor modality and SPECT protocol, there were no differences among the groups for event-free survival (Figure 2).

Predictors of Cardiac Events

Univariate and multivariate analyses for cardiac events (ACS and sudden death) were performed using clinical and imaging variables. Univariate predictors of cardiac events included hyperlipidemia, hypertension, DM and known CAD (all $P<0.01$), but the stressor for the SPECT was not included in our data (Table 2). Using the univariate analysis results, multivariate analysis was performed within these 4 predictors, and revealed DM and known CAD as predictors of cardiac events (Table 3). Thereafter, Kaplan-Meier analyses were performed on the basis of the presence of DM and known CAD.

Comparison of Survival Curves in Patients With Higher Predictors of Cardiac Events

Based on the multivariate analysis results, we compared the event-free survival rate between the stress-only protocol and stress-rest protocols on the basis of DM status. Figure 3A shows the cardiac event-free survival curves in patients with and without DM who showed normal perfusion on stress MPI. In the comparison of Kaplan-Meier event-free survival curves, there were no differences on the basis of SPECT protocol in patients with or without DM. Similar trends were observed in the comparison of the other higher predictor determined by multivariate analysis. Figure 3B shows the cardiac event-free survival curves in the patients with and without known CAD. As in the comparison based on DM, there were no differences on the basis of SPECT protocol in patients with and without known CAD. These results indicate that the stress-only protocol is suitable for the detection of future cardiac events even in patients with higher predictors, although patients with DM or known CAD have a higher incidence of cardiac events.

Discussion

The present study demonstrated all-cause mortality and cardiac events over a 2-year follow-up period in 1,125 patients who showed a normal SPECT study. We found that patients determined as having a normal SPECT on the basis of a stress-only protocol had mortality and cardiac events rates similar to those who had a normal SPECT on the basis of evaluation of both stress and rest images. This held true irrespective of patient age, sex, clinical risk factors, history of CAD or the stressor modality used in conjunction with the SPECT study. Also, in patients with the higher predictors of cardiac events, which were determined by multivariate analysis to be DM and known CAD, the stress-only protocol showed similar prognostic value for cardiac events. These findings support the stress-only protocol as having the ability to provide robust prognostic information from MPI with a shorter test time and less radiation exposure.

Of added benefit, there was a significant reduction in the radiopharmaceutical dose received by patients who had the stress-only protocol (600 MBq) vs. those who underwent additional rest imaging (740 or 1,200 MBq). In addition, our results indicate that additional rest imaging is not necessary in patients with a normal-appearing initial stress SPECT image. Selectively targeting rest imaging to appropriate patients should lower costs by eliminating unnecessary imaging time and radiopharmaceutical doses, improving laboratory throughput, and significantly lowering radiation exposure in a substantial percentage of patients.

Interpreting a Stress Study as Normal

The benefits of a stress-only protocol must be weighed against the potential for underdiagnosis of significant coronary stenosis, because patients with left main or 3-vessel disease might have a normal-appearing stress image or post-stress stunning.[2,11] Several recent technical advances over the past decade, such as ECG gating, reliable attenuation correction, and quantification of the perfusion images, have increased confidence in interpreting a study as normal from stress images alone.[12–14] In the present study, we diagnosed a patient as having a normal stress image only if the LV perfusion appeared visually homogeneous, the cavity size on gated SPECT was normal, and the LVEF on gated SPECT was ≥50% with normal regional wall motion. In the study by Berman et al,[11] all patients with significant left main stenosis had some abnormality on their stress examination: 97% with a perfusion defect >2%, 26% with a low LVEF (<50%), 24% with abnormal regional wall motion.

Comparison With Previous Studies

There are few published data addressing the feasibility of stress-only protocol imaging and subsequent patient outcome from Western countries.[9,15–18] Gibson et al evaluated patients with low to intermediate probability of CAD and showed that the overall cardiac event rate was low at 0.6% in the cohort with normal stress SPECT images.[15] Recently, Chang et al reported all-cause mortality in 16,854 patients who showed normal gated stress SPECT and showed that the stress-only protocol had similar diagnostic power for detection of mortality to that of the stress-rest protocol.[9] Importantly, most of the patients in those studies were stressed with exercise. In the present study, however, adenosine stress was performed in 56% of the cohort and similar diagnostic power was found for predicting future cardiac events as compared with previous studies. In the comparison with J-ACCESS trial by Matsuo et al, the cardiac event rate was similar in the group of patients with normal stress MPI.[19] It is important to reemphasize that this is the first report on the utility of a stress-only protocol in stress MPI, using a Japanese database in which the cardiac mortality rate is cardiac mortality rate is thought to be lower, even for a single database trial.

SPECT for Risk Assessment

Two decades of clinical experience has established the role of stress MPI in the routine clinical management of patients with suspected or known CAD and is an important decision-making strategy. A normal SPECT is generally recognized in the group with less than 1% annual risk for cardiac death and nonfatal myocardial infarction and a low (0.5%) cardiac mortality.[20] In this present study, we demonstrated that the stress-only protocol had similar diagnostic power for prediction of future cardiac events to that of the usual stress-rest protocol, even with the adenosine stress protocol. Also, even in patients with DM and known CAD, which were higher predictors selected by multivariate analysis, the diagnostic power to predict cardiac events was similar between the stress-only and stress-rest protocols. Patients with those cardiac risks might also have a higher incidence of chronic kidney disease in conjunction with ischemic heart disease and therefore require repeat diagnostic imaging. To avoid unnecessary iodinated contrast media and radiation exposure, the stress-only protocol can be easily applied to the management of such patients.

Clinical Implications

In our experience, a normal stress-only SPECT MPI with both exercise and pharmacologic stress has an excellent prognosis (both for cardiac mortality and cardiac events) when used for the evaluation of suspected CAD and is no different from the prognosis of a normal stress-rest study. Selective use of stress-only imaging thus appears justified in low to intermediate risk patients with suspected CAD to both save time and reduce radiation exposure. Based on the published data and our experience, we propose that an effective stress SPECT MPI protocol for patients with suspected CAD is firstly stress imaging, followed by rest imaging only in patients with abnormal stress perfusion. Test time, radiation dose and imaging cost will be thus decreased in a substantial number of patients. The stress-only protocol may find its greatest potential in large-volume hospital where a reader is readily available for immediate image interpretation.

Study Limitations

Because this study was retrospective, there were significant differences in the baseline characteristics of the patients in the stress-only and stress-rest protocols. Compared to the stress-rest group, the stress-only group was younger and had fewer risk factors of CAD. However, despite the lack of randomization and the differences in baseline risk, raw cardiac event rates were consistently identical between the imaging protocols and across the subgroups. Also, despite its retrospective design, this study evaluated a consecutive series of patients for whom the same nuclear cardiologists used the same criteria for interpreting a study as normal.

Conclusions

Patients determined to have a normal SPECT on the basis of a stress-only protocol has a similar low mortality rate as those undergoing stress and rest imaging. Our results indicate that patients who have a normal-appearing initial stress SPECT do not require additional rest imaging. This imaging strategy will significantly reduce radiation exposure in a substantial number of patients.

Disclosures

Conflict of Interest: None declared.

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