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Prognostic value of ECG-gated thallium-201 single-photon emission tomography in patients with coronary artery disease

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Background: The phenomenon of reversible impairment in LV function has been well described and is known as myocardial stunning. ***Objective:*** Thallium-201 myocardial perfusion gated SPECT was used to evaluate myocardial stunning and its incremental prognostic value in patients with coronary artery disease. ***Patients and Methods:*** Fifty-six patients (aged 63 ± 11 years) with coronary artery disease were included in this study. All subjects underwent exercise thallium scintigraphy. ECG-gated SPECT was obtained both at post-stress (10 minutes after the injection of 111 MBq of thallium at the time of peak exercise) and at rest (180 minutes). The left ventricular ejection fraction (LVEF) and end-systolic and end-diastolic volume (ESV, EDV) were determined by a quantitative gated SPECT (QGS) program. ***Results:*** Follow-up was complete in all patients (mean 569 days). The magnitude of the depression of post-stress LVEF relative to the rest LVEF was correlated with the severity of ischemia ($p < 0.05$). The group with a median LVEF of more than 45% had a significantly higher event-free rate ($p < 0.01$). ***Conclusion:*** Assessment of post-stress left ventricular function by gated-SPECT provides incremental prognostic information and is useful in predicting cardiac events in patients with suspected or definite coronary artery disease.

Key words: QGS, thallium, stunned myocardium

INTRODUCTION

PERSISTENCE of functional abnormalities after an episode of ischemia has been demonstrated in experimental animal models and in humans.[1,2] This phenomenon of reversible impairment in left ventricular function has been well described and is known as myocardial stunning.[2] By definition, stunning is reversible contractile functional abnormalities persisting after myocardial perfusion has returned to the pre-ischemic condition. Persistence of left ventricular dysfunction is known to be related to the degree of ischemia induced and to the duration of ischemia. Recently, R-wave gating with myocardial perfusion tomography has become an established diagnostic tool, permitting computation of left ventricular ejection fraction (LVEF) and volumes. Germano et al., developed an automatic algorithm for ECG-gated single-photon emission computed tomography (SPECT) to assess left ventricular function.[3,4] The addition of gating to routine myocardial perfusion SPECT provides accurate and reproducible information on left ventricular function at rest and after exercise. Tl-gated SPECT may provide regional and global functional parameters including end-diastolic volume (EDV) and end-systolic volume (ESV) as well as LVEF without extra cost. However the incremental prognostic value of post-stress stunning in patients with coronary heart disease has not been fully evaluated to date.

This study quantitatively evaluated the post-stress cardiac function and incremental prognostic value in patients with coronary artery disease using Tl-201 ECG-gated scintigraphy.

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METHODS

Patient Characteristics

Fifty-six patients (46 men and 10 women, aged 63 ± 11 years) with coronary artery disease, hospitalized at our

university hospital, were eligible for enrollment in this study. None of the patients had significant coronary vasospastic angina. The patients with severe arrhythmia, idiopathic cardiomyopathy, and valvular heart disease were excluded. Revascularizations on first catheterization (n = 14) and within 90 days after nuclear testing (n = 2) were censored from the prognostic portion of the analysis.[5]

Tl-201 Single Photon Emission Computed Tomography (SPECT)

Exercise Tl-201 imaging was performed during the same hospitalization period in all patients. A graded treadmill exercise was performed according to the Bruce protocol. Heart rate, rhythm, and blood pressure were monitored during exercise, including recording of the 12-lead electrocardiogram at 1 minute intervals throughout exercise. Incremental exercise testing was continued until the onset of either anginal chest pain, ST-segment depression ≥2 mm, fatigue, or target heart rate. At peak exercise, patients received Tl-201 at a dose of 111 MBq intravenously. The exercise was continued for an additional 60 seconds to allow for adequate circulation of the isotope. Imaging was begun within 10 minutes of the completion of exercise and was repeated after a 3-hour delay.[6] A three-headed rotating gamma camera (GCA-9300 A/DI, Toshiba Medical) equipped with a high-energy, general-purpose collimator and a medical image processor GMS-5500 U/DI (Toshiba Corporation, Tokyo) was employed for image processing. The gamma camera rotated, collecting 90 projections over 360°. The projection data were reconstructed into 64 × 64 matrix images using the filtered back projection method with a Butterworth filter (order 5, cut-off 0.5 cycles/pixel) and a ramp filter. For gating, 8 frames per cardiac cycle with a re-fixed RR interval and a 40% window were used. Acquisition was repeated in the resting state.

For data analysis, the QGS program, previously described and validated by Germano et al.,[3] was applied to process short-axis tomograms to determine LVEF and end-systolic and end-diastolic volume (ESV, EDV). To assess regional wall motion, the myocardium was divided into seven segments according to the American Heart Association criteria: anterobasal, anterior, apical, inferior, posterior, septal and lateral segments. Using a cinematic display mode on QGS, regional wall motion was semi-quantified using a four-point scale (0 = normal, 1 = mild hypokinesia, 2 = moderate to severe hypokinesia, 3 = akinesia or dyskinesia) in the 7 segments of the LAO and RAO projections. Two cardiologists assessed the total score as well as the wall motion score (WMS). Post-stress functional depression was defined as a worsening as WMS on stress image.

SPECT Image Interpretation

The left ventricle was divided into 13 segments as shown in Figure 1 (6 on the basal short-axis view, 6 on the mid-short axis view, and one apical segment on vertical long axis view).[6] A 4-point scoring system by visual interpretation (3, normal; 2, mildly reduced; 1, severely reduced; 0, no activity) was used.[6] Perfusion change was defined as (rest total perfusion score – exercise total perfusion score), which reflects the severity of ischemia. Segmental perfusion change was also defined as (rest perfusion score – exercise perfusion score) in each segment. The agreement rate between the two observers was 95% for SPECT image interpretation. All studies were evaluated by consensus between 2 experienced observers. A segment was considered ischemic if reversibility was observed between exercise and rest images.

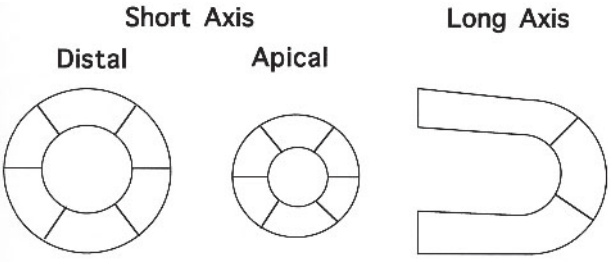

Fig. 1 The basal and distal left ventricular levels of the short-axis view and apical portions of the long-axis view of SPECT were divided into 13 radial segments. Segmental images were scored on a 3 (normal tracer uptake) to 0 (absence of activity) scale: 3, normal; 2, mildly decreased tracer uptake; 1, severely decreased tracer uptake; 0, absence of activity.

Cardiac Catheterization and Angiography

Angiography was performed through the femoral artery by the Judkins' technique within 2 weeks of the radionuclide study, using a Philips cineangiographic system (Philips Medical Systems, Tokyo, Japan). Multiple views of both coronary arteries were obtained. All angiograms were visually evaluated by two independent observers, according to AHA guidelines.[7,8] Contrast ventriculography in the right and left anterior oblique projections was performed to assess regional wall motion at rest. Left ventricular volume and ejection fraction were calculated according to the area-length method.[9]

Statistical Analysis

All values are presented as mean values ± standard deviation. Scheffé's F test for multiple comparisons was applied to detect significant differences as defined by ANOVA. Linear regression analysis was used to determine the correlation between LVEF by QGS and LVEF by LVG. Using unpaired t-test, variables were compared between patients with cardiac events (cardiac death and hospitalization due to angina pectoris or severe arrhythmia) and patients without cardiac events. Categorical data were compared using the chi-square test. The prognostic value of each variable was tested by Cox proportional

hazards regression analysis. The Kaplan-Meier method was used to calculate the cumulative event-free rate in groups of patients that were divided by the median value of each QGS parameter. Student's t-test was used for comparison of paired data, and p values of less than 0.05 were considered significant.

Table 1 Baseline clinical characteristics of the study population

	1 vessel n = 38	2 vessels n = 9	3 vessels n = 9
Age (years old)	61 ± 2	67 ± 3	70 ± 3
max HR (/min)	140 ± 4	123 ± 7	130 ± 5
max systolic BP (mmHg)	199 ± 6	187 ± 12	190 ± 9
rest systolic BP (mmHg)	119 ± 3	118 ± 5	121 ± 5
rest diastolic BP (mmHg)	67 ± 2	68 ± 5	58 ± 2
Total cholesterol (mg/dl)	189 ± 7	163 ± 31	205 ± 12
Triglyceride (mg/dl)	120 ± 14	193 ± 29	143 ± 14
HDL-cholesterol (mg/dl)	45 ± 2	40 ± 24	47 ± 7
LDL-cholesterol (mg/dl)	107 ± 6	106 ± 20	156
Blood sugar (mg/dl)	114 ± 9	117 ± 27	113 ± 8
HbA_{1C} (%)	7.2 ± 0.5	5.4 ± 0.3	6.5 ± 0.9
Hypertension, n (%)	12 (32)	3 (8)	2 (5)
Beta-blocker, n (%)	26 (68)	6 (66)	7 (78)
Nitrate, n (%)	25 (66)	5 (56)	5 (56)
Calcium-channel blockers, n (%)	22 (58)	4 (44)	2 (22)

HR, heart rate; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein

Table 2 Correlation between perfusion abnormalities and myocardial stunning

	With PSFD	Without PSFD
segPC ≥ 2 (moderate or severe ischemia)	45	18
segPC = 1 (mild ischemia)	40	79
segPC = 0 (without ischemia)	19	189

n = 390 segments (30 patients)
segPC, segmental perfusion change; PSFD, post-stress functional depression

Table 3 Relationship between clinical data and cardiac events

	Event (–)	Event (+)
Number (n)	44	12
Age (y.o.)	68 ± 8	62 ± 11
Male, n (%)	38 (86%)	8 (14%)
Prior CHF, n (%)	4 (9%)	2 (16%)
Prior PCI, n (%)	3 (7%)	4 (33%)
Prior CABG, n (%)	1 (2%)	1 (8%)
LVEF rest (%)	51 ± 10	47 ± 15#
LVEF ex (%)	53 ± 12	45 ± 15#

CHF, congestive heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction. #, $p < 0.05$ vs. Event (–)

RESULTS

Classification of patients

Subjects were grouped on the basis of the results of coronary angiograms: 1-vessel disease (38 cases), 2-vessel disease (9 cases), 3-vessel disease (9 cases). Baseline clinical characteristics are summarized in Table 1.

Correlation in LVEF

On overall analysis of 26 patients who underwent left ventriculography, the resting LVEF on thallium-gated SPECT linearly correlated with that on ventriculography, with coefficients of $r = 0.893$ for LVEF ($p < 0.01$). A good correlation was obtained between EDV by QGS and EDV by LVG ($r = 0.67$, $p < 0.001$).

LVEF from post exercise to rest

In the 3-vessel group, post-exercise LVEF was significantly impaired compared to that at rest (43 ± 4.7 vs. 46 ± 4.2, $p < 0.05$). In the 1-vessel and 2-vessel groups neither was significantly impaired. The mean differences in LVEF between post-exercise and rest in coronary artery disease

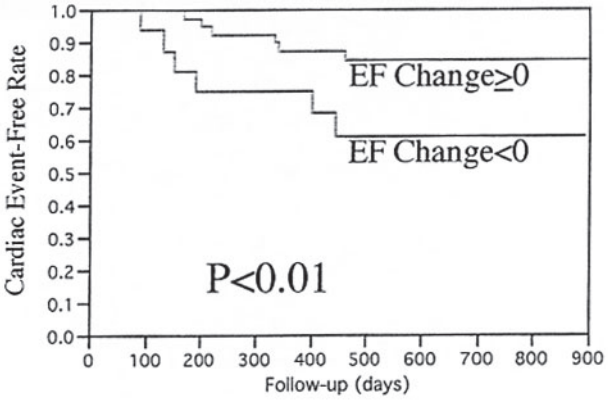

Fig. 2 Cardiac event-free curves for groups of patients with different median QGS-LVEF are shown. The group with post stress functional depression had a poorer prognosis ($p < 0.01$).

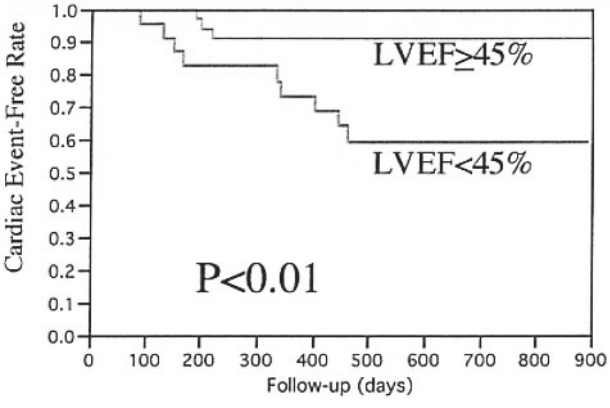

Fig. 3 The group with a median LVEF of more than 45% had a significantly lower event-free rate ($p < 0.01$).

were 2.2 ± 0.9%, 0.5 ± 1.7%, and −2.9 ± 1.5%, respectively (1 vessel, 2 vessels, 3 vessels). The change in LVEF in the 3-vessel group was significantly higher than that of 1-vessel disease or 2-vessel disease (−7.1 ± 1.1% vs. −0.1 ± 2.6%, $p < 0.01$).

Correlation between perfusion abnormalities and myocardial stunning

The magnitude of the depression of post-stress LVEF relative to the resting LVEF correlated with the severity of ischemia estimated using perfusion images ($p < 0.05$). Table 2 shows the correlation between perfusion abnormalities and myocardial stunning in 30 patients with reversible perfusion defects. Segments manifesting post-stress functional depression were associated with ischemic segments showing reversible perfusion defects. Of 26 patients without reversible perfusion defects, fixed perfusion abnormalities were observed in 20 patients.

Follow-up of subjects

Follow-up was complete in all patients (mean 569 ± 226 days). Coronary artery bypass grafting due to angina pectoris (n = 1), percutaneous coronary intervention due to angina pectoris (n = 4), non-fatal myocardial infarction (n = 4) or heart failure (n = 3) occurred during the follow-up period, but none of the patients died during that period. The relationship between clinical data and cardiac events is shown in Table 3. There were significant differences in resting LVEF and exercise LVEF between the groups with and without cardiac events ($p < 0.05$). Kaplan-Meier analysis shows that the group with post-stress functional depression had a poorer prognosis as shown in Figure 2 ($p < 0.01$). Cardiac event-free curves for groups of patients with different median QGS-LVEF are shown in Figure 3. The group with a median LVEF of more than 45% had a significantly higher event-free rate (Fig. 3). Kaplan-Meier analysis shows that the group with post-stress ventricular dilatation had a poorer prognosis ($p < 0.05$).

DISCUSSION

This study demonstrated that post-stress function testing by QGS provides incremental prognostic information in patients with coronary artery disease. The present data demonstrated that there was a high degree of correlation in left ventricular function between Tl-gated SPECT and left ventriculography.

The accuracy of quantitative gated myocardial perfusion SPECT for evaluating left ventricular function has been well established.[2,3,10–15] Tadamura et al. showed a good relation between ECG gated LVEF and three-dimensional magnetic resonance imaging in 20 patients (13 with an earlier infarction), although there was a small underestimation of LVEF (3.5%) by gated SPECT.[10] Maunoury et al. found a good correlation between Tl-201 gated SPECT and Tc-99m sestamibi gated SPECT ($r = 0.93$).[11] Reliability of the algorithm in the presence of perfusion abnormalities was further confirmed in this study.

Post-ischemic stunning has been well documented in animal models and in humans.[2,16] The phenomenon of post-ischemic stunning consists of the presence of abnormal regional function in the absence of necrosis. Persistence of functional abnormalities is certainly proportional to the degree of ischemia induced. Several echocardiographic and radionuclide studies have demonstrated post-stress stunning in clinical settings.[16–18] In the previous study using Tc-99m sestamibi gated SPECT, it was reported that LVEF after exercise was depressed in patients with reversible myocardial ischemia compared to LVEF at rest.[17] EDV is reportedly increased after exercise, with post-stress dilatation of the left ventricle serving as a marker of severe and extensive coronary artery disease.[18] However, optimal time post injection for Tc-99m sestamibi-gated SPECT was reported to be more than 30 minutes to allow for hepatobiliary tracer clearance. In this situation, standard stress SPECT acquisition seems to be too late to detect transient changes in cardiac function. That makes it difficult to recognize myocardial stunning in the clinical setting. In contrast, exercise thallium study can begin the acquisition of SPECT imaging soon after exercise and evaluate the severity of ischemia.[6,19] The feasibility of the use of thallium-201 in ECG-gated SPECT will easily facilitate assessment of myocardial stunning during exercise. Therefore, the prognostic value of post-stress EF may not be solely due to baseline ventricular dilatation and dysfunction, but also to transient worsening of ventricular function in patients with exercise-induced ischemia. In addition to viability assessment,[20–24] post-stress stunning may be a predictor of cardiac events in patients with coronary artery disease. And post-stress LVEF provides incremental value in the prediction of cardiac death.[25]

A limitation of the automated quantification algorithm in tracking myocardial edges might contribute to underestimation of LVEF. This study included only a few patients with akinetic or dyskinetic wall motion abnormalities. QGS software allows automatic edge contouring even in the absence of perfusion using smoothness, the isocontours of the coordinate system and the geometry of the defect boundaries as constrains. However, a limitation of this study is that care must be taken to evaluate such lesions. We used exercise redistribution imaging as the resting thallium imaging. Tc-99m MIBI image is reported to be superior to thallium redistribution image in terms of evaluation of wall motion and wall thickening.[26] However, LVEF, EDV and ESV can be determined reliably from gated thallium SPECT. In ischemic heart disease, it is important to measure regional dysfunction as well as global function, since normal myocardium becomes hyperkinetic during exercise. Germano et al. demonstrated a good agreement between visually-assessed Tl-201 and

Tc-99m gated images with respect to segmental wall motion and thickening.[4] It is also reported that wall motion and wall thickening determined by QGS were significantly correlated with the respective parameters determined by magnetic resonance imaging. Furthermore diastolic dysfunction after exercise was recently reported in patients with ischemic heart disease.[14] Further study is needed to determine the prognostic value of regional wall motion, wall thickening and diastolic function.

Assessment of post-stress left ventricular function by gated SPECT provides incremental prognostic information and is useful in predicting cardiac events in patients with coronary artery disease.

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