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 —

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Background Although the detection of wall motion abnormalities gives incremental value to myocardial perfusion single-photon emission computed tomography (SPECT) in the diagnosis of extensive coronary artery disease (CAD) and high-grade single-vessel CAD, whether or not it is useful in the diagnosis of mild, single-vessel CAD has not been studied previously.

Methods and Results Separate acquisition, dual isotope ECG-gated SPECT was performed in 97 patients with a low likelihood of CAD (Group 1) and 46 patients with single-vessel CAD (Group 2). Mild CAD was defined by stenosis of 50–75% (Group 2a, n=22) and moderate to severe CAD was defined by stenosis ≥76% (Group 2b, n=24). Myocardial perfusion and wall motion were graded by a 5 point-scale, 20-segment model. The sensitivity of myocardial perfusion alone was 50% for Group 2a, 83% for Group 2b and 67% for Group 2 as a whole. The overall specificity was 90%. When the wall motion analysis was combined, the sensitivity was increased to 82% in Group 2a and 92% in Group 2b.

Conclusion The ability to detect a wall motion abnormality immediately after exercise gives incremental diagnostic value to myocardial perfusion SPECT in the identification of mild, single-vessel CAD. (Circ J 2005; 69: 301–305)

Key Words: ECG-gated SPECT; Single-vessel disease; Wall motion abnormality

Prolonged regional myocardial dysfunction following exercise-induced ischemia has been identified as a sensitive marker of ischemia in both an experimental model1 and patients with known coronary artery disease (CAD).1–4 Nevertheless, the correlation between a wall motion abnormality detected by ECG-gated single-photon emission computed tomography (SPECT) and the angiographic data has not been fully evaluated. ECG-gated SPECT provides information on global as well as regional systolic function5,6 in addition to regional myocardial perfusion. Because a regional wall motion (RWM) abnormality may persist for 30–240 min following exercise, ECG-gated SPECT, acquired within 60 min after exercise cessation, has the potential to detect post-stress RWM abnormality in patients with multivessel CAD and high-grade coronary artery stenosis in the proximal coronary artery segments.5–9 However, the value of wall motion analysis using ECG-gated SPECT in patients with mild, single-vessel CAD has not yet been evaluated and because a RWM abnormality is most apparent in the early phase of the post-exercise period, we speculated that wall motion analysis shortly after exercise might give incremental diagnostic value to myocardial perfusion SPECT in patients with mild, single-vessel CAD.

Methods

Patient Population

The study group consisted of 97 normal subjects (Group 1: 57 men, 42 women; age 60±11 years) and 46 patients with angiographically documented single-vessel CAD (Group 2: 40 men, 6 women; age 61±9 years) who underwent separate acquisition, dual isotope ECG-gated SPECT. Group 1 consisted of patients with atypical chest pain who were classified as having a low likelihood of CAD according to the American Heart Association/American College of Cardiology classification for assessment of cardiovascular risk using multiple-risk-factor assessment equations.10 In all the patients of Group 1, coronary CT angiography was performed using a Siemens SOMATOM Volume Zoom with the image reconstruction method developed in our laboratory11 and it revealed no significant coronary artery stenosis in their major coronary arteries. The diagnostic accuracy of coronary CT angiography in comparison with invasive coronary angiography has been proved to be excellent, with a sensitivity of 94% and specificity of 97%...
in our laboratory. Patients in Group 2 were divided into the following 2 subgroups according to the angiographic severity of stenosis: Group 2a consisted of 22 patients with mild single-vessel CAD, which was defined as coronary artery stenosis of $50–75\%$ by quantitative coronary angiography; Group 2b consisted of 24 patients with high-grade single-vessel CAD, which was defined as coronary artery stenosis $\geq 76\%$ (76–100%). All the patients in Group 1 and 2 met the following criteria: (1) normal myocardial perfusion at rest (summed rest score (SRS) $<3$), (2) no akinesic or dyskinetic wall motion at rest, (3) no pathological Q waves on ECG, (4) no complete left bundle-branch block, (5) no previous coronary artery bypass surgery and (6) no paced cardiac rhythm. Patients with a known history of acute myocardial infarction were excluded.

**Acquisition Protocol**

We used the separate acquisition, dual isotope ECG-gated SPECT protocol with rest $^{201}$TI/exercise $^{99m}$Tc-tetrofosmin. The concept and technical details of this protocol have been described previously. In brief, $^{201}$TI (111 MBq) was injected intravenously at rest and SPECT imaging was started 10 min later. $^{99m}$Tc-tetrofosmin (740 MBq) was then given at peak exercise. Post-exercise SPECT imaging was initiated within 2 min of ceasing exercise. Acquisitions were performed using a 2-detector camera (E-CAM, Siemens, Germany) with 8-frame gated imaging, 64 projections over 180° for 35 s/projection. Projection images were filtered using a 2-dimensional Butterworth filter order 10 ($^{201}$TI) or 5 ($^{99m}$Tc), and a cutoff frequency of 0.36 cycle/cm ($^{201}$TI) or 0.46 cycle/cm ($^{99m}$Tc). For $^{201}$TI imaging, 2 energy windows were used, including a 30% window centered on the 70 keV peak and a 20% window centered on the 167 keV peak. For $^{99m}$Tc-tetrofosmin imaging, a 15% window centered on the 140 keV was used. Images were acquired using a 64x64 image matrix. Post-exercise image acquisition was completed within 17 min of exercise cessation in all patients.

**Exercise Protocol**

Beta-blockers and calcium antagonists were discontinued 24 h prior to the study and nitrates were discontinued 3 h prior to the study. A symptom-limited bicycle ergometer exercise test was performed. $^{99m}$Tc-tetrofosmin was injected at peak stress, and exercise at the same level was continued for an additional 60 s.

**Image Interpretations**

Myocardial perfusion SPECT images were scored semi-quantitatively using a 20-segment model of the left ventricle (Fig 1) with a 5-point scale system (0=normal uptake, 1=mild hypoperfusion, 2=moderate hypoperfusion, 3=severe hypoperfusion and 4=no uptake). In this model, the left anterior descending artery (LAD) distribution territory comprised 10 segments (segments 1–3, 7–9, 13–14, and 19–20), that of the left circumflex artery (LCX) comprised 6 segments (segments 5–6, 11–12, and 17–18) and the right coronary artery (RCA) comprised 4 segments (segments 4, 10, and 15–16). The summed stress score (SSS) was the sum of all scores on the post-exercise scan; the SRS was the sum of all scores on the rest scan; and the summed difference score (SDS) was calculated as the difference between them. If the SDS $\geq 3$ it was considered abnormal. Semi-quantitative analysis of RWM was performed by visually assessing the endocardial border excursion during systole. Left ventricular wall motion was scored by the 5-point scale, 20-segment model ($0$=normal, $1$=mild hypokinesia, $2$=severe hypokinesia, $3$=akinesia and $4$=dyskinesia). Summed stress wall motion score (SSSm) was the sum of all scores on the post-exercise scan; the summed rest wall motion score (SRSm) was the sum of all scores on the rest scan; and the summed difference wall motion score (SDSm) was calculated as the difference between them; SDSm $\geq 2$ was considered abnormal. A wall motion abnormality was defined as a segmental wall motion score $\geq 1$ in at least in 2 segments. The left ventricular end-diastolic volume, end-systolic volume and ejection fraction were calculated automatically by the quantitative ECG-gated SPECT system. Cohen’s $\kappa$ was calculated to determine the interobserver variations for the perfusion score and wall motion score and was revealed as 0.92 and 0.87, respectively, indicating good agreement.

**Coronary Angiography**

Coronary angiography was performed within 30 days (2–30 days) of the scintigraphic study in Group 2. Initially, angiographic results were visually interpreted by at least 2 experienced angiographers unaware of the scintigraphic data. Next, the percent luminal narrowing was quantitatively assessed by measuring the diameter at the region of maximum luminal narrowing and in the proximal and distal reference segments. Significant coronary artery stenosis was defined as luminal narrowing $\geq 50\%$ in the proximal portions of the LAD, LCX and RCA.

**Statistics**

Continuous data are expressed as the mean value±standard deviation. Comparisons were made using Student’s t-test for normally distributed variables and categorical data were assessed using the Fisher’s exact probability test. A $p$-value <0.05 was considered statistically significant. Sensitivity, specificity, and positive and negative predictive values were determined for SSS and SDS, as well as for SSSm and SDSm, for predicting angiographic stenoses. To compare the diagnostic accuracy of perfusion SPECT alone and for the combination of perfusion SPECT and wall motion analyses, McNemar’s chi-square test were used to determine the difference in the sensitivity and specificity.
Results

Exercise and Global LV Functional Characteristics

Patient characteristics are shown in Table 1. The location of CAD did not differ between the two groups. All the patients in Group 1 and 38 of the 46 patients in Group 2 (18 of 22 patients in Group 2a and 20 of 24 patients in Group 2b) achieved a peak exercise heart rate ≥85% of their age-adjusted maximal predicted heart rate.

Myocardial Perfusion and RWM Analysis (Table 2)

The SRS were similar among Groups 1, 2a and 2b. The SSS and SDS were greater in Group 2b than in Group 1 although they did not differ between Group 1 and Group 2a. The SSSm and SDSm in Group 2a were significantly greater than those in Group 1. End-diastolic and end-systolic volumes were comparable among the 3 subgroups at rest and did not differ between resting and after exercise. The ejection fraction was similar between Groups 1 and 2a, but was significantly lower in Group 2b than in Group 1.

Diagnostic Accuracy

The sensitivity and specificity of myocardial perfusion and wall motion for angiographic stenoses of 50–75% (Group 2a) and stenoses >76% (Group 2b).
alone and the combination of perfusion and wall motion analyses are shown in Fig 2. Using myocardial perfusion alone, the sensitivity was 50% in Group 2a and 83% in Group 2b. The overall sensitivity in Group 2 was 67%; 7 patients in Group 2a and 2 in Group 2b exhibited a wall motion abnormality without perfusion abnormality (Fig 3). When the positive test was defined by the presence of either perfusion abnormality or wall motion abnormality, the sensitivity increased to 82% in Group 2a, 92% in Group 2b and 87% in Group 2 as a whole. The specificity was 90% when only myocardial perfusion was considered. When the negative test was defined by the absence of perfusion abnormality and the absence of wall motion abnormality, the specificity was 87%. The McNemar’s chi-square test revealed that the sensitivity was increased when a wall motion abnormality was taken into account in Group 2a patients (p=0.016), but not in Group 2b patients (p=0.5). The incremental diagnostic value of detecting a wall motion abnormality was also observed in Group 2 patients as a whole (p=0.0039).

**Discussion**

The major finding of this study is that detecting a stress-induced wall motion abnormality immediately after exercise cessation adds incremental diagnostic value to the performance of myocardial perfusion alone in patients with mild, single-vessel CAD.

Although myocardial perfusion SPECT can predict long-term prognosis in patients with CAD, angiographic studies and recent observations by intracoronary ultrasound have suggested that the majority of patients with acute coronary syndrome have coronary artery luminal narrowing less than 50%, and that plaque texture features, such as the presence of lipid cores and thin fibrous caps, are more relevant to plaque rupture than luminal narrowing. Therefore, detecting mild ischemia is as important as the management of patients with suspected CAD as is detecting severe myocardial ischemia caused by high-grade or multivessel CAD. It is well documented that an exercise or pharmacologically induced wall motion abnormality is a sensitive marker of myocardial ischemia, but although a decrease of only 10–20% in subendocardial flow is sufficient to provoke regional wall motion abnormality, it is insufficient to produce an observable myocardial perfusion defect on myocardial perfusion SPECT, which cannot distinguish between the subendocardial and transmural perfusion status. However, wall motion analysis by ECG-gated SPECT appears to have little value in the detection of mild CAD. For example, Emmett et al reported that the sensitivity of wall motion analysis by ECG-gated SPECT is less than 20% in patients with 50–79% coronary stenosis. Usually, image acquisition is begun 15–45 min after exercise and completed 30–60 min after exercise in order to avoid the noise from high isotope accumulation in the liver, gallbladder, spleen and intestines. In an experimental model of single-vessel CAD, Homans et al showed that post-ischemic myocardial stunning persists only 15–30 min after exercise and in humans, Ambrosio et al showed that post-exercise myocardial stunning might persist for 120 min, but the time span between exercise cessation and regional functional recovery depended on the angiographic severity; that is, less severe angiographic lesions were associated with more prompt functional recovery. In the present study, we demonstrated an improved sensitivity for detecting single-vessel, mild CAD by analyzing wall motion immediately after exercise: post-exercise data acquisition was completed within 17 min after exercise cessation in all patients.

One might argue that the increased noise from motion artifacts immediately after exercise might hamper accurate wall motion analysis; none of the present patients was excluded because of appreciable motion artifacts. Pharmacological stress is thought to be better for avoiding motion artifacts, but may result in increased abdominal isotope uptake. Another problem with early data acquisition is incomplete isotope washout from the liver, which might lead to misinterpretation in the inferior myocardial segments because of liver–heart artifacts; however, none of our patients showed such artifacts. Although the extraction fraction of 99mTc-tetrofosmin is lower than that of 99mTc-sestamibi its washout rate from the liver is higher than that of 99mTc-sestamibi so 99mTc-tetrofosmin might be more suitable for early data acquisition.

In conclusion, we demonstrated that wall motion analysis added incremental value to myocardial perfusion SPECT alone for detecting myocardial ischemia in patients with mild, single-vessel CAD.

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**References**

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