Post-stress Global and Regional Left Ventricular Function in Ischemic Patients as Detected by Gated-SPECT Myocardial Perfusion Scintigraphy

Abstract

Objective: This study was performed to elucidate the residual effects of exercise on post-exercise global and regional left ventricular function in subjects with scintigraphic evidence of myocardial ischemia, and its implications on the detection of stunning.

Materials and methods: Two-day exercise/rest 99mTc-tetrofosmin gated-SPECT myocardial perfusion scintigraphy was performed in three groups of patients, namely patients without ischemia or prior infarction, patients with ischemia, and patients with prior infarction. The ischemic group was further stratified into patients with ischemia, and patients with prior infarction. The ischemic group was further stratified into

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Results: The patient population consisted of 30 normal control subjects, 50 ischemic patients, and 23 patients with scintigraphic evidence of myocardial infarction. Stress LVEF and EDV was representative of rest LVEF and EDV, respectively, in all patients’ groups. No statistically significant difference was observed in the LVEF and EDV values in the ischemic group between the stress and the rest conditions. Regional WT was, on the other hand, statistically different in stress images when compared to rest images (P=0.006); however, this difference disappeared in patients with mild ischemia.

Conclusion: LV regional dysfunction is more sensitive than impairment in global LVEF for the detection of post-ischemic stunning. WT abnormalities were significant only in patients with moderate to severe ischemia. We conclude that it is not expected for stress-induced WT abnormalities to improve the interpretation of stress myocardial perfusion study.

Key words: Ischemia, Ejection Fraction, Wall Thickening, Scintigraphy

Introduction

Electrocardiographically (ECG)-gated myocardial perfusion SPECT was developed in the late 1980s, and since then has rapidly evolved into a standard imaging modality for myocardial perfusion imaging. In its position paper of March 1999, the American Society of Nuclear Cardiology recommended the routine incorporation of ECG-gating during SPECT perfusion scintigraphy. Gated SPECT studies allow simultaneous assessment of perfusion and function in a single-injection, single-acquisition sequence.

Because of their high count rates and stable myocardial distribution over time, the 99mTc-based perfusion tracers allow the evaluation of regional myocardial wall motion and wall thickening throughout the cardiac cycle. The development of automated algorithms to quantitatively assess accurately and in a virtually operator-independent manner left ventricular (LV) volume and ejection fraction (EF), and even regional myocardial wall motion and thickening from gated SPECT, has also contributed to its widespread use. These advances have made SPECT imaging a premier method of noninvasive evaluation of myocardial blood flow and cardiac function in a variety of clinical situations.

Gated-SPECT measurement of left ventricular function has been validated versus a variety of techniques, such as equilibrium blood pool studies, contrast ventriculography, first pass ventriculography, and magnetic resonance imaging. Either or both of the acquisitions composing the stress/rest sequence can be gated, although the common practice is to gate only the post-stress image. The independent additive value of global LV dysfunction (LVEF) for the diagnosis of severe and extensive coronary artery disease (CAD), as evaluated by post-stress gated SPECT, has been demonstrated by several studies. These studies indicate that global LV function obtained from post-stress gated acquisitions are not representative of baseline LV global function in patients with stress-induced ischemia, and that both rest and stress images should be gated routinely, as long as feasible.

Post-exercise global dysfunction may underestimate the true incidence of stunning. Contractile dysfunction caused by an ischemic insult is typically regional; global LVEF is not impaired until at least 25% of the LV myocardium is ischemic. Thus, it is suggested that post-ischemic regional dysfunction may be more sensitive than global dysfunction in detecting stunning. The present study was performed to elucidate the residual effects of exercise on post-exercise global and regional LV function in subjects with scintigraphic evidence of myocardial ischemia using a single-tracer two-day protocol. To this end, relationships between post-exercise and resting LV global and regional function in different perfusion groups were investigated by employing a two-day exercise/rest 99mTc-tetrofosmin gated-SPECT protocol. LVEF and systolic wall thickening (WT) were considered as objective indices of LV global and regional function, respectively.

Materials And Methods

Study Population

Patients referred to the Regional Center of Nuclear Medicine of the University of Pisa to perform myocardial scintigraphy over a nine-month period were retrospectively classified into three groups, and only those who fitted the selection criteria were included in the study. The first group included patients referred to perform gated myocardial SPECT after atypical chest pain. Stress ECG was negative or non diagnostic for ischemia. None had a previously documented CAD or other cardiac disease. These patients had normal exercise/rest perfusion scintigraphic findings and no evidence of regional ventricular dysfunction on gated-SPECT. The second group included patients with clinically documented prior myocardial infarction without any interventional procedure or heart event between the infarction and the scintigraphic study. These patients had fixed perfusion defects on scintigraphy. The third group included patients with reversible myocardial perfusion defects indicating myocardial ischemia after exercise-induced stress, without any clinical or scintigraphic evidence of prior infarction. All patients were in pharmacological wash-out (nitrates and β-blockers). None of the ischemic patients had undergone percutaneous transluminal angioplasty nor aorto-coronary bypass graft, nor was any of these patients affected by left bundle branch block, cardiomyopathy, or atrial fibrillation.

Exercise and Imaging Protocol

A two-day exercise-rest myocardial perfusion imaging protocol was followed. Each subject underwent 25 watt-minutes per step graded exercise, and a dose of 740 to 925 MBq (20-25 mCi) 99mTc-tetrofosmin (Myoview, GE Healthcare, UK) was injected at peak exercise. The endpoint of exercise was when the patient reached 85% of age-predicted maximal heart rate, or when chest pain, marked ST-segment depression on the ECG (horizontal or downsloping >2 mm), exercise-limiting leg fatigue, or dyspnea occurred. Post-exercise images were acquired 1 hour after radio-tracer injection. A dose of 740-925 MBq (20-25 mCi) 99mTc-tetrofosmin was injected at rest the day after exercise and imaging was completed.
performed 1 hour later. Sixty-four projections (40 seconds each) were acquired with a 64×64 matrix over a 180° circular orbit from right anterior oblique 45° view to the left posterior oblique 45° view using a 90° dual-head gamma camera (Optima NT, GE Healthcare, Milwaukee, USA) equipped with LEHR collimator and set at 140 KeV±10%. ECG-gating was based on 8 frames per R-R interval and a gated tolerance of 60%.

All data were processed at a workstation (ELGEMS Entegra v.2.5) using a commercial software QPS/QGS developed by Cedars-Sinai (Los Angeles, USA)15. The gated SPECT projection data sets were constructed using an iterative OSEM algorithm with Butterworth "post-filtering" (cut-off 0.4 cycles/cm and order 8 for summed data; 0.3 cycles/cm and order 8 for gated data). No attenuation correction was performed.

Data Interpretation

All perfusion images were visually interpreted using a semi-quantitative method by the consensus agreement of two experienced observers who were informed on patients’ clinical data. Expert visual semi-quantitative scoring of the perfusion images was performed on non-gated images; however, gated images were made available at this session to allow for exclusion of attenuation defects. The post-exercise and rest images were interpreted for the presence, extent, severity and reversibility of perfusion defects using a 20-segment model of the left ventricle18. Visual scoring using a 5-point scoring system (0 = normal perfusion; 1 = equivocal or mildly reduced; 2 = moderate reduction; 3 = severe reduction; 4 = absent perfusion) was performed19. The summed stress score (SSS) was the sum of all scores on the stress scan; the summed rest score (SRS) was the sum of all scores on the rest scan; and the summed difference (i.e., reversibility) score (SDS) was calculated as the difference between the summed stress and rest scores. SDS less than 8 was considered as indicative of mild ischemia. SDS ≥ 8 was considered as equivalent of moderate-severe ischemia20.

QGS was applied to the reconstructed short-axis tomograms to assess global left function (LVEF) and regional wall thickening (WT). QGS images are automatically scored for motion and thickening for each myocardial segment. A scale of 0–3 is used for grading wall thickening (0 = normal, 1 = mildly reduced, 2 = moderately to severely reduced, 3 = no thickening). A summed stress score for wall thickening (SSSWT) was determined from the sum of the scores on the stress-gated images, which reflects the degree and extent of post-exercise regional wall thickening abnormality. The Summed Rest Score for Wall Thickening (SRWTS) was calculated as the sum of the scores on the rest images, thus reflecting the degree and extent of fixed regional wall thickening abnormality. The Summed Difference Score (SRWTS) was calculated as the difference between SSSWT and SRSWT. QGS stress/rest end diastolic volume and LVEF were also recorded for both the rest and stress images. Delta LVEF was defined as stress LVEF minus rest LVEF.

Statistical analysis

Data is presented as mean ± standard deviation. Student paired t test was used to compare paired data (post-exercise changes in LVEF, WT and perfusion scores) within a group. Data were analyzed using SPSS software for windows version 11.5.

Pearson correlation was employed to correlate perfusion (SDS) and function (EF%, SRWTS) data. A P-value <0.05 was considered statistically significant. Ninety-five percent Confidence Intervals (CI, mean±2SD) were calculated to describe systemic differences over the ranges of LVEF observed.

Results

Patients

The study included three distinct patients’ groups. The first negative control group consisted of 30 patients (14 men, age 61±12.6 years). The second infarction control group consisted of 23 subjects (22 men, age 63±9 years) with mean SSS of 13. The third group consisted of 50 patients (39 men, age 65±11 years). In this ischemia group, 29 patients had SDS < 8 and 21 had SDS ≥ 8.

Rest and post-stress LVEF

Correlation between LVEF at stress and at rest was excellent in normal subjects (r = 0.934, P<0.01) as well as in the infarction group (r = 0.952, P<0.01), and ischemia group (r = 0.807, <0.01) (Figure 1). Mean LVEF at stress in ischemia patients was 59.66% ± 10.07 SD, significantly lower than in the normal subjects (67.43% ± 8.77; P <0.01).

Figure (1) Correlation between LVEF at stress and at rest in the ischemia group (r=0.807, P <0.01)

Post-exercise changes in LVEF

In the normal group, post-exercise EF was minimally but significantly higher than rest EF (mean difference 2.667 mL, P = 0.0115). In this group, the mean delta ejection fraction (EF, defined as stress minus rest EF in the individual patients) was 2.67% (95% CI [0.65-4.69]). In the infarction group no exercise-induced change in EF was found. The mean EF in the infarction group was -0.26% (95% CI [-2.63-2.11]. No significant difference between stress and rest LVEF was observed in the whole ischemia group or subgroups, even when only those with SDS ≥ 8 were considered. The mean EF in the individual ischemic patients was -0.32% (95% CI [-2.10-1.46]) (see Figure 2). There was no statistically significant correlation between EF and SDS (r = -0.265, P = 0.063), even when separately considering the individual ischemic patients was -0.32% (95% CI [-1.40-0.76]).

The mean EV values and significance of post-exercise induced changes in all patient groups are presented in Table (1).
Post-stress global and regional left ventricular function in ischemic patients as detected by gated-SPECT myocardial perfusion scintigraphy

### Table (1)

<table>
<thead>
<tr>
<th>Group</th>
<th>Stress (%)</th>
<th>Rest (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarction</td>
<td>48.9% ± 10.8</td>
<td>49.2% ± 11.4</td>
<td>NS</td>
</tr>
<tr>
<td>Normal</td>
<td>67.4% ± 9</td>
<td>64.8% ± 9</td>
<td>0.0115</td>
</tr>
<tr>
<td>Ischemia</td>
<td>59.6% ± 10</td>
<td>59.9% ± 10</td>
<td>NS</td>
</tr>
</tbody>
</table>

Legends: Table (1) Mean ejection fraction (%) ± SD in all three patient groups

### Post-exercise changes in wall thickening

All patients in the negative control group had 0 stress- and rest-WT scores as defined in the inclusion criteria. In the infarction group there was no significant difference in WT values between the stress and the rest studies. In the ischemia group there was a statistically significant difference between SSSWT and SRSWT when all patients were considered (P = 0.038). When those with mild ischemia were considered, this difference was not significant, while it was statistically significant for those with SDS 8 (P = 0.007). There was also good correlation between ischemia severity (SDS) and reversible wall thickening abnormality (SRWTS) (r = 0.63, P<0.01) for the whole ischemia group; this correlation disappeared in patients with mild ischemia, but was maintained when only patients with moderate to severe ischemia were considered (r = 0.678, P<0.01) (Figure 3).

Considering that the ischemia group accounted for a total of 1000 segments, reversible myocardial perfusion defects were encountered in 291 segments, 29% of them demonstrating post-exercise-induced wall thickening abnormality.

All segments that demonstrated exercise induced wall thickening abnormality demonstrated also stress induced perfusion defects, except for 30 segments, in the vascular territory of stress induced ischemia, where abnormal wall thickening was evident in the stress images despite normal stress perfusion.

### Discussion

A completely automated, quantitative algorithm (QGS) for the measurement global left ventricular function (EF) and regional function (wall motion and thickening) from 3-dimensional gated myocardial perfusion SPECT has been developed. Three-dimensional endocardial and epicardial surfaces are determined for gated and ungated data sets. Myocardial thickening is determined as percent increase in myocardial thickness (distance between endocardial and epicardial surfaces, normal to the mid-myocardial surface) from end-diastole to end-systole.

Although this quantitative approach was developed for post stress 99mTc-sestamibi imaging, it is believed that the same thresholds can be applied to resting 99mTc-tetrofosmin as well. Measurements by this algorithm is well correlated with semiquantitative expert visual interpretation. Wall thickening correlates with 99m Tc-sestamibi myocardial uptake better than wall motion analysis, therefore in this study we considered segmental wall thickening rather than segmental wall motion.

Gated SPECT studies can be acquired both after stress and at rest, and it has been demonstrated that this method provides reproducible information on LVEF and EDV. At the time of acquisition, myocardial distribution and uptake of the tracer reflects perfusion at the moment of tracer injection (exercise or rest); in contrast, the acquisition of left ventricular function is a measure of real time function.

Since pooled analysis of 99mTc-sestamibi SPECT imaging yielded a 90% sensitivity in the detection of CAD, the first group of patients was considered as a negative control group. The ejection fraction in this group was minimally but significantly higher in post-exercise than at rest. As a matter of fact, studies using radionuclide ventriculography have revealed a significant increase in EF after exercise; this was attributed mainly to catecholamine-stimulated myocardial contractility. In this study we encountered a persistent increase in EF even at one hour after exercise.

Post-ischemic reversible contractile dysfunction, known as myocardial stunning, is common in patients with coronary artery disease.
A limited number of studies have shown that post-ischemic dysfunction can affect global left ventricular function (LVEF) as determined by gated SPECT on post–stress gated acquisitions; this stress-induced difference, however, is modest and rarely exceeds confidence limits. In our study we failed to demonstrate a depressed post-exercise LVEF in the ischemic group, this is probably attributed to variables regarding acquisition protocols; particularly time lapse between stress tracer injection and image acquisition, reference method used to establish the diagnosis of coronary artery disease and criteria of population selection for the study. Most studies that demonstrated global post-ischemic left ventricular dysfunction have used 32P for gated stress imaging (which implies early post-stress imaging) or started imaging 15–45 minutes after 99mTc tracer injection. In our study stress images were acquired one hour after tracer injection, which implies more time available for recovery of left ventricular function. These studies used angiography as reference method, therefore; patients with 3-vessel disease were included and global depression of left ventricular function is more likely, in our study, patients were selected on the basis of the presence of reversible perfusion defects, which implies lower probability of 3-vessel disease.

Prolonged regional myocardial dysfunction after exercise-induced ischemia has been documented experimentally in patients with coronary artery disease. Ambrosio et al. demonstrated that regional systolic dysfunction may persist for 30 to 240 min after exercise and, depending on the severity of ischemia, the resolution of post-ischemic left ventricular dysfunction may persist for 30 to 240 min after post-exercise regional dysfunction assessed by abnormal wall motion abnormalities, mild/moderate compromise of transmural blood flow, and mild/moderate compromise of subendocardial blood flow, could result in only a mild/moderate perfusion abnormality if any, but significant wall motion impairment, which may persist after exercise. Another possible explanation to this finding would be the partial redistribution of 99mTc-tetrofosmin with time. Schulz et al. reported that the relative washout fraction per hour for tetrofosmin was 8.3% ± 9.9% in areas with a stress-induced defect. It was suggested recently that that early tetrofosmin images acquired at 15 minutes post stress could have an important clinical impact, identifying ischemia more accurately in terms of severity and extension. This issue, however, is still open for further clinical and experimental investigation.

Conclusions

In our study population LV global function measured by LVEF, obtained from one-hour post-exercise gated SPECT, represents baseline LVEF in patients with prior infarction or in patients with scintigraphic evidence of reversible perfusion defects. Significant post-exercise regional dysfunction assessed by abnormal wall thickening and consistent with the concept of stunning, occurs in patients with reversible perfusion defects. The incidence and magnitude of regional stunning are determined by the severity of ischemia induced by exercise. LV regional dysfunction is therefore more sensitive than impairment in global LVEF for the detection of post-ischemic stunning, yet it is not expected to help improving the interpretation of myocardial perfusion study. Further investigations are needed for better understanding the pathophysiology underlying abnormal segmental thickening in the presence of normal perfusion.

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