Original article

Myocardial perfusion in patients with ST depression during the recovery phase of treadmill stress tests

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RESUMEN

Objetivo: determinar la incidencia y características de las anormalidades en la perfusión miocárdica en pacientes con depresión de ST en recuperación únicamente, usando tomografía computada por emisión de fotón único (SPECT) con Tc-99m.
Antecedentes: el significado de la depresión de ST en recuperación después de la prueba de esfuerzo sigue siendo motivo de controversia. Tal hallazgo se ha clasificado como falso positivo, falso negativo y signo no concluyente de arteriopatía coronaria.
Pacientes y métodos: se analizaron 50 pacientes que se sometieron a una prueba de esfuerzo y tomografía computada por emisión de fotón único (SPECT) con Tc-99m y demostraron depresión ST sólo en recuperación. El grupo consistió en 28 hombres y 22 mujeres, con edad promedio de 61 ± 9 años. Se valoraron las anormalidades en la perfusión, la distribución reversa, la relación corazón-pulmón, los cambios en el tamaño de la cavidad y la función global.
Resultados: la frecuencia cardiaca pico media fue de 139 ± 18 latidos por minuto (88% ± 14 de la frecuencia cardiaca máxima pronosticada). Sesenta porciento de los pacientes tenían datos de arteriopatía coronaria en forma de anormalidades de la perfusión fijas o reversibles. Las anormalidades de la perfusión fijas se encontraron en tres pacientes (6%), siete (14%) tenían defectos de la perfusión fijas y reversibles y 20 (40%) mostraron únicamente isquemia. Se observó isquemia en la pared anterior en 10 pacientes, en la pared inferior en 12, en la pared lateral en 5, en el apex en 8 y en el septum en uno. La extensión promedio de las anormalidades de la perfusión fueron 3.7 ± 2 segmentos (de 20).
Conclusiones: se encontraron datos de arteriopatía coronaria en 60% de los pacientes con depresión de ST en recuperación. El hallazgo más común fue isquemia en 54% de los pacientes, y las paredes anterior e inferior fueron las dañadas con más frecuencia. La extensión media del daño miocárdico fue moderada, lo que implica significado pronóstico.
Palabras clave: prueba de esfuerzo, recuperación, Tc-99m, perfusión miocárdica.

ABSTRACT

Objectives: To determine the incidence and characteristics of myocardial perfusion abnormalities in patients with ST depression in recovery only, using Tc-99m gated-SPECT.
Background: The significance of ST depression in recovery only after exercise treadmill testing (ETT) remains controversial. Such finding has been classified as a false positive, false negative and inconclusive sign of CAD.
Methods: Fifty patients who underwent ETT and Tc-99m gated-SPECT and demonstrated ST depression only in recovery were analyzed. The group consisted of 28 men and 22 females, mean age of 61 ± 9 years. Perfusion abnormalities, reverse redistribution, heart/lung ratio, changes in LV cavity size and global function were assessed.
Results: The mean peak heart rate (PHR) was 139 ± 18 bpm (88% ± 14 of the predicted maximal heart rate). Sixty % of the patients had evidence of CAD in form of either fixed or reversible perfusion abnormalities. Fixed only perfusion abnormalities were found in 3 patients (6%), seven (14%) had fixed and reversible perfusion defects and 20 (40%) showed ischemia only. Ischemia was observed in the anterior wall in 10 patients, inferior wall in 12, lateral wall in 5, apex in 8 and septum in 1 patient. Mean extent of the perfusion abnormalities were 3.7 segments (out of 20) ± 2.
Conclusions: Evidence of CAD was found in 60% of the patients with ST depression in recovery only. The most common finding was ischemia in 54% of the patients, and the anterior and inferior walls were most frequently involved. The mean extent of myocardial involvement was moderate, which implies prognostic significance.
Key words: Exercise treadmill test, recovery, Tc-99m, myocardial perfusion.

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This report describes the incidence and characteristics of perfusion abnormalities using technetium-99 gated-SPECT in 50 patients with ST depression in recovery only during exercise treadmill test. Sixty percent of the patients had perfusion abnormalities, ischemia being the most common perfusion abnormality. Mean extent of the perfusion abnormalities by semiquantitative analysis was 3.7 segments (out of 20) ± 2 and a mean percent of total stress extent area (TSA%) of 15% ± 10 (range: 2 to 46%). Ischemia was observed in the anterior wall in 10 patients, inferior wall in 12, lateral wall in 5, and in apex in 8.

The significance of ST depression at recovery only after an exercise treadmill test is controversial.[1-10]

The typical clinical and electrocardiographic changes that indicate the presence of coronary artery disease includes: Reproduction of the patient's symptoms, fatigue, decrease in systolic blood pressure $\geq$ 20 mm Hg, ventricular arrythmias, and ST-segment depression.[11] However, in 1.4% to 8.5%[1-4,8,9] of the patients who undergo exercise treadmill test, the ST segment depression occurs only after the exercise phase of the stress test. Such ST changes have been considered false positive,[5,10,12,13] non-conclusive,[4,6] true positive,[1,2,3,8,9] or significant in the sense that when included it increased the diagnostic yield of the stress test.[3] Stress and rest myocardial perfusion imaging using modern Tc-99 labeled agents and Single Photon Emission Tomography (SPECT) technique can objectively detect and assess myocardial perfusion abnormalities secondary to coronary artery disease. Both myocardial injury and stress induced ischemia can be detected with high sensitivity and specificity, and the abnormalities can be quantified. The incidence and type of perfusion abnormalities using this widely available technique in patients with ST depression in recovery only, has to our knowledge not been reported in the literature. The role of SPECT myocardial perfusion imaging in the work up algorithm of patients with ST depression in recovery is thus unclear.

The aim of this study was to determine the incidence of perfusion abnormalities detected by SPECT myocardial perfusion imaging in patients with ST depression in recovery period only, and to determine the extent, severity and localization of these perfusion abnormalities.

PATIENTS AND METHODS

Patient population

From October 1999 to May 2000, 50 consecutive patients referred for evaluation of known or suspected coronary artery disease who had: *a)* a normal baseline ECG, *b)* an exercise treadmill test with ST depression in recovery only, *c)* a myocardial perfusion study the same day and *d)* who had not undergone a coronary intervention within the last month before the test were prospectively enrolled in the study. Patients with left bundle branch block or T wave inversion in recovery were excluded. Baseline patient characteristics are described in Table 1.

Table 1. Demographic data of the patients

	Male	*Female*	*All*	*p*
Sex (n)	28	22	50	NS
Age (years)	61 ± 9	61 ± 10	61 ± 9	NS
Hypertension	9	12	21	NS
Diabetes	3	3	6	NS
History of myocardial infarction	6	4	10	NS
History of percutaneous transluminal coronary angioplasty	8	0	8	< 0.05
History of coronary artery bypass graft surgery	3	0	3	NS
Nitrates	10	6	16	NS
Betablockers	15	8	23	NS
Digoxin	0	1	1	NS
Calcium channel blockers	5	5	10	NS
Angiotensin converting enzyme ihhibitors	4	6	10	NS
Gated SPECT ejection fraction	62 ± 7	70 ± 10	66 ± 9	NS

Treadmill protocol

After informed consent obtained, all patients performed symptom or sign limited exercise treadmill test with Bruce or modified Bruce protocols. During the test, 12-lead ECG's were recorded before, during and after exercise at intervals of 2 minutes. Blood pressure readings were

performed in supine, standing and every 2 minutes during the exercise period and every 2 minutes in recovery. An ECG was also recorded in standing position immediately after the exercise to obtain the best possibly motion free tracings after peak stress. The PR segment was considered as the isoelectric line and the ST segment was measured 80 milliseconds after the J junction. The ST changes were considered positive if a ST depression of ≥ 1mm either horizontal or downsloping was detected. Patients with motion artifacts that did not allowed an adequate reading of the ECG were excluded.

Myocardial perfusion imaging

A stress-rest imaging protocol was used. Eight mCi Tc-99m Tetrofosmin was administered at peak stress (defined as maximal possible effort, moderately severe chest pain, dyspnea or fatigue) and the test continued for 30-60 seconds. Stress imaging was performed 20-40 min post tracer administration. Two to 3 hours later 24 mCi Tc-99m Tetrofosmin was injected rest. Rest imaging was performed 20-40 min post tracer administration.

A 3-headed camera (Prism, Picker Int., Cleveland Ohio) equipped with high resolution collimators was used. Data were acquired in 64x 64 matrix, over 180° from LPO 45 to RAO 45, 32 angles, 25 sec/angle for the stress study, and 20 sec/angle for the rest study. All studies were reconstructed using filtered back projection (ramp). A low pass filter was applied (order 5.0 with cutoff 0.23 for rest studies and order 5.0 with cutoff 0.25 for stress studies). The data were reformatted to vertical long, short and horizontal long axes (6 mm) according to the individually determined anatomical cardiac long axis. Software zoom was applied for display and visual assessment purposes, and coronal slices were added hereby generating perfusion images representing regional myocardial perfusion in the basal, mid and apical thirds of the myocardium. Midventricular sagittal and transaxial slices were also created for visualization of the apex and the walls in longitudinally context. The stress and rest studies were carefully aligned to insure that the corresponding myocardium in the two studies was compared.

The rest SPECT acquisition was gated to the R wave and the cardiac cycle was divided into 8 frames with an acceptance window of ± 10% around the mean R-R interval during 1 minute prior to the study.

Assessment of regional myocardial perfusion

The LV myocardium was divided into 20 segments and each segment was scored using a 5 point score (0 = no perfusion, 1 = severe decreased perfusion, 2 = moderatedly decreased perfusion, 3 = mild perfusion defect and 4 = normal perfusion). Quantitative analysis of the percentage of total myocardium affected during stress (percentage of total stress extent area = TSA%) was performed using the CEqual method.[14]

Stress heart/lung uptake

Stress heart/lung ratios were determined by measuring the mean counts in a 5x5 pixel ROI over the region of the heart with the highest tracer uptake in the anterior view, and over the pulmonary segment just above the heart. An abnormal lung uptake was considered when the ratio (H/L ratio) was > 0.45.[15,16]

Assessment of stress/rest LV cavity size ratio

Non-gated LV volumes were also determined in rest and stress study using the QGS software. A stress/rest volume ratio was calculated to detect the presence or absence of an increase in LV volume during stress, which is a reflection of subendocardial ischemia.[17,18] An abnormal volume ratio was considered when the volume ratio was > 1.20.[19]

Evaluation of global myocardial function

A commercially available automated myocardial gated-SPECT processing software (QGS)[20] was used to determine LVEF.

Statistical methods

All values are given as mean ± SD. Relationship between variables was analyzed using simple linear regression analysis. Fisher's exact test was used for comparison between groups. A p value of less than 0.05 was considered significant.

RESULTS

Exercise treadmill test

Fifty out of 1,150 (4.3%) patients studied in our laboratory during the study period, demonstrated ST depression in recovery only. Overall this population showed good exercise time, with a non-significant higher exercise time

Table 2. Exercise test results

	Male	Female	All	p
Exercise duration (min)	8.23 ± 3	6.29 ± 11	7.31 ± 3	NS
Peak heart rate (bmp)	138 ± 7	140 ± 19	139 ± 18	NS
% of predicted max	85 ± 11	92 ± 17	88 ± 14	NS
Δ heart rate (%)	110 ± 38	106 ± 43	108 ± 40	NS
Peak blood pressure (mmHg)	173 ± 29	174 ± 36	173 ± 32	NS
Δ blood pressure (%)	34 ± 22	32 ± 22	33 ± 22	NS
Rate pressure product	23,752 ± 5,250	24,624 ± 7,598	24,136 ± 6,334	NS
Δ Rate pressure product (%)	181 ± 90	172 ± 69	177 ± 81	NS
ST depression onset (min)	2.6 ± 1.06	2.4 ± 1.05	2.51 ± 1.05	NS
ST depression (mm)	1.3 ± 0.3	1.3 ± 0.2	1.32 ± 0.4	NS
Duration (min)	7.2 ± 3	9.4 ± 7	8.1 ± 5.1	NS

in male patients when compared to females (Table 2). The peak heart rate achieved was good in both gender groups, overall reaching an average of 88% ± 14 of the maximal predicted heart rate for age. The increase from basal to peak heart rate (Δ HR) was 108% ± 40, with a mean peak blood pressure of 173 ± 32 mmHg, a delta blood pressure (Δ BP) of 33% ± 22 and a mean rate pressure product of 24,136 ± 6,334.

Seventy percent of the patients had no adverse signs or symptoms and stopped the test due to fatigue, exercise induced chest pain was seen in 12% of the cases, shortness of breath in 12% of the cases, and shortness of breath and chest pain in 6% of the cases. Two patients (4%) demonstrated a decrease in blood pressure during exercise. There was no relation between symptoms, and the extent of the perfusion abnormalities.

The ST-segment depression in recovery only ranged from 1 to 2 mm, mean onset was 2.5 ± 1.05 min (range: 42 sec. to 5 min.). The mean duration of the ECG changes was 8.1 ± 5.1 minutes (range 3 to 35 minutes). There was no significant relation between the time of onset of the ST changes, their duration and the extent of perfusion abnormalities (r = -0.10 and -0.05 respectively).
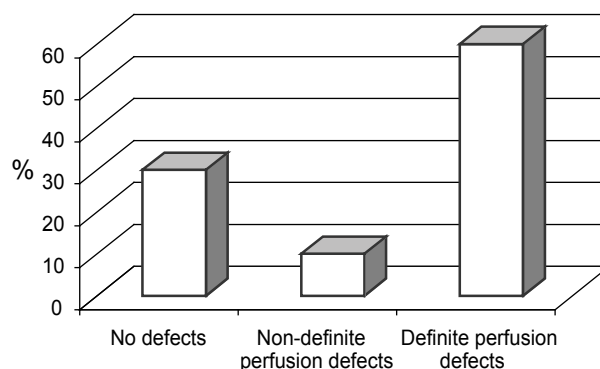
Myocardial perfusion

Definite fixed or reversible perfusion abnormalities was found in 30 (60%) of the patients, 3 patients (6%) had fixed perfusion defects with no stress induced ischemia, 7 (14%) had fixed and reversible perfusion abnormalities and 20 (40%) showed stress induced ischemia only (Figure 1). Among the patients with fixed-only perfusion defects 1 had 1 vascular territory involved and 2 had 2 territories involved. Among the patients with stress induced ischemia, 15 had 1 vascular territory involved, 4 had 2 vascular territories involved and 3 vascular territories were involved in one case (Figure 2). Five out of 9 patients with both rest and stress perfusion abnormalities had peri-infarct ischemia and 4 had stress induced ischemia in other territory than the one showing the rest perfusion abnormality.

The mean ejection fraction (EF%) was 66% ± 9, and there was no significant difference among patients with or without ischemia, their extent, symptoms or duration of the ST depression.

The presence of reverse redistribution (defined as the improvement of a rest perfusion abnormality during stress) was observed in 3 patients only. The heart/lung ratios were found to be increased in 12 (24%) of the patients, of whom 8 either had a fixed or reversible perfusion defects while 4 had no perfusion abnormalities. Four patients had increased LV cavity size during stress of whom 3 had either fixed or reversible perfusion defects.

The localization of the reversible perfusion defects (Figure 2) was the septum in 1 patient, the anterior wall in 10 cases, inferior wall in 12, lateral wall in 5 and apex in 8 cases. The localization of the fixed perfusion abnormalities was the septum in 1 patient, anterior wall in 2, lateral wall in 2 cases, inferior in 6 and apex in 3 cases.

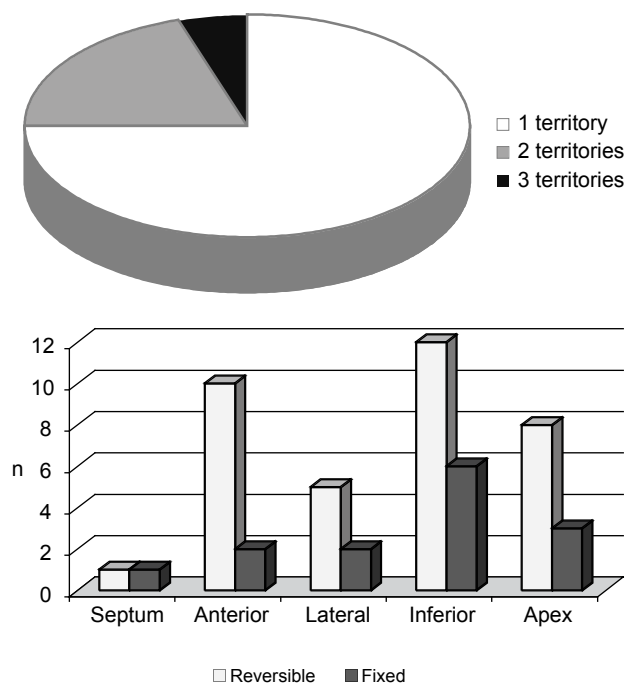**Figure 1**. Incidence and type of perfusion abnormalities.

Figure 2. Anatomical localization of the perfusion defects.

Extent of perfusion abnormalities

The extent of the perfusion abnormalities was assessed by visual semiquantitative analysis using a 20-segment model and quantitatively by the CEqual method.[14] The mean number of segments with fixed perfusion abnormalities was 3.4 ± 1.1 segments (range: 2 to 5) (Figure 3). The mean number of segments with reversible perfusion abnormalities was 3.7 ± 2 segments (range: 2 to 10) (Figure 3). The quantitative analysis showed a mean percent of total stress extent area of $15\% \pm 10$ (range: 2 to 46%).

The patients who did not experience chest pain had a significantly higher extent of ischemia by semiquantitative and
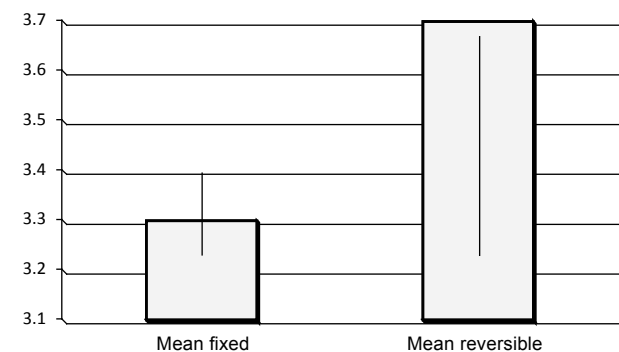

Figura 3. Semiquantitative extent of perfussion abnormalities (n = number of segments).

quantitative analysis, when compared to the patients who experienced chest pain during the stress test (p <0.003).

Pretest likelihood of coronary artery disease

The pretest likelihood of coronary artery disease[11] was very low in 10%, low in 14%, intermediate in 54% and high in 22% of patients with ST depression in recovery only. The presence of definite perfusion abnormalities in each of these patient groups is shown in Table 3.

Table 3. Pretest likelihood of coronary artery disease and incidence of perfusion abnormalities among patients with ST depression in recovery only

Likelihood	n (%)	Perfusion abnormalities (%)
Vey low	5 (10)	4 (80)
Low	7 (14)	5 (71)
Intermediate	27 (54)	18 (67)
High	11 (22)	3 (27)*
n	50	28

* p < 0.001 *vs* the frequency of perfusion abnormalities in the other groups.

Anatomical correlation

Although anatomical correlation was not the aim the present study, angiographic data available in 17 patients was analyzed. Fifteen patients (88%) had significant (>70%) coronary artery stenosis in at least one territory. Three patients had 1 vessel affected and 12 patients had multivessel disease (8 with 2 vessel disease, 2 with 3 vessel disease and 2 patients had left main and three vessel disease).

DISCUSSION

Patients with coronary artery disease who undergo exercise treadmill testing, typically develop ST depression during exercise,[21] however 1.4-8% of the patients develop ST depression in recovery only.[1-4,8,9] The diagnostic significance of ST depression that occurs in the post-exercise period only is unclear, the finding has been described as both a true[1,2,8,9] and a false positive[5,10,12,13] sign of coronary artery disease. The prognosis significance of this finding was investigated by Rywik et al[1] in 825 healthy volunteers, in whom they found similar event rates (angina, myocardial infarction and death) at 9 years of follow-up among subjects who developed ST depression during recovery only, and those with ST-depression during exercise.

One of the proposed mechanisms for ST changes in recovery is increased blood flow through the collateral circulation[22] distal to a coronary artery occlusion,[6] a phenomenon often cited as being responsible for reverse redistribution in myocardial perfusion images. This phenomenon was observed in only 3 (6%) of the patients in the present study. Shinmura et al[5] proposed that an imbalance of the sympathetic and parasympathetic system may be the cause of the occurrence of the ST depression during recovery only, and suggested that it might not be related to myocardial ischemia. This theory is difficult to prove, but seems quite unlikely if significant ischemia were to be found in these patients, as were the case in the present study.

Savage et al[9] suggested in their analysis of 62 patients with recovery only ST depression, that this phenomenon could be explained by changes in the body position. The rationale being, that a change from the upright to supine position, with the subsequent increase in preload, according to Laplace's law leads to an increase in myocardial wall stress and higher myocardial oxygen consumption. In addition, the increase in preload results in a reduction of the effective perfusion pressure gradient affecting for the subendocardial blood flow, leading to subendocardial ischemia. Accordingly if true, the LV cavity size in myocardial perfusion images should increase when compared to the cavity size at rest. In the present study such increase in LV cavity size was detected in only 4 (8%) of the patients, and 3 of these had definite regional perfusion defects, highly suggestive of epicardial coronary artery disease rather than subendocardial ischemia. Furthermore, the mean onset of the ST depression in the present study was 2.5 min, much later than one would expect if the changes were due to body position related changes in demand and supply. The onset of the ST depression ranged from 42 seconds to 5 minutes, suggesting that 5 minutes observation in recovery would insure that all patients with ST depression in recovery should be detected.

The ST depression observed in the patients in present study was not associated with any symptoms, and there was no correlation between the magnitude or duration of the ST depression and the extent of the perfusion abnormalities. Both of these findings are remarkable and difficult to explain by conventional cardiac pathophysiology. All patients appear to have silent ischemia, and the ischemia is not quantitatively or temporally related to the ECG signs of ischemia, suggestive of a unique patient entity or ischemic syndrome. In the present study the regional perfusion analysis demonstrated perfusion abnormalities in 60% of the patients by both semiquantitative and quantitative technique. The extent of the perfusion abnormalities was 3.7 ± 2.0 segments and percent of total stress extent area was $15\% \pm 10\%$. Perfusion abnormalities of this magnitude are generally considered moderate in extent, and have been shown to have significant prognostic implication.[23]

Surprisingly, the subgroup of patients with low or intermediate pre test likelihood of coronary artery disease (Table 3) and ST depression in recovery only, were the groups with the highest incidence of perfusion abnormalities. A likely explanation could be that these patients presents with atypical symptoms, which place them in the low or intermediate group, because they have an atypical ischemic syndrome, the ischemic component of which is demonstrated in the present study. If the tracer had been injected in recovery when the ECG signs of ischemia appeared one might have identified more patients with ischemia or possibly more severe and extensive ischemia, than found with the present conventional protocol.

The specificity of ST depression in recovery only, with myocardial perfusion SPECT imaging as the reference, was 60% in the present study. In a meta analysis of 114 published studies comprising 24,074 patients Gianrossi[24] found the specificity of ST depression during stress to be 77% (range 17-100%). It therefore seems reasonable to consider the subgroup of patients with ST depression in recovery only no different from the patients who develop ST depression during exercise, regarding management decisions. Modern myocardial SPECT perfusion imaging, with sensitivity in the low 90-ties and specificity in the low 80-ties, is more cost effective in patients with intermediate (20-80%) pre-test likelihood of coronary artery disease. Patients with low or intermediate pre test likelihood of coronay artery disease and ST depression in recovery only, falls in the intermediate post stress test likelihood group (67-81%) and would thus benefit from myocardial perfusion imaging.

Anatomical correlation was not the primary objective of the present study, however angiographic data was available in 17 patients. Fifteen of the 17 patients (88%) had significant coronay artery disease; multivessel disease was the most common finding, in agreement with the findings of other studies.[1,2,8]

CONCLUSION

The incidence of perfusion abnormalities in patients with ST depression in recovery only is similar to what has been reported in patients with ST depression during exercise. More than half of these patients have evidence of perfusion abnormalities, the most common being stress induced ischemia. In the population studied, the inferior and anterior walls were involved most often. The perfusion abnormalities detected were moderate in extent, thus carrying significant prognostic implications. Imaging studies are justified and needed for further classification and management of patients with ST depression in recovery only.

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