SRYAHWA PUBLICATIONS

Archives of Cardiology and Cardiovascular Diseases
ISSN: 2638-4744 | Volume 6, Issue 1, 2024
https://doi.org/10.22259/2638-4744.0601003

RESEARCH ARTICLE

Predictive Value of Positive Exercise Testing only during Recovery Phase: Comparison with ECG-Gated SPECT

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Received: 02 May 2024 Accepted: 06 June 2024 Published: 13 June 2024
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Abstract

Purpose: The ST segment depression occurring only in the recovery phase of an exercise testing (ET) (↓STr) is relatively rare (2.3-15%). This study aimed to investigate possible associations between ↓STr and ECG-gated SPECT imaging alterations.

Methods: Observational study (April 2010–December 2012), including 92 consecutive patients with known or suspected CAD with ↓ST anytime (≥1 mm) during recovery on ET, and who underwent ECG-gated SPECT. Mean age was 60±9.9 years, 74 (80.4%) male. A 5-point score (0-normal; 4-no uptake) and a 6-point score (0-normal; 5-diskinesia) assessed perfusion and wall motion; LVEF assessed after ET. From ET data, ↓STr, blood pressure (BP), heart rate (HR), time of tolerance to exercise, functional capacity (MET), time to onset of ↓STr, and presence of arrhythmias were evaluated.

Results: Abnormal perfusion was found in 58 patients (63%), 60% had ischemia – either isolated or associated with fixed defect, 31 (33.7%) abnormal wall motion; LVEF mean 57.8±11.6%, ↓STr 184.9 ± 92.4 s, magnitude 1.2±0.3 mm, 10.4±2.7 MET; 16 pts (17.6%) had angina, 58 pts (63%) ventricular arrhythmias. There were significant differences between ↓STr on ET and perfusion regarding male gender (p<0.001, PPV=73%); early time of onset ↓STr [(< 3min) p=0.011, PPV=76.2%]; increased systolic BP ≤30mmHg during ET (p=0.002, PPV=91.3%); and typical angina (p=0.025, PPV=87.5%). Transient defect was associated with male gender (p=0.01), hypertension (p=0.04), and smoking (p=0.03). The PPV was 64% for ↓STr to the presence of perfusion or wall motion abnormalities, and LVEF decrease.

Conclusions: ↓STr on ET showed strong association with ECG-gated SPECT alterations.

Keywords: Exercise Stress Testing, Myocardial Perfusion Imaging, St Segment Depression, Recovery Phase.

1. Introduction

Exercise stress test (ET) has been used frequently for assessment of suspected or known CAD, and exercise induced ST segment depression is considered the hallmark of ECG diagnosis of CAD[1,2]. While the diagnostic and prognostic value of ST segment depression occurring during ET is well recognized, the current literature is scarce in studies that investigated the clinical significance of ST segment depression that appears only in the recovery[3-12]. In the daily

Citation: Andréa M. Falcão, William A. Chalela, Maria C. P. Giorgi, *et al.* Predictive Value of Positive Exercise Testing only during Recovery Phase: Comparison with ECG-Gated SPECT. Archives of Cardiology and Cardiovascular Diseases. 2024; 6(1):14-23.

practice, ST depression only in the recovery phase presents low prevalence, ranging from 2.3 to 15%[3-10,13], and has not been valued in most cases. Some studies in symptomatic patients comparing abnormal ST segment during exercise and in the recovery phase showed both high sensitivity and specificity for obstructive CAD when compared with cardiac catheterization[7]. Little is known about the factors that could be involved in these two different ST behaviors. On the other hand, few studies[10,12] investigated its association with myocardial ischemia on myocardial perfusion scintigraphy (ECG-gated SPECT). Hence, the aim of this study was to assess whether there are any associations between ↓STr and ECG-gated SPECT imaging alterations and the PPV of the recovery-only ST segment depression during ET.

2. Methods

The study was performed at the Department of Nuclear Medicine and Molecular Imaging of the Heart Institute of the University of Sao Paulo Medical School Hospital and was approved by the institutional ethics review board. All patients signed an informed consent to take part in the study and to have its results published as well.

2.1 Study Design

Observational study. We analyzed the data obtained at the Department of Nuclear Medicine database from consecutive individuals that had a clinical indication to undergo ECG-gated SPECT and ET in patients with suspected or known CAD.

- *The inclusion criteria:* The inclusion criteria were sinus rhythm and interpretable electrocardiogram for ischemic changes, positive ET and ST segment depression only in the recovery phase.
- *Exclusion criteria:* Unstable angina, recent myocardial infarction, pacemaker rhythm, atrial fibrillation or flutter, left bundle branch block, significant valve heart disease, and use of digitalis.

ST segment depression was defined as ≥1.0 mm (0.1 mV) horizontal or downsloping ST segment depression occurring 80 ms after the J-point in at least two contiguous leads, consistent with the current practice guidelines.[1,2]

2.2 Exercise Testing

Patients underwent ET on a GE model CASE 2100 (GE Medical Systems, Wisconsin, USA) treadmill. ET consisted of a symptom-limited exercise treadmill according to the Bruce protocol. ECG, blood pressure (BP) and heart rate (HR) were recorded at rest, during each exercise stage, and every minute until the 6th during recovery. The interruption criteria of ET were the same described in the current guidelines[1,2].

We analyzed the following parameters during ET: time to onset of ↓ST in the recovery phase (↓STr) and magnitude of (↓STr); exertional angina; abnormal increase in systolic blood pressure during exercise (SBP ≤ 30 mmHg); maximal heart rate (HR) achieved (≥85%); time of tolerance to exercise (TTE); functional capacity in MET; and ventricular arrhythmias (frequent premature ventricular complexes, couplets or nonsustained ventricular tachycardia). We considered the three minutes point in the recovery phase as the *cut-off* to classify ST segment depression as early (≤ 3 min) or late (> 3 min).

Patients were instructed to fast for 4 hours and abstain from caffeine and cigarettes for 24 hours, to discontinue beta-blockers or calcium channel blocker medications for 3 days and long-acting nitrates for 6 hours before the exam.

2.3 ECG-Gated SPECT Myocardial Perfusion Imaging (MPI)

ECG-Gated SPECT myocardial perfusion imaging (MPI) technetium-99m sestamibi at rest and during stress was performed on all patients using one-day protocol. Tomographic images were acquired using a dual-head gamma camera equipped with high-resolution parallel-hole collimators (Cardio MD, GE Medical Systems, Wisconsin; or Forte, Philips Medical Systems, Cleveland, Ohio - USA). Rest images were acquired 50 minutes after the intravenous injection of 10 mCi of Tc-99m sestamibi, and stress were performed 15 to 30 minutes after peak stress injection of 30 mCi of Tc-99m sestamibi. Left ventricular ejection fraction (LVEF) was determined from ECG-gated post stress Tc-99m myocardial perfusion images (4D QGS, version 2012.2). ECG-gated SPECT interpretation was performed at the time by one experienced Nuclear Medicine medical doctor, using a semi-quantitative 5-point score analysis in the 17-segments model (0-normal, 1-mild uptake, 2-moderate, 3-severe, and 4-no uptake) for relative myocardial perfusion distribution, and 6-point score for regional wall motion (0-normal, 1-mild hypokinesia, 2-moderate, 3-severe, 4-akinesia, and 5-dyskinesia), according to the American Society of Nuclear Cardiology guidelines[14]. The perfusion images were analyzed in conjunction with the left ventricle regional wall motion and thickening. Summed stress

scores (SSS), summed rest scores (SRS), and summed difference scores (SDS) were determined. An SDS of < 2 was considered as no ischemia, 2-6 indicates mild ischemia, 7-10 moderate, and >11 as severe ischemia. LVEF dysfunction was considered when < 50%.[14]

2.4 Statistical Analysis

Descriptive analysis was performed using measures of position and dispersion for quantitative variables (mean and standard deviation), and percentages for qualitative variables. In a second step, we studied which variables, observed in patients with ST segment depression only in the recovery phase were associated with higher positive predictive value (PPV) related to myocardial perfusion alterations using Fisher's exact test for qualitative variables. Additionally, the Mann-Whitney test was used to compare the variable time to onset of ↓STr. P value ≤ 0.05 indicated statistical significance. Finally, the PPV of ET with its respective 95% confidence interval was presented.

3. Results

Data from ninety-two subjects were included in the study. The prevalence of ST segment depression in the recovery phase in our population was 1.5%. Mean age was 60.0 ± 9.9 years (37-88y), 74 (80.4%) male and 18 (19.6%) female. In this group, 19 pts (20%) had a history of previous CABG, 24 pts (25%) myocardial infarction (MI), and 32 pts (35.2%) PCI. Hypertension and dyslipidemia were the more prevalent risk factors in this population (77.53% and 62.92%, respectively). The baseline characteristics for all patients are listed in Table 1.

Table 1. *Clinical characteristics and exercise test results*

Variables	All (n = 92)
Age (37-88y)	60.0 ± 9.9 years
Male	74 (80.4%)
Weight (42 - 115 Kg)	74.6±14.0
BMI (17.4 - 40)	26.6±4.0
Diabetes	24 (25.8%)
Smoking	34 (37.0%)
Hypertension	71 (77.5%)
Dyslipidemia	58 (62.9%)
Obesity	21 (22.8%)
Previous events	(-)
CABG	19 (20%)
MI	24 (25%)
PCI	32 (35%)
Medications	(-)
Betablockers	62 (67.4%)
Calcium antagonists	10 (10.9%)
Nitrates	15 (16.3%)
ECG-Gated SPECT	(-)
Mean LVEF post stress % (20% - 84%)	57.8 ± 11.6
< 50% LVEF post stress	15 (16.3%)
LV wall motion abnormalities	31 (33.7%)
Mild/moderate Hypokinesia	17 (18.5%)
Severe hypokinesia, akinesia or dyskinesia	14 (15.2%)
Exercise Test	(-)
TTE (259 - 918 s)	546 ± 130.5
Δ SBP (10 – 130 mmHg)	48.6 ± 24.0
Δ DBP (-30 – 40 mmHg)	0.6 ± 12.3

↓STr (16 – 420 s)	184.9 ± 92.4
Resting HR (BPM)	72.8 ± 11.6
Peak HR (BPM)	149.2 ± 15.0
Resting SBP (mmHg)	135.6 ± 17.0
Peak SBP (mmHg)	184.3 ± 24.8
Exercise capacity (4.6 – 19.8 MET)	10.4 ± 2.7
↓ST in recovery magnitude (1.0 – 2.0 mm)	1.2 ± 0.3
Exertional angina	16 (17.6%)

BMI – body mass index, BPM – beats per minute, CABG – coronary artery bypass graft surgery, LVEF – left ventricle ejection fraction, ΔDBP - increase in diastolic blood pressure, HR - heart rate, MET - functional capacity, MI – myocardial infarction, PCI – percutaneous coronary intervention, ΔSBP – increase in systolic blood pressure, ↓STm – magnitude of ST segment depression, ↓STr - time to onset of ↓ST in recovery; TTE - time of tolerance to exercise.

3.1 Exercise Test Data

Eighty patients (87%) achieved at least 85% of the maximum predicted HR. The mean TTE was 546±130.5 s (range 259 to 918 s) and the mean time to the onset of ↓STr was 184.9 ± 92.4 s (range 16 to 420 s). We observed that 48 pts (52.2%) showed a late onset (> three minutes) of ↓STr. The magnitude of ↓STr was 1.2 ± 0.3 mm (range 1.0 to 2.0 mm), and exertional angina was observed in 16 pts (17.6%). The mean increase in SBP was 48.64±23.4 mmHg (range 10 to 130 mmHg), and in diastolic blood pressure (DBP) was 0.6±12.3mmHg (range -30 to 40 mmHg), although 24 pts (26.14%) showed abnormal increase in SBP (≤ 30 mmHg) during ET. The mean functional capacity was 10.4 ± 2.7 MET (range 4.6 to 19.8 MET), and exercise-induced ventricular arrhythmias were a common finding, observed in 58 pts (63%). Data are disclosed in Table 1.

3.2 ECG-Gated SPECT-MPI

We observed that ↓STr showed association with SPECT-MPI abnormalities in 58 pts (63%), and 34 pts (37%) had normal perfusion images. Nearly 60% (n= 35) of those pts with abnormal perfusion showed isolated ischemia or ischemia associated with fixed defects, and 23 pts (40%) showed only fixed defects. Moderate to severe ischemia was observed in 23 pts (25%). ECG-gated SPECT perfusion abnormalities were found in 73% of the male gender, whereas only in 22% of the female pts, which agrees with false-positive ET results in women.

Mean LVEF, end systolic and end diastolic volumes in post stress images were 57.8±11.6%, 43.4 ± 30.7ml and 95.7 ± 45.5ml, respectively. Left ventricular regional wall motion abnormalities were found in 31 pts (33.7%), and 61 pts (66.3%) had normal wall motion. Mild/moderate hypokinesia was found in 17 pts (18.5%); severe hypokinesia, akinesia or dyskinesia in 14 pts (15.2%), and 15 pts (16.3%) showed decreased LVEF on post stress phase.

3.3 Comparison of ET and ECG-Gated SPECT-MPI

There was statistically significant association between early onset ↓STr and any perfusion defect at ECG-gated SPECT (p=0.01). Marginal association with the presence of ischemia (p=0.06) was found, for early and late ↓STr**.**

Exercise test variables that showed significant association with ↓STr were: male gender (p<0.001), increase in SBP ≤ 30 mmHg during ET (p=0.02), early onset ↓STr (p=0.04), and angina (p=0.02) (Table 2). Although frequent, there was no statistically significant association between any complex arrhythmias and perfusion alterations (p=0.24), nor with functional capacity (p=0.24), probably because the mean functional capacity was >10 MET.

Patients who presented with only transient defects on ECG-gated SPECT showed statistically significant association with male gender (p=0.01); hypertension (p=0.04); smoking (p=0.03), and marginal significance with increase in SBP ≤ 30 mmHg during ET (p=0.09). We also found that fixed perfusion defects were associated with exertional angina (p=0.02) and SBP ≤ 30 mmHg (p=0.02). (Table 2)

The PPV of the ↓STr on ET was 64% for any alteration on myocardial perfusion, regional LV wall motion or LVEF. (Table 2)

Early appearance (≤ 3 min) of ↓STr, exertional angina, and abnormal SBP ≤ 30 mmHg during ET showed the highest PPV for any abnormality on ECG-Gated-SPECT, (76.2%, 87.5%, and 91.3%, respectively).

Table 2. *P-values results for the association between myocardial perfusion abnormalities with demographic data and exercise testing parameters*

Variables	Any perfusion defect	Ischemia	Ischemia or ischemia with fixed defects	Fixed defects
Male gender	**<0.001**	**0.01**	**0.003**	**0.06**
Hypertension	0.07	**0.04**	0.07	0.54
Diabetes	0,45	0.63	1.00	0.08
Dyslipidemia	0.65	1.00	0.82	0.78
Obesity	1.00	1.00	0.62	0.57
Smoking	0.12	0.03	0.13	1.00
Functional capacity	0.24	0.16	0.41	1.00
Increase in SBP ≤ 30 mmHg	**<0.001**	0.09	0.22	**0.02**
Time to onset of ↓STr	**0.04**	0.66	0.29	**0.09**
Angina	**0.02**	0.27	0.28	**0.02**
Ventricular Arrhythmias	0.10	0.16	0.43	0.93

MET - functional capacity; SBP - systolic blood pressure; ↓STr - time to onset of ↓ST in recovery.

Male gender also showed high association with any SPECT-MPI alterations (PPV 73%), (true-positives results by ET). This was not found in the female gender, which is known to show more false-positive results in the recovery. (Figure 1)

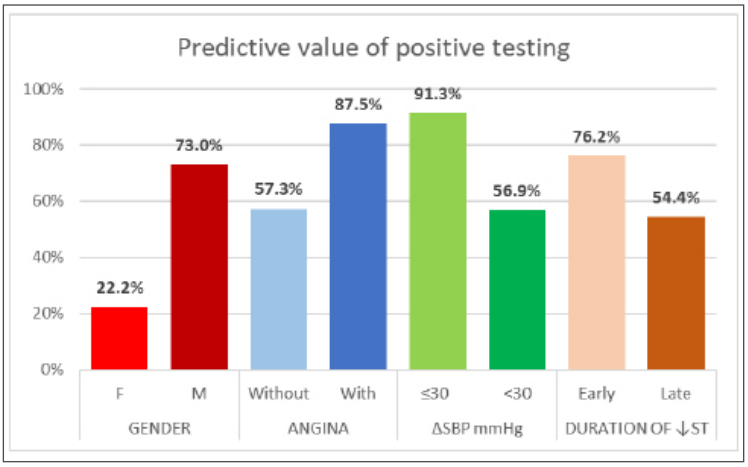

Figure 1. *Positive predictive value for any perfusion defect in relation to gender, exertional angina, abnormal increase in SBP and early or late time to onset of ¯STr; F = female, M = male, DSPB = increase in systolic blood pressure during exercise, ¯STr = ST segment depression in the recovery phase*

3.4 Cardiac Catheterization

Forty-three patients underwent invasive evaluation, by cardiac catheterization (n=41) and by noninvasive evaluation by CCTA (n=2). We found two- or three-vessel disease (≥ 50%) in 76%; one-vessel disease in 12%; normal coronary arteries in only 7%, and myocardial bridges in 5%.

4. Discussion

Our main finding was that the appearance of ↓STr should be valued, since we found a significant association with any perfusion defects, either fixed or transient, by ECG-Gated SPECT. There was higher PPV especially in males, and in those who presented with angina during ET, depressed response of SBP during exercise (that would express severity in relation to ischemia or ventricular function), and early time of appearance of ↓STr. This emphasizes the importance of the observance of multifactorial analyzes of an ET, beyond ST segment depression. We did not find differences between genders related to time of appearance of ↓STr, but there were more false-positive results in women. Our data also showed that the diagnostic power of ↓STr is very similar to that induced during the exercise.

Moreover, Laukkanen and cols[15] reported that ↓STr was a stronger predictor of sudden cardiac death in comparison with the ones occurring during exercise in men with any conventional risk factors.

Although uncommon, this finding should be carefully assessed when evaluating the results of an ET, since it seems to be able to identify asymptomatic high-risk patients who could benefit from further appropriate management.

The value of ECG-gated SPECT in the assessment of prognosis in patients with known or suspected CAD is well established[16]. The high percentages of severe perfusion defects and/or wall motion abnormalities in the study population indicate that a significant number of patients with ↓STr phase either have severe CAD or should undergo further investigation.

The first study that correlates ↓STr with scintigraphic incidence of ischemia was performed using planar Thallium-201 imaging[3]. Moreover, two other studies assessed ECG-gated SPECT in patients with ST segment depression only in the recovery phase. Soto and cols[10] demonstrated that only 17 patients exhibited ↓STr (3% of the whole population) in a study cohort of 566 patients, and ischemia on MPI was found in 65% of them. In the other study, 50 consecutive patients referred for evaluation of known or suspected CAD and ↓STr, the presence of fixed or reversible perfusion defects was found in 60%[12]. Our data is in agreement with what has already been described. Fifty-six percent of patients with perfusion abnormalities had moderate-severe ischemia, while 52% of those with regional LV wall motion abnormalities showed severe motility alterations. Additionally, we found a PPV of 64% when analyzing ↓STr in any myocardial perfusion, regional wall motion or LVEF abnormalities.

The existing literature about the prevalence of ↓STr of ET reports a variance from 2.3 to 15%[3-12]. This variability can be probably explained mainly by differences in the study population[3-11], although the adoption of different definition criteria for interpretation cannot be excluded. The ST segment changes occurred in the recovery have the same meaning, not only in diagnosis but also in prognosis, of those occurring during exercise[7,8]. The diagnostic and prognostic power of ↓STr seems to be similar to those changes observed during stress.

Little is known about the actual role of each factor during the onset of ST segment depression The following factors may be involved in the ischemic response only in the recovery phase: continued abnormal lactate production[17,18], mechanical dysfunction after induced ischemia, decrease in coronary output after exercise, electrophysiological changes at cellular level in the ischemic region, and effects of physical training.[19-23]

On the other hand, we did not find severe ST segment depression (> 0.2 mV), as we usually observe during an ET. Probably, ST segment depressions could be smaller due to lower heart rates than during exercise heart rates.[24-26] This study found a magnitude of 1.2 mm of ↓STr on average, although nearly 63% of them had myocardial perfusion abnormalities. It is important to remember that some of ST segment depressions appeared later than the third minute of the recovery phase. We also did not find any association either of ventricular arrhythmias or functional capacity with myocardial perfusion abnormalities. All the patients had a good performance for the expected age (10.4 MET), parameters frequently associated with ET prognosis[27,28].

We highlighted the results from a 55-year-old gentleman with previous anteroseptal MI successfully treated with PCI who was referred for ECG-gated SPECT for clinical follow up. He also had a positive family history of CAD and hypertension.

The patient's ECG and BP prior and during exercise were found to be normal. During the 5th min of the recovery, a significant ST depression was observed in DII, DIII, aVF, V6 (downsloping ↓ST 1,0 mm), that improved without medical intervention at the 11th minute (Figures 2A, 2B and 2C). Myocardial perfusion imaging showed mild ischemia in the inferior wall (SDS = 4), and fixed defect in the septal and anteroseptal walls (Figure 3). After completing the stress images, the patient experienced severe chest pain and hypotension (BP=70X40 mmHg). The ECG showed ST segment elevation in the anterior wall (Figure 4). The patient was transferred to the cath-lab for urgent coronary angiography that showed acute proximal occlusion of LAD and 50% of RCA. The patient underwent drug-eluting stenting in LAD with good results (Figures 5A, 5B and 5C). This was an unusual case where the onset of ↓ST occurred very late along the recovery phase and the patient evolved with acute coronary syndrome. The lack of perfusion defects on the anterior wall may be related to the delay between the radiopharmaceutical injection and the start of the ischemic alterations.

These data came to reinforce the importance of the observation of ECG in the post exercise phase, that should be performed for at least six minutes as recommended by the current guidelines on exercise testing[1,2].

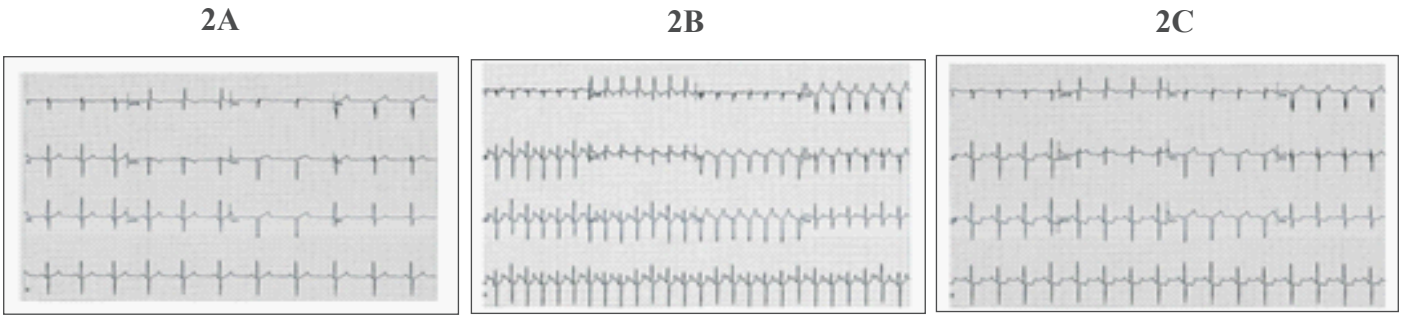

Figure 2. *A. Rest ECG of a 55-y.o. man previously treated with PCI for anteroseptal MI and normal exercise test. B. Peak exercise ECG. C. ECG at the 5th min (5 min, 46 s) in the recovery phase.*

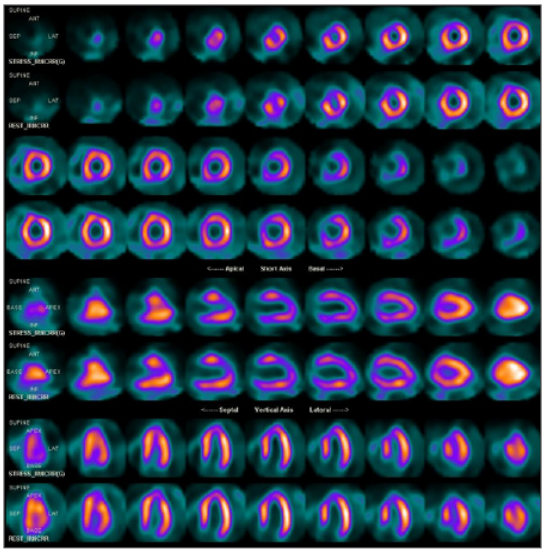

Figure 3. *Myocardial perfusion imaging showing a fixed defect in the anteroseptal wall and mild ischemia in inferior wall.*

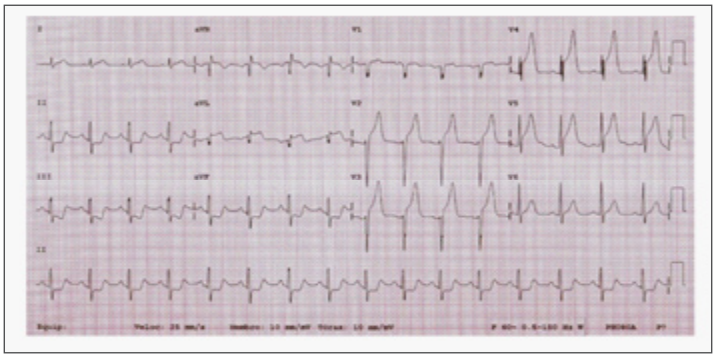

Figure 4. *ECG at 40 min after exercise test showing ST segment elevation in the anterior wall. The patient had severe chest pain and hypotension (BP=70X40 mmHg)*

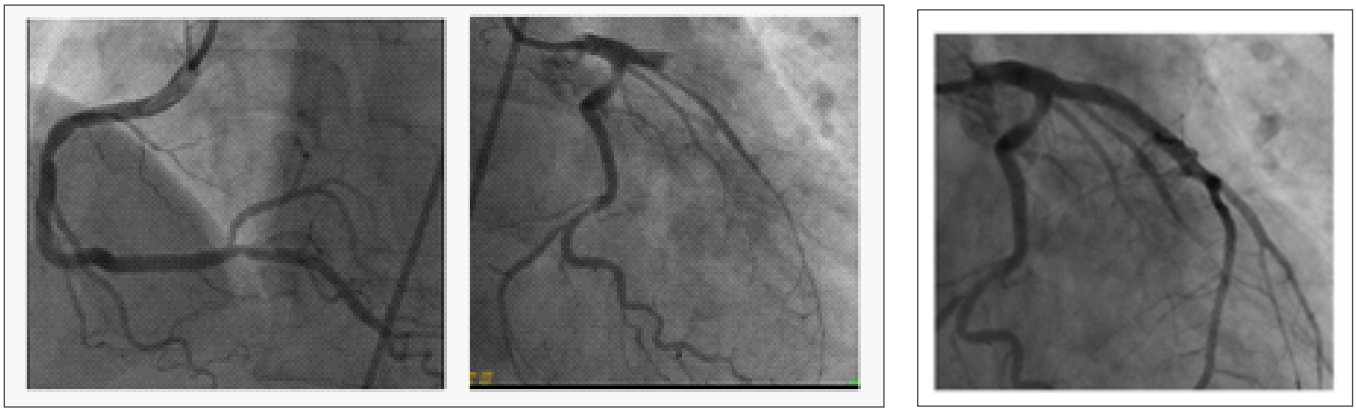

Figure 5. *A and B. Cardiac catheterization showing 50% of RCA and total occlusion in proximal LAD, that probably occurred post exercise test; C. LAD treated with pharmacological stenting, showing final result (Post PCI).*

4.1 Study Limitations

Our study has some limitations. First of all, this was a single-center observational study performed with a select population of patients with ST segment depression only in the recovery phase of ET. Its results may not be applicable to all such CAD patients, given the great diversity of clinical situations in which this can be present yielding different results. Moreover, cardiac catheterization or CCTA was not available in all patients, but we could analyze the data from most of them whose ECG-Gated SPECT images presented alterations. Usually, the absence of relative perfusion defects in myocardial perfusion imaging studies is associated with not significant CAD[14]. Also, most of the patients were taking anti-ischemic drugs that could suppress myocardial ischemia and modify the results of stress myocardial perfusion imaging and ST segment alterations as well[29-32]. Moreover, we did not use any attenuation correction software for the analyses. Transient ischemic dilatation (TID) and LV volumes during rest images that would provide information about LV function at rest were not assessed, since we were focused on ST segment behavior. Finally, we did not perform any follow up of these patients.

The data about cardiac catheterization or CCTA was obtained in <50% of the patients, but these data are also in agreement with other reports in patients with ↓STr.[13]

5. Conclusion

ST depression during recovery should be considered since we observed a strong association with ECG-gated SPECT alterations, especially regarding abnormal increase in SBP during exercise, chest pain, early onset of ↓STr, or male gender.

These are important findings and justify the additional assessment by ECG-gated SPECT when this ST behavior is present.

Knowledge Gain

ST segment depression during recovery phase of an ET had a strong association with ECG-gated SPECT alterations.

Statements and Declarations

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Datasets

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

AMF was responsible for the elaboration of the project, ECG data collection and processing, manuscript writing and review. WAC was responsible for the elaboration of the project, review and contribution to the manuscript. MCPG was responsible for the elaboration of the project and review of the manuscript. LOA provided assistance with data collection. RI was responsible for the ECG data collection and processing, elaboration of the manuscript. JCM was responsible for the imaging data collection and processing, elaboration of the manuscript. NLP was responsible for the ECG data collection and processing, elaboration of the manuscript. RKFº was responsible for the elaboration of the project and review of the manuscript. SB-N was responsible for the coordination and elaboration of the project, manuscript writing and review. All authors read and approved the manuscript.

Ethics Approval

The study was performed at the Department of Nuclear Medicine and Molecular Imaging of the Heart Institute-HCFMUSP, in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of HOSPITAL DAS CLÍNICAS, FACULDADE DE MEDICINA, UNIVERSIDADE DE SAO PAULO (University of Sao Paulo Medical School Hospital).

Informed consent was obtained from all individual participants included in the study.

Acknowledgments

We gratefully thank doctors Renan Irabi and Marcel Costa for processing the study data, and Mr. Marcio Diniz for the statistical analysis.

Funding

The authors declare that no funds, grants, or other support were received during the

preparation of this manuscript.

Abbreviations

Cardiac computed tomography angiography	CCTA
Coronary artery disease	CAD
Coronary artery bypass graft grafting	CABG
Exercise Testing	ET

Left anterior descending coronary artery	LAD
Metabolic equivalent	MET
Percutaneous coronary intervention	PCI
Positive predictive value	PPV
Right coronary artery	RCA
Systolic blood pressure	SBP
ST segment depression in recovery phase	↓STr
Electrocardiography Gated Single photon emission computerized tomography - myocardial perfusion imaging	ECG-gated SPECT MPI

6. References

1. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee to Update the 1997 Exercise Testing Guidelines. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol. 2002 Oct 16;40(8):1531-40. doi: 10.1016/s0735-1097(02)02164-2. Erratum in: J Am Coll Cardiol. 2006;48(8):1731.
2. Meneghelo RS, Araújo CGS, Stein R, Mastrocolla LE, Albuquerque PF, Serra SM et al. Sociedade Brasileira de Cardiologia. III Diretrizes da Sociedade Brasileira de Cardiologia sobre Teste Ergométrico. Arq Bras Cardiol 2010;95(5 supl.1):1-26.
3. Savage MP, Squires LS, Hopkins JT, Raichlen JS, Park CH, Chung EK. Usefulness of ST-segment depression as a sign of coronary artery disease when confined to the postexercise recovery period. Am J Cardiol. 1987;60(16):1405-6. doi: 10.1016/0002-9149(87)90632-1.
4. Karnegis JN, Matts J, Tuna N, Amplatz K. Comparison of exercise-positive with recovery-positive treadmill graded exercise tests. Am J Cardiol. 1987;60(7):544-7. doi: 10.1016/0002-9149(87)90302-x.
5. Lachterman B, Lehmann KG, Abrahamson D, Froelicher VF. "Recovery only" ST-segment depression and the predictive accuracy of the exercise test. Ann Intern Med. 1990;112(1):11-6. doi: 10.7326/0003-4819-112-1-11. Erratum in: Ann Intern Med 1990;113(4):333-4.
6. Tsuchihashi K, Hikita N, Satoh N, Nagao K, Tanaka S, Iimura O. Isolated post exercise delayed ST depression as a sign of severe ischemia: the influence of percutaneous transluminal coronary angioplasty. Can J Cardiol. 1992;8(10):1050-4.
7. Lanza GA, Mustilli M, Sestito A, Infusino F, Sgueglia GA, Crea F. Diagnostic and prognostic value of ST segment depression limited to the recovery phase of exercise stress test. Heart. 2004;90(12):1417-21. doi: 10.1136/hrt.2003.031260.
8. Rywik TM, Zink RC, Gittings NS, Khan AA, Wright JG, O'Connor FC, et al. Independent prognostic significance of ischemic ST-segment response limited to recovery from treadmill exercise in asymptomatic subjects. Circulation. 1998;97(21):2117-22. doi: 10.1161/01.cir.97.21.2117.
9. Casella G, Pavesi PC, Di Niro M, Medda M, Rubboli A, Lezha M, et al. ST sottolivellato nella fase di recupero del test da sforzo in pazienti stabili con pregresso infarto miocardico [ST segment depression during recovery after treadmill exercise test in stable patients with previous myocardial infarction]. G Ital Cardiol. 1996;26(12):1401-13. Italian.
10. Soto JR, Watson DD, Beller GA. Incidence and significance of ischemic ST-segment depression occurring solely during recovery after exercise testing. Am J Cardiol. 2001;88(6):670-2. doi: 10.1016/s0002-9149(01)01812-4.
11. Froelicher VF, Thompson AJ, Longo MR Jr, Triebwasser JH, Lancaster MC. Value of exercise testing for screening asymptomatic men for latent coronary artery disease. Prog Cardiovasc Dis. 1976;18(4):265-76. doi: 10.1016/0033-0620(76)90022-0.
12. De La Peña-Almaguer E, Desai MY, Mannting F. Myocardial perfusion in patients with ST depression during the recovery phase of treadmill stress tests. Medicina Universitaria 2009;11(42):22-8.
13. Michaelides AP, Fourlas CA, Giannopoulos N, Aggeli K, Andrikopoulos GK, Tsioufis K, et al. Significance of QRS duration changes in the evaluation of ST-segment depression presenting exclusively during the postexercise recovery period. Ann Noninvasive Electrocardiol. 2006;11(3):241-6. doi: 10.1111/j.1542-474X.2006.00110.x.
14. Tilkemeier PL, Bourque J, Doukky R, Sanghani R, Weinberg RL. ASNC imaging guidelines for nuclear cardiology procedures: Standardized reporting of nuclear cardiology procedures. J Nucl Cardiol. 2017;24(6):2064-2128. doi: 10.1007/s12350-017-1057-y. Epub 2017 Sep 15.
15. Laukkanen JA, Mäkikallio TH, Rauramaa R, Kurl S. Asymptomatic ST-segment depression during exercise testing and the risk of sudden cardiac death in middle-aged men: a population-based follow-up study. Eur Heart J. 2009;30(5):558-65. doi: 10.1093/eurheartj/ehn584. Epub 2009 Jan 23.
16. Saraste A, Knuuti J. ESC 2019 guidelines for the

diagnosis and management of chronic coronary syndromes: Recommendations for cardiovascular imaging. Herz. 2020;45(5):409-420. doi: 10.1007/s00059-020-04935-x.

17. Parker JO, Chiong MA, West RO, Case RB. Sequential alterations in myocardial lactate metaboli, S-T segments, and left ventricular function during angina induced by atrial pacing. Circulation. 1969;40(1):113-31. doi: 10.1161/01.cir.40.1.113.
18. Ihlen H, Simonsen S, Thaulow E. Myocardial lactate metabolism during pacing induced angina pectoris. Scand J Clin Lab Invest. 1983;43(1):1-7.
19. Okin PM, Ameisen O, Kligfield P. Recovery-phase patterns of ST segment depression in the heart rate domain. Identification of coronary artery disease by the rate-recovery loop. Circulation. 1989;80(3):533-41. doi: 10.1161/01.cir.80.3.533.
20. Tomoike H, Franklin D, McKown D, Kemper WS, Guberek M, Ross J Jr. Regional myocardial dysfunction and hemodynamic abnormalities during strenuous exercise in dogs with limited coronary flow. Circ Res. 1978;42(4):487-96. doi: 10.1161/01.res.42.4.487.
21. Remme WJ, van den Berg R, Mantel M, Cox PH, van Hoogenhuyze DC, Krauss XH, et al. Temporal relation of changes in regional coronary flow and myocardial lactate and nucleoside metabolism during pacing-induced ischemia. Am J Cardiol. 1986;58(13):1188-94. doi: 10.1016/0002-9149(86)90379-6.
22. Homans DC, Sublett E, Dai XZ, Bache RJ. Persistence of regional left ventricular dysfunction after exercise-induced myocardial ischemia. J Clin Invest. 1986;77(1):66-73. doi: 10.1172/JCI112303.
23. Gullestad L, Jorgensen B, Bjuro T, Pernow J, Lundberg JM, Dota CD, et al. Postexercise ischemia is associated with increased neuropeptide Y in patients with coronary artery disease. Circulation. 2000;102(9):987-93. doi: 10.1161/01.cir.102.9.987.
24. Lehtinen R, Sievänen H, Viik J, Turjanmaa V, Niemelä K, Malmivuo J. Accurate detection of coronary artery disease by integrated analysis of the ST-segment depression/heart rate patterns during the exercise and recovery phases of the exercise electrocardiography test. Am J Cardiol. 1996;78(9):1002-6. doi: 10.1016/s0002-9149(96)00524-3.
25. Bigi R, Cortigiani L, Gregori D, Fiorentini C. The Stress-Recovery Index for the risk stratification of women with typical chest pain. Int J Cardiol. 2008;127(1):64-9. doi: 10.1016/j.ijcard.2007.06.001. Epub 2007 Aug 9.
26. Rodriguez M, Moussa I, Froning J, Kochumian M, Froelicher VF. Improved exercise test accuracy using discriminant function analysis and "recovery ST slope". J Electrocardiol. 1993;26(3):207-18. doi: 10.1016/0022-0736(93)90039-g.
27. Lee V, Perera D, Lambiase P. Prognostic significance of exercise-induced premature ventricular complexes: a systematic review and meta-analysis of observational studies. Heart Asia. 2017;9(1):14-24. doi: 10.1136/heartasia-2016-010854.
28. Gulati M, Black HR, Shaw LJ, Arnsdorf MF, Merz CN, Lauer MS, et al. The prognostic value of a nomogram for exercise capacity in women. N Engl J Med. 2005;353(5):468-75. doi: 10.1056/NEJMoa044154.
29. Gianelly RE, Treister BL, Harrison DC. The effect of propranolol on exercise-induced ischemic S-T segment depression. Am J Cardiol. 1969;24(2):161-5. doi: 10.1016/0002-9149(69)90398-1.
30. Zoghbi GJ, Dorfman TA, Iskandrian AE. The effects of medications on myocardial perfusion. J Am Coll Cardiol. 2008;52(6):401-16. doi: 10.1016/j.jacc.2008.04.035.
31. Castellanet MJ, Greenberg PS, Ellestad MH. Comparison of S-T segment changes on exercise testing with angiographic findings in patients with prior myocardial infarction. Am J Cardiol. 1978;42(1):29-35. doi: 10.1016/0002-9149(78)90980-3.
32. Paine TD, Dye LE, Roitman DI, Sheffield LT, Rackley CE, Russell RO Jr, et al. Relation of graded exercise test findings after myocardial infarction to extent of coronary artery disease and left ventricular dysfunction. Am J Cardiol. 1978;42(5):716-23. doi: 10.1016/0002-9149(78)90089-9.