Short Communication

True-Positive Exercise Electrocardiogram / False-Negative Thallium-201 Scintigram: A Proposal of a Mechanism for the Paradox

JOHN E. MADIAS, M.D., PREDRAG KNEZ, M.D., MOE THU WIN, M.D.

Mount Sinai School of Medicine of the New York University, and Cardiology Division of Elmhurst Hospital Center, New York, New York, USA

Summary: A 72-year-old man with exertional angina had a strongly positive exercise electrocardiogram (EECG) with a negative thallium-201 myocardial perfusion scintigram (TI). Arteriography revealed triple-vessel coronary artery disease, for which he underwent aortocoronary bypass grafting. Repeat EECG was negative, and it was again associated with a negative TI. The false-negative TI on the first test was felt to be due to a rare phenomenon of homogeneously distributed reversible exercise-induced myocardial ischemia, leading to a uniform radiotracer count density. The even distribution of ischemia would also be expected to render a false-negative EECG, due to electrocardiographic cancellation, and this is frequently the case. However, in the patient presented herein, we propose that the ischemic cardiac apex rendered the EECG strongly positive because its position was not opposed by an ischemic muscular region, and thus an uncanceled ischemic ST-segment vector was generated. This hypothesis is supported by our recent work showing the unique role of the ischemic apex (among all the other myocardial territories) in rendering the EECG positive.

Key words: electrocardiogram (ECG), exercise ECG, thallium scintigraphy, ECG cancellation, true-positive exercise ECG, false-negative thallium test

Introduction

Discordance in the interpretation of the exercise electrocardiogram (EECG) and the associated thallium-201 myocardial perfusion scintigraphy (TI) is common. Particularly prevalent is the occurrence of a false-negative EECG, with a true-positive TI.^{1,2} The latter situation can be explained in certain cases by competing ischemic myocardial planes leading to an ischemic ST-segment counterpoise and rendering a false-negative EECG.^{3–6} Conversely, a false-positive EECG with a true-negative TI is occasionally found in premenopausal women without coronary artery disease (CAD), and it constitutes a yet unexplained EECG aberration.^{7,8}

We are presenting herein a patient with a yet another very rare discrepancy, that is, a true-positive EECG with a false-negative TI. In addition, we are proposing a mechanism for this paradox, which explains the findings in this case and may provide, along with the ischemic ST-segment counterpoise concept,^{3–6} some plausible explanations for the frequent discordance between the EECG and TI.

Case Report

A 72-year-old man with a past history of hypertension reported exertional angina with a left upper extremity weakness after walking 5 to 6 blocks, particularly uphill. An exercise test (ET) performed at another institution was reported as negative for angina and positive for ischemic changes in the EECG and TI, with the latter showing redistribution abnormalities in the inferolateral wall. On physical examination heart rate was 74 beats/min and blood pressure was 160/95 mmHg. The only abnormalities noted were an accentuated A2, an S4 sound, and a 3/6 systolic ejection murmur along the left sternal border. Nifedipine and metoprolol were administered. A two-dimensional (2-D) echocardiogram showed normal size and function of the left ventricle; mild left ventricular hypertrophy; mild mitral, aortic, and tricuspid regurgitation; and an estimated pulmonary artery systolic pressure of 30 mmHg.

Address for reprints:

John E. Madias, M.D.
Chief, Division of Cardiology
Elmhurst Hospital Center
79-01 Broadway
Elmhurst, NY 11373 USA

Received: July 6, 1999

Accepted with revision: September 2, 1999

An ET/TI was performed, employing the standard Bruce protocol. The patient exercised for 8 min and stopped because of fatigue. He achieved a peak heart rate of 110 beats/min (74% of the predicted value), and a peak blood pressure of 180/110; peak double product was 19.8×10^3 mmHg·min⁻¹. The EECG (Fig. 1) revealed horizontal ST-segment depression in leads II, III, aVF, V₃–V₆, first noted on the 4th min of the ET. The ST-segment depression reached a level of 2–3 mm at peak exercise. Downsloping ST-segment depression of 1 mm continued to be present on the 5th min of the recovery period and while the heart rate was 60 beats/min.

The associated qualitative single-photon emission computed tomography (SPECT) TI was consistent with normal findings according to the official report of Nuclear Medicine Department (Fig. 2). In addition, we employed a quantitative analysis of the stress, rest, relative washout, and redistribution “bull’s eye” maps (1st, 2nd, 3rd, and 4th, respectively, bottom row and starting from the left of Fig. 2), using a format which included two concentric rings. The inner circle represented the apex and had a diameter equal to 1/3 of the diameter of the entire polar image. The radionuclide count density mean $\pm$ standard deviation values for the five regions of each map (apex, anterior, inferior, septal, and lateral), normalized to the territory with the highest count density of each map, indicated ho-

mogeneous perfusion of all myocardial regions at stress and rest, without significant differences in relative washout or redistribution. The color-coded areas of the maps, and the small positive or negative mean values of the five regions of the relative washout and redistribution polar maps, indicated homogeneous washout/redistribution (Fig. 2).

In spite of the negative results of TI, we proceeded with cardiac catheterization because of the patient’s history and the strong ischemic response in the EECG. The test showed subtotal occlusion of the right coronary artery, 70% long stenosis of mid-left anterior descending coronary artery, with 90% stenosis of the first diagonal and subtotal occlusion of the second diagonal branch; there was also a 70% discrete stenosis of the left circumflex coronary artery, with a subtotal occlusion of its first marginal and a 90% stenosis of its second marginal branch (Fig. 3). These findings were consistent with severe triple-vessel CAD. Contrast ventriculography revealed an ejection fraction of 80%, with a normal regional contraction pattern. The patient underwent bypass graft, employing the left internal mammary artery, and three vein grafts.

The patient had a normal ET/TI test (Bruce protocol) 7 months after his first such procedure. He stopped at 9 min because of fatigue, and he achieved a peak heart rate of 145 beats/min (98% of his predicted value), a peak blood pressure of 208/120, and a peak double product that was 30.16×10^3 mmHg·min⁻¹ (Fig. 4). The associated TI (Fig. 5), analyzed as described above, was consistent with normal findings. The patient has been asymptomatic for the past 15 months, works full time, and is followed in our clinic.

FIG. 1 Before revascularization: Exercise electrocardiogram at rest and peak stress, revealing marked ST-segment depression in leads II, III aVF, and V₄–V₆; of note is the ST-segment elevation in aVR, frequently recorded in association with generalized subendocardial ischemic injury.

Discussion

Our patient had a history of angina, a strongly positive EECG (Fig. 1), severe CAD (Fig. 3), but a negative TI (Fig. 2). Positivity of TI for exercise-induced reversible ischemic defects hinges upon a transient state of heterogeneous regional coronary blood flow during stress. It is theorized that in the presence of triple-vessel CAD of equal severity, a homogeneous hypoperfusion may ensue, rendering a false-negative TI. However, such an occurrence is deemed very unlikely, since multiple coronary stenoses of the same degree are uncommon in the same patient and, even if present, they are not expected to impart similar regional flow deprivation. Inequalities of regional flows, provided by vessels with stenoses of similar severity, are due to collaterals, compressive forces, and other still unidentified mechanisms.²

Why was the TI negative in our patient, in the presence of reversible myocardial ischemia, as assessed by the transient ST-segment changes in the EECG? It is apparent that ischemia was present, but it did not manifest as such in the TI. Several causes of false-negative TI scans have been identified. A rare patient with multivessel CAD has a negative TI, due to a submaximal ET, or the effect of antianginal therapy.² Our patient did indeed reach only 75% of his maximal predicted heart rate and was on therapy with atenolol at the time of the ET. However, he developed strongly positive EECG early in

FIG. 2 Before revascularization: Myocardial slices from short axis (upper panel), vertical long axis (left middle panel), and horizontal long axis (right middle panel) from stress (top rows) and rest (bottom rows) of single-photon emission computed tomography images; stress, rest, relative washout, and redistribution bull's eye polar maps are shown in the bottom panel. The numbers in the five regions (apical, anterior, inferior, septal, and lateral) of polar maps refer to mean $\pm$ standard deviation of radionuclide count density, adjusted for the region with the highest such density. The findings are consistent with homogeneous myocardial perfusion during stress and rest.

the course of ET, with persisting ischemic changes during recovery, indicating that his response did not represent an example of a false-negative TI due to inadequate ischemic stress.

This is unequivocally corroborated by his negative EECG at a higher than originally attained work load (Fig. 4) following revascularization. Thus, the only remaining explanation for

FIG. 3 Coronary arteriograms. (A) Right anterior oblique projection (RAO) reveals severe obstructive disease of the left anterior descending coronary artery (LAD) and left circumflex coronary artery (LCF). (B) Left anterior oblique projection (LAO) show severe obstructive lesions of the right coronary artery (RCA).

FIG. 4 After revascularization: Exercise electrocardiogram at rest and peak stress depicting normal findings.

the absence of transient defects in the stress TI of our patient (Fig. 2) was that he represented a very rare example of balanced hypoperfusion.²

Why was the EECG positive in our patient who had equally ischemic cardiac planes opposite each other, resulting in balanced hypoperfusion? Why did the EECG not follow the TI in revealing balanced ischemia? Indeed, it has been suggested previously that false-negative EECGs occasionally occur in the presence of severe triple-vessel CAD and diffuse ischemia due to cancellation of the ischemic ST-segment vectors.⁷ Similarly, using quantitative TI analysis, we have shown that there is a high rate of false-negative EECG when territories facing each other reveal comparable myocardial ischemia.³⁻⁶ This seeming paradox can be attributed to the modulating effect of the ischemic cardiac apex on the response of the EECG.

Accordingly, even if all the ischemic ST-segment vectors from cardiac territories facing each other were canceled out, this would not apply to the apex, which by virtue of its location opposite the atrioventricular valvular rings (a region devoid of muscular elements) remains electrically unopposed (Fig. 6). This is a corollary of the observation that myocardial infarctions involving the apex are not associated with Q waves in the ECG, since there is no muscular element opposite the apex to pull the early 0.04 s vector away from the necrotic region.^{9,10} In addition, ST-segment elevation in aVR reflects generalized subendocardial ischemic injury detected by what is considered an intracardiac lead,⁸ and it was present in our patient (Fig. 1).

FIG. 5 After revascularization: For explanation see Fig. 2. Findings are consistent with homogeneous myocardial perfusion during stress and rest.

FIG. 6 A schematic rendition illustrating the mechanism by which generalized ischemia of the myocardium (producing a false-negative thallium single-photon emission computed tomography scan) is associated with ischemic changes in the exercise electrocardiogram (EECG). In spite of the cancellation effect on the ST vectors imparted by the counterpoised equally ischemic planes of the main body of the left ventricle, the apical ischemic ST-segment vector remains unopposed (no muscle at the valvular plane), and thus leads to a positive EECG.

Lead aVR is poised opposite to lead V₅, and both should be considered leads on a line parallel to the cardiac anatomic longitudinal axis perpendicular to the apex, rendering essentially electrically reciprocal information. The unique role of the apex in registering ischemic ECG responses during ET has been noted by Ellestad,⁸ who advocated that the ST-segment vector passes through the apex and is directed cephalad to the valvular plane; also, Blackburn *et al.*¹¹ had recommended a bipolar ECG lead, with the positive electrode at the V₅ position (such a lead faces the heart's apex) as the best lead for detecting is-

chemia. Finally, results from a consecutive series of 267 patients with Tl-diagnosed myocardial ischemia revealed that the ischemic apex (among all the other cardiac territories) is the only independent determinant of positivity of the EECG;¹² however, this remains still speculative and needs to be corroborated by more work and/or other investigators.

References

1. Zaret BL, Wackers FJ: Nuclear cardiology. Part I. *N Engl J Med* 1993;329:775-783
2. Iskandrian AS, Verani MS: *Nuclear Cardiac Imaging. Principles and Applications*. Edition 2, pp.12, 73-143, 81, 96, 97, 99, 101, 105, 110, 114, 115. Philadelphia: F.A. Davis Co., 1987
3. Madias JE, Sheth K: Ischemic ST-segment counterpoise: One mechanism of false electrocardiographic response to exercise stress testing. *Am J Noninvas Cardiol* 1994;8:194-199
4. Madias JE, Mahjoub M, Valance J: The paradox of negative exercise stress ECG / positive thallium scintigram. *J Electrocardiol* 1996;29:243-248
5. Madias JE, Khan M, Manyam B: The role of "ischemic ST-segment counterpoise" rendering the response of exercise electrocardiogram falsely negative. *Clin Cardiol* 1997;20:489-492
6. Madias JE, Tziros C, Khan M, Manyam B, Gujral I: Positive thallium-201 perfusion scintigraphy/negative exercise ECG: "ischemic ST-segment counterpoise" as an explanation (abstr). *J Invest Med* 1997;45:213A
7. Froelicher VF: *Exercise and the Heart. Clinical Concepts*, 2nd Ed., p. 81-145, 303. Chicago: Year Book Medical Publishers Inc., 1987
8. Ellestad MH: *Stress Testing: Principles and Practice*, 4th Ed., p. 104,330,487. Philadelphia: F. A. Davis Co., 1996
9. Hurst JW: *Cardiovascular Diagnosis. The Initial Examination*, p. 3603. St. Louis: Mosby-Year Book, 1993
10. Hurst JW, Anderson RH, Becker AE, Wilcox BR: *Atlas of the Heart*, p. 6.9. New York, NY: J. B. Lippincott Co., 1998
11. Blackburn H, Taylor HL, Vasquez CL, Puchner TC: The exercise electrocardiogram during exercise: Findings in bipolar chest leads of 1,449 middle-aged men, at moderate work levels. *Circulation* 1966;34:1034-1043
12. Madias JE, Tziros C, Knez P, Solanki N, Tunio JH, Sutandar A, Akbar S, Kaminetsky A, Win MT, Medepalli L: Transient ischemia of the apex (among other territories) as the only independent determinant of positivity of exercise ECG (abstr). *Circulation* 1998; 98(suppl I):I-293