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Varying prognostic significance of "ischemic ST depression" during vasodilator stress testing in patients with normal SPECT/PET myocardial perfusion imaging

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Electrocardiographic (ECG) recording of the bioelectrical activity of the heart has remained virtually unchanged for more than a century. However, advances in knowledge led to more and more diagnostic and prognostic information being obtained from the same ECG recordings. Thus, despite continuous progress in noninvasive diagnostic methods, simple and cheap ECG technology still has an important role in clinical practice, particularly in the diagnosis of coronary artery disease and in the assessment of prognosis in patients with various types of coronary artery disease.

In coronary artery disease, prognosis is related to the degree of left ventricular dysfunction, severity of coronary atherosclerosis, widely considered electrical instability, and non-coronary coexisting conditions. Objective assessment of the degree of coronary artery involvement is the most effective way to determine prognosis but requires invasive methods (coronary angiography, intravascular ultrasound) and/or sophisticated, expensive and not always widely available non-invasive modalities (CT, MRI). The degree of coronary artery involvement translates into the severity of perfusion defects and thus the utility of methods that allow assessment of these parameters (SPECT, PET). Significant perfusion abnormalities result in myocardial ischemia that affects ST segment in the ECG tracing. In this regard, we mostly rely on the ST segment evaluation during stress testing (exercise test or pharmacological stress with dipyridamole, adenosine, and dobutamine). The prognostic value of this assessment depends on the degree in which ST segment changes reflect objective phenomena determining prognosis. It is known that ST segment depression and its slope depend on qualitative and quantitative characteristics of action potentials and their spatial and temporary interrelation during both repolarization and depolarization phases [1]. Abnormal ECG findings may result from ischemia (with the latter not necessarily dependent on coronary artery disease), but they may also reflect other factors [1, 2], thus leading to false positive results, particularly in women and patients with hypertension [2–6]. To reduce the rate of false positive results, diagnostic criteria of "ischemic ST depression" were limited to strictly defined qualitative findings (horizontal or down-sloping ST segment depression) and quantitative parameters (at least 1 mm ST depression at 80 ms after the J point) [1]. This in turn resulted in an increased rate of false negative results. Thus, up-sloping ST segment depression of at least 1.5 mm is also considered "ischemic ST depression" by some authors. One may approach this trade-off between sensitivity and specificity in different ways, but we can never reach 100% sensitivity and specificity at the same time. Such a trade-off inevitably leads to the detection of "ischemic ST changes" in patients without coronary artery disease. The prognostic value of such ECG changes is small.

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With these caveats in mind, we avoid performing ECG stress testing in patients with a high likelihood of a false positive or false negative result. In these circumstances, we use perfusion imaging with radionuclide stress testing that in most cases allows, by extrapolation of gathered information, evaluation of the severity of coronary artery involvement which is an objective prognostic parameter. During these studies, ECG is also usually recorded. Does it have a prognostic value in such situation? Already in the 1990s it was accepted that regardless of the ST segment changes, perfusion abnormalities detected by SPECT indicate worse prognosis, and their absence is associated with minimal mortality risk of < 1% per year [7–11]. Thus, SPECT imaging was considered to have superior value compared to ECG [12, 13]. However, in 2003 Abbott et al. [14] Klodas and et al. [15] published reports that questioned this belief. They showed a significant risk of a cardiac event (with a yearly risk of death or myocardial infarction of 5–10%) in patients with no perfusion abnormalities in SPECT but with "ischemic ST depression" during dipyridamole or adenosine stress. These reports were first to suggest a prognostic value of "ischemic ST changes" with negative SPECT findings. Authors suggested that such a situation may occur in patients with multivessel coronary artery disease resultung in true positive ECG findings and false negative perfusion imaging with SPECT. These false negative results (undetected but present perfusion abnormalities) may by explained with the occurrence of so-called "balanced ischemia" or "perfectly balanced" decrease in perfusion of the coronary artery tree due to a "perfectly balanced" symmetric distribution of stenotic coronary artery lesions [10, 11, 16–19]. In response to these reports, in this issue of the "Cardiology Journal" Hage et al. [20] present a study conducted in a group of 73 patients with ischemic ST depression but without perfusion abnormalities detected by SPECT during adenosine stress. During the mean follow-up of 5 years, cardiac mortality in these patients was less than 1.3%. This is another long-term follow-up study, but the first one performed in such a large group of patients that confirms a superior prognostic role of SPECT over ECG: with normal (true negative) SPECT findings, the presence of concomitant ischemic (false positive) ST changes in ECG does not have an adverse effect on prognosis. Thus, ST changes that were found in this study group but were not associated with perfusion abnormalities in SPECT should be considered not related to myocardial ischemia. It should be stressed that this conclusion might apply only to *this* particular study group as available data suggest that it was a population with a low pretest likelihood of coronary artery disease but with a significant likelihood of false positive ST segment changes (81% women, 74% patients with hypertension). Overall, these reports suggest that the same findings of "ischemic ST depression" might have varying prognostic value in patients with a negative result of stress SPECT imaging.

In 2005, Chow et al. [21] published results of a 2-year follow-up of patients with negative PET imaging with dipyridamole stress, demonstrating a very good prognosis in this group (no cardiac deaths, yearly myocardial infarction risk of 0.6%). The presence of "ischemic ST changes" had no effect on prognosis. Thus, a (truly) negative result of PET clarified the true value of "ischemic ST changes" which in such a case should be considered a false positive finding. This might be explained by the fact that the study group included 83% women and 61% patients with hypertension. Of interest, the pretest likelihood of coronary artery disease in this group was similar to that in populations studied by Abbott et al. [14] and Klodas et al. [15] while prognosis in patients with no perfusion abnormalities in SPECT or PET but with "ischemic ST changes" was dissimilar. Also, the interpretation of these "ischemic ST changes" was different. Contrary to what some might think, the results reported by Chow et al. [21] do not contradict findings of Abbott et al. [14] and Klodas et al. [15], as PET might detect perfusion abnormalities missed by SPECT [22], thus reducing the number of false negative SPECT results associated with true positive ECG findings. With PET, more true positive results are obtained that indicate actual perfusion abnormalities accompanied by true "ischemic ST depression" seen in ECG. In result, negative PET finding are usually true negatives, and any accompanying "ischemic ST changes" are false positives that have no significant prognostic value. One might suspect that verification of findings reported by Abbott et al. [14] and Klodas et al. [15] using PET would divide the group with "significant ST depression" and negative SPECT findings into two subgroups: with and without perfusion abnormalities. The former would mostly include patients with multivessel coronary disease while the latter would include women with false positive "ischemic ST changes". The prognosis in the former group would be poor but much better in the latter.

The prognostic value of "ischemic ST changes" as seen during stress tests depends on the probability that these changes reflect prognostically

adverse significant coronary stenoses. The importance of "ischemic ST changes" in case of normal stress SPECT imaging is related to the balance between the pretest likelihood of coronary artery disease and the probability of a false positive result in a given population. In a population with a low likelihood of multivessel coronary artery disease and a high probability of a false positive "ischemic ST depression", the latter should be considered spurious and prognostically insignificant, while the true prognosis is indicated by true negative SPECT findings. In contrast, in a population with a low probability of a false positive "ischemic ST depression" but high likelihood of multivessel coronary artery disease that might result in the occurrence of "balanced ischemia", one might reasonably expect a false negative SPECT finding and a true positive ECG finding, and the latter may suggest worse prognosis. The use of PET significantly reduces the probability of obtaining a false negative result and thus a negative result of this imaging modality indicates good prognosis regardless of the presence of "ischemic ST depression" that in such a situation should be considered a false positive finding.

The prognostic value of each test depends on the likelihood it accurately reflects real phenomena determining prognosis. This is expressed by sensitivity and specifity, as well as by the rates of occurrence or no occurrence of a cardiac event. It should be remembered, however, that according to the Bayes theorem, the prognostic value of a method may vary depending on the pretest likelihood of a given condition in the studied population. The prognostic value of "ichemic ST depression" during vasodilator stress testing in patients with normal SPECT/PET myocardial perfusion imaging may vary depending not only on the severity of coronary artery involvement, but also on age, gender, the degree of left ventricular dysfunction, and the severity of electrical instability. This issue deserves further studies.

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References

1. Zipes DP, Braunwald E. Braunwald's heart disease: A textbook of cardiovascular medicine. 7th Ed. Philadelphia, WB Saunders, 2005.
2. Hlatky MA, Pryor DB, Harrell FE Jr, Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. Am J Med, 1984; 77: 64–71.
3. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol, 1999; 83: 660–666.
4. Morise AP, Beto R. The specificity of exercise electrocardiography in women grouped by estrogen status. Int J Cardiol, 1997; 60: 55–65.
5. Rovang KS, Arouni AJ, Mohiuddin SM, Tejani A, Hilleman DE. Effect of estrogen on exercise electrocardiograms in healthy postmenopausal women. Am J Cardiol, 2000; 86: 477–479.
6. Henzlova MJ, Croft LB, Diamond JA. Effect of hormone replacement therapy on the electrocardiographic response to exercise. J Nucl Cardiol, 2002; 9: 385–387.
7. Amanullah AM, Berman DS, Erel J et al. Incremental prognostic value of adenosine myocardial perfusion single-photon emission computed tomography in women with suspected coronary artery disease. Am J Cardiol, 1998; 82: 725–730.
8. Kamal AM, Fattah AA, Pancholy S et al. Prognostic value of adenosine single-photon emission computed tomographic thallium imaging in medically treated patients with angiographic evidence of coronary artery disease. J Nucl Cardiol, 1994; 1: 254–261.
9. Hachamovitch R, Berman DS, Kiat H et al. Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia. Am J Cardiol, 1997; 80: 426–433.
10. Hage FG, Dubovsky EV, Heo J, Iskandrian AE. Outcome of patients with adenosine-induced ST-segment depression but with normal perfusion on tomographic imaging. Am J Cardiol, 2006; 98: 1009–1011.
11. Chow BJ, Wong JW, Yoshinaga K et al. Prognostic significance of dipyridamole-induced st depression in patients with normal 82rb pet myocardial perfusion imaging. J Nucl Med, 2005; 46: 1095–1101.
12. Gibbons RJ, Hodge DO, Berman DS et al. Long-term outcome of patients with intermediate-risk exercise electrocardiograms who do not have myocardial perfusion defects on radionuclide imaging. Circulation, 1999; 100: 2140–2145.
13. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. A prognostic score for prediction of cardiac mortality risk after adenosine stress myocardial perfusion scintigraphy. J Am Coll Cardiol, 2005; 45: 722–729.
14. Abbott BG, Afshar M, Berger AK, Wackers FJ. Prognostic significance of ischemic electrocardiographic changes during adenosine infusion in patients with normal myocardial perfusion imaging. J Nucl Cardiol, 2003; 10: 9–16.
15. Klodas E, Miller TD, Christian TF, Hodge DO, Gibbons RJ. Prognostic significance of ischemic electrocardiographic changes during vasodilator stress testing in patients with normal spect images. J Nucl Cardiol, 2003; 10: 4–8.
16. Marshall ES, Raichlen JS, Tighe DA, Paul JJ, Breuninger KM, Chung EK. ST-segment depression during adenosine infusion as a predictor of myocardial ischemia. Am Heart J, 1994; 127: 305–311.
17. Ho KT, Miller TD, Christian TF, Hodge DO, Gibbons RJ. Prediction of severe coronary artery disease and long-term outcome in patients undergoing vasodilator spect. J Nucl Cardiol, 2001; 8: 438–444.

18. Iskandrian AS, Heo J, Lemlek J et al. Identification of high-risk patients with left main and three-vessel coronary artery disease by adenosine-single photon emission computed tomographic thallium imaging. Am Heart J, 1993; 125: 1130–1135.
19. Lette J, Bertrand C, Gossard D et al. Long-term risk stratification with dipyridamole imaging. Am Heart J, 1995; 129: 880–886.
20. Hage FG, Heo J, Iskandrian AE. Adenosine-induced ST segment depression with normal perfusion. Cardiol J, 2009; 16: 121–126.
21. Chow B, Wong J, Yoshinaga K et al. Prognostic significance of dipyridamole-induced ST depression in patients with normal Rb PET myocrdial perusion imaging. J Nucl Med, 2005; 46: 1095––1101.
22. Go RT, Marwick TH, MacIntyre WJ et al. A prospective comparison of rubidium-82 PET and Thalium SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in diagnosis of coronary artery disease. J Nucl Med, 1990; 31: 1899–1905.