IMAGES IN CARDIOLOGY

False Negative Myocardial Perfusion Imaging: Regular Exercise Tolerance Test Coming to the Rescue

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Abstract

A case of a patient with critical coronary artery disease is presented where a regular exercise tolerance test was positive whereas myocardial perfusion imaging was (false) negative. ***Rhythmos 2021; 16(3):62-64.***

Key Words: coronary artery disease; myocardial ischemia; exercise tolerance test; myocardial perfusion imaging; coronary angiography; percutaneous coronary intervention; coronary stenting; gated SPECT

Abbreviations: CAD = coronary artery disease; ECG = electrocardiogram; ETT = exercise tolerance test; MPI = myocardial perfusion imaging; RCA = right coronary artery; SPECT = single photon emission computed tomography

A 73-year-old gentleman with history of hypercholesterolemia was referred for evaluation for possible coronary angiography after discrepant results of functional testing. The patient had atypical symptoms over the past 6 months with occasional episodes of chest discomfort occurring at rest, for which he was initially subjected to a regular exercise tolerance test (ETT) 3 months earlier. During that test, at maximal exercise (92% of predicted heart rate), there was 1.5-mm ST depression noted in the inferolateral leads (**Fig**. 1, dotted circles). No action was initially taken and he was advised to have myocardial perfusion imaging (MPI), which was performed one month later. The electrocardiography (ECG) part of the test was again positive for inferolateral ischemia; however, the ungated MPI was reported negative for ischemia showing normal myocardial perfusion (**Fig**. 2). Images from the ECG-gated MPI showed mostly perfusion defect in the inferior wall (**Fig**. 3), albeit apparent perfusion defects can be artifactually created simply because of low image count density; anyhow, these images were obtained to assess ventricular function, not perfusion. Echocardiography was normal with no regional wall motion abnormalities; left ventricular ejection fraction was at 60%. The patient was subsequently scheduled to undergo coronary angiography.

Coronary angiography was performed via the right radial artery and showed no critical stenoses in the left coronary arteries; a long complex lesion with an 80-95% critical stenosis was detected in the proximal-to-mid segment of the right coronary artery (RCA) (**Fig**. 4, left panel). This was followed by ad-hoc successful coronary stenting with 3.5/28 mm drug-eluting stent which restored patency to the RCA (**Fig. 4**, right panel).

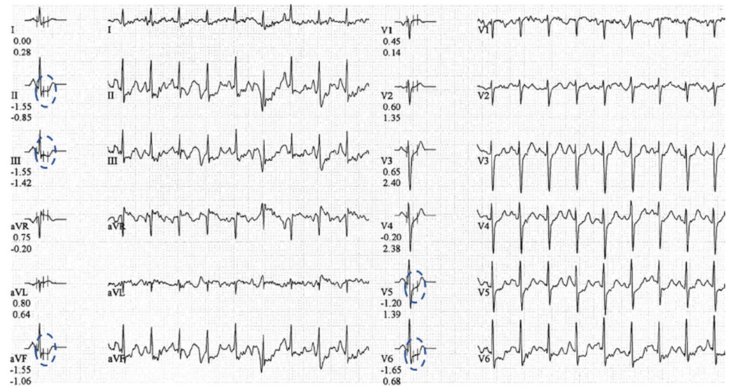

Figure 1

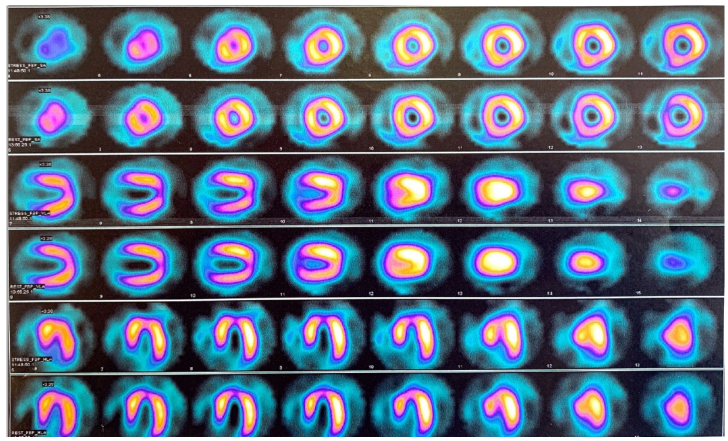
Figure 2

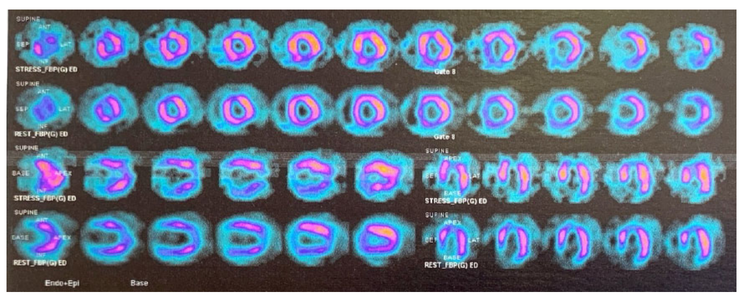
Figure 3

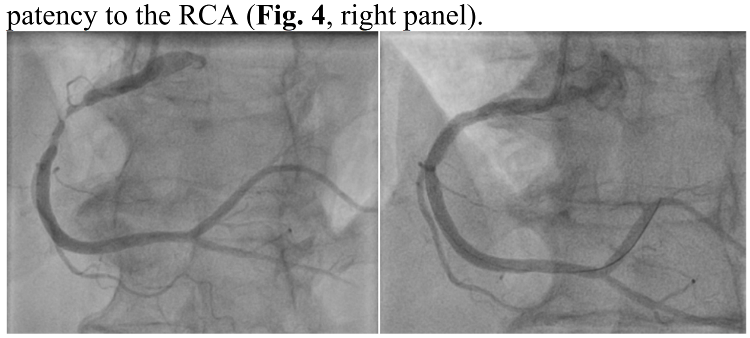
Figure 4

The post-procedural course was uneventful and the patient was discharged home the next day.

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We herein present a case of critical single vessel (RCA) coronary artery disease (CAD) which was missed by myocardial perfusion imaging (MPI) and was detected by regular exercise tolerance testing (ETT). The patient underwent coronary angiography and successful revascularization via coronary stenting of a critical long and complex lesion of the RCA.

*Single-photon emission computed tomography (*SPECT) MPI, widely employed clinically, can provide critical diagnostic information on CAD;[1,2] individuals with negative MPI have <1% incidence of major cardiovascular events for a year.[3] However, false-negative MPI may be encountered in patients with angiographically significant CAD, such as in the present case.

The induction of ischemia during functional testing depends on the severity of stress imposed (i.e., submaximal exercise can fail to produce ischemia) and the severity of the impedance to the coronary flow commensurate with the degree of vessel stenosis.[4] Indeed, stress was maximal (>85% of maximum age-predicted heart rate) and coronary lesion was critical in the present case and thus could not account for the false negative result of MPI. Pitfalls or limitations of MPI resulting in a false negative test may include lower sensitivity due to inadequate exercise (<85% of predicted maximal heart rate); inadequate pharmacological stress; preceding intake of coffee or tea interfering with adequate pharmacological stress effect by blocking the action of the pharmacological agents; a lower dose of radio-tracer; small area of perfusion defect; ischemia caused by left circumflex or its branches; balanced ischemia in presence of three-vessel CAD; and/or collateral circulation.[5-10] Again, none of these reasons and limitations could account for the false negative result of MPI in our patient, who had a critical, long and complex, single-vessel (RCA) lesion. Interestingly, it has been reported that the sensitivity of MPI decreases significantly with a small number of diseased vessels.[7]

In the present case, the regular ETT was positive for ischemia albeit in the absence of typical symptomatology, which could easily have led to dismissal of the ETT findings and acceptance of the PMI results; however, a clinical approach prevented it from happening.[11]

Importantly, limitations of noninvasive diagnostic tests range from evidence on technical quality through test accuracy (sensitivity and specificity of test, as well its interpretation). Indeed, there are multiple factors such as imaging noise, limited spatial resolution, cardiac and respiratory motion blur that can degrade the quality of the reconstructed images, and thereby adversely affect the diagnostic accuracy in MPI from SPECT.[12] In order to reduce the extent of cardiac motion blur, cardiac-gated acquisitions with various techniques to eliminate the influence of cardiac motion are often employed, wherein the acquired data are dissected and binned into a number of intervals within the cardiac cycle according to the ECG signal.[13-17] While this can drastically limit the cardiac motion blur within the individual intervals, it also lowers the data counts and thus leads to enhanced reconstruction noise. In this context, gated studies are primarily used for functional assessment of the left ventricular wall motion and thickening, while ungated studies are used for assessment of perfusion defects.[18]

Gated SPECT is expected to improve resolution associated with the beating heart; however, this may not be true of the qualitative evaluation of the summed (ungated) data. A significant feature of gated SPECT is the ability to distinguish fixed myocardial defects due to scar from an attenuation artifact; this is achieved with the simultaneous assessment of perfusion and regional systolic thickening, with the latter being absent in a scar.[19] However, ungated SPECT acquisition may underestimate regional myocardial uptake when myocardial wall motion is good, therefore, ECG-gated data should be acquired for accurate assessment of regional myocardial uptake of 99mTc-MIBI.[20] Nevertheless, there are several limitations and potential artifactual pitfalls of ECG-gated data.[21, 22] As the technique divides tracer counts into intervals within the cardiac cycle (usually 8 or 16), a study with low summed tracer counts can produce very low counts in the individual interval images that do not allow a proper diagnosis. Also, proper gating requires a regular cardiac rhythm; irregular rhythm, such as frequent extrasystoles or atrial fibrillation, can result in lower counts in the end-diastolic frames, and render the exam uninterpretable.[21]

Although the false-negative MPI in the presence of a positive ETT is unusual, it should not be ignored.[9, 23] Positive ETT with reproduction of symptoms indicates a high probability of critical CAD, irrespective of perfusion defects.

The patient presented herein had atypical symptoms and ECG evidence of ischemia on regular exercise ECG but ungated MPI did not show ischemia. It would be logical to dismiss the findings of ETT, the sensitivity of which (~70%) [24] is known to trail that of MPI (~88%)[1] and not proceed with coronary angiography. However, clinical acumen prevailed [11] and the patient was subjected to cardiac catheterization, which confirmed single vessel disease with a critical complex lesion of the RCA, which was successfully managed with coronary stenting.

ETT is a major noninvasive diagnostic test for CAD, which is readily available, easy to interpret and its findings should not be ignored regardless of the negative/normal findings of "more sensitive" testing, such as MPI, especially in the absence of factors favoring false-positive ETT results (age, gender, baseline ECG, valvular heart disease, etc).[4] Thus, the combination of ETT and MPI can increase the diagnostic accuracy of stress MPI, as demonstrated in our case and in two other cases, with the difference being that our patient had single-vessel disease while the other patients had severe three-vessel CAD.[9, 23]

In ***conclusion***, MPI can miss high-risk CAD with untoward consequences; regular ETT may occasionally circumvent such a limitation of MPI, as demonstrated in the present case, and its findings should not be ignored. Whether ECG-gated MPI may provide an alternative to the ungated MPI remains doubtful, at least for the false-negative ungated MPI cases, as the low tracer counts in the gated frames might enhance sensitivity but can significantly decrease specificity, whereas wall motion abnormalities may not be observed.

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