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Clinical detection of myocardial ischemia

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Abstract: Myocardial ischemia involves several pathophysiologic mechanisms. To assess suspected myocardial ischemia in relation to obstructive coronary artery disease (CAD)—the most frequent case—the reference test would be an electrocardiogram (ECG) exercise stress test; in the event of inconclusive results, an imaging (either radionuclide or echocardiographic) stress test can be indicated. Pharmacologic stress tests with imaging are indicated in patients unable to exercise. The same tests can be applied in patients with suspected microvascular angina; in such patients, a diagnostic clue would be induced angina and ECG changes in the absence of regional wall motion abnormalities on echocardiographic stress testing. Spasm provocation tests using either acetylcholine or ergonovine might be necessary to detect myocardial ischemia in patients in whom this is caused by coronary epicardial, or even microvascular, spasm. ECG Holter monitoring can be helpful to identify and characterize myocardial ischemic episodes that occur during daily life. ■ *Heart Metab*. 2020;81:32-35

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In patients with ongoing anginal chest pain, a standard 12-lead electrocardiogram (ECG) is the elective method to detect myocardial ischemia. The diagnosis of myocardial ischemia caused by transient episodes of chest pain, and possible myocardial ischemia in asymptomatic or even apparently healthy subjects, is, in clinical practice, based mainly on results from noninvasive diagnostic cardiac stress tests.

Most of these tests are specifically aimed at identification of myocardial ischemia secondary to obstructive coronary artery stenoses, which are usually triggered by conditions that increase myocardial oxygen consumption (MVO_2)—mainly physical exertion. This is the most frequent reason behind testing for myocardial ischemia in clinical practice. Accordingly, the biggest indication for these tests is for subjects with suspected effort angina; exercise with increasing workloads is the most obvious stressor to induce increased MVO_2 in this context.

However, pharmacologic stressors can be used as an alternative to exercise to induce myocardial ischemia, in particular in patients who cannot exercise or who are expected not to achieve significant levels of physical effort. The pharmacologic stressors most frequently used in clinical practice include: (i) the sympathomimetic drug dobutamine (dose, 5 to 40 µg/kg/min); and (ii) adenosine (dose, 140 µg/kg/min) or its analogs dipyridamole (dose, 0.56 to 0.84 mg/kg) and regadenoson (dose, 400 µg). Dobutamine, similarly to exercise, acts by increasing MVO_2. Adenosine and its analogs dipyridamole and regadenoson mainly act by inducing coronary steal of blood flow by myocardial regions perfused by normal or less-obstructed cor-

onary vessels from myocardial regions perfused by coronary arteries with the most critical stenoses.[1]

The diagnostic methods most frequently used to detect myocardial ischemia in patients with suspected obstructive coronary artery disease (CAD) in clinical practice include ECG exercise stress testing (ECG-EST) and imaging cardiac stress testing, which typically include radionuclide and echocardiographic stress tests (*Figure 1*).

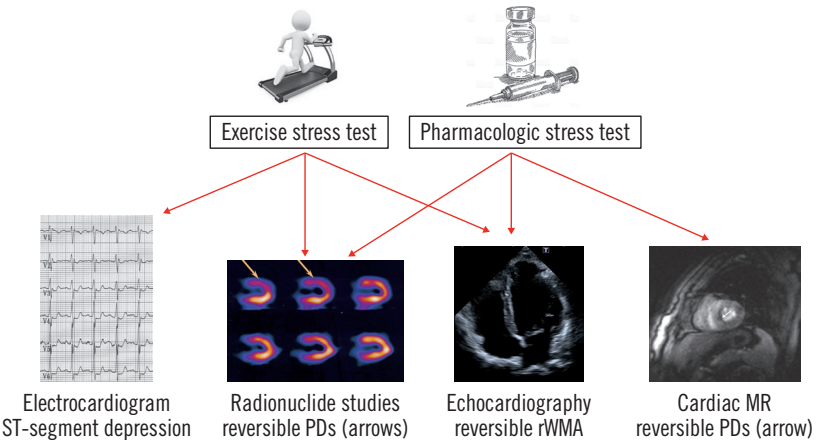

Figure 1 *Main noninvasive methods for myocardial ischemia detection.*
Abbreviations: *MR, magnetic resonance; PD, perfusion defects; rWMA, regional wall motion abnormalities*

The most typical ECG sign of myocardial ischemia during EST is the induction of horizontal or downsloping ST-segment depression. Radionuclide exercise or pharmacologic stress testing (with either ^{201}thallium or ^{99m}Tc-sestamibi) identify myocardial ischemia via the detection of perfusion defects at peak exercise that normalize under resting conditions, and echocardiographic stress testing allows diagnosis of myocardial ischemia when a transient impairment of contractility (hypokinesia, akinesia, or dyskinesia) is induced by the stressor in one or more regions of the left ventricle.

More sophisticated imaging methods have also been proposed to detect myocardial ischemia by stress tests, including positron emission tomography, cardiac magnetic resonance imaging (*Figure 1*), and computed tomography coronary angiography (CTCA); however, they are unlikely to be used as reference methods due to their higher costs and limited availability.[2]

For several decades, the ECG-EST has been the reference test for the detection of myocardial ischemia in patients with suspected obstructive CAD. Imaging stress tests have, on the other hand, been indicated as second-line tests to clarify equivocal or uninterpretable results of ECG-EST; they have also been indicated as first-line tests in patients with uninterpretable basal ECG (eg, patients with left bundle branch block, a pacemaker, relevant ST-segment abnormalities at baseline, etc), with pharmacologic imaging stress tests also indicated first-line in those unable to exercise.[3]

However, in recent years, as some studies have reported the better diagnostic accuracy of imaging stress tests over ECG-EST, several authors have suggested that these tests should always be preferred for the detection of myocardial ischemia related to obstructive CAD; in fact, imaging stress tests are recommended as first-line tests (together with CTCA) in the most recent ESC guidelines on chronic coronary syndromes.[4]

This recommendation does not seem justified, however. ECG-EST has several advantages over imaging methods, including its easy and wide availability, very low costs, and repeatability, which also make it the most ideal test for clinical follow-up of patients. Of note, radionuclide tests also involve radiation exposure, and left ventricle wall motion abnormalities on echocardiographic stress testing may be inadequately assessed in 10% to 20% of cases due to a suboptimal echo-window. Furthermore, echocardiographic stress testing may present a higher interoperator variability in the interpretation of wall motion abnormalities.

Most importantly, whereas diagnostic accuracy of ECG-EST has been derived from large studies on widely unselected subjects, studies reporting diagnostic accuracy of imaging stress tests usually included populations selected according to previous first-line tests and are therefore conditioned by referral bias.[5] Accordingly, in the absence of adequate controlled studies directly comparing the diagnostic accuracy of noninvasive diagnostic tests in unselected patients, the exact differences in the diagnostic accuracy of the different methods remains to be established.

Moreover, the management of patients based on ECG-EST does not seem to be associated with a substantially different clinical outcome from that based on imaging stress tests,[6,7] as well as CTCA.[8]

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Detection of myocardial ischemia vs obstructive CAD

A relevant issue that should be considered when comparing the accuracy of stress tests for the detection of myocardial ischemia is that the gold standard for their evaluation, ie, the presence of obstructive CAD on angiography, is, in fact, not ideal; stress tests can detect myocardial ischemia, not the presence of stenoses on angiography. Significant coronary stenoses do not necessarily result in myocardial ischemia, and myocardial ischemia might exist without stenosis (eg, it could be due to coronary spasm or coronary microvascular dysfunction).

Thus, in patients with microvascular angina (MVA), as diagnosed according to typical angina and presence of reduced coronary flow reserve in the presence of normal or near-normal coronary arteries on angiography,[9] typical signs of myocardial ischemia can be detected by ECG-EST and radionuclide stress tests, though these would, in fact, be considered false positive results if one takes the presence of obstructive CAD as the reference finding. Of note, ECG-EST in this setting seems to reveal myocardial ischemia more frequently than scintigraphic stress tests, and both reveal myocardial ischemia more frequently than echocardiographic stress tests, which usually yield negative results in this condition because of the patchy distribution of myocardial ischemia.[10,11]

Myocardial ischemia caused by coronary artery spasm

Whereas standard stress tests can detect myocardial ischemia related to critical atherosclerotic coronary stenosis or coronary microvascular dysfunction resulting in impaired coronary flow reserve, they are usually unhelpful for detecting myocardial ischemia caused by coronary artery spasm, which may occur both at the site of significant or nonsignificant stenosis, or even in normal coronary segments. Typically, myocardial ischemia caused by epicardial spasm occurs at rest, predominantly during the night or early hours of the day and results in transmural myocardial ischemia, as indicated by ST-segment elevation during angina attacks.[12] In these cases, in fact, EST can induce the spasm and therefore myocardial ischemia in a subset of patients, but in most patients, induction of spasm-related myocardial ischemia can only be obtained by pharmacologic intravenous (ergonovine) or intracoronary (ergonovine, acetylcholine) provocation tests. Usually, these tests are performed under ECG control, although echocardiography has been used in some studies.[13]

Of note, in angina patients with normal coronary arteries or nonsignificant coronary stenosis, acetylcholine or ergonovine provocation tests may induce myocardial ischemia in the absence of epicardial spasm, suggesting that coronary microvascular spasm is the cause of symptoms in these patients.[14,15]

Detection of spontaneous myocardial ischemia episodes

Whereas provocation tests are usually employed to detect the inducibility of myocardial ischemia, continuous ECG Holter monitoring (ECG-HM), usually for 24 to 48 hours, could be applied on several occasions to detect spontaneous episodes of myocardial ischemia during daily life. In patients with myocardial ischemia related to obstructive CAD, or even in patients with reduced coronary flow reserve related to impaired coronary microvascular dilatation, ECG-HM is less sensitive than diagnostic stress tests for documenting myocardial ischemia, but it may give relevant information about the myocardial ischemia burden, as assessed by both number and severity of myocardial ischemia episodes during normal daily activities, most of which are usually silent.[16]

Importantly, ECG monitoring can be particularly helpful to detect myocardial ischemia caused by coronary artery spasm. In patients with a sufficient number of angina episodes, ECG-HM may identify episodes of transmural myocardial ischemia (as indicated by ST-segment elevation) (*Figure 2*), most of

Figure 2 *ST-segment elevation with complete atrioventricular (AV) block and AV nodal rhythm during chest pain and presyncope, detected by 24-hour ECG Holter monitoring in a patient with Prinzmetal's variant angina.*

which, again, are silent. Timely ECG-HM may aid the correct diagnosis in about 50% of patients with variant angina.[17] ■

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