Moving Toward the Optimal Test for the Assessment of Myocardial Ischemia

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The past 2 decades have produced an unprecedented amount of research toward defining the optimal approach to patients with suspected coronary artery disease (CAD). This has led to an enormous increase of knowledge, and the improved outcomes in patients with cardiovascular diseases have contributed significantly to longevity.

There is increasing agreement on various aspects of how to assess patients with suspected CAD and how to guide them toward revascularization, for example:

1. The diagnosis of CAD can be based on anatomy or function. Both have strong prognostic value, which may be additive rather than competitive. Medical therapy is guided toward reducing and stabilizing plaque as well as reducing myocardial ischemia.
2. Revascularization should be guided by functional assessment. It is well understood and generally agreed that patients without hemodynamically relevant coronary artery stenosis should not be revascularized. There are data but no consensus on which method should be used to prove hemodynamic significance.
3. Pretest likelihoods are frequently overestimated. This can be seen by the high number of negative tests in imaging and in the catheterization laboratory as well as the high number of healthy patients in many studies designed to assess pathways for assessing patients with suspected CAD, such as the recent PROMISE trial.[1] The most recent European

Society of Cardiology guidelines[2] adapted the pretest likelihoods to accommodate for this observation. Although stress testing should precede invasive angiography in most cases, the high number of negative stress tests (and computed tomography angiographies) remains worrying.

In contrast, we are still asking ourselves very basic questions:

1. Is exercise a better test than pharmacological stress?
2. Is wall motion imaging better than perfusion imaging?
3. Are there relevant differences among various imaging modalities?

Some of these questions cannot be answered without answering some of the others, for example, the use of a different reference standard will lead to a different answer in comparing imaging modalities, or perfusion imaging may react differently to changing the type of stress than wall motion imaging (Table). Because of the near endless possibilities for combination, it is unlikely that a single strategy will perform best, especially when considering various pretest likelihoods and patient populations. Except for rare patients with stable symptoms for CAD and high pretest likelihood, a stress test should be performed before proceeding with invasive angiography. According to most current guidelines, the choice of stress and the choice of imaging depend on local availability and local expertise; however, differences are starting to crystallize as data accumulate. Cardiovascular magnetic resonance (CMR) shows preferable results to single–photon emission computed tomography (SPECT) imaging in large single– and multicenter studies for the diagnosis of myocardial ischemia with perfusion imaging,[3,4] for the detection of myocardial infarction,[5] and for picking up other abnormalities that may be prognostically relevant.[6] Although the diagnostic accuracy can always be discussed by challenging the reference standard used, these differences in diagnostic accuracy are also slowly starting to result in differences in outcomes. CMR picks up myocardial infarction with the highest accuracy,[7] and patients with a previously unknown myocardial infarction have an increased event rate and mortality.[8] Recently, the 5-year follow-up data from the CE-MARC study demonstrated a strong and independent

Table. Comparison of Different Stressors in Ischemia Testing

	Exercise	Dobutamine	Adenosine/Regadenoson
Mechanism of action	Physiological stimulation, positive inotrope, positive chronotrope, increase of blood pressure and rate pressure product, coronary vasodilation, induction of true myocardial ischemia, usually used for wall motion imaging	Positive inotrope, positive chronotrope, increase of blood pressure and rate pressure product, coronary vasodilation, induction of true myocardial ischemia, usually used for wall motion imaging	Coronary vasodilation, compensatory increase of heart rate, no induction of true myocardial ischemia, usually used for perfusion imaging
Advantages	Physiological, true ischemia, correlation of imaging findings with symptoms	Highly reproducible, excellent achievement of target heart rate also in patients unable to exercise, no motion artifacts, normal breathing pattern, allows measurement of wall motion viability and perfusion in 1 stress test	Highly reproducible, low rate of significant side effects, minimal increase of heart rate and (nearly) normal breathing pattern resulting in excellent image quality, rapid test
Disadvantages	Depends on patients' ability to exercise, peak stress frequently not achieved, image quality frequently reduced (for echo or cardiovascular magnetic resonance)	Reduction of EDV and ESV with less pronounced wall motion abnormalities than exercise	Contraindicated in severe asthma, difficult to assess whether peak stress was achieved. no induction of true ischemia, less sensitive for wall motion imaging

EDV indicates enddiastolic volume; ESV, endsystolic volume.

predictive value of CMR perfusion imaging for future major adverse cardiac events that was superior to SPECT imaging.[9]

The multicenter EXACT trial presented in this issue[10] adds to this information. Raman et al examined 94 patients with a sophisticated dual-imaging exercise stress protocol. All patients were stressed on a magnetic resonance (MR) conditional treadmill ergometer and were imaged under stress and at rest with CMR and with technetium Tc 99m SPECT. Patients who did not undergo clinically indicated invasive angiography were assessed with computed tomography angiography as the reference standard. Patients were followed up for 1 year for outcome. CMR is not optimally suited for exercise imaging. Several reports have used MR conditional supine bicycle devices; however, because of the spatial restraints of the MR scanner, imaging needs to be performed after stopping the exercise and moving the patient into the scanner. In addition, supine bicycle ergometric stress seems not to be feasible for a relatively large number of patients. In the EXACT trial, the authors tried to overcome this limitation by using upright treadmill exercise positioned immediately beside the MR scanner and achieved 97% of age-predicted maximum heart rate. Patients were then rapidly moved into the MR scanner, and free-breathing non–cardiac-triggered cine imaging was performed, followed by first-pass perfusion imaging. The authors found sensitivity of 79% and specificity of 99% for a CMR readout based on perfusion and wall motion and sensitivity of 50% and specificity of 94% for SPECT. Correlation of CMR with angiography was strong, whereas SPECT and angiography showed only moderate correlation. CMR and SPECT differed in the detection of previous myocardial infarction (7 patients with scar in MR but not SPECT and 9 patients with fixed defect in SPECT but normal CMR late gadolinium enhancement), and CMR picked up 9 patients with important findings beyond ischemia, including 2 patients with hypertrophic cardiomyopathy and 1 patient with left ventricular thrombus. Outcomes were favorable in all patients. This first multicenter study on treadmill exercise testing for CMR demonstrates feasibility, useful accuracy, and a favorable comparison to SPECT imaging in patients routinely referred to exercise stress imaging. The authors can be congratulated for putting together a sophisticated protocol including anatomical coronary artery imaging in this patient group, providing another piece of the puzzle in the quest for the optimal test in patients with suspected CAD.

Three questions come up immediately. First, in the current study, wall motion was performed before perfusion imaging in the MR scanner because cine imaging could be performed untriggered without breath holding, enabling early imaging in all patients. This resulted in a delay of only 25 seconds between ending stress and starting imaging, with a heart rate of 83% of age-predicted maximum heart rate for wall motion imaging. Nevertheless, wall motion imaging was suboptimal because of breathing motion and did not contribute significantly to the overall diagnostic accuracy of the combined CMR protocol. In general, the scientific data on wall motion imaging versus perfusion imaging is limited because SPECT imaging is not optimally suited for wall motion assessment, and echocardiography is less accurate for perfusion imaging. Early data based on CMR,[11] which combines the ability of wall motion and perfusion imaging, demonstrated higher accuracy of perfusion imaging than wall motion imaging during adenosine stress and higher accuracy of wall motion imaging in comparison to perfusion imaging during dobutamine stress.

The first finding can be explained by the ischemic cascade because adenosine does not induce true myocardial ischemia and thus limited wall motion abnormalities; the second finding can be explained by technical limitations because, at the time of the study, CMR perfusion imaging was not possible during the high heart rates induced by dobutamine stress. More recent studies performing accelerated perfusion imaging during dobutamine stress have been highly favorable.[12] It is important to realize that CMR perfusion imaging is a real-time technique and thus is more affected by artifacts that wall motion imaging usually obtained during several heartbeats. The real-time imaging approach for wall motion chosen in the EXACT trial to allow imaging during free breathing and without ECG triggering eliminates the main advantage of CMR cine imaging in comparison to perfusion imaging. Because the wall motion imaging was performed first, perfusion was done with a significant delay of 46 seconds after terminating stress, with a heart rate of 76% of age-predicted maximum heart rate. It is possible that perfusion imaging performed as the first step would improve accuracy; this could potentially be done with pulse oxymetric triggering for more robustness. Despite these limitations, CMR correlated more closely with invasive angiography and demonstrated higher accuracy than SPECT imaging in the current study, further contributing to the above-mentioned notion.

Second, the authors stressed the importance of exercise stress testing to allow reproduction of symptoms and their correlation with ECG and imaging findings, comparison of functional capacity to the extent of ischemia, and use of the Duke treadmill score for prognostication. Unfortunately, they did not provide data on the additional (if any) information obtained by either of the 2 imaging tests on top of the pure exercise information or the contribution of the exercise information (if any) to the results of the imaging tests. In a previous study with incremental testing using an exercise tolerance test and CMR perfusion imaging,[13] the imaging test provided independent value in patients with high pretest likelihood and incremental value in patients with low pretest likelihood and positive exercise tolerance test (ST segments or symptoms) as well as in patients with intermediate pretest likelihood and a negative exercise tolerance test or only positive by symptoms or ST segments. Patients with low pretest likelihood and normal exercise tolerance test or intermediate likelihood and symptomatic and ST-segment–positive exercise tolerance test did not require additional imaging testing. Performing such an algorithm in the combined setting might be an effective approach. In general, the question of whether pharmacological or physical stress is the better approach remains scientifically unanswered.

Third, an important question remains the costs of the presented approach. This will be answered in a later study but is important; the use of an ergometer adjacent to the MR scanner may be required for achieving adequate heart rate during the CMR scan but also prolongs the time that the MR scanner cannot be used for imaging. A stress protocol of 8.5 minutes with a recovery time of 6 to 8 minutes, as observed in the EXACT trial, may be similar to a dobutamine stress scan but is significantly longer than an adenosine stress test, which can be done in $\approx$5 to 7 minutes.

In summary, the current study adds multicenter feasibility and reasonable accuracy of treadmill exercise perfusion CMR to our armamentarium of tests for the assessment of stable CAD. Although this provides us with more options, it also generates additional questions. The quest for the optimal test continues.

Disclosures

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