

INTRODUCTION

Coronary artery disease (CAD) is narrowing of small blood vessels supplying the heart due to plaque build up and can result in angina, damage to cardiac muscle and death. CAD is a leading cause of death in adults over the age of 35 years. Because of its high prevalence timely diagnosis and treatment is crucial. Earlier detection and treatment of patients with known or suspected CAD results in better outcomes and decreased mortality. Apart from clinical history and risk factors noninvasive imaging tests can help in determining the presence, extent and location of coronary atherosclerosis and myocardial ischemia. A wide array of functional as well as anatomic noninvasive tests including exercise treadmill (TMT), stress echo, Myocardial perfusion imaging modalities like single photon computed tomography (SPECT) & PET, multislice CT angio (MSCT) and stress cardiac MRI (CMR) have shown utility in the diagnosis of CAD. Available tests have advantages and limitations and none can be considered suitable for all the patients. Noninvasive test selection is challenging for many clinicians and a controversial topic for practice guidelines. Current guidelines for imaging stable chest pain of suspected cardiac etiology do not yet incorporate recent randomised trials comparing functional versus anatomical testing strategies. In this review we attempt to discuss the advantages, costs, diagnostic accuracy and appropriateness of each available modality in a stable symptomatic patient with suspected ischemic heart disease and provide a concise approach to non-invasive

test selection based on recent guidelines and emerging evidence.

PATIENT SELECTION FOR NON-INVASIVE TESTING

Clinical classification of chest pain

According to symptoms chest pain can be classified as per Diamonds criteria shown below in table 1 as typical, atypical angina and non angina chest pain.

Quantification of "intermediate" pretest probability of Ischemic Heart Disease (IHD) and role in test selection

The history along with age should be used to quantify the pretest probability (PTP) of underlying coronary artery disease and will determine the eligibility for specific noninvasive testing. While there is no strict definition of intermediate pretest probability the ACC/AHA uses the value of 10-90% while the ESC stratifies patients into four groups: <15%, 15%–65%, 66%–85% and >85%.

Sensitivity - the true positive rate - of most modalities is around or below 85% and specificity - the true negative rate - is approximately or below 85%, thus a key message is that specific non-invasive testing to establish diagnosis of SCAD is only recommended for patients with intermediate clinical likelihood of SCAD (15-85%), but not for individuals with higher PTP >85% or lower PTP <15%.

Strong clinical evidence of SCAD with comorbidities and quality of life making revascularization an unlikely option should be put on medical management without need to confirm the diagnosis.

Typical angina and depressed left ventricular ejection fraction (LVEF) <50% should prompt direct referral for invasive coronary angiogram (ICA) as part of a more aggressive approach.

FUNCTIONAL TESTING VERSUS ANATOMIC TESTING

Functional Testing

Detection of CAD by assessing the hemodynamic significance of an epicardial coronary artery lesion. Ischemia is based on the principle of imbalance between oxygen demand and supply. Functional tests include exercise treadmill testing (TMT), stress echo, SPECT, PET and CMR. **Exercise Tread mill testing (TMT):** Is a time honored simple and generally safe and least costly of all the non invasive tests available. It has a higher specificity of 85-90% suggesting a higher efficacy for exclusion rather than confirmation of diagnosis of SCAD. It is a useful test in intermediate PTP between 15-65% in patients

Table 1: Diamonds Clinical Classification for Chest Pain

Typic angina (definite)	Meets all three of the following characteristics: 1. Substernal chest discomfort of characteristic quality and duration 2. Provoked by exertion or emotional stress 3. Relieved by rest and / or nitrates within minutes
Atypical angina (probable)	Meets two of these characteristics
Non-anginal chest pain	Lacks or meets only one or none of the characteristics

Table 2: Sensitivities and Specificities of non invasive tests for detection of CAD (Data from ACC/AHA 2012 & ESC 2013 guidelines)

	ACC/AHA 2012		ESC 2013	
	Sensitivity	Specificity	Sensitivity	Specificity
Exercise Treadmill	0.66	0.77	0.45-0.50	0.80-0.90
Exercise or Pharm Echo	0.76	0.88		
Exercise Echo			0.80-0.85	0.80-0.88
Pharmacological Echo			0.79-0.83	0.82-0.86
Exercise or Pharm SPECT	0.88	0.77		
Exercise SPECT			0.73-0.92	0.63-0.87
Pharm SPECT			0.90-0.91	0.75-0.84
EXER or Pharm Pet	0.91	0.82		
Pharm PET			0.81-0.97	0.74-0.91
Dobutamine CMR			0.79-0.88	0.82-0.86
Pharma CMR			0.67-0.94	0.61-0.85
CT Angio			0.95-0.99	0.64-0.93

with interpretable normal resting ECG without baseline ST-T abnormalities. TMT is absolutely contraindicated in patients with acute myocardial infarction within 2 days, unstable angina, severe symptomatic aortic stenosis, uncontrolled arrhythmias with hemodynamic instability, decompensated heart failure, acute pulmonary embolism/infarction, myocarditis or pericarditis or active endocarditis, acute aortic dissection, acute non-cardiac disorder that may affect exercise performance like infection, renal failure and thyrotoxicosis and inability to get consent.

Stress imaging: The addition of imaging to exercise TMT provides incremental benefit for the accurate diagnosis of CAD with an acceptable increase in cost. The diagnostic endpoint of stress imaging is either of LV wall motion abnormalities and endocardial systolic thickening (stress echo, stress CMR) or myocardial perfusion (SPECT, PET, CMR).

Pharmacological stress testing using dobutamine or with vasodilator stress agents like adenosine, dipyridamole or selective A2A receptor agonists like regadenoson, binodenoson and apadenoson is preferable over TMT in case of (1) inability to exercise to an adequate level of workload (2) Baseline ECG features like LBBB, ventricular paced rhythm, pre-excitation syndromes, repolarization abnormalities due to LVH and digoxin. Advantages of stress echo include wide availability, relatively low cost and lack of ionizing radiation.

Myocardial perfusion scintigraphy using SPECT: Can be done with either Technetium 99m or thallium 201. Reduced regional tracer uptake during stress compared with preserved perfusion at rest is the hallmark of reversible myocardial ischemia on SPECT. Additional markers of significant CAD include transient ischemic dilatation of LV during stress and extensive RWMA.

SPECT has better sensitivity whereas stress echo has higher specificity (Table 2). Advantages of SPECT include

good quality imaging despite presence of lung disease. In patients with resting ECG abnormalities it is preferable to do vasodilator stress SPECT. Limitations of SPECT include exposure to radiation, long imaging protocol, high costs, artifacts related to respiratory motion, breast tissue and sub-diaphragmatic attenuation.

Myocardial perfusion scintigraphy using PET: PET can uniquely quantify blood flow thus allowing diagnosis of microvascular angina. Advantage of PET over SPECT is lower radiation, higher resolution and fewer attenuation artefacts with better image quality even in obese patients.

Cardiac Magnetic resonance stress imaging: CMR may detect either ischemia induced RWMA (dobutamine stress CMR) or myocardial perfusion (vasodilator stress CMR).

Advantages of perfusion CMR include lack of radiation, high spatial resolution, ability to perform absolute quantification of perfusion with limited operator dependence and additional information on cardiac structure. However CMR is costly with limited availability and expertise.

ANATOMICAL IMAGING

Invasive angiographic assessment of the lumen is the gold standard for the detection of obstructive disease but is associated with a small risk of complications because of its invasive nature. In properly selected group of patients noninvasive anatomic evaluation of the coronary tree may be a more accurate screening technique than functional imaging. It is also of value when functional testing is non-diagnostic or in certain populations like LBBB where functional imaging may have suboptimal diagnostic performance. Available noninvasive techniques include MSCT angio (CTA) and MR angiography (MRA).

Coronary CTA: Has a sensitivity of 95-99% and specificity of 64-83% with the diagnostic performance being higher in patients with lower range of intermediate PTP (15-50%) and is therefore most useful for ruling out (high negative predictive value) rather than conforming the diagnosis.

Table 3: Advantages and Disadvantages of Cardiac Imaging Modalities

Test	Availability	Feasibility	Portable	Versatility	Reproducible	Axial resolution in mm	Testing time mins	Approx cost RS
Stress Echo	Very High	High (limited in obese and COPD) Operator skill dependent	Yes	High (Anatomy & Lv Function)	Medium	1	30-45 Mins	2,500
SPECT	High	High (Limited In Young Women)	No	Medium (LV Function)	High	6-8	2.5-3 Hrs	8,000
PET	Low	High (Limited In Young Women) Flow Quantification	No	Medium (LV Function)	High	2-4	30-45 Mins	10,000
CMR	Low	High (Limited In Claustrophobic Patient) No Ionising Radiation	No	High- (Anatomy, LV Function & Valves) Precise Scar Imaging	High	0.5-1	45-60 Mins	10,000
CTA	Medium	High (Limited In Patients with CKD & Arrhythmia) Radiation Risk	No	Medium (Anatomy LV Function Valves) Limited Assesment with Extensive Calcium	Medium Low NPV In Higher PTP	0.4-0.7	30 Mins	7,000

Proper patient selection includes non-obese patient with adequate breath holding capacity with heart rate less than 65 in sinus rhythm with Agatson calcium score less than 400 with normal or near normal renal function. Contraindications include renal dysfunction, prior contrast allergy, pregnancy and inability to cooperate

The sensitivities and specificities of various available noninvasive tests for the detection of CAD as reported in the ACC/AHA 2012 guidelines and ESC 2013 guidelines is shown in Table 2 below.

GENERAL APPROACH FOR TEST SELECTION

In patients with clinically suspected SCAD following key questions need to be answered to determine patient suitability for non-invasive testing, type of stress (exercise or pharmacological) and functional vs anatomic testing:

1. What is the clinical pretest probability for SCAD?
2. Would the patient benefit from revascularisation? It is more reasonable to optimes medical management

in the presence of significant comorbidities or poor QOL.

3. Can the patient exercise adequately? Does the patient have any contraindication to TMT? This would help to decide on pharmacological stress.
4. Is resting ECG interpretable?
5. Does the patient have any contraindication to pharmacological stress testing? If the patient is not a candidate for exercise or pharmacological stress testing an anatomical strategy with coronary computed tomography (CTA) should be considered.

The strength and weakness of various imaging modalities is shown in Table 3 below:

CHOOSING THE TEST: WHAT DO THE GUIDELINES SAY?

ACC/AHA 2012 GUIDELINES: ETT for patients with intermediate PTP of IHD and exercise stress with nuclear MPI or echocardiogram for those with intermediate to high PTP of IHD who have uninterpretable ECG (class I). For patients unable to exercise pharmacological

918 stress with nuclear MPI or echocardiography is class I recommendation. The guidelines discourage the use of pharmacological stress with nuclear MPI, echo or CMR for patients who can exercise with an interpretable ECG and low PTP(class III)

There are currently no strong class I recommendations for CTA as the initial test.

CTA can be considered for patients who cannot exercise or for those with prior normal functional test but ongoing symptoms, an inconclusive functional test or unable to undergo stress MPI or echo (class IIa).

While no recommendations are made for PTP more than 90% it is reasonable to send such patients for invasive coronary angiogram.

ESC 2013 GUIDELINES

Exercise TMT is class I recommendation as the initial test for patients with suspected CAD and symptoms of angina and intermediate PTP of CAD of 15-65%. Stress imaging (echo, CMR, SPECT or PET) is strongly recommended as initial option if local expertise and availability permit (class I).

In patients without typical angina and high PTP 65-80% imaging stress test is recommended as initial test for diagnosing CAD (class I).

While there are no recommendations for pharmacological stress test exercise TMT is recommended over pharmacological testing whenever possible (class I)

Similar to ACC guidelines there are no strong recommendations for CTA as initial test. In patients with non-conclusive TMT or stress imaging test or those with contraindications to stress testing with low-intermediate PTP 15-65%. CTA can be considered (class IIa)

Class III recommendations include using CTA for patients with prior revascularization and not using as a screening test in asymptomatic individuals.

CONCLUSION

Optimal test selection for the diagnosis of CAD in stable patients with chest pain begins with the history

and physical examination and assessment of pretest probability of CAD using validated tools. Patients who are both and intermediate pretest probability of CAD and who are revascularization candidates should be sent for noninvasive testing. Either a functional or anatomical strategy is reasonable for many patients and the choice of test may be driven by the presence of important patient factors.

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