SEMPI Priority Clinical Area: Coronary Artery Disease (CAD)

INTRODUCTION

Coronary heart disease (CHD) or ischemic heart disease (IHD) is the leading cause of death in men and women in the US (Mozaffarian et al., 2016). The 2016 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) has recently reported that 15.5 million persons ≥20 years of age in the USA have CHD (Mozaffarian et al., 2016). Coronary artery disease (CAD) is generally used to refer to atherosclerosis affecting the coronary arteries and is often used synonymously with CHD/IHD. Markedly accelerated growth in the use of cardiac imaging, especially for CAD/IHD, has led to new rules mandating more careful use of radionuclide or nuclear medicine (NM), computed tomography (CT), and magnetic resonance (MR) cardiac imaging. As such, numerous guidelines and appropriate use criteria are being developed to assist clinicians in their diagnostic approach to CAD/IHD.

Clinical Assessment/Risk Stratification

Clinically, patients presenting with suspected cardiogenic chest pain are categorized as having stable or unstable angina. Patients with stable angina are risk-stratified based on their pre-test probability of CAD as being low (<15%), intermediate (15-85%), or high (>85%). Bayesian principles are then applied to guide the selection of further cardiac workup. If the pre-test probability is low, consideration is directed towards non-CAD causes of chest pain. If the pre-test probability is high, invasive rather than non-invasive testing is indicated. In the group with an intermediate (15%-85%) pre-test probability, non-invasive testing is the primary modality used for further evaluation (Albus et al., 2017). For patients with a low-to-intermediate pre-test probability, exercise stress testing without imaging is often sufficient. However, patients with intermediate-to-high pre-test probability as well as certain other patient populations (such those with known CAD) generally warrant an imaging study. Patients who cannot exercise or have an uninterpretable electrocardiogram (ECG) require pharmacologic stress testing, which necessitates an imaging component.

In patients with symptoms concerning for heart disease, the cardiac workup is driven by a clinical determination of the pre-test probability for CAD, which estimates the likelihood of CAD based upon risk factors such as characterization of chest pain (typical vs. atypical angina), age, gender, etc. (Balfour et al., 2017). Several algorithms and risk prediction models have been validated for this purpose, including the Diamond–Forrester (DF) score, the Duke Clinical Score (DCS), the CAD Consortium Basic and Clinical scores, and the Marburg Heart Score (Diamond et al., 1979; Mancini et al., 2014; Pryor et al., 1993; Bittencourt et al., 2016; Haasenritter et

al., 2012). The CAD Consortium models have demonstrated that the DF and DCS scores overestimate the risk of CAD among contemporary patient populations (Bittencourt et al., 2016; Papireddy et al., 2018). Recently, a variety of risk 'calculator' tools have been devised (calculating 10-year risk for atherosclerotic cardiovascular disease and risk stratifying of symptomatic patients using pre-test probability estimates) (ACC, 2018; Bayliss, 2009; CAD Consortium, 2018).

RADIOLOGICAL AND NON-RADIOLOGICAL EVALUATION

Non-Invasive Cardiac Assessment/Imaging

The goal of cardiac testing is to help stratify patients thought to be at risk for symptomatic coronary artery disease (CAD). Risk stratification of chest pain also includes interpretation of the history, physical exam findings, electrocardiogram (ECG) and, when indicated, cardiac biomarkers levels as well as a variety of noninvasive tests. These tests include exercise stress testing, pharmacologic stress testing, myocardial perfusion imaging (MPI), stress echocardiography, and cardiac computed tomography (CT) scanning, magnetic resonance (MR), and positron emission tomography (PET) scanning.

Exercise Stress Test: Exercise stress testing is the most widely used modality for the workup of CAD. It involves use of a bicycle or treadmill to increase cardiac workload in a protocolized, stepwise fashion. Historically, American professional society guidelines have recommended exercise ECG testing as the initial diagnostic tool in patients with low and intermediate pre-test probabilities of coronary artery disease (CAD), given that they are able to exercise and have an interpretable resting ECG (Cheezum et al., 2015; Fihn et al., 2012; Mancini et al., 2014). Recent updates to the National Institute for Health and Care Excellence (NICE) guidelines no longer recommend the use of exercise ECG in this setting due to its purported limitations in sensitivity and specificity (Dancy et al., 2018). However, real-world clinical data from insurance claims suggest that this modality is comparable to stress imaging studies (e.g., myocardial perfusion scintigraphy or stress echo) as well as noninvasive anatomic studies (e.g., coronary CT angiography) in identifying obstructive CAD as well as predicting major adverse cardiac events (Roifman et al., 2017).

Pharmacologic Stress Test: Pharmacologic stress testing involves the induction of coronary hyperemia using intravenous coronary vasodilators (e.g., dipyridamole, adenosine, regadenoson) which decrease coronary vascular resistance or adrenergic agonists (e.g., dobutamine) which increase chronotropy and inotropy. Pharmacologic stress testing requires an imaging portion, as abnormalities in cardiac perfusion and/or wall motion are used to discern ischemia.

Nuclear Myocardial Perfusion Imaging (MPI) Stress Test: Both stress echo (see below) and stress MPI can be useful in patients at intermediate pre-test risk of CAD and those with an **uninterpretable resting ECG**. The choice between these two modalities is based, in part, on the availability of equipment and expertise. It should be noted that a perfusion abnormality precedes LV dysfunction which precedes ECG abnormalities and angina such that echocardiography captures the ischemic changes later as compared to single-photon emission computed tomography-myocardial perfusion imaging **(SPECT-MPI).** Exercise is the preferred mechanism of stress with either MPI or echo imaging, as exercise capacity is an important predictor of outcomes (Gurunathan et al., 2018). As patient limitations frequently preclude exercise, pharmacologic stress induction with vasodilatory or adrenergic agents has evolved as a comparable diagnostic tool.

Stress Echocardiography: Both stress echo and stress MPI (see above) can be useful in patients at intermediate pre-test risk of CAD and those with an **uninterpretable resting ECG**. Cardiac stress echocardiography involves imaging the heart via duplex & Doppler ultrasonography while inducing stress via exercise or pharmacologic means. Stress echocardiography helps to assess regional wall motion abnormalities and visualize contractile reserve in infarcted areas while also providing a prognostic value for predicting "hard" outcomes (Chelliah et al., 2010). Stress echocardiograms can be enhanced by the addition of contrast for improved visualization. Exercise is the preferred mechanism of stress with either MPI or echo imaging, as exercise capacity is an important predictor of outcomes (Gurunathan et al., 2018). As patient limitations frequently preclude exercise, pharmacologic stress induction with vasodilatory or adrenergic agents has evolved as a comparable diagnostic tool.

Cardiac Magnetic Resonance Perfusion Imaging: Cardiac stress myocardial perfusion magnetic resonance (MR) imaging combines gadolinium contrast-based MR with a pharmacologic stressor agent (e.g., adenosine or dobutamine) in order to identify CAD and assess for ischemia in patients with intermediate risk for CAD (Task Force Members et al., 2013). Noninvasive cardiac stress MR demonstrates high concordance with invasive fractional flow reserve (FFR) obtained by coronary angiography (Greenwood et al., 2012; Takx et al., 2015). It remains unclear, however, whether this cardiac imaging modality can identify those patients who would benefit from percutaneous or surgical revascularization rather than medical management alone. In a 2019 review, vasodilator stress CMR had sensitivities/specificities for detecting clinically significant CAD of 67-94%/61-85% while those of dobutamine stress CMR ranged from 79-81%/81-91% (Iwanaga, 2019). The MR-INFORM trial reported that a noninvasive stress CMR-based strategy is not inferior to an invasive coronary angiography-based strategy for revascularization management, but follow-up was limited to only one year and cardiac events occurred less frequently than current incidence/prevalence rates support (Nagel et al., 2019).

Cardiac Computed Tomography (CT Calcium Scoring and Cardiac CT Angiography): Cardiac computed tomographic angiography (CCTA) has a high negative predictive value for CAD; thus, it can reliably exclude obstructive CAD in low-to-intermediate risk patients. However, there remains concern that the limited anatomical information provided by CCTA is of lesser utility in comparison to the prognostic and functional information provided by other non-invasive studies, especially those with exercise components. The PROMISE and SCOT-HEART studies suggest that initial CCTA evaluation strategy improves diagnostic certainty as well as guides the selection of pharmacological or invasive treatment strategies for patients with clinically suspected CAD (Adamson & Newby, 2019). Based on these and similar studies, the United Kingdom's NICE guidelines now recommend that all patients with stable angina or patients with non-typical angina and an abnormal EKG should first be investigated with CCTA (Moss et al., 2017; Neglia et al., 2015). However, European (ESC) guideline recommends reserving CCTA for patients with a low risk of CAD and functional imaging test for patients with an intermediate risk (15-85%) of CAD (Task Force Members et al., 2013; Genders et al., 2011; Knuuti et al., 2018). The 2012 guidelines from the American Cardiology Society on stable chest pain recommend initial clinical evaluation of the pretest probability of CAD. Patients able to exercise with interpretable resting ECGs and a low to intermediate likelihood of CAD are recommended to have an exercise ECG stress test. Patients with an uninterpretable ECG and intermediate to high likelihood of CAD, are recommended to have functional imaging tests (Wolk et al., 2014).

Controversy remains regarding the role of **coronary artery calcium (CAC) scoring** as a cardiac event risk-assessment tool. In 2003 and 2007, two observational studies provided evidence that a CAC score provides independent incremental risk assessment in the prediction of all-cause mortality in patients with CAD when added to traditional CVD risk factors (Shaw et al., 2003; Budoff et al., 2007). Subsequent studies have found that while the absence of coronary artery calcification has a robust negative predictive value (NPV) for future cardiovascular events, a positive CACS is less helpful given a low specificity (Sarwar et al., 2009). Additionally, a calcium score of zero could help to identify a subset of patients in whom life-long preventive pharmacotherapy (statins, aspirin) would **not** provide benefit (Blaha et al., 2016). The US Preventive Services Task Force (USPSTF) published a consensus report concluding that clinical trial evidence is insufficient to support use of CACS for incremental changes to risk assessment, and further questions whether such incremental changes provide meaningful clinical benefit (Lin et al., 2018). Alternatively, a CACS greater than 0 warrants initiation/continuation of statin therapy in those with a CVD risk assessment of 7.5-20% (Greenland et al., 2018; Gupta et al., 2017; Miedema et al., 2018; Arnett et al., 2019). Recent data from the MESA trial indicate that a CACS strongly predicts cardiovascular risk with the same magnitude of effect in all races, age groups, and in both sexes (Budoff et al., 2018). The Coronary Artery Calcium Consortium reported findings from a multicenter observational cohort study analyzing 14,169 patients with low

cardiovascular risk scores (less than 5%) and a **family history of coronary heart disease** and found that a CAC score can identify those patients who would benefit from preventive pharmacotherapy (Dudum et al., 2019). The same Consortium studied 22,346 younger adults (aged 30-49) and found that a CACS greater than 100 (versus 0) was independently associated with significantly increased risk of CHD, cardiovascular disease, and all-cause mortality (Miedema et al., 2019). CT without contrast is recommended for coronary artery calcium (CAC) assessment in asymptomatic adults who are at low to intermediate risk, as determined by the latest risk score (validated ACC/AHA risk calculator) and risk modifiers, to further stratify risk for pharmacotherapy decision-making.
Positron emission tomography-myocardial perfusion imaging (PET-MPI): PET-MPI represents a newer imaging modality for functional assessment of ischemic burden in patients with coronary artery disease. As such it can facilitate revascularization planning. Advantages of PET-MPI include **absolute** quantification of coronary perfusion (SPECT can only provide **relative** measurements), sharper image production and associated improved interpretation, and marginally increased (vs SPECT-MPI/stress ECHO) sensitivity and specificity for detecting CAD. Disadvantages include reliance on isotopes that require costly equipment to produce at each site, and the inability to have patients exercise with PET because the isotope tracers have such short half-lives (minutes) compared to SPECT-MPI (hours). Without the ability to exercise the patient, critical functional capacity information that earlier types of nuclear studies and echo studies provide (in combination with treadmill ECG), are lost. At present, consensus is lacking as to whether PET-MPI alone should drive revascularization decisions.

SUMMARY

Noninvasive cardiac testing is used as part of a broader scheme of risk stratification for patients with chest pain and coronary artery disease. Patient characteristics and local resources dictate which of the cardiac tests are chosen. Although variability exists in how well noninvasive cardiac tests correlate with angiographic findings, most of the tests are useful for determining short-term risk of myocardial infarction and cardiovascular death.

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