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Noninvasive Imaging for the Assessment of Coronary Artery Disease

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Abstract

Noninvasive cardiac imaging is a cornerstone of the diagnostic work-up in patients with suspected coronary artery disease (CAD), cardiomyopathy, heart failure, and congenital heart disease. It is essential for the assessment of CAD from functional and anatomical perspectives, and is considered the gate-keeper to invasive coronary angiography. Cardiac tests include exercise electrocardiography, single photon emission computed tomography myocardial perfusion imaging, positron emission tomography myocardial perfusion imaging, stress echocardiography, coronary computed tomography angiography, and stress cardiac magnetic resonance. The wide range of imaging techniques is advantageous for the detection and management of cardiac diseases, and the implementation of preventive measures that can affect the long-term prognosis of these diseases. However, clinicians face a challenge when deciding which test is most appropriate for a given patient. Basic knowledge of each modality will facilitate the decision-making process in CAD assessment.

Keywords: Noninvasive, imaging, coronary artery disease, assessment, diagnosis

1. Introduction

Noninvasive cardiac imaging is crucial for coronary artery disease (CAD) assessment. The increasing global burden of CAD is a major contributor to the marked growth in the use of noninvasive imaging [1]. In recent years, the development of state-of-the-art hardware and software technologies has broadened the perspective and dimension of noninvasive imaging. This is advantageous to hybrid imaging in CAD assessment, with the introduction of anatom-

ical, physiological, or combined approaches. These techniques allow clinicians to move beyond the dichotomous concept of the presence or absence of CAD by increasing their understanding of the unique pathophysiologic processes in CAD, including subclinical atherosclerosis, plaque vulnerability, myocardial blood flow (MBF), and scar detection.

Invasive coronary angiography (ICA), an anatomical test, is considered the gold standard method for the diagnosis of CAD. Nevertheless, the risk of complications precludes the routine use of ICA and it is only indicated in patients with a high pre-test probability of the disease [2]. Because most patients have low or intermediate pre-test probabilities of disease, noninvasive testing should be considered first, serving as a selection process for ICA. Clinicians can choose from a wide range of noninvasive tests, including exercise electrocardiography (ECG), single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), positron emission tomography (PET) MPI, stress echocardiography (SE), coronary computed tomography angiography (CCTA), and stress cardiac magnetic resonance (CMR). Therefore, clinicians are frequently faced with the apparently difficult clinical question: "What is the right test?" However, there are no right tests! The test to be used should be selected for each patient after considering the patient's characteristics, genetic and environmental factors, predisposition, risk factors, and comorbidities. Cardiac testing is generally unnecessary in asymptomatic patients except in high-risk occupations or before starting antiarrhythmic drugs.

A basic understanding of the principles, diagnostic, and prognostic accuracy, and the strengths and limitations of each imaging technique is essential. The clinician must then adopt a structured approach, which will help choose the appropriate test to use after considering the risk and benefit profile of each test. The establishment of a diagnosis of CAD will influence the perceived likelihood of a future cardiac event and warrant secondary prevention to slow or prevent disease progression. The absence of CAD on imaging will reassure the patient, and encourage the clinician to adopt a primary prevention strategy. Hence the ultimate goal is for the chosen test to address the clinical question with a high level of certainty. The theme of this chapter is to provide a comprehensive guide to selecting the appropriate imaging test in patients with suspected CAD.

2. Basic concepts for choosing cardiac imaging tests

2.1. Classification of chest pain

There can be varied presentation of chest pain, including jaw pain, epigastric pain, indigestion, shortness of breath, or reduced effort tolerance. Atypical presentations are commonly seen among diabetics, female, and the elderly. Chest pain can be classified using the criteria below [3]:

Criteria:

1. Substernal chest pain or discomfort

- 2. Provoked by exertion or emotional stress
- 3. Relieved by rest ± nitroglycerin

Typical angina: (1) + (2) + (3)

Atypical angina: (1) + (2) or (1) + (3)

Nonanginal chest pain: (1) or none.

2.2. Pre-test and post-test probabilities

Bayes’ theorem proposes the use of a combined pre-test probability and test result to determine the post-test probability of disease [4]. This will help the clinician to determine whether a positive test result is a “true positive” or a “false positive” and whether a negative test result is a “true negative” or a “false negative”. For example, a positive test result is likely to be a “true positive” result in a 70-year-old patient with typical angina or a “false positive” result in a 40-year-old female with nonanginal chest pain. Meanwhile, a negative test result is likely to be a “true negative” result in a 35-year-old man with atypical chest pain or a “false negative” result in a 60-year-old man with prior myocardial infarction (MI) and typical angina. Pretest probability can be estimated using the Diamond and Forrester classification [5] (Table 1).

Age	Gender	Typical	Atypical	Nonanginal
(years)		Angina	Angina	chest pain
≤ 39	Men	Intermediate	Intermediate	Low
	Women	Intermediate	Very low	Very low
40-49	Men	High	Intermediate	Intermediate
	Women	Intermediate	Low	Very low
50-59	Men	High	Intermediate	Intermediate
	Women	Intermediate	Intermediate	Low
≥ 60	Men	High	Intermediate	Intermediate
	Women	High	Intermediate	Intermediate

Table 1. Diamond and Forrester Pre-Test Probability of Coronary Artery Disease by Age, Sex, and Symptoms. High: >90% pre-test probability. Intermediate: between 10% and 90% pre-test probability. Low: between 5 and 10% pre-test probability. Very low: <5% pre-test probability [5].

2.3. Appropriate use criteria

The appropriate use criteria (AUC) defines appropriate imaging for the different clinical indications. The AUC for test selection among symptomatic patients with suspected CAD [2] (Table 2).

Indication for noninvasive testing in	Exercise	Stress	Stress	Stress	CCTA
symptomatic patients	ECG	MPI	Echo	CMR	
Low pretest probability of CAD ECG interpretable AND able to exercise	A	R	M	R	R
Low pretest probability of CAD ECG uninterpretable OR unable to exercise		A	A	M	M
Intermediate pretest probability of CAD ECG interpretable AND able to exercise	A	A	A	M	M
Intermediate pretest probability of CAD ECG uninterpretable OR unable to exercise		A	A	A	A
High pretest probability of CAD ECG interpretable AND able to exercise	M	A	A	A	M
High pretest probability of CAD ECG uninterpretable OR unable to exercise		A	A	A	M

Table 2. Appropriate Use Criteria for noninvasive testing in symptomatic patients for CAD assessment. A= appropriate, M= maybe appropriate, R= rarely appropriate. Uninterpretable ECG refers to resting abnormalities such as ST-segment depression (≥ 0.10 mV), complete left bundle branch block (LBBB), pre-excitation, digoxin use, or ventricular paced rhythm [2].

3. Non-invasive imaging tests

This section will focus on the unique principles, diagnostic and prognostic accuracy, strengths, limitations, representative cases and clinical pearls for each imaging modality.

3.1. Exercise electrocardiography

3.1.1. Background

Exercise ECG is a well-established and validated functional test used for CAD assessment. It has been used for more than 50 years, despite the increasing use of other imaging modalities. It is the first-line test in patients with suspected CAD who are able to exercise and who have an interpretable resting ECG [2]. Studies have demonstrated a lower diagnostic accuracy of exercise ECG in women because of their lower prevalence of CAD. However the risk of major adverse cardiac events (MACE) in women with good functional capacity and a normal resting ECG was not different between those who underwent exercise ECG compared with exercise SPECT MPI, and exercise ECG was considered a cost-effective strategy [6].

3.1.2. Principles

Exercise ECG evaluates the physiological response of the heart to a controlled level of exercise. The latter can be prescribed using specific exercise protocols such as Bruce and Naughton. Exercise ECG and hemodynamic-specific variables are shown to have diagnostic and prognostic value in the assessment of CAD. These variables include ST deviation, exercise capacity, percentage of the maximum age-predicted target heart rate (HR), heart rate recovery (HRR), blood pressure (BP) response, and the Duke Treadmill Score (DTS) [7].

Abnormal ST deviation is defined as ≥ 1 mm (0.1 mV) of downsloping or horizontal ST-segment depression (J point + 80 ms); or ≥ 1 mm of ST segment elevation in leads without pathological Q waves (except aVR). The J-point is defined as the junction of the QRS complex and the ST-segment. The ST deviation should be seen in three or more consecutive beats in the same lead to be considered significant [8, 9]. An upsloping ST-segment depression is considered an “equivocal” response and is not suggestive of myocardial ischemia [10]. High risk features include ST-segment depression ≥ 2 mm at < 5 metabolic equivalents (METs) in ≥ 5 leads and ≥ 5 minutes into recovery [11]. ST-segment elevation in two or more contiguous leads can help localize the site of significant ischemia, unlike ST-segment depression [12]. In the presence of prior Q waves, ST-segment elevation of > 1.0 mm (J point +60 ms) is considered abnormal. This could represent reversible ischemia in the peri-infarct zone or ventricular dyskinesia or akinesis of a segment of the left ventricle. This finding has been demonstrated among patients with anterior ($\sim 30\%$) and inferior ($\sim 15\%$) infarctions [13, 14].

Exercise capacity (a marker of cardiorespiratory fitness) is an estimate of the maximal oxygen uptake for a given workload, and is measured in METs [15]. The prevalence of significant ischemia was 0.4% and 7.1%, based on the workload achieved (≥ 10 METs and < 7 METs), respectively, on exercise SPECT MPI [16]. Hence, patients who are able to achieve a high workload (≥ 10 METs) on exercise ECG, may not require additional functional imaging.

The maximum age-predicted HR is usually described as “220-age”. The inability to achieve 85% of the maximum age-predicted HR was associated with decreased survival [17].

HRR is calculated as the peak HR achieved (HR at 1 min) [18]. An abnormal HRR is defined as a decrease in the HR of < 12 bpm in the first minute of recovery, and is predictive of mortality.

A normal blood pressure (BP) response is defined as an increase in systolic BP and an increase or decrease in diastolic BP during exercise. A decrease in systolic BP of > 10 mmHg may suggest the presence of acute left ventricular dysfunction owing to ischemia [7]. An abnormal BP response may be a specific marker for left main (LM) or triple vessel disease (TVD) [19].

The DTS is calculated as exercise time (minutes) – (5 \times ST depression in mm) – (4 \times angina index) (0= no angina; 1= nonlimiting angina; 2= limiting angina) [20]. DTS can be categorized into low risk ($\geq +5$), intermediate risk (-10 to $+4$) and high risk (≤ -11).

The absolute and relative contraindications for undergoing and termination of an exercise ECG, respectively, is illustrated in Table 3 and Table 4 [9].

Absolute	Relative
Acute myocardial infarction (<48 hours)	Obstructive left main stenosis
Unstable angina	Moderate aortic stenosis
Decompensated heart failure	Hypertrophic obstructive cardiomyopathy with severe resting gradient
Active endocarditis	
	Significant tachyarrhythmias or bradyarrhythmias
Uncontrolled cardiac arrhythmias	High degree atrioventricular (AV) block
Severe symptomatic aortic stenosis	Recent stroke or transient ischemic attack
Acute pulmonary embolism	Mental impairment with limited ability to cooperate
Acute myocarditis or pericarditis	Uncontrolled BP >200/100 mmHg
Acute aortic dissection	Uncorrected medical conditions, e.g. significant anemia, important electrolyte imbalance, and hyperthyroidism
Physical disability that precludes safe and adequate testing	

Table 3. Absolute and relative contraindications for undergoing exercise ECG [9]

Absolute	Relative
ST segment elevation (> 1.0 mm) in leads without preexisting Q waves (other than aVR, aVL and V1)	Marked ST displacement (horizontal or downsloping of >2 mm measured 60 to 80 ms after the J point)
Drop in systolic BP >10 mmHg, despite an increase in workload, in the presence of ischemia	Drop in systolic BP >10 mmHg, despite an increase in workload, in the absence of ischemia
Moderate to severe angina	Worsening chest pain
Central nervous system symptoms (e.g. ataxia, dizziness)	Fatigue, shortness of breath, wheezing, leg cramps or claudication
Signs of poor perfusion	Tachyarrhythmias, including multifocal ectopy, ventricular triplets, supraventricular tachycardia
Sustained ventricular tachycardia (VT), 2nd or 3rd degree AV block	Bradyarrhythmias that potentially become more complex or result in hemodynamic instability
Technical difficulties in monitoring the ECG or BP	BP >250/115 mmHg
Patient's request to stop	Development of bundle branch block which is indistinguishable from VT

Table 4. Absolute and relative indications for termination of exercise ECG [9]

3.1.3. Diagnostic and prognostic accuracy

A meta-analysis evaluating the accuracy of exercise ECG reported a sensitivity of 68% and specificity of 77% for the detection of CAD [21]. The discriminatory cut-off point of 1 mm (0.1

mV) of horizontal or downsloping ST-segment depression had a sensitivity of 68% and specificity of 77% [22]. The frequency of significant CAD in patients with low, intermediate, and high DTS was 19.1%, 34.9%, and 89.2%, respectively. In patients with LM or TVD, the frequency of significant CAD was 3.5%, 12.4%, and 46% in patients with low, intermediate, and high DTS, respectively [23]. The 5-year survival rates in patients with a DTS of ≤ -11 and $\geq +7$, were 67% and 93%, respectively[24]. In a recent study of 58,020 adults without CAD, the peak METs and the percentage of the maximum predicted HR were highly predictive of survival [25].

In relation to other imaging modalities, significant risk predictors for hard cardiac events in asymptomatic or symptomatic low-risk patients without CAD included abnormal SPECT findings (hazard ratio [HR] = 1.83), ischemia detected by exercise ECG (HR = 1.70), decreasing exercise capacity (HR = 1.11), decreasing DTS (HR = 1.07), and increasing severity of the coronary calcium score (CS) (HR = 1.29). The CS improved the long-term risk prediction for CAD when stratified according to the Framingham Risk Score [26].

3.1.4. Strengths and limitations

The strengths and limitations of an exercise ECG are shown in Table 5.

Strengths	Limitations
Cheap	Low sensitivity
Widely available	Low specificity
No radiation exposure	Unable to localise ischemic territory
No injection	
Short procedural time	
Assess exercise capacity	

Table 5. Strengths and limitations of exercise ECG

3.1.5. Case example 1

A 71-year-old man presents with atypical chest pain, able to exercise, and a normal resting ECG. Risk factors include ex-smoker and hypertension. Pretest probability of CAD is intermediate. Based on the AUC, exercise ECG is considered an appropriate test. Resting ECG revealed sinus rhythm at a HR of 61 bpm (Figure 1A). He underwent exercise ECG using Bruce protocol. He exercised for 7 minutes 31 seconds and achieved 10.1 METs. At 6 minutes into the exercise and at a HR of 121 bpm, ECG demonstrated 1 mm horizontal ST-segment depression in leads II, III, aVF, V3 to V6 and reached a maximum of 3 mm at peak stress at HR of 151 bpm in leads II, III, and aVF (Figure 1B). The changes resolved at 1 minutes 50 seconds during recovery. Test was terminated due to fatigue. He developed chest pain at recovery. The

calculated DTS = -11.5. Conclusion: Abnormal exercise ECG with a high DTS. He was referred for ICA.

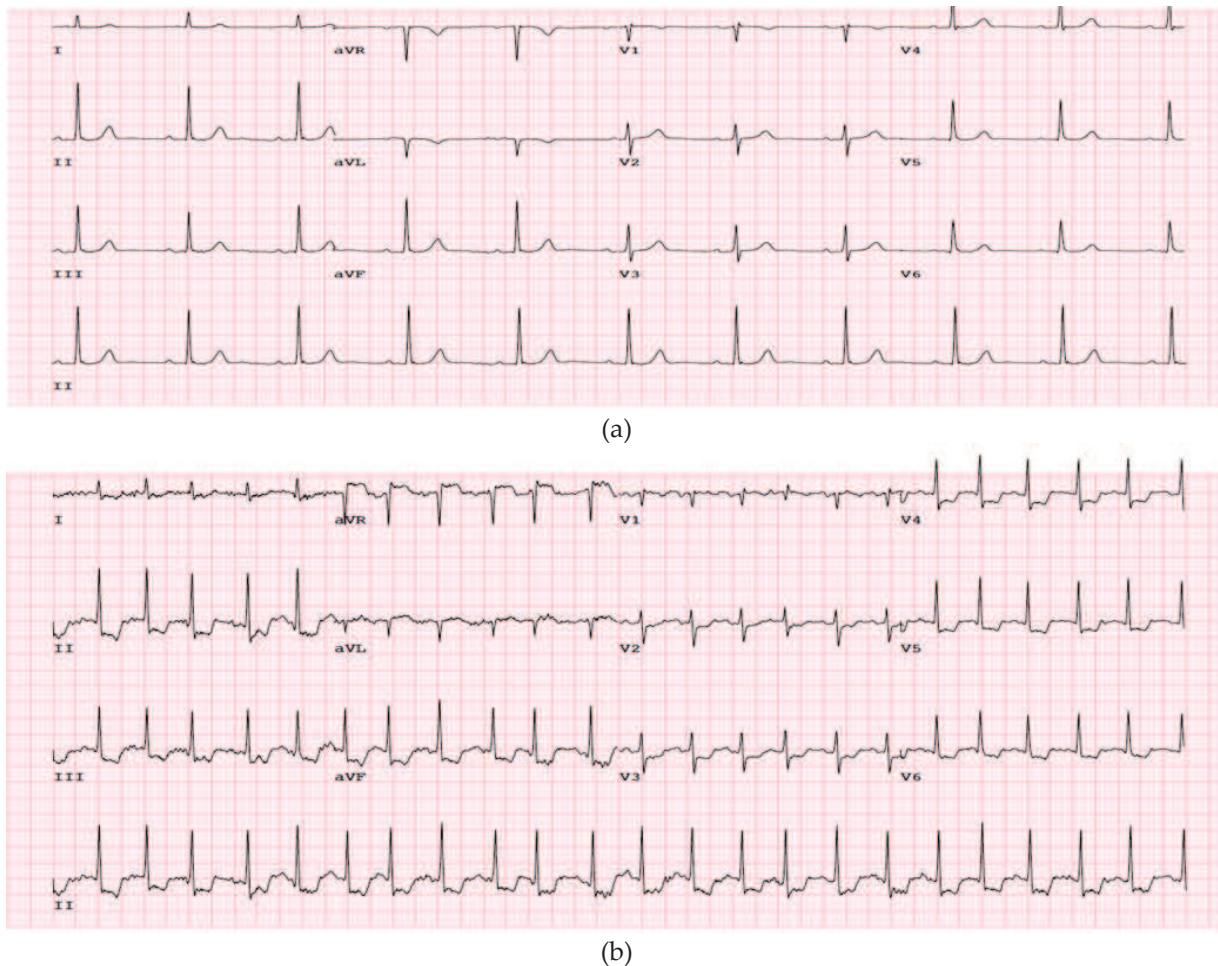


Figure 1. (a) Normal resting ECG. (b) Maximum of 3 mm horizontal ST segment depression seen in leads II, III and aVF, 2 mm ST segment depression in leads V3 to V6, at peak stress.

3.1.6. Clinical pearls

1. The J-point is defined as the junction of the QRS complex and the ST segment.
2. Achieving 85% of age predicted HR should not be an indication for test termination.
3. Exercise ECG with a high DTS may warrant ICA.
4. Exercise duration and METs achieved are strong predictors of prognosis.
5. The modification in ECG lead placement during exercise ECG compared to standard ECG may result in shift of the frontal axis to the right, increasing the voltage in the inferior leads, disappearance of Q waves in a patient with prior inferior infarct, or produce artifactual Q waves in normal subjects.

3.2. Single photon emission computed tomography

3.2.1. Background

There is robust evidence supporting the use of SPECT MPI in the workup and risk stratification of patients with suspected or known CAD because of its high diagnostic and prognostic value [27]. The development of solid state detector cameras compared with conventional SPECT (Anger) cameras offer improved signal resolution and shorter image acquisition time, which increases laboratory throughput [28, 29]. The switch from the standard, filtered back projection reconstruction method to iterative algorithms, which include depth independent resolution recovery, noise regularization, and scatter and attenuation correction, has improved the signal-to-noise ratio and image quality. This also allows for low-dose imaging using a standard acquisition time with reduced radiation exposure to the patient and operator, without compromising image quality and accuracy in the detection of CAD [30–32]. This is consistent with the American Society of Nuclear Cardiology's goal to reduce the radiation dose to ≤ 9 mSv in 50% of MPI studies by 2014.

3.2.2. Principles

SPECT MPI uses radionuclide-labeled compounds that emit γ ray photons. SPECT perfusion radiotracers include 201-Thallium (Tl-201, half-life $[t_{1/2}] = 73$ hours), and 99m-Technetium (^{99m}Tc , $t_{1/2} = 6$ hours)-labeled sestamibi or tetrofosmin. Tl-201 is produced from a cyclotron and ^{99m}Tc is produced by a molybdenum-99- ^{99m}Tc generator.

SPECT MPI can be performed using exercise or pharmacological stressors. Exercise is preferred for patients who can exercise at an adequate workload, aiming for a minimum of 85% of the maximal age-predicted HR and 5 METs [33]. A submaximal exercise workload decreases the sensitivity of exercise SPECT MPI for the detection of CAD. Exercise usually increases MBF by 2–3 times of resting flow [24, 34].

A pharmacological stressor should be used in patients who are unable to exercise or those with baseline ECG abnormalities (pre-excitation, paced ventricular rhythm, LBBB). Pharmacological stressors include intravenous vasodilators (adenosine, dipyridamole or regadenoson) or dobutamine, a β -adrenoceptor agonist. Vasodilators activate the adenosine A2A receptor and cause coronary arteriolar vasodilatation. Vasodilators increase MBF by 3–5 times in normal coronary vessels, an increase termed as the coronary flow reserve. Meanwhile, dobutamine increases MBF similar to that induced by exercise. In the presence of flow limiting stenosis, the coronary vessel is maximally vasodilated at baseline. Hence, the administration of a vasodilator is unable to augment coronary flow. MPI assesses the regional flow heterogeneity in normal and diseased coronary vessels [35]. Generally, vasodilators do not cause myocardial ischemia because MBF increases, albeit with some variability in all coronary artery beds with a minimal or no increase in the rate-pressure product, a measure of myocardial oxygen demand. In patients with extensive CAD, ischemia can be induced by the coronary steal phenomenon [33]. Vasodilators may also activate other adenosine receptors (A1, A2B, and A3) resulting in bronchospasm (A2B and, A3) or AV conduction delay (A1). Regadenoson is a selective A2A receptor agonist that is better than other vasodilators in patients with moderate chronic obstructive pulmonary disease (COPD) or asthma [36, 37].

For pharmacological stress SPECT MPI, contraindications include asthma or COPD with active wheezing, 2nd or 3rd degree AV block without a pacemaker or sick sinus syndrome, systolic BP <90 mmHg, use of methylxantines (e.g., aminophylline or caffeine) <12 hours, known hypersensitivity to the vasodilator, acute myocardial infarction (MI) and acute coronary syndrome [33].

3.2.3. Diagnostic and prognostic accuracy

The diagnostic accuracy of all noninvasive tests is subject to the post-test referral bias, also known as the verification bias. This increases the sensitivity and reduces the specificity of the test. A normalcy rate is used as a surrogate for specificity. It is defined as the percentage of normal perfusion scans in patients with a low likelihood (<10%) of CAD based on the results of clinical and ECG stress tests [38–40]. A pooled analysis of 4,480 patients with known or suspected CAD showed that exercise SPECT MPI had a mean sensitivity of 87% and a specificity of 73% for the detection of >50% stenosis [41]. The normalcy rate of SPECT MPI is around 84% [38]. Standard MPI studies include a combination of stress and rest protocols. The use of a stress-only protocol with a “normal” stress study can reduce the radiation dose by 40% and detected similar event rates [42–44]. A “normal” stress-only study is defined as homogenous perfusion, summed stress score (SSS) of <3, normal left ventricular (LV) cavity size, function, and wall motion [43].

The prognostic value of a normal pharmacological stress MPI test is independent of the radiopharmaceutical used [45]. A meta-analysis of 19 SPECT MPI studies comprising 39,000 patients demonstrated a low annual event rate of 0.6%, for hard cardiac events such as cardiac death or nonfatal MI in patients with a normal test result [46]. However, the prognostic value is based on the studied population. For example, the annual event rate among individuals with a normal test result was higher among diabetic patients than in non-diabetic subjects (0.5% vs. 1.7%, respectively, $p < 0.005$). Diabetic patients with a LV ejection fraction (LVEF) of $\leq 45\%$ had the worst outcome [47]. High-risk MPI variables include large perfusion defect size and extent, transient ischemic dilatation (TID), post stress stunning, increased right ventricular uptake, and increased lung uptake especially with Tl-201. A normal perfusion on exercise SPECT MPI was associated with a low event rate (<1% per year) in subjects with a low or intermediate DTS, compared in subjects with an intermediate DTS and high-risk SPECT variables or those with a high DTS and a normal perfusion [48].

3.2.4. Strengths and limitations

The strengths and limitations of SPECT using ^{99m}Tc-labeled sestamibi or tetrofosmin are shown in Table 6.

3.2.5. Case example 2

A 60-year-old female with hypertension presented with atypical chest pain. Pre-test probability of CAD is intermediate. Pharmacological (dipyridamole) SPECT MPI was performed due to an uninterpretable resting ECG that showed a LBBB. The test is considered appropriate based on the AUC. SPECT MPI demonstrated normal perfusion (Figure 2).

Strengths	Limitations
Widely available	Low specificity
High sensitivity	Lower spatial resolution
Expensive	Prone to attenuation artifacts
Well validated	Long procedural time (≈4 hrs)
Exercise and pharmacological stress	Longer half life of tracers
Improved specificity with gated SPECT	Increase hepatobiliary uptake
	Radiation exposure

Table 6. Strengths and limitations of ^{99m}Tc-labelled sestamibi or tetrofosmin SPECT MPI

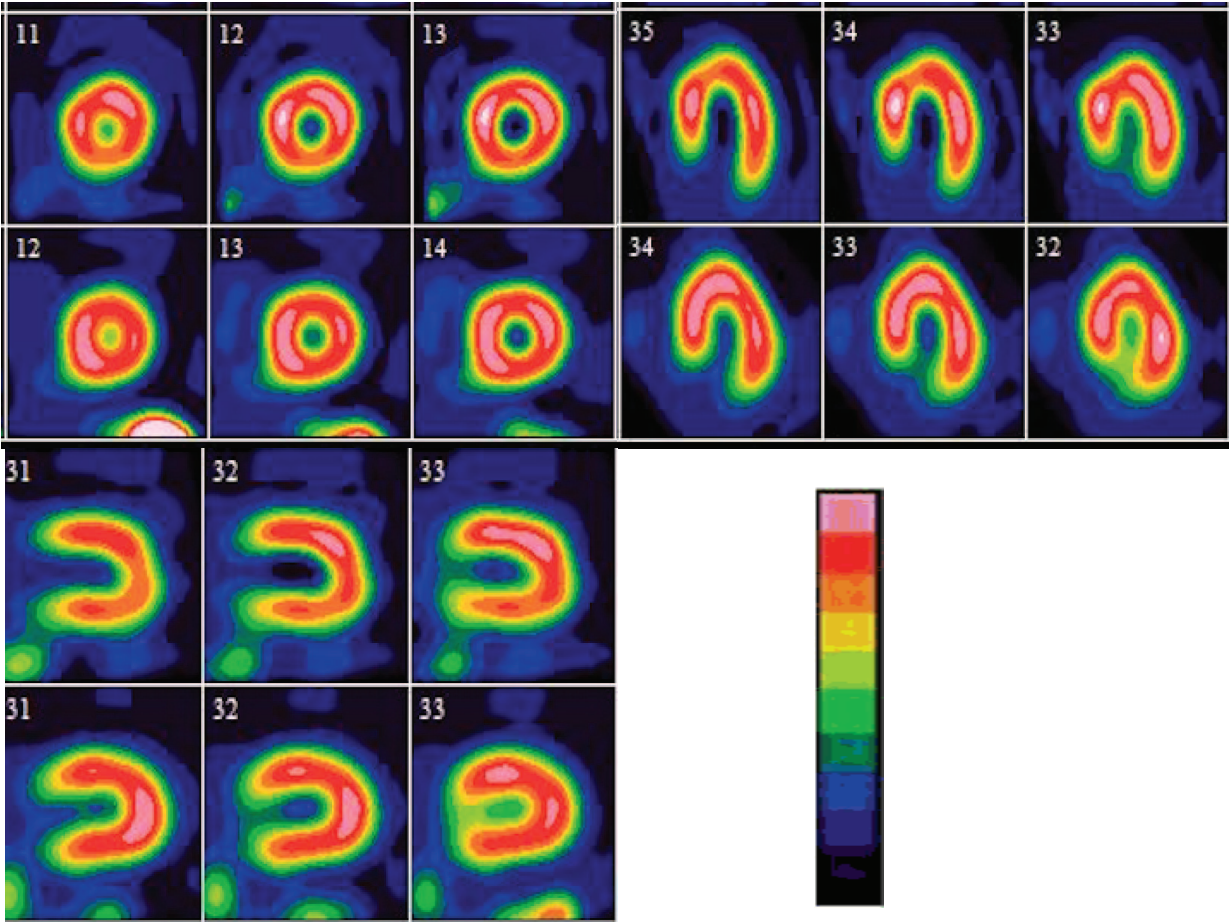


Figure 2. Stress (top row) & Rest (bottom row) images in the short axis (SA), horizontal long axis (HLA) and vertical long axis (VLA) show normal homogenous tracer uptake. Gated images showed normal left ventricular ejection fraction (not shown). This is a normal SPECT MPI study.

3.2.6. Case example 3

A 58-year-old man with a history of hyperlipidemia presented with typical angina (Canadian Cardiovascular Society Class 2). Pre-test probability of CAD: High. He underwent exercise SPECT MPI, which is considered an appropriate test based on the AUC. Baseline ECG showed sinus rhythm (Figure 3A) and resting BP of 140/90 mmHg. At 2 minutes in Bruce protocol, he developed significant ST-segment depression (Figure 3B). A significant BP drop from 140/90 mmHg to 80/60 mmHg during exercise was present and the test was terminated. The ECG changes persisted 5:50 minutes into recovery, and BP gradually returned to baseline. He achieved a total of 5 METS. He remained asymptomatic of chest pain. Calculated DTS was -17 (high risk). SPECT MPI findings as described in Figure 3C. He was referred for ICA (Figure 3D).

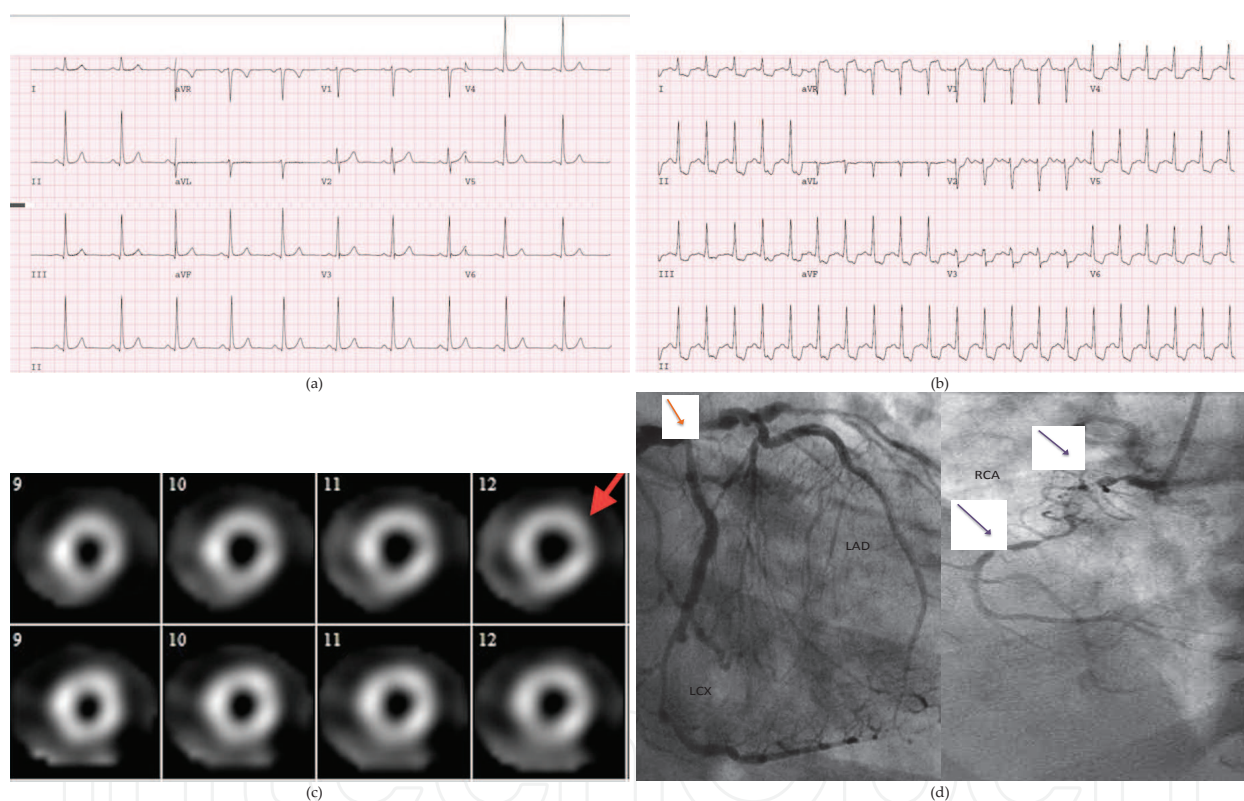


Figure 3. (a) Resting ECG showed normal sinus rhythm (b) ECG showed 3 mm ST segment depression in leads 1, aVF and V3, and a maximum of 4 mm ST segment depression leads II, V4 to V6. (c) Stress (top row), Rest (bottom row) in the SA slices: Mild reduction in tracer uptake in the mid to distal anterolateral walls (arrow) which normalized at rest. This was consistent with mild ischemia in the left circumflex (LCX) artery/ left anterior descending artery territory (LAD). TID is defined as the ratio of ungated LV volumes at stress and rest was present (1.21). TID is due to extensive subendocardial ischemia post stress that resolves on the rest images. ICA showed distal left main 90%, ostial LAD 90%, first diagonal 90%, first obtuse marginal 100%, second obtuse marginal 100%, right coronary artery 100%, and subsequently referred for CABG. This example clearly illustrates, despite a mildly abnormal perfusion (i.e. mild reduction in myocardial tracer uptake), the associated presence of high risk variables such as TID, and a high DTS, identifies a high risk scan. (d) Significant stenosis in the ostial LAD (orange arrow) and occluded proximal RCA with diffuse disease (purple arrows).

4. Clinical pearls

1. Combination of low-level exercise with dipyridamole can improve image quality and reduce symptoms resulting from drug effects.
2. High-risk findings include large defect size and extent, TID, post-stress stunning, increased right ventricular uptake, and increased lung uptake.
3. The prognosis of a normal MPI study is dependent on the study population.
4. A normal SPECT perfusion scan with ischemic ECG changes during vasodilator stress is associated with a significant cardiac event rate (~2% per year) and should be followed up with further cardiac imaging (PET MPI or CCTA).
5. Avoid antianginal medications such as beta-blockers, calcium channel blockers, or nitrates at least 48 hours prior to stress MPI for ischemia detection in suspected CAD.

4.1. Positron emission tomography

4.1.1. Background

PET MPI has superior temporal and spatial resolution, greater count sensitivity, and accurate attenuation correction compared with SPECT. These features translate into greater diagnostic image quality with fewer equivocal results, especially in obese subjects for example [49, 50]. The latest generation of PET cameras are combined with CT usually with ≥ 16 slices, and provide 3-dimensional imaging. Integrated PET (emission scan)/CT (transmission scan) systems facilitate sequential scanning, faster acquisition of transmission images, and enable functional and anatomic assessments in a single study [51–53]. These features make PET a useful clinical choice, but widespread utilization is limited by cost.

4.1.2. Principles

PET imaging is based on the detection of positron emission from radionuclide decay. After emission, the positron travels a short distance before it collides with an electron, resulting in mutual annihilation. This annihilation results in the production of 2 γ photons of 511 keV that travel in nearly opposite directions. The simultaneous detection of both photons by the detector of a PET camera is called coincidence detection [51–53].

Examples of cardiac PET radiotracers include rubidium-82 (^{82}Rb ; $t_{1/2} = 76$ s), nitrogen-13 ammonia (^{13}N - Ammonia; $t_{1/2} = 9.96$ min), and oxygen-15 water (^{15}O - H_2O ; $t_{1/2} = 2$ min). A shorter $t_{1/2}$ allows a lower radiation dose per test. Radiotracers are produced by a cyclotron, except for ^{82}Rb , which is eluted from a strontium-82 (^{82}Sr)/ ^{82}Rb generator.

Ischemia is detected in the same way as for SPECT MPI. The fundamental difference in uptake kinetics of radiotracers used in SPECT and PET explain the superior sensitivity of PET for the detection of CAD. The ideal radiotracer is ^{15}O - H_2O , which has linear uptake by myocardial tissue with increasing blood flow and “no roll-off” phenomenon. $^{99\text{m}}\text{Tc}$ - labeled tracers have a much lower extraction fraction. At high MBF, $^{99\text{m}}\text{Tc}$ - labeled tracers are characterized by a roll-

off phenomenon to a greater degree, unlike PET radiotracers [54]. At high MBF levels during stress, the relative difference in myocardial tracer uptake may be reduced leading to an underestimation of the regional flow heterogeneity between normal and diseased coronary arteries. With dynamic imaging of the tracer kinetics in PET MPI, it is feasible to measure the myocardial flow reserve (MFR), which is defined as the ratio of absolute MBF during stress compared to MBF at rest. An abnormal global MFR is indicative of diffuse atherosclerosis or microvascular dysfunction.

4.1.3. Diagnostic and prognostic accuracy

PET MPI showed superior sensitivity and diagnostic accuracy, compared to SPECT [55, 56]. A meta-analysis of three different stress perfusion modalities determined the pooled sensitivity, specificity, and area under the curve of SPECT (88%, 61%, and 0.86, respectively), CMR (89%, 76%, and 0.90, respectively) and PET (84%, 81%, and 0.92, respectively) for the detection of CAD [57].

PET MPI can be used to determine prognosis, revealing annual event rates for cardiac death and nonfatal MI of 0.4%, 2.3%, and 7.0% for SSS values of <4 (normal), 4–7, and >8, respectively [58]. A similar trend was noted when subjects were stratified according to the percentage of ischemic LV myocardium, with a relative hazard for cardiac death of 2.3%, 4.2%, and 4.9% for the strata of 0.1–9.9%, 10–19.9%, and ≥ 20%, respectively [59]. Parameters that measure the extent of ischemia have been shown to guide the decisions regarding revascularization [60]. An abnormal global MFR (<2.0) was associated with an increased incidence of MACE compared with a normal MFR (1.3% vs. 4.7%, $p = 0.03$), independent of a normal perfusion and a CS of 0 [61].

4.1.4. Strengths and limitations

The strengths and limitations of PET MPI are shown in Table 7.

Strengths	Limitations
High spatial resolution	Expensive
Robust attenuation correction	Not widely available
Improved diagnostic accuracy in the obese	Radiation exposure
Alternative for an equivocal SPECT study	Unable to assess exercise capacity
Short half life of tracers	Pharmacological stress
Absolute MBF	
Assessment of calcium on CT	

Table 7. Strengths and limitations of PET MPI

4.1.5. Case example 4

A 68-year-old female with obesity, hypertension and an ex-smoker presented with chest pain. Noncontrast CT showed a CS of 715. CCTA was not performed. A persantine ^{82}Rb PET MPI was performed (Figure 4A) and gated images were acquired at stress and rest (Figure 4B). Coronary calcium was visualised on CT and MBF was abnormal (Figure 4C).

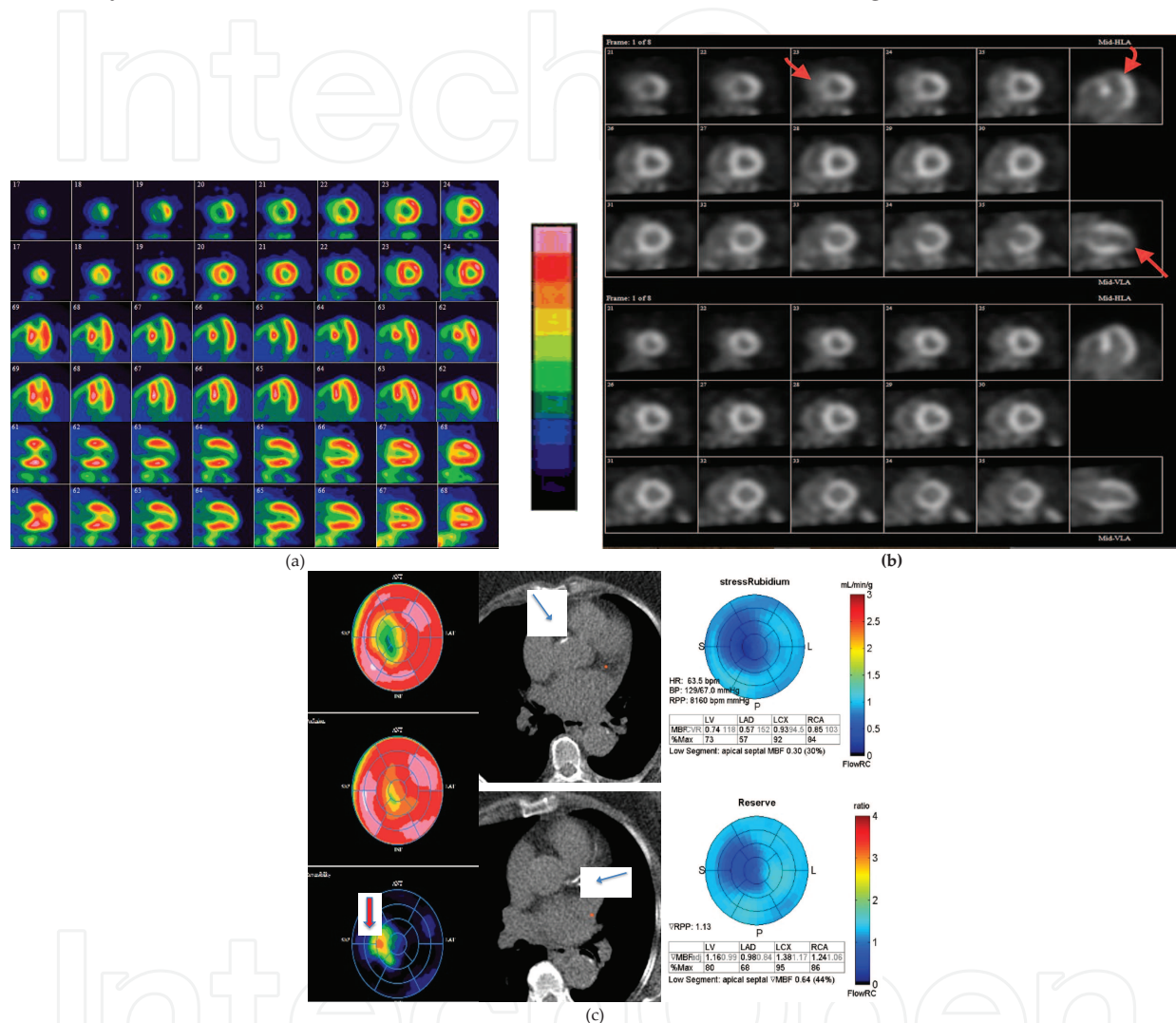


Figure 4. (a) Following stress, there is mild to moderate reduction in tracer uptake in the apical (distal) segments of the septum and anterior wall, and apex, which predominantly improves at the rest. This is consistent with a moderate sized area of moderate ischemia in the distal LAD territory. Stress images (rows 1, 3, and 5) and rest images (rows 2, 4, and 6). (b) Gated stress (top 3 rows) and gated rest (bottom 3 rows) during PET MPI. Normal LVEF and wall motion at rest. Following stress, there is mild hypokinesis in the apical (distal) septum and apex consistent with stress induced ischemia (red arrows). Stress acquisition during PET MPI is acquired at peak stress, and hence presence of regional wall motion is specific for ischemia. This differs from post-stress acquisition during SPECT which is delayed by 30 to 45 minutes. (c) Polar map shows the extent of reversible ischemia in the LAD territory (red arrow). CT shows presence of coronary calcification in the RCA (top, blue arrow), LCX and LAD (bottom, blue arrow). MBF demonstrate marked reduction in stress flow in the areas of reduced perfusion (global MBF=0.74 ml/min/g), as depicted by the polar map which is labelled as stress Rubidium. Global MFR is reduced at 1.16, and 0.99 (after correction for RPP). There is reduced regional MFR in all three coronary artery territories (LAD=0.98, LCX=1.38, and RCA=1.24), as seen on the polar map labelled as Reserve. The MFR finding is suggestive of underlying triple vessel disease. Measurement of MBF is corrected for rate-pressure product (RPP), and depicted in the shade of gray, next to the uncorrected values.

4.1.6. *Clinical pearls*

1. PET imaging is based on positron annihilation and coincidence detection of paired 511 keV γ photons.
2. PET has higher diagnostic accuracy compared to SPECT in the assessment of obstructive CAD.
3. PET is an excellent choice for imaging in the obese and those with an equivocal SPECT.
4. Abnormal global MFR suggest diffuse atherosclerosis or microvascular dysfunction.
5. Patient motion can result in significant misregistration artifact between the emission and transmission scans.
6. Normal PET perfusion and MFR confer an excellent prognosis.

4.2. Stress echocardiography

4.2.1. *Background*

SE is a robust, versatile imaging modality for CAD assessment. Advances in digital image acquisition, strain imaging, tissue harmonics, and contrast agents have increased the use of SE. In particular, the advances in tissue harmonics and contrast agents have greatly improved the visualization of endocardial borders, and diagnostic accuracy of SE for the detection of wall motion abnormalities (WMA) [62–64]. Because SE is highly operator- dependent, those who perform the test should have adequate training and experience to meet the level of competency required for performing and interpreting this test [65].

4.2.2. *Principles*

The fundamental principle for the detection of myocardial ischemia is the development of new or worsening WMA during stress [65, 66]. Based on the ischemic cascade, WMA appear after perfusion abnormalities and precede the manifestation of ECG changes and symptoms. Thus, SE has decreased sensitivity and superior specificity compared to perfusion-based imaging for the detection of CAD. Images are acquired at rest and stress. The images are compared on a four-screen setup side-by-side for WMA, LV cavity size and LVEF.

The stress component may be exercise (treadmill or bicycle) or pharmacologically (dobutamine or dipyridamole). An adequate level of stress using exercise requires a minimum target of 85% of the age-predicted HR, and is preferably symptom-limiting, considering the additional prognostic value of the subject's exercise capacity. Bicycle SE (supine or upright ergometry) allows simultaneous image acquisition during peak stress, and the measurement of Doppler information. During treadmill exercise SE, the stress images are acquired within 60–90 seconds post stress. The contraindications and indications for terminating an exercise SE are similar to those of exercise ECG.

Pharmacological SE using dobutamine is preferred over dipyridamole for wall motion assessment [65], although either stressor can be used [67]. The dose for dipyridamole in SE is

higher at 0.84 mg/kg over 10 minutes, compared to the dose used in nuclear perfusion imaging at 0.14 mg/kg/min over 4 minutes. A typical dobutamine infusion rate is at 5 micrograms/kg/min and increasing at a 3-minute interval to 10, 20, 30, and 40 micrograms/kg/min, aiming to achieve 85% of the age-predicted target HR. Atropine can be used to achieve the desired target HR. The induction of ischemia is due to an increase in myocardial oxygen demand. Deformation analysis using the tissue velocity index (TVI) and two-dimensional speckle tracking (ST)-based strain imaging have been proposed using dobutamine SE [68, 69]. However, TVI- and ST-based analysis conferred no additional diagnostic value over WMA for detection of ischemia [70].

Indications for terminating the test include the de novo or worsening of WMA, significant arrhythmias, hypotension, severe hypertension, and intolerable symptoms. For image interpretation, normal wall motion is defined as normal wall thickening and endocardial excursion. Visual assessment of wall motion can be categorized and scored as follows: 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic or aneurysmal. Please note that a score of "5" is no longer applicable. Each segment using the 16 segment LV model (i.e., apical cap not included) is scored and the wall motion score index (WMSI) is calculated. A normal WMSI equals to "1". $WMSI = \text{Total wall motion score} / \text{Total number segments visualised}$. Unlike in MPI that utilizes the 17 segment model, for WMA assessment the 16 segment model is preferred. A WMSI of >1.7 corresponds to a perfusion defect of $>20\%$ on MPI. If feasible, the right ventricular wall motion should be assessed and presence of WMA suggest greater extent of CAD.

Normal: normal at rest; hyperdynamic at stress

Ischemia: normal at rest; inducible new or worsening WMA (hypokinesis, akinesis or dyskinesis) at stress

Infarction: fixed abnormality at rest and stress

4.2.3. Diagnostic and prognostic accuracy

The development of WMA depends on the extent of stenosis detected by ICA, and occurs at a cut-off relative diameter of 54% for exercise SE, 58% for dobutamine SE, and 60% for dipyridamole SE [71]. The sensitivities and specificities for the detection of CAD were 85% and 77%, respectively, for exercise SE, 80% and 86%, respectively for dobutamine SE, and 78% and 91%, respectively, for dipyridamole SE [71, 72]. SE had a similar diagnostic accuracy to that of SPECT MPI for the detection of CAD [73, 74]. However, because of its greater specificity, SE showed a better discriminatory capacity for the diagnosis of LM and TVD [75]. For patients presenting at an emergency department with chest pain, nondiagnostic ECG, and negative cardiac biomarkers, the overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of SE for the diagnosis of CAD were 90%, 92%, 78% and 97%, respectively. Moreover, exercise SE had a better specificity than dobutamine SE [76].

A normal exercise SE result is associated with an excellent prognosis with an annual event rate of cardiac events of 0.54% [77]. The best discriminator of increased risk of cardiac events was $WMSI \geq 1.25$ and ≤ 6 METs in both genders [78]. There was no difference in the prognostic

value of dobutamine SE and dipyridamole SE [79, 80]. Therefore, the choice between these techniques may depend on institutional practices. With regards to LV cavity size, an abnormal stress LV end-systolic volume (LVESV) (i.e., no change or an increase) was associated with an increase risk of cardiac events compared with a decrease in the LVESV (2.9% vs. 1.6%) [81].

4.2.4. Strengths and limitations

The strengths and limitations of SE are shown in TABLE 8.

Strengths	Limitations
Cheap	Poor echo window (obese, COPD)
Widely available	Reduced sensitivity in detection of posterior wall ischemia
No radiation	Foreshortened LV apex
Portable	Operator dependent
Contrast echo improves endocardial definition	
Exercise and pharmacological stress	
Medium procedural time	

Table 8. Strengths and limitations of stress echocardiography

4.2.5. Case example 5

65-year-old woman with rheumatoid arthritis and hypertension presented with heartburn and indigestion of increasing severity for 1 month. An exercise SE with contrast was performed at rest. She experienced a similar episode of heartburn and nausea at 2 minutes into exercise. The test was stopped and stress images were acquired immediately (Figure 5A). Rest and stress images are shown as still frames captured at end-systole (Figure 5B i-iv). The patient was admitted in view of a positive SE at low workload. ICA showed ostial LAD 70%, mid LAD 90%, proximal LCX 80%, and mid RCA 100%. She was referred for CABG.

4.2.6. Clinical pearls

1. Normal wall motion at rest does not rule out the presence of obstructive CAD.
2. Abnormal regional wall motion can be seen in the presence of ischemic or nonischemic etiology.

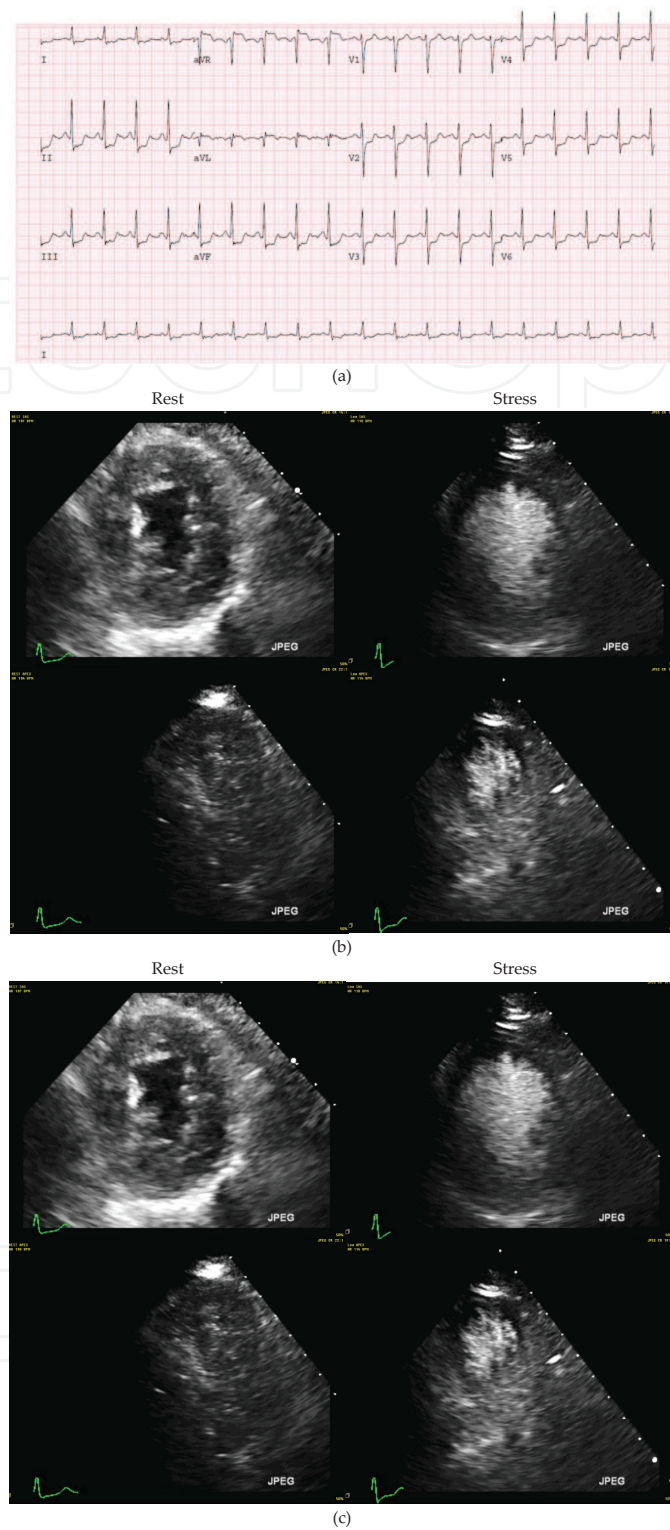


Figure 5. (a) ECG during episode of chest pain demonstrated diffuse 2 mm ST segment depression in leads II, III, aVF, V2 to V6 and ST elevation in aVR. (b) SE using contrast showing images captured at end-systole during rest and stress. The LV in different views are illustrated in the following sequence from top to bottom (i) parasternal long axis, (ii) 2-chamber, (iii) short axis, (iv) apical, demonstrate regional WMA in the anterior, anteroseptum, apex and lateral walls. Note the stress induced LV cavity dilatation, at peak stress which is suggestive of underlying triple vessel disease.

3. The absence of radial motion of the mitral valve annulus can result in a reduction in motion of the basal inferior or inferoseptal segments resulting in a false-positive study.
4. A common cause of a false negative test is a suboptimal stress level.

4.3. Coronary computed tomography angiography

4.3.1. Background

CCTA has come a long way from electron beam CT to the present multidetector CT system, with continually increasing detector rows (i.e., = slices) from 4-slices to 320-slices in some systems. A 64-slice CT system is the minimum requirement for coronary imaging. Other developments include iterative reconstruction, dual-source CT, prospective scanning, tube current modulation, and a z-flying focal spot [82]. These innovations have led to significant improvements in spatial and temporal resolution, radiation dosimetry, and image quality, which are prerequisites for coronary imaging. The ability to visualize subclinical atherosclerosis and characterize plaques has led to techniques for quantifying the extent of the atherosclerotic burden [83].

4.3.2. Principles

CCTA can determine the extent of coronary atherosclerosis and estimate the severity of coronary artery stenosis. The major components of a CT scanner include the table, X-ray tube, detector array and the gantry that rotates the X-ray tube and detector array around the patient. The ability to image a beating heart requires a high temporal resolution, which is defined as the time taken to obtain a complete data set for image reconstruction. The typical temporal resolution of CT is 280–420 ms. Data covering 180° are needed to construct one image, termed “half scan reconstruction”. Accordingly, the temporal resolution of a single-source CT system is half the time required for the gantry to rotate 360°. For a dual-source CT (DSCT), the temporal resolution is one-quarter of the gantry rotation time, because data covering 90° are sufficient for image acquisition. A DSCT has a temporal resolution of 75 ms (compared to 20–30 ms for ICA) [84].

The ability for CT to discriminate two structures is called the spatial resolution, which is measured in line pairs per centimeter (lp/cm). The typical spatial resolution of CT is 10 lp/cm, which is equivalent to 0.5 mm (compared to 0.1 mm for ICA). CT data are acquired as isotropic voxels enabling the images to be viewed in multiple planes with similar spatial resolutions [85]. The spatial resolution of CT is less than ideal to accurately quantitate the degree of stenosis, hence a grading method is used [86]:

Normal: 0%; Minimal: <25%; Mild: 25–49%; Moderate: 50–69%; Severe: 70–99%; Occluded: 100%.

ECG gating is essential to minimize cardiac motion by synchronizing image acquisition to the cardiac cycle. There are two types of scanning modes. In prospective ECG-triggered scanning, data acquisition is triggered by the R waves on the ECG. Its advantage is the low radiation

dose, typically 3–5 mSv. Disadvantages include image reconstruction limited to the desired phase and functional evaluation is not possible. In retrospective ECG-gated scanning, data acquisition are acquired throughout the cardiac cycle and the ECG signal is simultaneously recorded with the raw data. Advantages include image reconstruction can be performed at any point in the cardiac cycle and it is useful in patients with arrhythmias. Its main disadvantage is the high radiation dose, typically 10–12 mSv because the tube current remains “on” throughout image acquisition. The application of tube current modulation can reduce the radiation dose. The best phase for image acquisition is mid-diastole, when the heart is moving the least.

The images to be acquired are the initial scout image, which defines the scan length, followed by a non-contrast calcium scan and finally the contrast-enhanced CT images. The average scan length for native coronary artery imaging is 12–14 cm. Using a 64-slice scanner, images are acquired over a few cardiac cycles, as opposed to a 320-slice scanner where one cardiac cycle is sufficient because of the larger volume covered. Data can be reconstructed in two or three dimensions, although the two-dimensional axial views should serve as a reference for image interpretation.

Contrast enhancement in the ascending aorta can be tracked using a test bolus or automated bolus tracking. Both methods are acceptable and the choice between them may depend on the institutional protocol. About 80–100 ml of iodinated contrast is typically used. The target HR of 50–65 bpm can be achieved by oral or intravenous β -adrenoceptor blockers. Nitroglycerin spray is recommended to improve image quality by inducing coronary vasodilatation.

Calcium is measured using the Agatston score (i.e., CS), which correlates with the extent of the atherosclerotic plaque burden. Screening for CS are recommended in two groups of asymptomatic patients: (1) patients with low global coronary heart disease (CHD) risk and a family history of premature CAD and (2) patients with intermediate global CHD risk [87]. CT perfusion is still research-based, and will not be discussed in this review.

4.3.3. *Diagnostic and prognostic accuracy*

There is extensive literature describing the diagnostic and prognostic value of CCTA. The main advantage of CCTA is the ability to exclude disease from the differential diagnosis since CCTA has an excellent NPV. The ACCURACY trial demonstrated sensitivity, specificity, PPV, and NPV of 95%, 83%, 64%, and 99%, respectively, for the detection of $\geq 50\%$ stenosis, and 94%, 83%, 48%, and 99%, respectively, for the detection of $\geq 70\%$ stenosis. The NPV was high in patient- and vessel-level analyses [88]. The low PPV is due to its tendency to overestimate stenosis, while the presence of artefacts lead may lead to a false positive test. CCTA is considered appropriate for patients with low or intermediate pre-test probabilities of CAD, and a negative scan reliably indicates the absence of significant CAD. However, CCTA is of limited clinical value and functional imaging tests are more appropriate in patients with a high pre-test probability [89]. The presence of severe coronary calcification (CS >400) can reduce the diagnostic accuracy by overestimating the severity of stenosis owing to blooming artefacts [88]. Although there is no specific cut-off level to cancel a CCTA, CS of > 600–1000 is typically used for this purpose, considering the high likelihood of a nondiagnostic study.

The use of CCTA in the emergency department resulted in a shorter hospital stay, increased discharge rate [90, 91], and reduced time to CAD diagnosis [90], while patients with a negative scan had an excellent prognosis [92]. The all-cause mortality rate was 0.65% for normal CCTA, 1.99% for <50% stenosis, 2.9% for ≥50% stenosis, and 4.95% for LM ≥50%, TVD ≥70%, or two vessel disease with proximal LAD disease [93]. The excellent prognosis of a negative CCTA result was seen in other large series of patients [94]. The “warranty period” of a normal CCTA is ~7 years [95]. Coronary calcium has prognostic value beyond traditional risk factors with a hazard ratio of 3.89, 7.08, and 6.84 for CS of 1–100, 101–300, and ≥300, respectively, for coronary events [96].

4.3.4. Strengths and limitations

The strengths and limitations of CCTA are shown in Table 9.

Strengths	Limitations
Excellent negative predictive value	High calcium limits accuracy of assessing stenosis
High temporal resolution	Radiation exposure
High spatial resolution	Morbidly obese
Visualize coronary anatomy	Arrhythmias
Short procedural time	Allergy to iodinated contrast
Assessment of calcium score	Heart rate control
	Follow breath hold instruction
	Renal impairment (>2.0 mg/dl)
	No functional assessment

Table 9. Strengths and limitations of CCTA

4.3.5. Case example 6

A 71-year-old female with hypertension, hyperlipidemia, and an ex- smoker presented with atypical chest pain and LBBB. CCTA was performed. Findings included a CS of 269, and ≥70% stenosis (calcified and noncalcified plaque) with positive remodeling in the mid LAD (Figure 6). There was mild disease in ostium of the RCA. She was referred for ICA.

4.3.6. Case example 7

A 57-year-old man with hypertension. CCTA showed a CS of 524 with an occluded proximal RCA. He was referred for ICA and underwent percutaneous coronary intervention to the RCA (Figure 7 A-E).

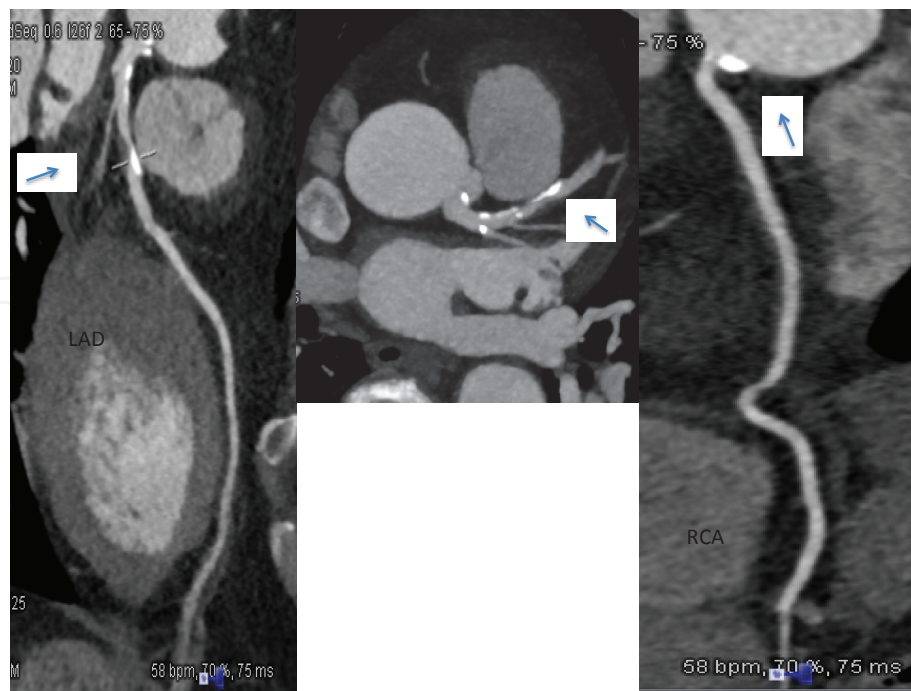


Figure 6. First two images of the curved multiplanar reformatted (MPR) and 2D-axial views demonstrate $\geq 70\%$ stenosis of the LAD (blue arrows). The third image (curved MPR) of the RCA showing a calcified plaque with minimal stenosis at the ostium (blue arrow).

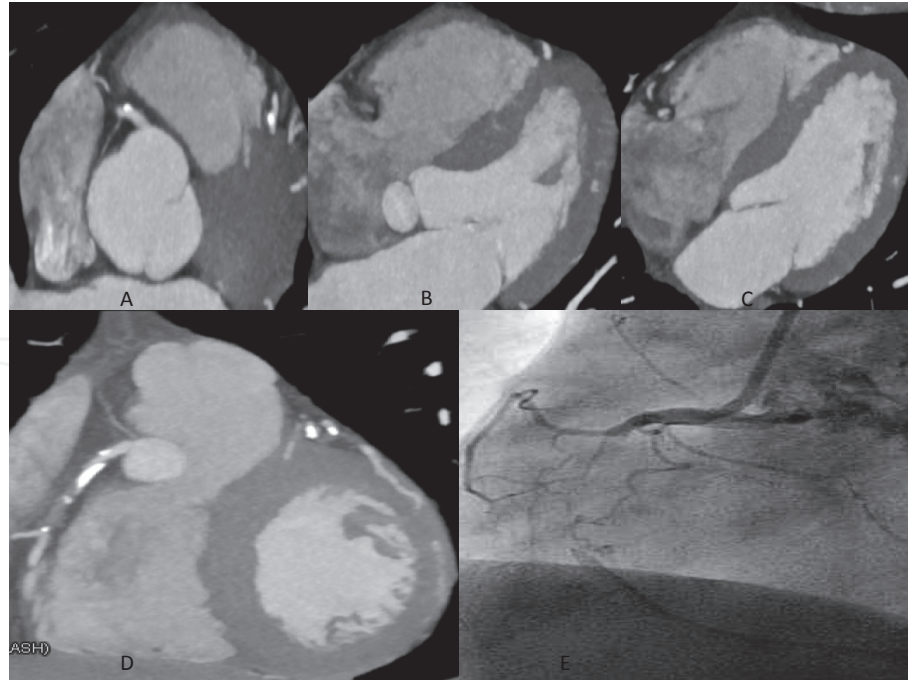


Figure 7. Axial slices from cranial to caudal demonstrate (A) contrast enhanced lumen in the proximal RCA, (B) absent of contrast enhancement and (C) reappearance of the contrast in the RCA. (D) Axial maximum intensity projection of the RCA demonstrate an occluded vessel and correlates with ICA (E).

4.3.7. Clinical pearls

1. An asymptomatic patient with a CS of 0 has a very low event rate of 0.1% per year [97].
2. Prospective ECG-triggered acquisition is preferred in view of the lower radiation dose.
3. Regular, low HR and obeying breath-hold instructions are essential for diagnostic image quality.
4. Appropriate timing of contrast injection is crucial for optimal enhancement as contrast non-uniformity in the distal coronary vessels can simulate stenoses.
5. Volume coverage in the z-axis for a 64-slice CT (0.625 mm detector width) is 4 cm (64 x 0.625), and a 320-slice CT (0.5 mm detector width) is 16 cm.

4.4. Stress cardiac magnetic resonance

4.4.1. Background

CMR has recently emerged clinically as a highly versatile technique with superior spatial and temporal resolution. The development of high field strength magnets (3T) and rapid imaging techniques such as gradient echo, echo-planar, and balanced steady-state free precession, have contributed to the feasibility of MR perfusion. The type of pulse sequence or hybrid sequences affect the contrast-to-noise ratio and the susceptibility to artifacts, which can affect image quality. In the context of MPI, CMR is a promising tool in parallel with well-established and validated modalities such as SPECT and PET MPI. The advantage of MR is its superior sensitivity for the detection of subendocardial perfusion defects without radiation exposure. The paramagnetic property of gadolinium (Gd)-based contrast agents can alter the local magnetic field in the tissue, which enables differentiation between normally and abnormally perfused myocardium. Arterial spin labeling and blood oxygen level-dependent techniques are new advances in perfusion imaging, but are still research-based. The use of coronary magnetic resonance angiography is not well established, except in some highly specialized centers, and will not be discussed here.

4.4.2. Principles

The fundamental basis of CMR perfusion imaging is the first-pass imaging of contrast transit through the LV myocardium. This exploits the effect of Gd on the T1 relaxation time of myocardial tissue [98]. Gd-based contrast agents are paramagnetic, extracellular agents that are rapidly taken up and rapidly washed out of the normal myocardium, but accumulate in damaged tissues with slower washout kinetics. Gd is highly toxic in its native state. Therefore, Gd chelators (e.g., Gd-DTPA) are used clinically. These agents shorten the T1 and T2 relaxation time constants that represent the decay of the MR signal. However, at low doses, T1 shortening is predominant. During first-pass perfusion, the normal myocardium (i.e., normal perfusion) shows substantial Gd uptake, and appears bright (i.e., hyperintense) owing to a short T1.

Ischemic myocardium (i.e., reduced perfusion) shows diminished Gd uptake and appears dark (i.e., hypointense) owing to a long T1 [98].

Similar to pharmacological stress SPECT or PET MPI, stress CMR requires the use of a pharmacological stressor, such as a vasodilator (e.g., adenosine, dipyridamole, and regadenoson) or dobutamine. Diseased coronary arteries, exhibit a lower peak myocardial signal intensity and increases in myocardial contrast transit time (e.g., signal upslope, arrival time, time-to-peak signal, and mean transit time)[99]. The difference in signal intensity can be quantitatively, semiquantitatively, or visually evaluated to identify possible perfusion defects. The use of adenosine and visual interpretation are common, and these approaches are discussed in further detail.

Historically, inducible ischemia was only assessed using stress and rest perfusion cine images. This method demonstrated a sensitivity, specificity, and diagnostic accuracy of 88%, 90%, and 89%, respectively, for the detection of significant CAD [100]. The caveat being, in patients with prior MI, the resultant perfusion deficit may include areas of prior infarct and may not reflect true inducible ischemia. Imaging with late Gd-enhancement (LGE) was used to detect prior infarction. A method combining first-pass stress and rest imaging with LGE demonstrated an overall accuracy of 0.88, or 0.96 for one-vessel disease, 0.75 for two-vessel disease, and 0.9 for prior coronary artery bypass graft, in the detection of significant stenosis [101].

A stress CMR study can be interpreted using the following algorithm [99]:

Step 1. Assess for LGE

Negative: Move to step 2.

Positive: CAD present.

Step 2. Assess stress perfusion

Negative: No CAD

Positive: Move to step 3.

Step 3. Assess rest perfusion

Negative: Inducible ischemia suggestive of CAD.

Positive: Likely artifact*

* Common being the Gibbs artifact, which is more pronounced on a 3T scanner. This usually occurs in the phase encoding direction and tends to be transient. If the segment of perfusion defect is also positive for LGE, then inducible ischemia cannot be assessed in the same segment.

An abbreviated adenosine stress CMR protocol [102]:

1. **LV structure and function module** – scout and cine imaging for cardiac structure and systolic function at rest.
2. **First pass stress perfusion module** – infusion of adenosine (140 mcg/kg/min over 4 minutes), followed by intravenous Gd (0.05 to 0.1 mmol/kg) and saline flush. Once the

contrast bolus has transited the LV myocardium, adenosine is stopped. Stress images are acquired for 40 to 50 heart beats.

3. **Rest perfusion module**– performed after 10 minutes to ensure sufficient clearing of Gd from the blood pool. Reinjection of a second dose of Gd. Rest images are acquired. Slice geometry, scan setting, and Gd dose should be similar to step (2).
4. **LGE module**– performed after 5 minutes of completion of step (3).
5. **Analysis**– visual interpretation using the 17 segment LV model. The stress and rest cine images are viewed side-by-side using equivalent slices, in addition to the LGE images.

(Some centers omit the rest perfusion module, if the first pass stress perfusion study is normal).

Adenosine ($t_{1/2} = 10$ s) is safe and well-tolerated. The potential adverse effects include flushing, chest pain, palpitations, breathlessness, transient episodes of heart block, hypotension, sinus bradycardia, and bronchospasm [102]. The contraindication to adenosine stress CMR (in addition to the general contraindication of any MR study) include known hypersensitivity to adenosine, known or suspected bronchoconstrictive or bronchospastic disease, 2nd or 3rd degree AV block, sinus bradycardia (HR <45 bpm), and systolic BP <90 mmHg [102].

4.4.3. Diagnostic and prognostic accuracy

Diagnostic accuracy of stress CMR in a population with high prevalence of CAD (57%) showed on an overall sensitivity of 89% and specificity of 80% for the diagnosis of significant obstructive CAD. Adenosine-based stress demonstrated better sensitivity than dipyridamole (90% vs. 86%), but with similar specificity (81% vs. 77%) [103]. Adenosine and dobutamine stress CMR have similar sensitivity and specificity [104]. Stress CMR showed no difference in diagnostic accuracy when compared to SPECT MPI for CAD detection [105]. The concordance and accuracy of stress CMR with 320-detector row CT, showed an excellent agreement (92%, kappa value = 0.81) in an intermediate risk cohort [106]. Adenosine perfusion was the most accurate component of the stress CMR study in predicting which patients had significant CAD, compared with resting WMA and LGE [107].

Negative findings on stress CMR are reassuring and associated with annualized event rates of 0.4% for MI and 0.3% for cardiovascular death. In patients with inducible ischemia, the annual event rates for MI and cardiovascular death were 2.6% and 2.8%, respectively. The concomitant presence of LGE was associated with a worse prognosis [108]. Other predictors of cardiac events were resting WMA, inducible WMA and LGE. Patients with inducible WMA (i.e., ischemia) experienced significant benefits from revascularization, compared with patients without inducible WMA (i.e., without ischemia) [109].

4.4.4. Strengths and limitations

The strengths and limitations of stress CMR are shown in Table 10.

Strengths	Limitations
Good contrast resolution	Expensive
No radiation exposure	Not widely available
Visualization of subendocardial ischemia and scar	Cardiac device/metallic implant
Transmurality of scar	Glomerular filtration rate <30 mls/min
Procedural time (~45 minutes)	Allergy to gadolinium
	Breath hold instructions
	Pharmacological stress
	Claustrophobia

Table 10. Strengths and limitations of stress CMR

4.4.5. Case example 8

A 65-year-old man with prior coronary artery bypass surgery presents with chest pain. An adenosine stress CMR was performed. For study interpretation, follow the steps as described in the text starting with LGE, stress and rest images. There is inducible inferior wall perfusion defect with no LGE (Figure 8).

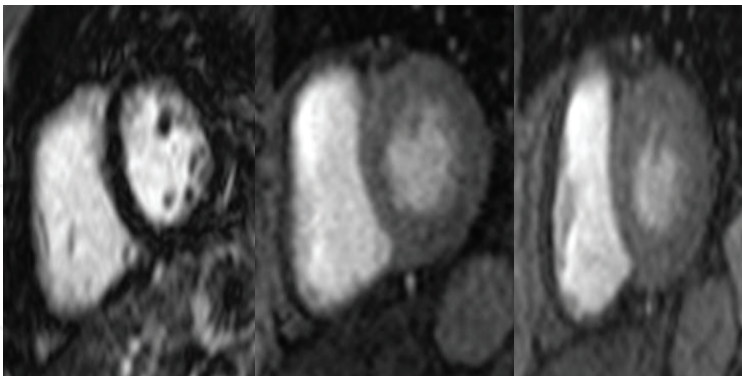


Figure 8. Left to right: 1st image: LV short axis LGE image show no evidence of scar. 2nd image: Stress first pass perfusion image demonstrate an inducible inferior wall perfusion defect. 3rd image: The corresponding rest image demonstrate no perfusion defect in the inferior wall.

4.4.6. Clinical pearls

1. Avoid caffeinated food and beverages, theophylline, and dipyridamole for 24 hours prior to stress CMR.

2. Stress CMR should be avoided in patients with a glomerular filtration rate (GFR) < 30 mls/min.
3. The presence of infarction on LGE (subendocardial or transmural in a coronary artery distribution) favors CAD, irrespective of perfusion findings.
4. Criteria for a perfusion defect is a persistent delay in enhancement pattern during first pass observed in at least 3 consecutive temporal images.
5. Perfusion defects should be graded according to transmurality.
6. Dark-rim artifact typically appear as dark lines at the blood pool-myocardium interface, and can mimic a perfusion defect (typically Gibbs artifact).

We have come to the end of our review on the essentials of noninvasive imaging modalities for the assessment of CAD. A proposed algorithm for test selection in suspected CAD is included (Figure 9). The following are four clinical scenarios commonly encountered in clinical practice and the suggested answers:

1. Would you perform a test in an asymptomatic 35-year-old woman who plans to participate in a marathon next month? She has a normal resting ECG with no cardiovascular risk factor.

Answer: No. Asymptomatic patients generally do not warrant cardiac testing. Her pretest probability of CAD is very low (<5%).

2. What is the next suitable test in a 60-year-old woman with morbid obesity who presents with chest pain? She completed 4 METs and achieved 70% of the maximum age-predicted HR following an exercise ECG.

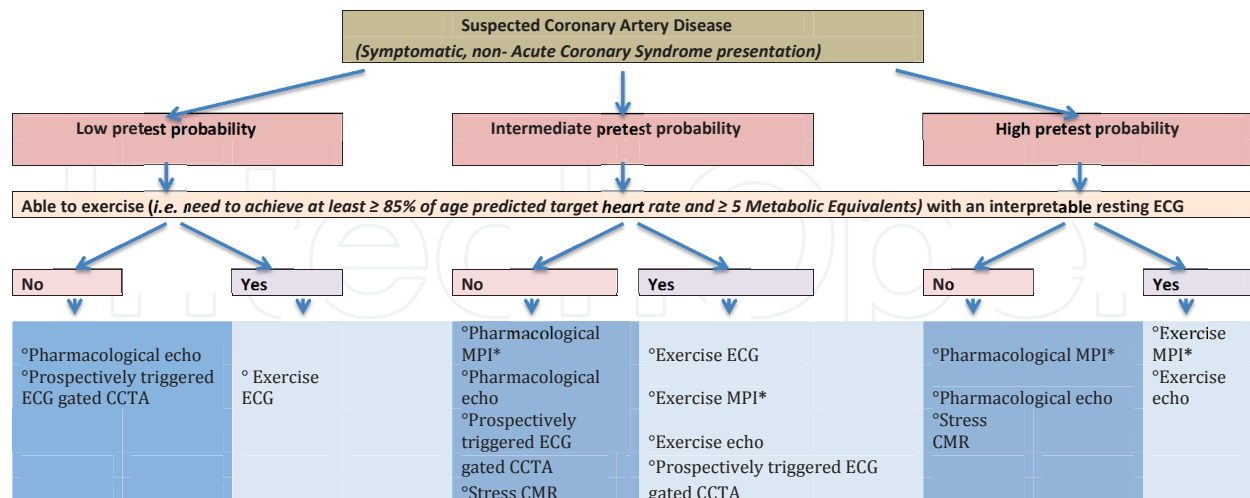
Answer: Inability to achieve an adequate stress level reduces the sensitivity of an exercise ECG. Her pretest probability of CAD is intermediate. In the presence of morbid obesity, PET MPI or CCTA would be considered a suitable alternative.

3. What test would you perform in a 75-year-old man with a sedentary lifestyle who presents with chest pain on exertion that is relieved with nitroglycerin spray? He has underlying COPD, diabetes, and hypertension. Baseline creatinine is 300 micromol/l.

Answer: Pretest probability for CAD is high ($\geq 90\%$) and the diagnosis of CAD is not in question. He has stable angina. First step would be to initiate medications such as aspirin, beta-blockers, calcium channel blockers, and statin therapy. Pharmacological SPECT or PET MPI for risk stratification is reasonable. Pharmacological SE can be performed if a good echo window can be obtained. In the presence of moderate ischemic burden, high risk variables on MPI, or worsening of symptom despite on optimal medical therapy, ICA is warranted.

4. Would you repeat another CCTA in a 50-year-old man with an active lifestyle presenting with atypical chest pain? He had a calcium score of 0 and a normal CCTA a year ago.

Answer: No. No testing is required. If symptoms persist, consider an exercise ECG.



ECG= electrocardiography; CCTA= coronary computed tomography angiography; MPI= myocardial perfusion imaging; CMR= cardiac magnetic resonance; BMI= body mass index. * BMI ≥ 30 kg/m²: PET MPI is preferred; BMI < 30 kg/m²: SPECT or PET MPI, depending on resource.

Patients with renal impairment (Creatinine > 2.0 mg/dl, avoid CCTA; if GFR < 30 mls/min, stress CMR is contraindicated.

For pharmacological MPI, use of low level exercise (1.7 mph, grade 0) is an option, in the absence of LBBB.

Figure 9. Proposed algorithm for test selection in suspected coronary artery disease.

5. Conclusion

Understanding the merits and limitations of each noninvasive imaging modality, together with local expertise and resources, will increase the clinician's confidence in selecting imaging tests for the assessment of CAD. This is crucial to avoid layered testing, unnecessary radiation exposure, and maintain a cost-effective approach. Functional and anatomical noninvasive tests are associated with similar cardiovascular outcomes in patients with low to intermediate risk [110]. The use of stress MPI to serve as a gatekeeper for ICA is well validated [111]. A detailed history and physical examination with sound clinical judgement and the integration of evidence-based guidelines are vital for selecting the right test. In summary, noninvasive tests are the cornerstone of CAD assessment. Although not covered in this chapter, such tests also serve as a guide for ischemia-driven ICA strategies.

6. Conflict of interest

The authors have no conflict of interest to disclose pertaining to the contents of this book chapter.

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