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Review

Chest Pain Evaluation: Diagnostic Testing

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ABSTRACT

Chest pain/discomfort (CP) is a common symptom and can be a diagnostic dilemma for many clinicians. The misdiagnosis of an acute or progressive chronic cardiac etiology may carry a significant risk of

RÉSUMÉ

La douleur ou la gêne thoracique sont des symptômes fréquents qui peuvent poser un dilemme diagnostique pour de nombreux médecins. Les erreurs de diagnostic d'une cause aiguë ou chronique progressive

Chest pain/discomfort (CP) is a common symptom and can be a diagnostic dilemma for many clinicians. There are numerous potential etiologies of CP, ranging across all organ systems (Table 1), and the misdiagnosis of an acute or progressive chronic cardiac etiology may carry a significant risk of morbidity and mortality.[1] Therefore, correctly identifying the cause of CP is essential.

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morbidity and mortality. This review summarizes the different options and modalities for establishing the diagnosis and severity of coronary artery disease. An effective test selection algorithm should be individually tailored to each patient to maximize diagnostic accuracy in a timely fashion, determine short- and long-term prognosis, and permit implementation of evidence-based treatments in a cost-effective manner. Through collaboration, a decision algorithm was developed (www.chowmd.ca/cadtesting) that could be adopted widely into clinical practice.

d'origine cardiaque peuvent d'ailleurs entraîner un risque considérable de morbidité et de mortalité. La présente synthèse porte sur les différentes options et modalités d'établissement du diagnostic et de la gravité d'une coronaropathie. Un algorithme efficace pour le choix des tests doit être adapté à chaque patient afin de maximiser l'exactitude diagnostique dans les plus brefs délais, de déterminer le pronostic à court et à long terme, et de permettre une mise en œuvre de traitements fondés sur des données probantes tout en tenant compte des coûts. Un algorithme décisionnel a donc été conjointement mis au point (www.chowmd.ca/cadtesting) et pourrait être largement adopté dans la pratique clinique.

New or sudden CP, or those with accelerating patterns (changes in frequency or intensity) may necessitate urgent assessment in the emergency department to rule out life-threatening etiologies such as an acute coronary syndrome, pulmonary embolism, or acute aortic syndrome. The investigation and management of acute CP in the emergency department is outside the scope of this review. This review will focus on patients with CP of a chronic and stable nature who are amenable to outpatient testing.

Assessment of CP starts with a thorough review of the CP characteristics including description, location, radiation, duration, associated symptoms, and precipitating and alleviating factors. The patient's age, pre-existing cardiac conditions, cardiovascular risk factors, and comorbidities, along with physical findings, should guide the differential diagnosis, clinical suspicion, and subsequent investigations. As coronary artery disease (CAD) remains a leading cause of death in developed countries, a missed diagnosis may lead to significant morbidity or mortality.[1]

Therefore, testing for the presence of CAD is often needed, but other chest pain etiologies should also be considered (Table 1). This review summarizes the different options and modalities for establishing the diagnosis and severity of CAD and a decision algorithm was developed (www.chowmd.ca/cadtesting) that could be adopted widely into clinical practice.

An effective test selection algorithm should be individually tailored to each patient to maximize diagnostic accuracy in a timely fashion, determine short- and long-term prognosis, and permit implementation of evidence-based treatments in a cost-effective manner.

Pretest Probability for Coronary Artery Disease

In patients with suspected CAD, the pretest probability of finding underlying obstructive CAD can be approximated using age, sex, and typicality of CP features.[2-8] However, traditional pretest probability prediction tools were derived from invasive coronary angiography (ICA) populations that no longer reflect the contemporary populations referred for noninvasive testing who have a lower prevalence of CAD.[7-10] More contemporary pretest estimates have used lower risk populations referred for coronary computed tomography angiography (CCTA). Furthermore, existing pretest probability calculators do not account for the varying array of less typical symptoms nor do they account for the presence of cardiac risk factors. How risk factors should be incorporated into a diagnostic algorithm is less certain, but their presence should heighten the clinician's level of suspicion for the presence of CAD.

Recent guidelines have suggested that low-risk individuals (pretest probability $< 15\%$) have a low prevalence of obstructive CAD and may not require testing, whereas investigations are warranted in those with a pretest probability of $\geq 15\%$.[7,11,12] Although a patient's pretest probability for CAD can be estimated using 3 variables (age, sex, and typicality of symptoms), current pretest probability models have limitations. As an example of the limitations of existing risk scoring tools, a 60-year-old woman with a history of diabetes, 30-pack year history of smoking, previous ischemic stroke, family history of premature CAD, and "typical" ischemic CP has a pretest probability of 16%, which is lower than a 50-year-old man without cardiac risk factors and with "atypical" CP (17%).[12] Thus guidelines and this review provide guidance but cannot replace overall clinical acumen.

Diagnostic Testing for CAD

When selecting the most appropriate cardiac test to investigate CP, several factors should be considered. In addition to test accuracy, patient-specific factors include contraindications to specific tests, known CAD, or previous revascularization, previous testing results, and patient preference (Tables 2 and 3). In addition, available modalities include anatomic and functional assessments of CAD, or both, and each clinical scenario should guide appropriate test selection. Also, the availability of newer imaging technology (hardware and software) that enhances diagnostic accuracy should be considered. When there is equipoise among modalities, other factors to consider are availability, timeliness of access, local expertise, and cost.

Anatomic vs functional testing

Historically, coronary anatomy and luminal stenosis identified by ICA was used to guide revascularization. However, the **F**ractional Flow Reserve vs **A**ngiography for **M**ultivessel **E**valuation (FAME) trial showed that anatomic stenosis does not consistently predict physiology, and practice has shifted "anatomic assessment" to one that includes "functional assessment." The discord between anatomy and function should also temper our interpretation of historical accuracy studies whereby noninvasive tests were gauged solely against coronary anatomy. Noninvasive stress tests (ischemia testing) have likely been disadvantaged when compared against anatomy alone as the gold standard. In these studies,

the absence of myocardial ischemia in the presence of epicardial stenoses was considered "false-negative," whereas ischemia in the absence of epicardial stenosis was considered "false-positive." Even chronically occluded epicardial stenoses may have sufficient collateralization to maintain overall normal myocardial blood flow. We now recognize the existence of ischemia with no obstructive coronary arteries (INOCA) from subtle plaque rupture/disruption or coronary artery ulceration (only appreciated on intracoronary imaging), coronary vasospasm, microvascular disease or dysfunction, nonatherosclerotic coronary artery disease, and myocardial disease.

Imaging Modalities: Anatomic Testing

Invasive coronary angiography

Traditionally, ICA has been considered the gold standard test for the detection of epicardial coronary artery disease. ICA is an invasive procedure with inherent risks and is an expensive and limited resource. For stable patients, it has typically been reserved for those with high risk or nondiagnostic findings on noninvasive testing or with unacceptable quality of life on medical therapy. Risk-stratification models have been proposed to help identify patients who would likely benefit from ICA although with limited effectiveness.[13] ICA may be considered in those with Canadian Cardiovascular Society (CCS) class II to IV angina despite medical therapy[14] or those with high-risk or inconclusive noninvasive test results.[14,15] Asymptomatic patients and those without high-risk features on noninvasive testing should not be routinely referred for ICA.[12,15]

ICA excels at identifying the presence and extent of CAD. A spatial resolution of 0.2 mm and temporal resolution of 20 msec provides the most accurate evaluation of epicardial coronary stenosis.[16] Cineangiography and basic quantitative techniques determine location, extent and severity of coronary stenosis, as well as plaque eccentricity and characteristics (thrombus, dissection, ulceration, and calcification), anomalous coronaries, assessment of bypass grafts, and visually abnormal resting flow.[17]

Coronary angiography alone without intracoronary imaging or physiological assessment may underestimate or overestimate the severity and extent of coronary disease. In effect, compensatory vessel remodelling as described by Glagov et al.[18] results in underestimated luminal stenosis until the cross-sectional area of the plaque approaches 40% of total vessel area.

Intravascular assessment of coronary physiology and morphology adds incremental information to ICA luminal assessment.[19] The FAME trial confirmed the potential discordance between anatomic stenosis and its functional significance, thus measuring coronary flow (fractional flow reserve [FFR], resting flow rate [RFR], or instantaneous wave-free ratio [iFR]) is considered standard of care for lesions of intermediate stenosis.[20] However, FFR is not without limitations, as it cannot assess microvasculature. Microvasculature assessment with the index of microvascular resistance (IMR) and coronary flow reserve (CFR) is useful for investigation of angina symptoms or myocardial ischemia despite the absence of significant stenosis and can help differentiate among INOCA, preserved coronary flow despite chest pain, or vasospastic angina.[19,21]

Table 1. Differential diagnosis of chest pain

Cardiovascular	- Myocardial ischemia/necrosis • Acute coronary syndrome, myocardial infarction, myocardial infarction with nonobstructive coronary arteries, spontaneous coronary artery dissection • Ischemia with nonobstructive coronary arteries, coronary vasospasm, coronary microvascular dysfunction • Cardiomyopathy (stress-induced, tachycardia-mediated, hypertrophic hypertensive) - Myocarditis/myopericarditis/pericarditis - Valvular • Aortic stenosis • Mitral valve prolapse - Pulmonary hypertension - Acute aortic syndromes
Respiratory	- Pulmonary embolism - Pneumothorax/hemothorax - Pneumomediastinum - Pneumonia - Bronchitis - Pleuritis - Malignancy
Gastrointestinal	- Cholecystitis - Pancreatitis - Hiatal hernia - Gastroesophageal reflux disease - Peptic ulcer disease - Esophageal spasm - Dyspepsia
Musculoskeletal	- Costochondritis - Chest-wall trauma/inflammation - Herpes zoster - Cervical radiculopathy - Breast disease - Rib fracture - Prolapsed intervertebral disc
Psychological	- Panic disorder - Anxiety - Depression - Somatization disorder
Other	- Hyperventilation syndrome - Carbon monoxide poisoning - Post-COVID syndrome - Lead poisoning - Thoracic outlet syndrome - Sickle cell crisis

Intracoronary imaging is an additional powerful tool for assessing luminal stenosis, plaque characterization, and stent optimization or for assessment of restenosis. Optical coherence tomography (OCT) has superior resolution compared to intravascular ultrasound (IVUS) (10-20 μm vs 100-150 μm) but less depth penetration (2 mm vs 4-8 mm).[21] Both provide coronary minimal luminal area (MLA),[22] but OCT is generally preferred for plaque characterization (thin-cap fibroatheroma, calcified nodules, plaque erosion/rupture) and stent failure.[23] These recent advances in physiological and anatomic assessment greatly increase the diagnostic value of ICA in stable patients.

There are no absolute contraindications to performing ICA. Relative contraindications include allergy to contrast media, renal dysfunction, acute stroke, severe anemia,

Table 2. Noninvasive test sensitivity and specificity for the diagnosis of obstructive coronary artery disease*

	Sensitivity	Specificity	Reference
Ischemia testing			
Exercise treadmill stress test (Supplememtal Fig. S1)	68%	77%	109,110
Single photon emission computed tomography (Tc-99m SPECT) (Supplemental Fig. S2)	88%	77%-85%	76,109,111
Stress echocardiography (Supplemental Fig. S3)	76%-85%	75%-89%	109,111,112
Positron emission tomography	90%-91%	82%-88%	76,109
Cardiac MRI (Supplemental Fig. S4)			113
•Perfusion	89%	80%	
•Wall motion	83%	86%	
Anatomic testing			
Coronary CT angiography (Supplemental Fig. S5)	94%-99%	79%-88%	114,115

CT, computed tomography; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography.

*Obstructive coronary artery disease as defined by invasive coronary angiography.Examples of abnormal tests are provided as supplemental figures.

active bleeding/severe bleeding disorder, decompensated heart failure, pregnancy, and inability of patients to cooperate.[24]

The invasive nature of ICA carries procedural risk (1.9%).[25] The most common local vascular complications after ICA (0.7%) include arterial dissection, hematoma, pseudoaneurysm, arteriovenous fistula, and limb ischemia.[26] Myocardial infarction (0.002%), coronary dissection (0.002%), pericardial effusion (0.009%), stroke (0.06%), and death (0.01%) are rare events in the modern era.[24,26] Canadian registry data suggest that acute kidney injury (AKI) can be up to 7.6%, with moderate to severe AKI (serum creatinine rise ≥100%), occurring in only 1.2%.[27]

Cardiac CT and coronary artery calcium

Electrocardiogram (ECG)-gated noncontrast-enhanced computed tomography (CT) can be used to assess the presence of coronary artery calcium (CAC), which is an early and specific marker of coronary atherosclerosis.[27] The absence of CAC confers an excellent cardiovascular prognosis, with a 2.2% event rate at 10 years.[28] However, this technique does not permit the direct visualization of the coronary lumen, and the absence of CAC does not exclude noncalcified obstructive plaque in all patients. Used selectively, CAC may be useful in low-risk symptomatic patients.[12,15,29]

Coronary CT angiography

CCTA is a noninvasive modality that directly images the coronary arteries and has now been endorsed as a first-line test for the diagnosis of CAD in stable patients by other cardiology societies based on its high sensitivity and negative predictive value.[7,12,15,30,31]

In addition, CCTA is the only noninvasive modality that can detect nonobstructive coronary atherosclerosis and plaque features (positive remodelling, low attenuation plaque (< 30 Hounsfield units [HUs]), spotty calcifications, and napkin-ring sign), which are associated with major adverse cardiovascular events (MACE), and tailoring therapy may improve outcomes.[32-36]

In patients with previous revascularization, CCTA should be used very selectively. Caution should be used in imaging patients with documented CAD and those with previous percutaneous coronary intervention (PCI), especially in those with multiple or small-diameter stents (< 3.0 mm).[37] CCTA can be used in patients with previous coronary artery bypass grafts (CABG) and is able to accurately assess for graft patency, but the assessment of the native coronary arteries can be more difficult because of diffuse coronary atherosclerosis and calcification.[37]

The **Pro**spective **M**ulticenter **I**maging **S**tudy for **E**valuation of Chest Pain (PROMISE) showed that CCTA is comparable with functional imaging and results in fewer false-positive referrals for ICA (27.9% vs 52.5%, respectively).[38] The **S**cottish **Co**mputed **T**omography of the **Heart** (SCOT-HEART) trial, at 5-year follow-up, showed that patients investigated by CCTA had improved outcomes and was likely related to refinement of medical therapy.[36] Moreover, the **I**nternational **S**tudy of **C**omparative **H**ealth **E**ffectiveness With **M**edical and **I**nvasive **A**pproaches (ISCHEMIA) trial suggested that CCTA is an excellent modality for assessment of patients with stable chest pain and moderate-to-severe ischemia based on functional testing. The agreement between CCTA and ICA for excluding left main stenosis ≥ 50% was 97.1%, and the identification of patients with at least 1-vessel CAD with ≥ 50% stenosis was 92.2%.[39] Anatomic severity of CAD by CT was highly correlated to death (hazard ratio [HR], 2.72; 95% confidence interval [CI], 1.06-6.98) and myocardial infarction (HR, 3.78; 95% CI, 1.63-8.78).[40] Moreover, CCTA identified 21% of cases with moderate-to-severe ischemia that did not have epicardial stenosis of 50% or greater and were effectively eliminated by CCTA from inclusion in the trial to avoid inclusion of patients with INOCA.

Coronary CT angiography-derived fractional flow reserve (FFR_{CT}) provides assessment of lesion-specific ischemia, with a similar sensitivity but greater specificity compared with standard CCTA (0.87 vs 0.76 and 0.80 vs 0.61, respectively).[41] Also, CT perfusion (CTP) using vasodilator stress provides good sensitivity (0.82) and specificity (0.88) for detection of obstructive CAD. Both FFR_{CT} and CTP may reduce the need for downstream ICA but there are limited data supporting their impact on MACE.[42]

False-positive CCTA results can be as high as 28%.[38] Image quality can be limited from technical factors (spatial and temporal resolution, blooming artifacts) and patient factors (high heart rate, elevated body mass index [BMI], arrythmias, movement). Real-world multicentre accuracy studies suggest variable accuracy across studies and centres, and—ideally—CCTA should be performed in centres in which expertise is readily available.[43]

Potential contraindications to CCTA include allergy to contrast media, severe renal dysfunction, contraindication to beta blockade or nitroglycerin, uncontrolled arrhythmias, pregnancy, clinical instability, and inability to follow commands and breath-hold instructions.[44] The incidence of intravenous contrast material-induced nephropathy is low in patients with normal renal function but is higher in patients with baseline renal insufficiency, diabetes mellitus,

Table 3. Contraindications and relative contraindications to testing

	Contraindications	Relative contraindications
Treadmill exercise	• Unable/unsafe to exercise • Uncontrolled hypertension (≥ 200/110 mm Hg) • Uncontrolled heart failure • Concurrent/recent ACS/MI/myocarditis/aortic dissection • Symptomatic aortic stenosis • Symptomatic hypertrophic obstructive cardiomyopathy • Severe pulmonary hypertension	• Unable to achieve target HR • Abnormal baseline ECG (ST changes > 1mm) • Left bundle branch block • Paced ventricular rhythm • Accessory pathway/delta waves
Pharmacologic stress: vasodilator	• Severe reactive airways disease • Second- or third-degree AV block • Hypotension (systolic BP < 90 mm Hg) • Recent dipyridamole use • Recent methylxanthine or caffeine use (< 24 hours)	
Pharmacologic stress: dobutamine	• Uncontrolled hypertension (≥ 200/110 mm Hg) • Uncontrolled heart failure • Concurrent/recent ACS/MI/myocarditis/aortic dissection • Symptomatic severe aortic stenosis • Symptomatic hypertrophic obstructive cardiomyopathy • Severe pulmonary hypertension	• Unable to achieve target HR • Abnormal baseline ECG (ST changes) • Left bundle branch block • Paced ventricular rhythm • Accessory pathway/delta waves • Contraindication to atropine use
Stress echocardiography	• Poor acoustic windows	• Allergy to contrast
SPECT myocardial perfusion imaging	• Contraindication to stress (above)	• Elevated risk associated with radiation exposure
PET myocardial perfusion imaging	• Contraindication to stress (above)	• Elevated risk associated with radiation exposure
Cardiac MR	• Contraindication to stress (above) • Non-MRI safe devices/implants	• Left-sided implantable electronic devices • Claustrophobia • Renal insufficiency (GFR < 30)
Coronary artery calcium score		• Elevated risk associated with radiation exposure
Coronary CT angiogram	• Known extensive coronary calcification	• Elevated risk associated with radiation exposure • Contrast allergy • Uncontrolled HR, non-sinus rhythm • Renal insufficiency (GFR < 30) • Contraindication to NTG

ACS, acute coronary syndrome; AV, atrioventricular; BP, blood pressure; CT, computed tomography; ECG, electrocardiogram; GFR, glomerular filtration rate; HR, heart rate; MI, myocardial infarction; MR, magnetic resonance; MRI, magnetic resonance imaging; NTG, nitroglycerin; PET, positron emission tomography; SPECT, single photon emission computed tomography.

cardiomyopathy, volume depletion, older age, and small BMI.[44,45] Radiation exposure from CCTA can vary based on technique, can be as low as < 1 mSv but averages between 3 to 5 mSV.[46] This dose is lower than or similar to other modalities using ionizing radiation.

Functional/Ischemia Testing

Ischemic cascade

The ischemic cascade has been used to explain the accuracy of different functional tests.[47] In this schema, stress-induced ischemia would first manifest in metabolic changes (myocardial preferential use of glucose as an energy substrate), followed by a reduction in perfusion, induction of diastolic and then systolic wall-motion abnormalities, with subsequent ECG abnormalities and clinical chest pain.

Exercise ECG stress test

Evaluation of stable CAD by exercise ECG stress testing (EST) has been performed for almost 90 years.[48] The enduring nature of this investigation is tied to its simplicity, availability, low cost, and ease of correlation with patients' symptoms.[4] In the modern formats of treadmill or ergometer exercise, EST remains a valid strategy for the investigation of chest pain but has recently been downgraded to Class II indication status within recent international and national guideline documents.[7,12]

Testing in very low-risk pretest probability (< 15%) patients is not advised because of the risk of false positive findings and the absence of meaningful change between pretest and post-test likelihood with the study results.[7,12] This is pertinent when using EST in patients when the pretest probability approaches the ends of the spectrum. Thus, as we choose to investigate those at extremes of pretest probability, a more accurate test is needed to sway decision making.[7,12,49]

EST does not diagnose subclinical nonobstructive atherosclerosis and, as such, suffers in comparison with other techniques when global atherosclerotic risk is sought.[50] Nevertheless, exercise capacity and blood-pressure responses can highlight increased risk, although their management does not have consensus in guidelines.[51-54] Furthermore, robust intervention outcome data examining the benefits of improved exercise capacity or tempered hypertensive responses are missing in comparison with trials considering primary prevention with statins.

Despite low diagnostic-accuracy concerns, EST has retained utility in clinical practice, in part because of its prognostic value.[55] This is achieved by the use of scoring algorithms such as the Duke Treadmill Score, which combines ECG changes, exercise capacity, and the presence of chest pain symptoms during the test.[56] The utility of EST-derived

prognostic scores also helps with functional imaging interpretation when other parameters might be considered low risk (eg, normal relative perfusion with positive EST).[57] Thus, although the accuracy of EST has been surpassed by techniques combining stress with imaging or by anatomic testing, EST continues to be relied upon for prognosis and can help decision making with regard to the urgency of further investigations.[58,59]

EST also has few contraindications to testing.[53] Diagnostic accuracy may be reduced in patients with abnormal resting ECGs or in those unable to achieve the target heart rate or rate pressure product > 25,000; however, EST may still be used in this setting to confirm symptoms, assess exercise capacity, and to assess therapeutic response.[60] The cumulative risk from repeated EST testing in patients to evaluate different therapeutic strategies is minimal, as there is no radiation exposure. Furthermore, the cost for repeated EST is estimated to be much lower than most comparison techniques, which has important health economic implications.[12]

The main disadvantage of EST is its lower diagnostic accuracy, having a sensitivity and specificity of approximately 77% and 68%, respectively, for detecting obstructive CAD.[60] This may reduce physician confidence in the diagnosis and may lead to the underdiagnosis and undertreatment of patients.[36,61]

There have been significant advances since the adoption of EST. Exercise testing to reproduce symptoms will likely remain an important tool to identify and correlate symptoms with activity and ECG changes. Although ECG changes occur later in the ischemia cascade, EST has simplicity, accessibility, and diagnostic and prognostic value, which supports its ongoing use as a pragmatic modality, especially with settings in which more advanced tests may not be readily available.

Exercise and pharmacologic stress

Functional cardiac imaging with echocardiography (ECHO), single photon emission computed tomography (SPECT), positron emission tomography (PET), and cardiac magnetic resonance imaging (CMR) require the concomitant use of a "stressor" (exercise or pharmacologic).

Two distinct approaches can be applied to induce myocardial ischemia: either exercise or pharmacology stress.[62] Exercise stress can be performed with treadmill or bicycle approaches with standardized protocols.[63] During exercise stress, patients are encouraged to exercise until fatigue or limiting symptoms develop. Standardized patient workloads have also been developed using prognostic data to identify patients who are at a low risk for future cardiac events and—by extension—unlikely to have obstructive CAD.[57]

Exercise Stress

Exercise protocols, either with treadmill or bicycle stress, assist in the direct correlation of exertional symptoms to ischemic findings (Table 2).[62,63] This can be helpful for both patients and their physicians. For patients, the ability to exercise to maximum capacity without inducing angina in the safety of a monitored environment can be reassuring and builds confidence. For physicians, when chest pain and typical ischemia features occur during testing, it can affirm the clinical diagnosis and assist in management decisions. Along with symptomatic data, exercise stress protocols also provide ECG and hemodynamic data to supplement imaging findings. The importance of such findings can further risk stratify patients, even in the presence of normal stress echocardiography or nuclear perfusion findings.[57,64] Exercise data may also help to detect other diagnoses for symptoms on exercise such as chronotropic incompetence, hypertensive response to exercise, or low exercise capacity. Exercise testing may not be applicable or practical in some patients. Patients with deconditioning or other physical limitations may not be able to achieve diagnostic heart rate thresholds of exertion. In addition, certain ECG abnormalities, such as left bundle branch morphology, ventricular-paced rhythm, delta waves, or significant resting ST depression may have associated wall-motion or perfusion abnormalities that can be exaggerated by rapid heart rates, precluding accurate interpretation or inducing artifact.[62,63] In the presence of relative or absolute contraindications to exercise stress, pharmacologic agents can be used.

Pharmacologic Stress

Pharmacologic stress can be performed using vasodilator agents or dobutamine (Table 2). Less frequently, combined protocols in nuclear perfusion imaging may use vasodilator stress with low-level treadmill exercise.[62] Three vasodilator agents are currently in clinical use: dipyridamole, adenosine, and regadenoson. These target the A2A adenosine receptors of the coronary vasculature to induce coronary vasodilation.[62]

Vasodilator stressors are less complicated to administer than exercise and dobutamine protocols. They are administered either as a bolus or infusion while the patient is monitored hemodynamically and with a continuous 12-lead ECG. They can facilitate the logistics of patient throughput in large-volume centres, as there are relatively few absolute contraindications, and their administration can be performed in a timely fashion. Absolute contraindications specific to vasodilator stress include second- or third-degree atrioventricular (AV) block without a pacemaker, bronchogenic expiratory wheezing, hypotension < 90 mm Hg systolic, recent use of dipyridamole medications, or known hypersensitivity to vasodilators.[62]

Dobutamine-induced stress is performed through protocols with close hemodynamic and 12-lead ECG monitoring. Dobutamine acts as an agonist at β-1 adrenoreceptors to increase heart rate and myocardial contractility. Contraindications to dobutamine stress for CAD assessment include symptomatic severe aortic stenosis or left ventricular (LV) outflow tract obstruction, uncontrolled atrial arrhythmias, uncontrolled hypertension, aortic dissection, or large aortic aneurysms.[63]

Selecting Exercise vs Pharmacologic Stress

Which stressor is chosen to assess the functional significance of suspected or known CAD depends on the patient, the imaging technique used, local expertise and availability. Patient factors such as specific contraindications to a particular stressor, inability to exercise, or having an abnormal resting ECG are often the starting point in determining choice of stressor. Stress-imaging modality is also a concern; some modalities are limited in their ability to accommodate certain stressor agents. Exercise stress with CMR is currently limited

because of the lack of nonferrous exercise equipment and space constraints within the scanner. Exercise is also limited with PET because of the short half-lives of the available radiotracers; however, phase 3 trials have been completed of a new PET tracer that could be used with exercise in the future. In contrast, exercise stress is preferred for stress echocardiography and SPECT myocardial perfusion imaging when adequate levels of exercise can be attained. Finally, an important determinant in the choice of stressor and imaging modality is local availability and expertise. Not all centres have access to every modality or stressor agent, and the decisions surrounding which test with what type of imaging will reflect the practicalities of what investigations can be performed in an expert manner in a timely fashion.

Stress echocardiography

Given its wide availability, safety, relatively low cost, and wide-ranging applications, echocardiography has evolved into a central role in the assessment of patients with both suspected and known CAD. Stress echocardiography (SE) combines transthoracic imaging with provocative stress protocols and records dynamic myocardial contractility in response to stress. Changes in wall motion are incremental to the clinical, hemodynamic, and electrocardiographic information and have very good diagnostic sensitivity and specificity for the detection of ischemia (Table 2). Treadmill protocols are the most frequently used in SE, but recumbent bicycle and pharmacologic protocols (most commonly dobutamine stress) can be used for patients unable to perform treadmill exercise or for whom the acquisition of imaging or Doppler information at the precise time of peak exertion is required.

When assessing diagnostic accuracy, SE has generally been compared with the results of contemporaneous coronary angiography. This raises issues of selection bias and is fundamentally problematic in that it compares the functional ischemia identified by SE with the anatomic information provided by angiography. However, such comparisons have demonstrated sensitivities and specificities of approximately 85% and 77%, respectively.

SE can also be used to diagnose ischemic mitral regurgitation. Usually performed with bicycle protocols, SE can uncover the full extent of regurgitation and clarify the cause of otherwise unexplained exercise limitation. Similarly, diastolic SE can be used to assess if diastolic dysfunction may explain exertional limitations or symptoms of dyspnea.

Although SE would not replace a complete transthoracic echocardiogram (TTE), resting SE images may identify other potential etiologies of CP, such as valvular heart disease, structural/congenital heart disease, right ventricular dysfunction, pulmonary hypertension, and obstructive hypertrophic cardiomyopathy.

There are no absolute contraindications to SE other than contraindications to the stress modality, but SE is dependent on adequate image acquisition. Therefore, it can be limited by certain patient body habitus, particularly when endocardial border definition is suboptimal. This limitation can be mitigated with the use of contrast agents, which has become more widely available. In addition, the detection of wall-motion abnormalities is demanding both from an image acquisition and interpretive perspective and can be even more challenging when resting regional wall-motion abnormalities are present or in the presence of dyssynchronous ventricular activation, particularly left bundle branch block. SE requires specific training for both sonographers and interpreting physicians and is optimally provided at high-volume facilities in which ongoing comparisons with angiography and other imaging modalities are available.

SPECT myocardial perfusion imaging

Globally, SPECT myocardial perfusion imaging (MPI) remains one of the most common and widely available imaging modalities for the assessment of CAD.[65] SPECT-MPI has high sensitivity, and with its ability to assess myocardial perfusion, wall motion, and LV ejection fraction, it remains a Class I indication for the diagnosis of CAD.[7,12]

As with other functional tests, SPECT should be considered in patients with intermediate and high pretest probability for CAD and in patients with established CAD or following revascularization.[7,12] Both exercise and pharmacologic agents can be used with SPECT, and, when possible, exercise offers advantages over pharmacologic approaches in terms of symptom assessment, image quality, functional capacity, and ischemia sensitivity.[66]

The specificity of SPECT continues to improve.[66] Gated SPECT imaging allows for an assessment of LV function, which is an important determinant of prognosis in CAD.[67] Gated SPECT has also improved the distinction of attenuation artifacts from myocardial ischemia or scar and thus also helped to reduce false positive findings.[68] The adoption of attenuation correction (AC) has reduced susceptibility to artifacts and false-positive interpretations.[69] Low-dose CT images provide incremental information by identifying the presence and extent of CAC. This further improves SPECT-MPI specificity and refines patient risk.[70] Identifying subclinical atherosclerosis with CAC may help with patient risk-factor modification and medical therapy.

Advances have occurred with regard to the detectors in SPECT cameras; recently introduced solid-state cadmium zinc telluride detectors are more sensitive, more efficient, and have better energy resolution than previous sodium iodide crystal detectors.[71] This has enabled radiation dose reduction and scan-time reductions.[72] The use of contemporary technology has reduced patient radiation exposure substantially from 20 mSv to 5-9 mSv at many centres.[66,73,74] Further reduction in radiation exposure has also been possible with stress-only protocols, through the use of AC correction and software applications such as iterative reconstruction.

In addition to promoting low dose imaging, solid state SPECT cameras have allowed for the introduction of SPECT dynamic blood flow imaging and measuring myocardial blood flow (MBF).[75] MBF may improve accuracy of SPECT and help identify patients with "balanced ischemia" and identify patients with inadequate vasodilator response.[68-70] SPECT may be less useful in patients with elevated BMI (> 40 mg/m^2) and patients at greater radiation risk.[50] Despite some limitations, SPECT-MPI has good sensitivity and specificity (Table 2) and remains an important modality used for diagnosis of CAD.[76]

PET-MPI

PET MPI is a powerful, well-validated technique for the assessment of patients with suspected clinically significant CAD. The latest American Heart Association/American College of Cardiology (AHA/ACC) guidelines for chest pain include PET as a Class I recommended modality.[7] It has both high sensitivity and high specificity, as demonstrated in a recent meta-analysis (Table 2), and provides significant prognostic value.[76-83] Image acquisition, either with ^{82}Rb or ^{13}N-NH_3, the 2 most commonly used PET-MPI radiotracers in North America, can be completed in 30 minutes, enabling both patient convenience and rapid patient throughput. This is particularly helpful for patients who find it difficult to remain supine for prolonged periods. Radiation exposure is also low, with effective doses of approximately 2-3 mSv, achievable using the appropriate protocols and modern 3-dimensional (3D)-PET equipment.[84] Although PET-MPI is first and foremost a functional modality, it should be noted that most modern PET systems are hybrid PET-CT systems. These have multiple advantages including fast, reliable attenuation correction and the added ability to assess for the presence of coronary calcification (either qualitative visual assessment or a full calcium score scan). Perhaps the greatest strength of PET-MPI, however, is its ability to quantify MBF and myocardial flow reserve (MFR) routinely and noninvasively.[78,79,83,85] Multiple software packages are now available to facilitate this, and these measurements have been shown to be accurate and reproducible.[86,87] Both regional and global MFR can be assessed. This powerful tool improves accuracy and risk stratification and enables detection of microvascular disease as well as balanced ischemia caused by multivessel obstructive CAD. It also helps validate adequate stressor response.[88] When combined with the other information provided by the test (relative perfusion, coronary calcification, and LV function), this provides the clinician with robust prognostic information.[78-80,83] PET-MPI also has the advantage of not being significantly limited by patient body habitus or being limited by heart rate or renal function.

One important limitation of PET-MPI is that current PET radiotracers have a short half-life and hence are challenging to combine with exercise stress; thus, it is usually performed with pharmacologic stress.[89] Furthermore, exercise PET precludes the measurement of absolute blood flow. An alternative technique using myocardial activity ratios has been described, which could potentially be combined with exercise, but this is currently limited to research and awaits further validation.[90] Therefore, in a patient in whom it is expected that diagnostic exercise stress is possible to assess for obstructive CAD, PET-MPI might not be the best first choice of modality at present. This may change in the future with the use of longer half-life tracers such as ^{18}F-flurperidaz, which—in preliminary studies—have shown promising results.[91-93]

Another group in which PET-MPI might be less evident is the very elderly. Data have suggested that the incremental value of PET-MPI is diminished in patients above 85 years of age.[94] The availability of PET-MPI remains limited in Canada. Although this is not a limitation of the modality itself, it remains an obstacle to its widespread use. Finally, misconceptions about the high cost of PET-MPI should not be seen as a limitation of this technique. Although initial costs for the acquisition of the equipment are high, PET-MPI has been shown to be cost effective, mainly because of a reduction in downstream testing and intervention,[95] and—in the case of ^{82}Rb generators—with fixed costs, cost efficiency can be achieved with greater patient throughput.

In totality, when available, PET-MPI is an excellent choice to assess the significance or cause of cardiac symptoms or the significance of an anatomic lesion in any patient. There is further value added in patients who have had previous equivocal testing; those with body characteristics that might adversely affect other testing modalities, including obesity or the presence of attenuating material (ie, breast implants or implantable cardioverter defibrillators [ICDs]); and in patients with suspected microvascular disease, diffuse CAD, or special populations such as detection of post-transplant vasculopathy.[80,96-98]

CMR imaging

CMR imaging is widely accepted as the gold standard noninvasive imaging modality for the evaluation of myocardial function, quantifying volumes, and characterizing myocardial tissue including ischemic scar. CMR offers a superior temporal and spatial resolution compared with other imaging modalities without the burden of poor acoustic windows, iodinated agents, or ionizing radiation. Stress CMR is an accurate and safe method to assess regional myocardial flow[99] and is a Class I recommended modality for evaluating patients with stable chest pain by the latest American guidelines for the evaluation of chest pain.[7] Stress CMR uses vasodilator agents—such as adenosine, regadenoson, or dipyridamole—to induce hyperemia before a bolus injection of a gadolinium-based agent (GBCA). Serial T1-weighted CMR images are acquired during the first pass of contrast material as the GBCA permeates through the myocardium. Myocardial signal is attenuated in abnormally perfused segments compared with normal segments at peak hyperemia. These stress images are sometimes compared with corresponding "resting" images to confirm inducible hypoperfusion. Myocardial scar (ischemic and nonischemic) is also assessed following perfusion, adding to the diagnostic yield of the study. In addition, for patients with previous myocardial infarction, the transmural extent of ischemic scar provides important information on myocardial viability and potential survival with surgical revascularization.[100-102]

Several prospective trials and meta-analyses confirm good diagnostic accuracy of stress CMR for the detection of CAD for both single-vessel (sensitivity 79%, specificity of 87%) and multivessel disease (sensitivity 87%, specificity 73%).[103] Stress CMR has also outperformed other imaging modalities when referenced FFR for per-patient (sensitivity 90%, specificity 94%) and per vessel (sensitivity 91%, specificity 85%)[99] and demonstrates an excellent positive predictive value (91%) and negative predictive value (94%) for the detection of significant CAD as defined by FFR.[104] Importantly, stress CMR is less susceptible to a false-negative result when investigating "balanced ischemia." Overall, the available data suggest that a negative stress CMR is associated with a $< 1\%$ annualized event rate[105,106] and results in a lower probability of unnecessary invasive coronary angiography.[107]

However, stress CMR may present a number of challenges in clinical practice including accessibility; difficulty performing exercise-based perfusion; claustrophobia; and left-sided implantable devices, hindering image quality.[108] There is also a relative lack of data on prognosis compared with other cardiac imaging modalities evaluating patients with CAD. Although at many centres renal dysfunction is no longer a barrier to administration of contrast material with newer macrocyclic GBCA, discussion with an imaging expert may be required.[108] Future progress in stress CMR is needed for streamlining clinical protocols, elaborating tools allowing the quantification of perfusion, and developing noncontrast-material approaches to perfusion (eg, blood oxygenation level-dependent imaging).

Decision Support Tool/Algorithm

With all the available diagnostic modalities, test selection can be difficult, especially as it requires the integration of patient factors, test accuracy (Table 2), contraindications (Table 3), technology (strengths and limitations), and local factors (local expertise and available technology). Although developing algorithms and decision support tools may assist clinicians in selecting an "ideal strategy," they are potentially limited by factors that cannot be well measured or quantified. Local expertise, available technology (hardware and software), costs, wait-times, and previous testing results should be factored when selecting the most appropriate test. Also, the other influences on diagnostic accuracy include technologic factors such as the use of contrast material with stress echocardiography, the use of cadmium zinc telluride detectors and attenuation correction with SPECT, different radiotracers, and time-of-flight with PET, 1.5 or 3T with magnetic resonance imaging (MRI) and single-source vs dual-source CT scanners. It would be difficult to account for all variability within a single decision support tool.

Despite the potential limitations, a decision support tool was designed to identify the test options most appropriate for each individual patient scenario to improve diagnostic accuracy, to minimize unnecessary downstream costs or resource utilization, and to avoid inappropriate repetitive testing.

Creating decision support tools are complex and difficult and likely explains the absence of a widely adopted tool for CAD testing. A decision support tool was developed (www.chowmd.ca/cadtesting) using the strengths and weakness of each modality and a Delphi technique that leveraged the knowledge of leading experts in cardiology and cardiac imaging. Such a decision support tool can be helpful for clinicians faced with numerous patient, technical, and facility factors to consider if it incorporates all pertinent variables. Patient factors that should be considered include age, sex, body habitus, typicality of chest pain, cardiac risk factors including family history of premature CAD, history of known CAD +/− revascularization modality, resting heart rate, presence of significant renal dysfunction, and previous testing results. In addition, patient contraindications to individual tests need to be considered (Table 3). When more than 1 option is appropriate, the final test selected should reflect local expertise, available local technology, and wait-times.

Conclusions

Choosing the best test for investigating patients with chest pain or discomfort can be challenging but should ideally be tailored to each individual, the local availability and expertise, and strengths and limitations of each diagnostic modality. A decision support tool was developed (www.chowmd.ca/cadtesting) that may be used to identify appropriate tests that would be diagnostic and feasible, while minimizing inappropriate downstream resource use and costs.

Ethics Statement

Ethics approval was not required for this review.

Patient Consent

The authors confirm that patient consent is not applicable. Patient consent was not needed as images were provided from different centres across Canada and were anonymized. The corresponding author does not have ways of identifying each individual patient

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Supplementary Material

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