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ACR Appropriateness Criteria® Chronic Chest Pain—High Probability of Coronary Artery Disease

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Imaging is valuable in determining the presence, extent, and severity of myocardial ischemia and the severity of obstructive coronary lesions in patients with chronic chest pain in the setting of high probability of coronary artery disease. Imaging is critical for defining patients best suited for medical therapy or intervention, and findings can be used to predict long-term prognosis and the likely benefit from various therapeutic options. Chest radiography, radionuclide single photon-emission CT, radionuclide ventriculography, and conventional coronary angiography are the imaging modalities historically used in evaluating suspected chronic myocardial ischemia. Stress echocardiography, PET, cardiac MRI, and multidetector cardiac CT have all been more recently shown to be valuable in the evaluation of ischemic heart disease. Other imaging techniques may be helpful in those patients who do not present with signs classic for angina pectoris or in those patients who do not respond as expected to standard management. The ACR Appropriateness Criteria® are evidence-based guidelines for specific clinical conditions that are reviewed every 2 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances in which evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

Key Words: Appropriateness Criteria, myocardial ischemia, coronary artery disease, cardiac magnetic resonance imaging, multidetector cardiac CT, radionuclide single photon-emission CT

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The ACR seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria® through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply society endorsement of the final document.

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SUMMARY OF LITERATURE REVIEW

Chronic chest pain of suspected cardiac origin is usually a consequence of myocardial ischemia, representing an imbalance between myocardial oxygen demand and coronary blood flow. This is usually caused by fixed, hemodynamically significant coronary stenosis due to atherosclerotic plaque formation leading to reduced myocardial perfusion, which can also be caused by coronary spasm, microvascular disease, or a combination of both. In the setting of high probability of coronary artery disease (CAD), flow-limiting epicardial coronary artery narrowing is likely. However, chest pain of myocardial ischemic origin can also occur in patients with relatively normal coronary arterial caliber but with conditions resulting in increased demand for oxygenation (eg, increased myocardial mass and workload due to systemic arterial hypertension or aortic stenosis). Although the syndrome of exertional angina pectoris is nearly always diagnostic of chronic CAD, nonischemic cardiac (eg, myocarditis, pericarditis) and extracardiac (eg, esophageal reflux or spasm) etiologies should also be considered in the setting of nonexertional or atypical chest pain.

In patients with chronic chest pain in the setting of high probability of CAD, imaging has major and diverse roles. First, imaging is valuable in determining and documenting the presence, extent, and severity of myocardial ischemia, hibernation, and scarring, on one hand, or the presence, site, and severity of obstructive coronary lesions on the other. Second, imaging findings are important in determining the course of management of patients with suspected chronic myocardial ischemia as well as for defining those patients best suited for medical therapy, angioplasty or stenting, or surgery. Third, imaging is also necessary to evaluate ventricular function and end-systolic volume, both of which are important in predicting the long-term prognosis and likely benefit from various therapeutic options. Imaging studies are also required to demonstrate abnormalities (eg, congenital or acquired coronary anomalies, severe left ventricular hypertrophy) that can produce angina in the absence of coronary obstructive disease due to atherosclerosis.

The imaging modalities historically used in evaluating suspected chronic myocardial ischemia are (1) chest radiography, (2) stress and rest radionuclide single photon-emission CT (SPECT) myocardial perfusion imaging (MPI), (3) radionuclide ventriculography with and without stress, and (4) catheter-based selective coronary angiography with or without left ventriculography. Stress echocardiography, PET, cardiac MRI, and multidetector cardiac CT have all been more recently shown to be valuable in the evaluation of ischemic heart disease (see Variant 1). In those patients who do not present with signs classic for angina pectoris, or in those patients who do not respond as expected to standard management, the exclusion of noncardiac causes of chronic chest pain requires the use of additional studies (eg, esophagography, upper gastrointestinal series, and biliary ultrasound).

Chest Radiography

Chest radiography is an inexpensive test that can rapidly demonstrate many noncardiac causes of chronic chest pain, including a variety of diseases of the mediastinum, pleura, or lung. It may also provide qualitative indirect information about left ventricular function as reflected in cardiac size and pulmonary vascular patterns (eg, pulmonary venous hypertension) [1]. However, chest radiography can neither establish nor exclude chronic ischemic heart disease. In addition, it (including fluoroscopy) is insensitive for the detecting coronary arterial calcification [2]. Chest radiography, therefore, is of limited value in symptomatic patients with high risk for CAD.

Imaging of Myocardium

SPECT. Stress SPECT MPI demonstrates relative myocardial perfusion defects, indicating the presence of myocardial ischemia. For this reason, it is considered an important first-line study in the evaluation of patients with chronic chest pain and high likelihood of CAD. By acquiring rest and stress perfusion scans, it is possible to demonstrate reversibility (ischemia) or irreversibility (infarction) of a myocardial perfusion defect. The territory of the perfusion defect identifies the likely culprit coronary artery and can distinguish between significant single-vessel and multivessel coronary arterial obstructions [3-12]. The magnitude of the abnormality and the presence of high-risk findings also assist in clinical decision making [13,14].

Presently, SPECT perfusion agents labeled with ^{99m}Tc, such as ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin, are used most commonly because of improved image resolution, higher count density, and more favorable dosimetry. The sensitivity and specificity of ^{99m}Tc SPECT in detecting CAD are equal to and usually superior to those of ^{201}Tl [15]. With the use of electrocardiographic gating, and with improved imaging protocols and image quality, the diagnostic accuracy of stress SPECT MPI for detecting angiographically significant CAD is high (sensitivity, 87%-89%; specificity, 73%-75%) [16]. More important, normal stress SPECT MPI results in patients with intermediate to high likelihood of CAD predicts a very low rate of cardiac death or nonfatal myocardial infarction (≤1% per year) [17]. Furthermore, SPECT MPI may be used for risk stratification in scenarios such as follow-up after percutaneous coronary intervention and coronary artery bypass grafting or evaluation before noncardiac surgery. Limitations of stress SPECT MPI are its relatively high cost and relatively high radiation dose.

Recently, new software algorithms such as iterative reconstruction, maximum a posteriori noise regularization, and resolution recovery, as well as new hardware

Table 1. Chronic Chest Pain — High Probability of CAD

Radiologic Procedure	Rating	Comments	Relative Radiation Level
SPECT MPI rest and stress	9	Strongest evidence. Fundamental test for reversible and irreversible ischemic disease. Can segregate out those who need next study (ie, coronary artery angiography). Fused SPECT and CCTA can accurately measure plaque burden and identify the hemodynamic functional significance of coronary stenoses.	☢☢☢☢
Arteriography coronary	8	Consider if high probability of CAD intervention is contemplated, and/or noninvasive studies are equivocal. In setting of high probability, provides opportunity to intervene.	☢☢☢
^{82}Rb PET heart stress	8	PET perfusion imaging has advantages over SPECT, including higher spatial and temporal resolution. Routine performance of both PET and SPECT not necessary. Fused PET and CCTA can accurately measure plaque burden and identify the hemodynamic functional significance of coronary stenoses.	☢☢☢
Ultrasound echocardiography transthoracic stress	8	Similar sensitivity to stress SPECT MPI but has advantage of no radiation. Some limitations due to LV anatomy, acoustic window, body habitus, and experience of the physician.	O
CTA coronary arteries with contrast	7	Very good accuracy and negative predictive value in low-risk to intermediate-risk groups. However, may have false-negatives in high-risk group, and negative studies may still require further diagnostic testing. Coronary calcification often found in older high-risk patients (especially males) can limit coronary luminal assessment.	☢☢☢☢
MRI heart with stress, with or without contrast	7	Accuracy equivalent or superior to stress SPECT MPI. Diagnoses hemodynamically significant CAD in patients with intermediate to high likelihood of having significant stenosis. Higher diagnostic accuracy than stress echocardiography. See statement regarding contrast in text under “Anticipated Exceptions.”	O
MRI heart function and morphology, with or without contrast	5	Versatile, used to evaluate anatomy, function, valvular disease, cardiomyopathies, and myocardial viability. Subendocardial scar with or without wall motion abnormalities supports diagnosis of CAD. Used before revascularization to evaluate viability. See statement regarding contrast in text under “Anticipated Exceptions.”	O
Ultrasound echocardiography transthoracic resting	4	Incomplete examination for high CAD risk, unless with stress, even if other etiologies may be present. May evaluate aortic and pericardial disease, valve and chamber abnormalities.	O
X-ray chest	3	Usual initial imaging study in cardiac patients. Although used frequently, chest radiography can neither establish nor exclude chronic ischemic heart disease. Insensitive for detecting coronary arterial calcification [1]. Limited value in patients with high risk for CAD.	☢
CT coronary calcium	3	Little value for defining cause of chronic chest pain in a particular patient. Cannot exclude significant disease even if negative; high scores suggest significant chronic coronary atherosclerotic plaque load but cannot identify the vessels implicated.	☢☢☢
CT chest with contrast	3	Excludes many noncardiac causes of chest pain. May diagnose source of pain such as pulmonary embolism, dissection, unstable LV aneurysms, etc.	☢☢☢
MRA coronary arteries	3	Useful in some cases but too many nonassessable segments given current technology. Less sensitive for disease beyond the proximal main branches.	O
Radionuclide ventriculography	2	Rarely still performed, largely unavailable, with limited expertise. Stress ventriculography can be combined with SPECT MPI.	☢☢☢
Ultrasound abdomen	1	Little value in this setting. Occasionally used when atypical chest pain raises suspicion of biliary disease.	O
CTA coronary arteries with contrast with advanced low-dose techniques	No consensus	Although there is growing evidence in support of use of these low–radiation dose CCTA techniques rather than traditional CCTA techniques, evidence of their applicability to patients with chronic chest pain and high probability of CAD is not yet adequate.	☢☢☢

Note: Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate. CAD = coronary artery disease; CCTA = coronary CT angiography; CTA = CT angiography; LV = left ventricular; MRA = MR angiography.

and detector materials, have become available, allowing image acquisitions at significantly shorter acquisition times (one-fifth to one-half) or alternatively at lower doses compared with conventional algorithms [18,19].

Stress radionuclide ventriculography consists of measurement of the ejection fraction and assessment of regional wall motion at rest and during stress. This technique can be used to identify patients with "balanced" 3-vessel disease, which can be missed on perfusion studies, as well as for differentiating attenuation artifacts from myocardial infarction [9]. Stress ejection fraction has also been shown to be an independent predictor of the risk for cardiac death [20,21]. However, radionuclide ventriculography is rarely used because it has largely been replaced by SPECT MPI; hence, the availability of and expertise with this method are very limited. In patients with typical angina (high pretest likelihood of disease), stress SPECT MPI is useful for estimating the extent (single-vessel vs multivessel disease) and severity of coronary stenosis, which has relevance for prognosis, choice among therapeutic options, and advisability of performing coronary arteriography.

PET. Myocardial PET imaging using ^{82}Rb or ^{13}N ammonium for assessing perfusion, or ^{18}F-2-fluoro-2-deoxy-D-glucose for evaluating metabolism, is now recognized as a useful method for the evaluation of ischemic heart disease. PET perfusion imaging has several advantages over SPECT, including higher spatial and temporal resolution, superior attenuation and scatter correction, and the capability to perform quantitative measurements. In a meta-analysis of 8 studies with 791 patients evaluated for CAD by PET perfusion imaging, overall sensitivity and specificity were determined to be 93% and 92%, respectively [22]. In the same article, 3 studies comparing ^{201}Tl SPECT with ^{82}Rb or ^{13}N ammonium PET were analyzed, and the overall accuracy of PET was 91%, compared with 81% for ^{201}Tl SPECT. Gated PET also provides assessment of left ventricular function and overall provides important diagnostic and prognostic data [23].

Newer hybrid PET scanners use CT for attenuation correction (PET/CT). After the completion of the PET study, coronary CT angiography (CCTA) can be performed. By coupling the PET perfusion examination findings to CCTA, PET/CT permits the fusion of anatomic coronary arterial and functional (perfusion) myocardial information and enhances diagnostic accuracy [24]. The fused examinations can accurately measure the atherosclerotic burden and identify the hemodynamic functional significance of coronary stenoses [25,26]. The results of the combined examinations can more accurately identify patients for revascularization [26]. In a study of 110 consecutive patients with combined stress ^{82}Rb PET perfusion imaging and CCTA, nearly half of significant angiographic stenoses (47%) occurred without evidence of ischemia, whereas 50% of PET studies with normal results were associated with some abnormality on CCTA [25].

Echocardiography. Stress 2-D echocardiography for contractility assessment is increasingly used for patients with suspected regional wall motion abnormalities secondary to regional ischemia, in part because of the ubiquity of 2-D echocardiography. When exercise is not feasible, pharmacologic stress echocardiography may be performed. A recent meta-analysis of 44 studies indicated that stress echocardiography has similar sensitivity to stress SPECT MPI (85% and 87%, respectively), with higher specificity (77% vs 64%) [27].

Administration of an echocardiographic contrast agent (ie, microbubbles) improves endocardial visualization at rest and more so during stress, leading to a higher confidence of interpretation and greater accuracy in evaluating CAD [28]. According to a recent meta-analysis of 435 patients, dipyridamole and dobutamine stress contractility echocardiography had similar accuracy, specificity, and sensitivity for detecting CAD [29]. This technique is limited by the fact that it sometimes yields nondiagnostic results and that suboptimal definition of some regions of the left ventricle can lead to subjective interpretation.

Resting transthoracic echocardiography can be useful if pericardial effusion or valvular or chamber abnormalities are suspected. Transesophageal echocardiography is generally not indicated for evaluating chronic angina; the expense of this study does not justify its use in this setting. However, it is sometimes used for assessing aortic pathology (eg, dissection, aneurysm, penetrating ulcer) in patients with chronic chest pain, although CT and MRI are less invasive and simpler to perform.

MRI. The use of MRI for evaluating general cardiac anatomy and function, and specific aspects of valvular disease, cardiomyopathies, myocardial viability, continues to evolve.

MRI myocardial perfusion techniques can be used to assess for significant CAD. The diagnostic accuracy of stress perfusion MRI has been evaluated in many studies and has been found to be equivalent, and in many cases superior, to stress SPECT MPI [30-40]. A recent meta-analysis of 37 studies with 2,191 patients undergoing both exercise and dobutamine stress MRI contractility evaluation and dipyridamole and adenosine MRI perfusion assessment found that imaging of stress-induced wall motion abnormalities had sensitivity of 83% and specificity of 86%; perfusion imaging demonstrated sensitivity of 91% and specificity of 81% [41].

Clinically, stress perfusion MRI has been used to diagnose hemodynamically significant CAD in patients with intermediate to high likelihood of having significant stenosis. Commonly, the technique is used in patients with poor acoustic windows that would be likely to limit the utility of stress echocardiography [42], and it has been shown to have higher diagnostic accuracy than dobutamine stress echocardiography [42,43]. The addition of delayed-enhancement MRI using a gadolinium agent is superior to stress perfusion MRI alone for detecting CAD [44]. In patients with poor echocardiographic examinations, dobutamine stress MRI can be used to forecast myocardial infarction or cardiac death [45].

However, MRI is not suitable for evaluating individual patients with chronic chest pain with high probability of CAD in the setting of implanted electronic devices (eg, permanent pacemakers, implantable cardioverter defibrillators). In addition, general reliance on MRI in assessing chronic chest pain is hindered by the limited availability of advanced facilities and experienced personnel.

Imaging of Coronary Arteries

CT. Multidetector CT as well as electron-beam CT can detect the presence and severity of calcification, a sign of coronary atherosclerosis [46-53]. The coronary calcium score is most commonly used for risk stratification in asymptomatic patients. The absence of coronary calcification is useful evidence against myocardial ischemia [46]. In a large study of 10,377 subjects, it was shown that coronary calcium score provides independent incremental information in addition to traditional risk factors in the prediction of all-cause mortality [54]. On the other hand, patients who present with chronic chest pain of suspected cardiac origin are typically older, with a significant proportion aged > 60 years. Because coronary calcium is so prevalent in this population, a "positive" coronary calcium score, even in the upper quartiles, cannot be used as strong evidence of myocardial ischemia.

There is also increasing use of CCTA, specifically contrast-enhanced electrocardiographically gated multidetector CT, to evaluate for CAD. Studies using 64-slice CCTA have shown high sensitivity and high negative predictive value (NPV) for treatable stenoses of the coronary arteries [55-57]. A recent meta-analysis to evaluate the diagnostic accuracy of 64-slice CCTA compared with conventional selective coronary angiography included 27 studies and 1,740 patients and found sensitivity, specificity, positive predictive value, and NPV of 86%, 96%, 83%, and 96.5%, respectively, by per segment analysis, and 97.5%, 91%, 93%, and 96.5%, respectively, by per patient analysis [58]. The 64-slice CCTA Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography trial found 95% sensitivity, 83% specificity, 64% positive predictive value, and 99% NPV [59].

The pretest probability of CAD affects the diagnostic performance of CCTA. The NPV of CCTA is significantly lower in patients with a high prevalence of CAD, and negative results on CCTA only reduce the estimated posttest probability of having obstructive disease to approximately 17% [60,61]. Because of this high residual posttest probability despite negative results on CCTA, many symptomatic high-probability patients are likely to still require invasive selective coronary angiography. Coronary CT angiography, therefore, may be of limited clinical value in the evaluation of the group with high estimated pretest probability. There is also continuing concern about the high radiation exposure with CCTA, which has led to new dose-limited protocols.

Recent advances in cardiac CT imaging technology allow further reduction of the radiation dose from CCTA [62]; available new dose-reducing techniques include prospective triggering [63-65], adaptive statistical iterative reconstruction [66], and high-pitch spiral acquisition [67]. However, these newer low-dose techniques may not be the appropriate choice in all patients because of their dependency on a combination of factors, including heart rate, rhythm, and clinical indication. Thus, although these techniques are promising in terms of reducing patient radiation dose, their overall accuracy and utility compared with standard coronary CT angiographic techniques are not yet completely defined.

MR Angiography (MRA). Although MRA of the pulmonary and systemic vessels has matured significantly in the past few years, MRA of the coronary arteries is still problematic because of their small size and incessant motion tied to the respiratory and cardiac cycles. At this time, coronary MRA should be limited to sites with extensive experience and appropriate capabilities to exclude disease in the proximal coronary arteries. At present, only CCTA can noninvasively visualize coronary arteries on a routine basis; in direct comparison, coronary MRA had similar sensitivity but significantly lower specificity and accuracy compared with CCTA [68].

Selective Coronary Angiography

Catheter-based selective coronary angiography remains the coronary imaging modality with the highest spatial and temporal resolution. Thus, although only projection images are obtained (as opposed to 3-D volumes on CCTA), selective coronary angiography is considered the gold standard for depicting the anatomy and the severity of obstructive CAD and some other coronary arterial abnormalities (eg, spasm) [69]. Moreover, it is needed to guide transluminal interventions.

There remains agreement that selective coronary angiography is indicated in patients in whom angina is not adequately managed by vigorous medical therapy and in those in whom left main stenosis or severe multivessel CAD is suggested by results of stress SPECT MPI or stress echocardiography.

Left ventricular catheterization and left ventriculography are generally indicated, but not always necessary, to define ventricular function in patients with angina. In many patients, left ventricular function can be evaluated better using noninvasive studies (eg, echocardiography, MRI).

Other diagnostic studies, such as hepatobiliary ultrasound, should be considered only after a cardiac etiology has been accurately excluded, using the imaging modalities and clinical evaluation described above.

SUMMARY

- The approach defined here for evaluating patients with chronic chest pain of probable cardiac origin is supported by a substantial body of literature.
- Stress SPECT MPI, stress PET, and stress echocardiography are used as frontline modalities to establish the diagnosis and assess the severity of myocardial ischemia.
- On the basis of the results of stress SPECT MPI, stress PET, or stress echocardiography or a patient's clinical response to medical therapy, the next procedure is usually selective coronary angiography.
- Given the underlying high prevalence of CAD in this patient population, the substitution of newer examinations (eg, MRI, CCTA) is promising for diagnosis but awaits the results of comparative studies and cost analysis. Their value may be seen in therapeutic planning (eg, myocardial "viability" assessment using MRI for evaluating myocardial perfusion, contraction, and scarring).

ANTICIPATED EXCEPTIONS

Nephrogenic systemic fibrosis is a disorder with a scleroderma-like presentation and a spectrum of manifestations that can range from limited clinical sequelae to fatality. It seems to be related to both underlying severe renal dysfunction and the administration of gadolinium-based contrast agents. It has occurred primarily in patients on dialysis, rarely in patients with very limited glomerular filtration rates (ie, <30 mL/min/1.73 m^2), and almost never in other patients. There is growing literature regarding nephrogenic systemic fibrosis. Although some controversy and lack of clarity remain, there is a consensus that it is advisable to avoid all gadolinium-based contrast agents in dialysis-dependent patients unless the possible benefits clearly outweigh the risk and to limit the type and amount in patients with estimated glomerular filtration rates < 30 mL/min/1.73 m^2. For more information, please see the ACR's *Manual on Contrast Media* [70].

RELATIVE RADIATION LEVEL INFORMATION

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, an relative radiation level indication has been included for each imaging examination. The relative radiation levels are based on effective dose, which is a radiation dose quantity that is used to estimate a population's total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the relative radiation level dose estimate ranges for pediatric examinations are compared with those specified for adults (Table 2). Additional information regarding radiation dose assessment for imaging examinations can be found in *ACR Appropriateness Criteria®: Radiation Dose Assessment Introduction* [71].

Table 2. Relative radiation level designations

Relative Radiation Level	Adult Effective Dose Estimate Range (mSv)	Pediatric Effective Dose Estimate Range (mSv)
O	0	0
☢	<0.1	<0.03
☢☢	0.1-1	0.03-0.3
☢☢☢	1-10	0.3-3
☢☢☢☢	10-30	3-10
☢☢☢☢☢	30-100	10-30

Note: Relative radiation level assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The relative radiation levels for these examinations are designated as not specified.

For additional information on ACR Appropriateness Criteria®, refer to http://www.acr.org/ac.

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