ACR Appropriateness Criteria Chronic Chest Pain—Low to Intermediate Probability of Coronary Artery Disease

Pamela K. Woodard, MD[a], Richard D. White, MD[b], Suhny Abbara, MD[c], Philip A. Araoz, MD[d], Ricardo C. Cury, MD[e], Sharmila Dorbala, MD[f,g], James P. Earls, MD[h], Udo Hoffmann, MD, MPH[i], Joe Y. Hsu, MD[j], Jill E. Jacobs, MD[k], Cylen Javidan-Nejad, MD[l], Rajesh Krishnamurthy, MD[m], Leena Mammen, MD[n], Edward T. Martin, MD[o,p], Thomas Ryan, MD[p,q], Amar B. Shah, MD[r], Robert M. Steiner, MD[s], Jens Vogel-Claussen, MD[t], Charles S. White, MD[u]

Chronic chest pain can arise from a variety of etiologies. However, of those potential causes, the most life-threatening include cardiac disease. Chronic cardiac chest pain may be caused either by ischemia or atherosclerotic coronary artery disease or by other cardiac-related etiologies, such as pericardial disease. To consider in patients, especially those who are at low risk for coronary artery disease, are etiologies of chronic noncardiac chest pain. Noncardiac chest pain is most commonly related to gastroesophageal reflux disease or other esophageal diseases. Alternatively, it may be related to costochondritis, arthritic or degenerative diseases, old trauma, primary or metastatic tumors, or pleural disease. Rarely, noncardiac chest pain may be referred pain from organ systems below the diaphragm, such as the gallbladder.

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, chronic chest pain, low probability of coronary artery disease, intermediate probability of coronary artery disease

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[a]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, Missouri.

[b]The Ohio State University College of Medicine, Columbus, Ohio.

[c]Massachusetts General Hospital, Boston, Massachusetts.

[d]Mayo Clinic, Rochester, Minnesota.

[e]Baptist Hospital of Miami, Kendall, Florida.

[f]Brigham and Women's Hospital, Boston, Massachusetts.

[g]Society of Nuclear Medicine and Molecular Imaging, Reston, Virginia.

[h]Fairfax Radiological Consultants, Fairfax, Virginia.

[i]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

[j]Kaiser Permanente, Los Angeles, California.

[k]New York University Medical Center, New York, New York.

[l]Washington University School of Medicine, St Louis, Missouri.

[m]Texas Children's Hospital, Houston, Texas.

[n]Advanced Radiology Services, Grand Rapids, Michigan.

[o]Oklahoma Heart Institute, Tulsa, Oklahoma.

[p]American College of Cardiology, Washington, District of Columbia.

[q]The Ohio State University Heart and Vascular Center, Columbus, Ohio.

[r]Westchester Medical Center, Valhalla, New York.

[s]Temple University Health System, Philadelphia, Pennsylvania.

[t]Johns Hopkins Hospital, Baltimore, Maryland.

[u]University of Maryland Hospital, Baltimore, Maryland.

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SUMMARY OF LITERATURE REVIEW

Chronic chest pain can arise from a variety of etiologies. However, of those potential causes, the most threatening is cardiac disease. Chronic noncardiac chest pain (nCCP) is most commonly related to gastroesophageal reflux disease (GERD) or other esophageal diseases [1]. Alternatively, it may be related to costochondritis, arthritic or degenerative diseases, old trauma, primary or metastatic tumors, or pleural disease. Rarely, nCCP may be referred pain from organ systems below the diaphragm, such as the gallbladder.

Nevertheless, cardiac disease must be a primary consideration during the evaluation of chronic chest pain. Chronic cardiac chest pain (CCP) may be caused by either atherosclerotic coronary artery disease (CAD) or other cardiac-related etiologies. The latter include ischemic syndromes in the absence of epicardial CAD as well as nonischemic cardiac pain. Some causes of non-CAD-related ischemia include aortic stenosis, hypertrophic cardiomyopathy [2], uncontrolled hypertension [3], interarterial anomalous coronary artery, and syndrome X [4,5]. Nonischemic etiologies of chronic CCP are most commonly related to the pericardium and include chronic pericarditis or primary or metastatic tumors.

In evaluating a patient presenting with chronic chest pain, a clinician must first determine the clinical probability of CAD, defined as the likelihood of having a >50% coronary stenosis. This is done by judging whether the chest pain is typical angina, atypical angina, or "noncardiac" and comparing it with the patient's age and gender according to previously reported findings [6,7]. Typical angina is characterized by substernal chest pain or discomfort that is provoked by exertion or emotional stress and relieved by rest or nitroglycerin [7]. However, a history of atypical angina (chest pain or discomfort that lacks one of the characteristics of typical angina [7]) may also be given.

To estimate a patient's probability of CAD, a history and physical examination, including laboratory tests for diabetes and hyperlipidemia and resting electrocardiography, are of value [4]. Patients whose age, gender, and type of chest pain indicate a high to intermediate probability of CAD should undergo a stress physiologic assessment: an exercise treadmill test, a stress nuclear medicine myocardial perfusion imaging (MPI) examination, or stress echocardiography for contractility assessment [8]. If the results of any of these are positive in a patient with symptoms indicating a high probability of CAD, coronary catheterization angiography should be considered. In some cases, however, a patient with stable angina may be treated medically [9].

In a patient with intermediate probability of CAD and positive results on stress imaging, multidetector coronary CT angiography (CCTA) or coronary catheterization angiography can be performed for direct coronary artery evaluation [10]. In patients unable to either exercise or receive pharmacologic stress agents, CCTA may be performed in lieu of stress imaging examinations. Those patients with a low probability of CAD and those in whom CAD has been excluded should be further evaluated for alternative causes of their chest pain. Screening chest radiography may be used to further narrow potential etiologies in these low-risk patients.

Guidelines exist in the literature for diagnosing chronic stable angina (ischemia-related chest pain) [11], yet there are no significant literature presentations of diagnostic algorithms that consider patients with chronic chest pain of determined nonischemic etiology. There are procedure-related reports that include such patients [12,13], but no randomized controlled trial to provide an evidence-based practice is available. When to order chest radiography, chest CT, barium swallow, bone scan, or virtually any diagnostic imaging in patients with chronic nCCP is poorly documented. As a result, the ordering of diagnostic tests is governed by the impression of the primary physician.

Approach to Patients With Chronic Chest Pain

In general, chronic chest pain is defined as chest discomfort that does not change over a period of time; it may wax and wane, but the intensity and duration generally show little change. For this reason, acute coronary syndrome, myocardial infarction, and aortic dissection are not considered in the differential diagnosis (Table 1).

However, findings of chronic chest pain may represent underlying CAD. A great many patients present with what has been characterized as "atypical chest pain." Moreover, 1-year mortality among patients with nonspecific or atypical chest pain has been shown to be higher than in control subjects [14]. For this reason, evaluation for CAD should be undertaken in patients with chronic chest pain in the setting of intermediate to high pretest probability of CAD. The principal imaging test used is stress single-photon emission CT (SPECT) MPI [15]. The intervention performed with a SPECT MPI scan is either exercise or pharmacologically induced to invoke perfusion or contraction abnormalities.

Overall, stress echocardiography is competitive with SPECT MPI. When echocardiography is performed, stress contraction abnormalities are induced by either exercise or inotropic stimulation (ie, dobutamine). In

sentation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

Dr Araoz performs core laboratory analysis for Medtronic, Inc (Minneapolis, Minnesota). Dr Cury is a consultant for Astellas Pharma US Inc (Northbrook, Illinois) and has received research grants from Astellas Pharma US Inc and GE Healthcare (Milwaukee, Wisconsin). Dr Dorbala has received a research grant from Astellas Pharma US Inc and is funded by a K23 grant from the National Institutes of Health (Bethesda, Maryland).

Corresponding author and reprints: Pamela K. Woodard, MD, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191; e-mail: woodardp@mir.wustl.edu.

Table 1. Clinical condition: chronic chest pain—low to intermediate probability of coronary artery disease

Radiologic Procedure	Rating	Comments	Relative Radiation Level
X-ray chest	9		☢
Ultrasound echocardiography transthoracic stress	8	To exclude ischemic cardiac disease.	O
SPECT MPI rest and stress	8	To exclude ischemic cardiac disease.	☢☢☢☢
CTA chest (noncoronary) with contrast	8	For pulmonary embolism and thoracic aortic aneurysm/dissection. To rule out pulmonary embolism and evaluate lung pathology.	☢☢☢
CTA coronary arteries with contrast	8	Can be used to assess for coronary atherosclerosis, anomalous coronary artery, and pericardial disease. High negative predictive value will exclude coronary artery disease and allow triage management to focus on more likely diagnoses. To eliminate unnecessary catheterizations.	☢☢☢☢
MRI heart with stress without and with contrast	8	Can be used in patients with poor echocardiographic window or indeterminate stress test results. See statement regarding contrast in text under “Anticipated Exceptions.”	O
CTA coronary arteries with contrast low-dose	8	Especially useful in younger patients in whom anomalous coronary artery is being considered.	☢☢☢
^{82}Rb PET heart stress	8	N-13 ammonia may be used if a cyclotron is available.	☢☢☢
MRI heart with stress without contrast	6	Dobutamine MRI heart stress test might be used in patients with poor echocardiography window or indeterminate stress test. Useful when MRI is desired but renal insufficiency precludes the use of gadolinium-based MRI contrast agents. Availability limited to centers with expertise.	O
X-ray barium swallow and upper GI series	6	If gastroesophageal reflux, esophagitis, achalasia, or esophageal tumor is considered a likely source of chest pain, the indication is higher.	☢☢☢
Ultrasound echocardiography transthoracic resting	6	Can be used to assess for valve disease or pericardial disease as a cause for chronic chest pain.	O
Ultrasound abdomen	6	If referred chest pain is thought to be caused by cholecystitis, stones, or biliary disease.	O
CT chest without contrast	6		☢☢☢
Coronary angiography with ventriculography	6	If ischemic cardiac disease remains in the differential diagnosis.	☢☢☢
MRI heart function and morphology without and with contrast	4	For determination of constrictive pericarditis. See statement regarding contrast in text under “Anticipated Exceptions.”	O
Ultrasound echocardiography transesophageal	4	If TTE is inadequate and there is no suspicion of esophageal disease.	O
^{99m}Tc V/Q scan lung	4	May be used in patients with suspected chronic pulmonary embolism in patients with iodinated contrast contraindications.	☢☢☢
^{99m}Tc 3-phase bone scan area of interest	4		☢☢☢
Arteriography pulmonary	4	If CT or V/Q scan imaging is inadequate and chronic pulmonary embolism is the principal suspected etiology or if concurrent pulmonary arterial pressures are to be obtained.	☢☢☢☢
MRI heart function and morphology without contrast	3	For determination of constrictive pericarditis. If contrast cannot be given.	O
MRI chest without and with contrast	3	Possibly for chronic pulmonary embolism in patients unable to undergo chest CTA.	O
CT coronary calcium	3	May be used in patient risk stratification. Zero score alone cannot be used to exclude ischemia.	☢☢☢
MRI chest without contrast	2	For noncardiac etiologies, including pleural disease.	O

Note: Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate. CTA = CT angiography; GI = gastrointestinal; MPI = myocardial perfusion imaging; SPECT = single-photon emission CT; TTE = transthoracic echocardiography; V/Q = ventilation/perfusion.

any situation in which a SPECT MPI study could be performed, exercise stress or dobutamine stress echocardiography may be substituted [16,17]. In certain cases, if aortic valvular stenosis is considered the cause of ischemia or if a pericardial effusion is in question, echocardiography at rest may be the preferred examination.

Dobutamine-stress functional cardiac MRI may also play a role in the assessment of chronic CCP [18]. This is especially so when the echocardiographic examination is nondiagnostic. In settings in which the study may be adequately monitored, dobutamine stress functional cardiac MRI provides high sensitivity and specificity for ischemia by the induction of wall motion abnormality [19]. However, adenosine stress cardiac MRI perfusion imaging is easier to perform and also has been shown to have relatively high sensitivity and specificity for the presence of CAD [19-21]. PET/CT may play a role similar to cardiac MRI in assessing patients with chronic indeterminate chest pain and at low to intermediate risk for CAD. Cardiac PET/CT has been shown to provide incremental prognostic value to historical and clinical variables [22] and may be of particular use in patients with equivocal or suboptimal SPECT MPI or echocardiographic results.

As described above, it should be noted that chronic CCP can occur in ischemic syndromes in the absence of epicardial CAD. The diagnosis of syndrome X, in particular, has been shown to best be made with adenosine stress perfusion cardiac MRI, which demonstrates diffuse subendocardial hypoperfusion [23]. Its utility in comparison with SPECT MPI may be because of its higher spatial resolution. Cardiac MRI without pharmacologic stress could also be performed if valve disease, pericardial disease, or tumor is thought to be the cause of CCP, especially if the echocardiogram is inadequate.

Most recently, coronary 64-slice CCTA has been used to assess both acute and chronic CCP [24-26]. Like stress SPECT MPI or echocardiography, it can also be used to assess patients with intermediate to high probability of CAD. However, it is especially useful and is used instead of SPECT MPI and/or echocardiography in patients with atypical chest pain and/or low to intermediate probability of CAD, in whom etiologies other than CAD are also in question [24,27]. It has particular utility for noninvasively and accurately demonstrating the origin and course of anomalous coronary arteries [28]. It may also be used in patients in whom SPECT MPI or echocardiographic examinations were nondiagnostic or the results were questionable.

Recent advances in cardiac CT imaging technology allow further reduction of the radiation dose from CCTA [29]; available new dose-reducing techniques include prospective triggering [30-32], adaptive statistical iterative reconstruction [33], and high-pitch spiral acquisition [34]. These new lower-dose techniques are the appropriate choice in properly selected patients who have low heart rates (<65 beats/min) and are in sinus rhythm.

Coronary calcium scoring is most commonly used for risk stratification in asymptomatic patients. A large study of 10,377 subjects showed that coronary calcium scoring provides independent incremental information in addition to traditional risk factors in the prediction of all-cause mortality [35]. Although a patient's calcium score provides independent information regarding the patient's baseline probability of having CAD, a high calcium score cannot be used as strong evidence of myocardial ischemia, and a zero calcium score cannot exclude it.

Cardiac catheterization may be used if the results of less invasive imaging were consistent with the presence of significant CAD.

Approach to Patients With Chronic Chest Pain of Determined Noncardiac Etiology

In attempting to stratify the diagnostic tests, chest radiography would almost certainly be indicated to exclude bony pathology or chest masses. Because GERD is the most common cause of nCCP (found in almost 60% of cases) [14,36], a barium swallow could be performed or, alternatively, esophageal pH monitoring, manometry, or endoscopy [1,12]. The remainder of the diagnostic imaging progression depends strongly on the clinical history and signs and symptoms of the patient. For instance, studies performed could include a chest CT scan (if CCTA was not already obtained) to exclude chest syndrome in a sickle-cell patient or a lung mass in a patient with chest pain, cough, and weight loss. Right upper quadrant ultrasound might be obtained in a patient with suspected gallstones or chronic cholecystitis. A bone scan could be obtained in a patient with a primary malignancy and pain on rib palpation.

Chronic pulmonary emboli can also cause chest discomfort, and in these patients, contrast-enhanced pulmonary CT angiography may be performed. Ventilation-perfusion scans may be performed as an alternative in patients with iodinated contrast contraindications. Invasive pulmonary angiography is a second alternative, especially if the pulmonary CT angiogram is inadequate or pulmonary arterial pressure measurements are required.

SUMMARY

- Whether or not chest pain is anginal should be initially determined.
- The patient's risk factors for CAD should be determined.
- If a patient is at high risk for atherosclerotic CAD and/or chest pain is determined to be anginal, chronic ischemia should be excluded by stress forms of SPECT or echocardiography, or the presence of flow-limiting CAD can be determined by CCTA. CCTA may be

particularly useful in patients with atypical chest pain in whom other etiologies are being considered.
- In patients with low to intermediate probability of CAD and in whom chest pain is determined by either history or imaging to be nonanginal, further testing depends on the clinical history, signs, and symptoms. Imaging may include assessment for cardiac disease of noncoronary origin, including valvular or pericardial disease.
- GERD is the most common cause of nCCP. If it is suspected, a barium swallow, esophageal pH monitoring, manometry, or endoscopy can be ordered.

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* [37].

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, a 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 population 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 lower 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* [38].

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

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 "Varies."

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