EMERGENCY MEDICINE PRACTICE
EMPRACTICE.NET
AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE

Chest Pain: Diagnostic Strategies To Save Lives, Time, And Money In The ED

June 2003
Volume 5, Number 6

Authors

Darren B. Bean, MD
Assistant Professor, Section of Emergency Medicine, Department of Medicine, University of Wisconsin Hospital, Madison, WI.

Michael Roshon, MD, PhD
Penrose–St. Francis Health Services, Colorado Springs, CO.

J. Lee Garvey, MD
Medical Director, Chest Pain Evaluation Center, Department of Emergency Medicine, Carolinas Medical Center, Charlotte, NC.

Peer Reviewers

Francis M. Fesmire, MD, FACEP
Director, Heart-Stroke Center, Erlanger Medical Center; Assistant Professor of Medicine, UT College of Medicine, Chattanooga, TN.

Joseph P. Ornato, MD
Professor and Chairman, Department of Emergency Medicine, Virginia Commonwealth University Health System, Richmond, VA.

CME Objectives

Upon completing this article, you should be able to:
1. compare and contrast different causes of chest pain, including the benign and the potentially lethal;
2. discuss factors in the patient history and physical examination that may suggest acute coronary syndromes, pulmonary embolism, or aortic dissection;
3. describe the rationale for different diagnostic studies in the work-up of a patient with chest pain; and
4. discuss cost-effective modalities used in chest pain patients, such as chest pain observation units.

Date of original release: June 1, 2003.
Date of most recent review: May 9, 2003.
See "Physician CME Information" on back page.

5:50 p.m.: Another busy evening in the ED. A medic crew rolls in with a 57-year-old female clutching her chest and complaining of horrible chest pain. She is tachycardic and hypertensive. Her blood pressure is 188/98 mmHg, and her pain is unrelieved with nitroglycerin. Her ECG shows non-specific ST changes laterally, and the chest radiograph reveals a generous aortic knob.

Just then, a 43-year-old truck driver presents complaining of "sharp" right-sided chest pain with associated dyspnea. He has normal vital signs and non-reproducible pain on examination. His chest radiograph and ECG are normal.

CHEST pain accounts for roughly 5%-7% of the total ED volume in the United States, or approximately 6 million visits per year.[1,2] More than 3 million patients are hospitalized annually for acute chest pain evaluation, and of those, roughly 70% prove not to have an acute coronary event, at an annual cost exceeding $3 billion.[1] Yet despite this vigilance, 0.4%-4.0% of patients with an acute myocardial infarction (AMI) are sent home from the ED, doubling their mortality compared to those admitted.[3-5]

Gone are the days of observation for myocardial infarction. To improve outcomes, we must act to open culprit arteries soon after ED presentation. Also gone are the days of routine admission to an intensive care unit for every patient with chest pain. Cost-effective strategies for evaluation are mandatory. These changes have thrust the emergency physician into a pivotal role.

The emergency physician must rule out or treat potentially life-threatening conditions such as acute coronary syndromes (ACS), pulmonary embolism (PE), aortic dissection, and esophageal rupture. The spectrum of ACS includes AMI (both ST segment elevation ["STEMI"] and non-ST segment elevation ["non-STEMI"]) and unstable angina. This issue of *Emergency Medicine Practice* provides a focused approach to the initial evaluation of chest pain patients, discussing both benign and potentially lethal etiologies. The following protocols provide a structured and cost-effective approach to chest pain evaluation.

Future issues of *Emergency Medicine Practice* will address the comprehensive management of specific conditions such as PE, aortic disasters, and ACS.

Critical Appraisal Of The Literature

Few areas of clinical practice have as many large, randomized trials as therapeutic cardiovascular medicine. Many of these trials have enrollments that exceed several thousand patients in each arm.

The literature regarding chest pain is divided into diagnostic and therapeutic efforts. In contrast to the treatment scenario, the evidence basis for the various testing methods is relatively meager. Risk stratification protocols have been applied to the ED population, but none of these is ideal. There are few data describing a level of risk that is so low that further testing is not warranted. Because the outcome of patients with missed MI can be catastrophic, the net cast must be tightly woven.

Current clinical policies outline generally agreed upon principles of chest pain evaluation, including serial serum markers, serial electrocardiography, and selective stress testing. The American College of Emergency Physicians, the American Heart Association, and the American College of Cardiology have all published management guidelines for ACS.[250-252] Using history, physical examination, and ECG, patients can be rapidly risk stratified as having high, intermediate, or low probability of coronary artery disease (CAD). The efficient application of these measures has been organized into structured protocols.[8-10,211] These protocols are designed to be sensitive in capturing patients with disease, while maintaining cost-effectiveness.

In a comprehensive review of the technologies used for identifying acute cardiac ischemia in the ED (available at (http://www.ahrq.gov/clinic/epcsums/cardsum.htm),[11] most studies evaluated the accuracy of the technologies. Only a few evaluated the clinical impact of routine use. Specific findings include the following:

- Prehospital 12-lead electrocardiogram (ECG) has moderate sensitivity (76%) and specificity (88%) for the diagnosis of acute cardiac ischemia. It has demonstrated a reduction of the mean time to thrombolysis by 33 minutes and short-term overall mortality in randomized trials.
- In the general ED setting, only the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) has demonstrated, in a large, multicenter clinical trial, a reduction in unnecessary hospitalizations without decreasing the rate of appropriate admission for patients with acute cardiac ischemia.
- The Goldman chest pain protocol has good sensitivity (about 90%) for AMI but has not been shown to result in any differences in hospitalization rate, length of stay, or estimated costs in the single clinical impact study performed.[12]
- Single measurement of biomarkers upon presentation to the ED has poor sensitivity for AMI, although most biomarkers have high specificity (over 90%). Serial measurements can greatly increase the sensitivity for AMI while maintaining specificity. *Biomarkers cannot identify most patients with unstable angina.*
- Diagnostic technologies to evaluate acute cardiac ischemia in selected populations, such as echocardiography, sestamibi perfusion imaging, and stress ECG, may have very good to excellent sensitivity; however, they have not been sufficiently well-studied to identify the best or most cost-effective strategy.

While electrocardiography has been a key element in identifying patients with ACS for over 50 years, it is relatively insensitive for diagnosis at presentation. Serial changes in electrocardiography and continuous ST segment monitoring may increase the yield.[13]

Even though troponin testing has become a standard for the definition of myocardial infarction, there is no standardization between the various assays for this test. The decision between troponin T and troponin I, as well as the timing of serial markers, remain controversial. The interval between the time the symptoms began and the time at which the markers are drawn remains crucial. The ACEP clinical policy states that the necessary interval needed to exclude MI on the basis of negative markers depends on the specific assay—from 8-12 hours for CK-MB activity, 6-10 hours for CK-MB mass and subform, and 8-12 hours for troponins.[250] The bottom line is that no one set of markers can exclude AMI within six hours of symptom onset.

Epidemiology And Etiologies

Each year, nearly 1.5 million people are discharged from U.S. hospitals with a diagnosis of acute coronary syndrome.[253] While approximately 30% of patients who present to the ED with non-traumatic chest pain are ultimately diagnosed with ACS, 70% of patients have a non-coronary condition. Because coronary artery disease remains the leading cause of death in the United States, the identification of acute coronary syndromes, including AMI and unstable angina, must be at the top of the radar screen for the emergency physician.

Fruergaard et al provide some data regarding the epidemiology of patients admitted for evaluation of chest pain who ultimately were found not to have AMI.[14,15] After comprehensive testing in a series of 204 patients (including pulmonary scintigraphy, echocardiography, exercise electrocardiography, myocardial scintigraphy, Holter monitoring, hyperventilation test, esophagogastroduodenoscopy, three-hour monitoring of esophageal pH, esophageal manometry, Bernstein test, physical examination of the chest wall and thoracic spine, bronchial histamine provocation test, and ultrasonic examination of the abdomen), more than 90% had a specific diagnosis at discharge.[14] These included gastroesophageal diseases (42%), ischemic heart disease (31%), chest-wall syndromes (28%), pericarditis (4%), pleuritis/pneumonia (2%), PE (2%), lung cancer (1.5%), aortic aneurysm (1%), aortic stenosis (0.5%), and herpes zoster (0.5%). Of those patients with gastroesophageal disorders, 30% had gastroesophageal reflux, 13% had esophageal motility disorders,

10% had peptic ulcer disease, and 5% were diagnosed with cholelithiasis. The remaining 10% of patients had no identifiable source of their chest pain.

One recent study noted the large number of patients with anxiety disorders who were admitted to an ED chest pain observation unit. Of 156 enrolled participants, 50 (32%) met criteria for panic disorder.[16] Having panic disorder or other psychiatric considerations, however, does not preclude the existence of CAD or other pathophysiology.

Pathophysiology

Chest pain syndromes are difficult to diagnose because the constellation of symptoms often cannot identify the organ system involved. The organ systems of the chest—musculoskeletal, cardiovascular, pulmonary, and gastrointestinal—share afferent pathways. Pathologic processes in any of these systems can result in a similar pattern of complaints. This vagueness is attributed to the visceral innervation and "cross talk" between various levels of the nervous system where these afferents arise. While most patients with ACS have some component of chest pain, other presentations—for example, difficulty breathing, nausea/vomiting, or arm or jaw pain—may be the patient's primary or associated concern.

It has been suggested that comorbid disease, particularly diabetes, alters the patient's perception of these signals. However, in one angioplasty study, the description by diabetic patients of chest discomfort during balloon inflation was very similar to that of non-diabetic patients.[17]

Effects of age and gender on symptom presentation in ACS are becoming more appreciated.[18-20] No hard-and-fast rules for "atypical" presentations of ACS can be made, except that the atypical may be more typical than originally appreciated.[21]

Differential Diagnosis: Immediate Life Threats

The differential diagnosis of chest pain is wide-ranging. (See **Table 1**.)

Acute Coronary Syndromes

Due to their frequency and lethality, acute coronary syndromes remain the number-one concern for the emergency physician. They account for a significant percentage of all patients who present to the ED with chest pain.

Misdiagnosed AMI is more likely to occur among younger patients, those with atypical symptoms, and those with less experienced physicians, who order fewer screening ECGs.[6] In a retrospective study of more than 10,500 patients evaluated for possible AMI or unstable angina, independent predictors of unrecognized cardiac ischemia included women younger than 55 (odds ratio [OR], 6.7), non-white race (OR, 2.2), a chief complaint of shortness of breath (rather than chest pain) (OR, 2.7), and a normal ECG (OR, 3.3).[4] Missed AMI accounts for one-quarter of all malpractice dollars paid against emergency physicians, representing the largest single diagnostic category.[4,7] While we have made important strides in the chest pain diagnostic dilemma, significant challenges remain.

Acute Pulmonary Embolism

PE remains one of the most insidious and deadly diseases encountered in emergency medicine. The incidence of PE in outpatients remains approximately 1 in 1000 per year.[22,23] These data indicate that the average emergency physician working 15 shifts per month would encounter approximately 2-4 cases of PE per year.

The mortality from untreated PE is as high as 30% but falls to 8% with timely diagnosis and treatment.[24,25] Risk factors for PE include increasing age, immobilization, recent surgery/trauma, previous history of thromboembolic disease, and active malignancy.[26]

"On 25 October 1760 George II, then 76, rose at his normal hour of 6 a.m., called as usual for his chocolate, and repaired to the closet-stool. The German valet de chambre heard a noise, 'louder than the royal wind,' and then a groan; he ran in and found the King lying on the floor, having cut his face in falling."—Thomas Bevill Peacock[32]

Aortic Dissection

Aortic dissection is an immediate threat to life that may require emergency surgical intervention. Most patients have either a structural abnormality of the aortic wall or long-standing hypertension, leading to an intimal tear. Blood dissects into the layers of the aortic wall, creating a false lumen. This false lumen may advance, occluding tributary

Table 1. Differential diagnosis of chest pain.

Potentially life-threatening causes of chest pain

- Acute coronary syndromes
  - Acute myocardial infarction
  - ST segment elevation AMI
  - Non-ST segment elevation AMI
  - Unstable angina
- Pulmonary embolism
- Aortic dissection
- Myocarditis (most common cause of sudden death in the young)
- Tension pneumothorax
- Acute chest syndrome (in sickle cell disease)
- Pericarditis
- Boerhaave's syndrome (perforated esophagus)

Common non-life-threatening causes of chest pain

- Gastrointestinal
  - Biliary colic
  - Gastroesophageal reflux
  - Peptic ulcer disease
- Pulmonary
  - Pneumonia
  - Pleurisy
- Chest wall syndromes
  - Musculoskeletal pain
  - Costochondritis
  - Thoracic radiculopathy
  - Texidor's twinge (precordial catch syndrome)
- Psychiatric
  - Anxiety
- Shingles

arterial branches and ultimately causing ischemia or infarction in vital organs such as the brain, heart, kidneys, or intestine. Retrograde dissection may compromise the aortic valve annulus, causing aortic insufficiency, or blood may dissect into the pericardial sac, producing cardiac tamponade.

Aortic dissections are most commonly classified using the Stanford classification system, using the location of the dissection in respect to the aortic arch. (The older DeBakey classification is not used as frequently.) Stanford type A is determined by any involvement of the ascending aorta, while Stanford type B involves only the descending aorta beyond the take-off of the subclavian artery. Dissections that involve both the ascending and descending aorta would be classified as type A. Dissections involving the aortic arch usually require immediate surgical intervention, whereas dissections involving the descending aorta are often given a trial of medical management.

Esophageal Rupture

Esophageal rupture (or Boerhaave's syndrome) is a rare but potentially lethal disease. Most cases of Boerhaave's syndrome occur after endoscopy or, less commonly, after vomiting.[34] In a recent review at a Rhode Island hospital, 44 cases were identified over a 15-year period (30 cases after endoscopic procedures).[34]

Most patients present with either chest or abdominal pain, and the most common finding on examination is diminished breath sounds.[34] The majority of patients are toxic-appearing. Hamman's crunch (audible crepitus associated with heart sounds), though very specific for mediastinitis, is rarely reported.[34] Subcutaneous air might be present in the chest or root of the neck. Chest radiography is the most sensitive screening tool. Pneumothorax, pneumomediastinum, and/or pleural effusion should trigger consideration of esophageal rupture.[34] (See **Figure 1**.) The combination of pneumothorax/pneumomediastinum and pleural effusion should trigger consideration of esophageal rupture. Swallowing studies (barium or gastrographin) are often an initial study of choice, but they may miss up to 25% of cases and should not be used to exclude the diagnosis.[35-37] Both endoscopy and CT scans of the chest may be helpful.

Figure 1. Pleural effusion secondary to a rupture of the esophagus.

Acute Chest Syndrome

Acute chest syndrome is the most common cause of death in sickle cell patients.[38] Patients over the age of 20 years and those presenting with neurological symptoms have the highest mortality.[38] Pulmonary infarction (16%), fat emboli (8%), chlamydia (7.2%), and mycoplasma infections (6.6%) are the most common etiologies, when identified.[38] However, despite rigorous testing, half of the patients with acute chest syndrome have no identifiable source.

Sickle cell patients presenting with chest pain should be presumed to have acute chest syndrome until proven otherwise. Progressive hypoxia, multilobar pneumonia on chest radiograph, and falling hemoglobin levels are the most common clinical findings.[38] Adults are more likely to be afebrile, present with severe chest pain with multilobar infiltrates by chest radiograph, and have a more severe illness. Children are often febrile, rarely complain of chest pain, and are likely to have respiratory symptoms (cough or dyspnea).[39] Because physical examination and history predict fewer than 40% of the patients ultimately found to have infiltrates on chest radiograph, any sickle cell patient complaining of chest pain or with respiratory symptoms should undergo chest radiography.[40,41] Still, half of patients diagnosed with acute chest syndrome have a normal initial chest radiograph.[40,41]

"On her headstone you'll find this refrain / 'She died as she lived, sniffing cocaine.'"—W.H. Auden[42]

Cocaine-Related Chest Pain

Chest pain associated with cocaine use is common. Up to one-quarter of patients evaluated for chest pain in urban EDs have detectable levels of cocaine or cocaine metabolites in their urine, while only 72% of those admit to cocaine use.[43-45] Hollander et al found that the likelihood of testing positive is 29% for patients 18-30 years old; 45% for patients 31-40 years old; and 18% for those 41-50 years old.[46]

Few patients evaluated for cocaine-related chest pain have AMI (6%), with an in-hospital mortality rate of less than 1%.[47,48] Most patients evaluated for cocaine chest pain continue to abuse the drug and will revisit EDs with recurrent chest pain, at an annual cost in the United States exceeding $83 million.[49] Despite this pattern of abuse, the subsequent risk for cardiac events (including AMI and cardiac death) remains low—less than 1% at one-year follow-up for patients evaluated for cocaine chest pain.[43]

Cocaine can cause myocardial ischemia resulting from hypertension, tachycardia, and coronary vasospasm. But of those patients with AMI, only half have epicardial atherosclerosis documented by angiography.[43,50,51] Other causes of cocaine chest pain include aortic dissection, pneumothorax, chest wall muscle spasm, or pneumomediastinum.

Apart from a history of drug use, there are no historical features that distinguish cocaine-related AMI from non-cocaine-related AMI, or uncomplicated cocaine chest pain.[43,52] The ECG can be deceptive, as over 40% of patients with cocaine chest pain will have ST elevation/J point

elevation that could be interpreted to meet criteria for fibrinolytic treatment.[53] However, only 6% will have abnormal cardiac markers.[48,53] Many of those patients with documented cocaine-induced myocardial necrosis will have a normal ECG or only nonspecific changes.[52]

A recent prospective study of 344 patients demonstrated the safety of a nine- to 12-hour observation period in patients with cocaine chest pain who are at low-to-intermediate risk of cardiovascular events.[54] Patients with cocaine-associated chest pain who had normal levels of troponin I, no new ischemic changes on ECG, and no cardiovascular complications (dysrhythmias, AMI, or recurrent symptoms) during the observation period were discharged home. During the 30-day follow-up period, none of the patients died of a cardiovascular event, and the four nonfatal MIs all occurred in patients who continued to use cocaine. While some centers will not perform cardiac stress testing in patients with recent cocaine use, several small studies indicate that it is safe,[55,56] and at least one trial performed dobutamine stress tests with no ill effects.[57] In Weber et al's study in the *New England Journal of Medicine*, stress testing before discharge ceased to be mandatory because of the very low rate of positive stress tests; patients were referred to their physicians for outpatient stress testing.[54]

Prehospital Care

Many emergency medical systems can obtain and transmit ECGs and pertinent history via cell phone or fax. The use of prehospital 12-lead ECGs transmitted to the receiving hospital can reduce the time to fibrinolytic administration, increase the number of patients treated, and ultimately reduce mortality from AMI.[58-60] The ED physician who receives an ECG with ST elevations across the precordium should prepare the ED staff for an expeditious work-up and reperfusion strategies. The goal for "door-to-needle" time is less than 30 minutes, and the "door-to-balloon" time is 60-90 minutes.[61]

Emergency Department Evaluation

Triage

Train triage personnel to rapidly identify patients who present with symptoms suggestive of ACS and immediately transport them to an acute care area of the ED. Standing orders for chest pain patients include establishment of IV access, oxygen administration and/or pulse oximetry, cardiac monitoring, an immediate 12-lead ECG, and, in some centers, chest radiography. The ECG should be available and interpreted within 10 minutes of the patient's arrival.[61]

Higgins et al studied the impact of a modified ED triage protocol where all patients presenting with undifferentiated chest pain over the age of 30 were sent to high-acuity areas where ECGs were rapidly obtained. Traditional triage by experienced nursing personnel led to 40% of patients with AMI being triaged inappropriately to low-acuity areas, leading to delays in patient care.[62] In contrast, implementation of chest pain triage protocols led to a significant reduction of time between arrival and the decision to treat.[62] In a study by Graff et al, any patient who presented to triage with any of five complaints bypassed the usual triage process and was brought back to a treatment area for an ECG, which was immediately shown to an emergency physician. Patients were candidates for immediate ECG if they were older than 30 years with chest pain (excluding respiratory infection or trauma) or older than 50 years with a rapid heartbeat, weakness, syncope, or difficulty breathing. Sensitivity for AMI improved from 67% to 93%, and time to treatment fell from 37 to 26 minutes.[63] The number of ED patients who received a stat ECG under this protocol, compared to the standard protocol relying on triage nurse judgment, rose only from 6.3% to 7.3%.

The Initial Clinical Examination

There is an expanding armamentarium for evaluating chest pain available to the emergency medicine physician, including serum markers, continuous ST segment monitoring, improved imaging technology, and computer protocols. Despite these advances, there are no rapid, easily attainable tests that exclude AMI or ACS on ED presentation. The sensitivity of the initial ECG ranges from 20%-60% for AMI.[64] Likewise, the sensitivity of plasma CK-MB within four hours of the onset of pain is notoriously poor for detecting AMI, and even worse for detecting unstable angina.[65] Because of these limitations, the cornerstones of the evaluation of patients presenting with chest pain remain the initial history, physical examination, and ECG. While this diagnostic triad is usually not sufficient to exclude ACS, it is the best information immediately available to risk-stratify patients.

"*The most important difference between a good and indifferent clinician lies in the amount of attention paid to the story of a patient.*"—*Farquhar Buzzard*[66]

History

When obtaining the history from a patient with chest pain, it may be helpful to group the interview questions to target the three most common life threats. Consider "ACS questions," "PE questions," and "aortic dissection questions." Each one has its own peculiar risk factors and suggestive historical findings.

Cardiac Questions

Arguably the two most important pieces of historical information are the easiest to obtain: age and gender. With advancing age, both the prevalence and the severity of CAD increase. In addition to the increased likelihood of significant CAD, advanced age is associated with increased mortality and complication rates. A combination of autopsy data and large angiography studies allows us to estimate the pretest probability of CAD in patients based on age and gender alone. This can be further refined based on classifying the chest pain as typical, atypical, or non-anginal.[67] (See **Table 2** on page 6) These data confirm that the pretest probability of CAD ranges widely but is still significant in patients commonly regarded as low risk. For instance, a 35-year-old man with non-anginal chest pain has an estimated pretest probability of CAD of roughly 5%.

Another significant element obtained from the initial history is whether the patient has a prior history of AMI or CAD. Not surprisingly, a prior history of AMI or CAD raises the risk of a subsequent coronary event fivefold.[68] Pain that is reported as the same as the pain experienced with prior AMI or as worse than prior angina carries an additional relative risk of 2.8.[69] If the patient has a cardiac history, inquire about prior stress tests, cardiac catheterizations, bypass surgery, stenting, and the like.

Character Of Pain

The literature regarding the importance of the character of pain is decidedly schizophrenic. Textbooks and review articles routinely emphasize the importance of this feature. Studies addressing missed MI often debunk the value of pain character and instead point to the atypical nature of ischemic symptoms in many patients. A few clinical features (such as pain radiating to both arms) are specific but not sensitive to cardiac disease.

Aside from a prior history of CAD, the historical features that are of greatest interest involve the nature, duration, and modifying factors of the pain, and associated symptoms. A number of studies have concluded that the presence of "typical" vs. "atypical" chest pain has no predictive value for AMI or ACS. Forty percent of patients with AMI present with atypical pain, and 35% of patients without AMI present with typical "cardiac pain."[70] In a retrospective study of 721 patients with an ultimate diagnosis of AMI, about half presented to the ED without chest pain. Shortness of breath, weakness/dizziness/syncope, and abdominal pain were frequent complaints, especially among the elderly.[71]

In an excellent article, Panju et al synthesized the data on the clinical features of patients with symptoms suggestive of ACS from 14 studies representing over 30,000 patients.[72] (See **Table 3** on page 7.) Patients with pain radiating to the left arm, right shoulder, or both arms, as well as patients with diaphoresis, were more likely to have an AMI (OR, 7.1 for patients with pain radiating to both arms). Patients with pain described as pleuritic, sharp or stabbing, positional, or reproduced with palpation had a decreased likelihood of having an AMI (OR, 0.2-0.3). Because these data were extracted from large cohorts of patients that included those who were clinically unstable and those with diagnostic ECGs on presentation, its clinical utility is marginal in some patients. For instance, in a patient with hypotension, ST segment elevation, and crushing substernal chest pain, the presence or absence of chest wall pain on palpation adds little to the examination.

A more problematic group of patients is those with an intermediate likelihood of ACS. Goodacre et al studied 893 patients with intermediate probability of ACS. They excluded high-risk patients who had new ECG changes consistent with ischemia or new left bundle branch block, those with comorbidity such as heart failure or arrhythmia or an alternative serious pathology, and patients with definite unstable angina. They also excluded those with minimal risk of coronary heart disease, such as those less than 25 years or whose pain was related to recent trauma. Goodacre showed that the duration of the pain and associated symptoms symptoms (nausea, vomiting, or diaphoresis) had no value in the diagnosis of ACS.[73] (See **Table 4** on page 7.) A burning or indigestion type of pain was associated with an odds ratio of 4.0 for ACS, while crushing pain was associated with an odds ratio of 0.9 in these intermediate-risk patients. The presence of chest wall tenderness was associated with a reduced risk for AMI (OR, 0.2).

The relationship between the duration of pain and AMI is also problematic. Physicians generally believe that very brief pain or persistent, unrelenting pain is unlikely to be ischemic. One study showed that while the likelihood of AMI is decreased for patients with duration of pain for less than five minutes or over six hours, a substantial number of these patients still subsequently prove to have AMI.[74]

The relief of pain by sublingual nitroglycerin has long been thought to be a helpful diagnostic tool to differentiate cardiac from non-cardiac etiologies of chest pain. A retrospective study evaluated 251 ED patients admitted for chest pain.[75] While 88% of patients with cardiac chest pain responded to sublingual nitroglycerin, *92%* of patients with noncardiac chest pain also had symptomatic improvement with sublingual nitroglycerin. More insidious is the misinterpretation of response to a GI cocktail. In one retrospective study of 97 patients who received a GI cocktail in the ED, 8 of 11 patients eventually admitted to the hospital with possible myocardial ischemia had partial or complete symptomatic relief after administration of a GI cocktail.[76] (Some patients in the study received co-administered medications such as morphine or nitroglycerin.)

Risk Factors

It is common practice to inquire about traditional cardiac risk factors (e.g., diabetes mellitus, hypertension, smoking,

Table 2. Pretest likelihood of CAD based on age, sex, and symptoms.

	Asymptomatic		Non-anginal chest pain		Atypical angina		Typical angina	
Age	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
30-39	1.9%	0.3%	5.2%	0.8%	21.8%	4.2%	69.7%	25.8%
40-49	5.5%	1.0%	14.1%	2.8%	46.1%	13.3%	87.3%	55.2%
50-59	9.7%	3.2%	21.5%	8.4%	58.9%	32.4%	92.0%	79.4%
60-69	12.3%	7.5%	28.1%	18.6%	67.1%	54.4%	94.3%	90.6%

Source: Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979 Jun 14;300(24):1350-1358.

hypercholesterolemia, and family history) in all patients who present to the ED with chest pain. However, these risk factors, identified in longitudinal studies such as the Framingham study, were intended to predict development of CAD over decades—not the likelihood of ACS in the setting of acute chest pain.

So how do these traditional coronary risk factors predict ACS in the patient with acute chest pain? In a study by Jayes et al, none of the traditional risk factors were associated with an increase in risk of acute cardiac ischemia in women.[77] In men, diabetes and family history were associated with increased relative risk—2.4 and 2.1, respectively. Another study confirmed that traditional CAD risk factors are of little value in the evaluation of low-risk patients with acute chest pain and that having more risk factors did not significantly increase risk.[78] More importantly, the absence of risk factors does not exclude acute cardiac ischemia as an etiology for the patient's pain.

Medications And Drug Use

The patient's medications may be illuminating, especially if they are on anti-anginal or anti-arrhythmic drugs. Questions regarding recent cocaine use are often high-yield; in one study, 30% of patients 18-50 years old evaluated for chest pain tested positive for cocaine.[45]

Non-ACS Conditions

The history is critical in identifying life-threatening causes of chest pain other than AMI or ACS. While not always definitive, a carefully acquired history can help differentiate between ACS, aortic dissection, PE, Boerhaave's syndrome and myocarditis or pericarditis.

Aortic Dissection

The International Registry of Acute Aortic Dissection (IRAD) has shed new light on clinical features, physical examination findings, and mortality of acute aortic dissection.[33] Twelve large referral centers in six countries enrolled a total of 464 patients in the registry. Patients with this disease are most commonly male (75%), in their seventh decade of life, and have a history of hypertension (70%). Other risk factors include Marfan's syndrome, atherosclerosis, prior dissection, or known aortic aneurysm.

The pain is usually sudden in onset (83%), severe or "worst ever" (90%), and often characterized as sharp (64%) or tearing (50%).[33] The pain is slightly more likely to be in the anterior chest (60%) than back (53%), and less likely to be migratory (16%) or radiating (28%) in nature. While migratory pain may occur in a minority of patients, suspect aortic dissection in patients who have a changing clinical picture, such as those complaining of chest, then back, then abdominal pain. Patients who complain of chest pain along with a neurologic deficit may have a dissection occluding a cerebral or spinal artery.

Therefore, it's helpful to address three basic concerns regarding a patient's pain: the quality (sudden and severe), radiation (especially to the back), and intensity at onset (maximal). One retrospective study showed that when all three questions were asked, physicians correctly diagnosed thoracic aortic dissection in 30 of 33 patients (91%); if one or more of these aspects were omitted, the correct diagnosis was suspected in fewer than half of all patients ($P < 0.001$).[79]

Table 3. Analysis of clinical predictors of acute myocardial infarction in unselected patients.

Clinical feature	LR (95% CI)
Pain in chest or left arm	2.7
Chest pain radiation	
Right shoulder	2.9 (1.4-6.0)
Left arm	2.3 (1.7-3.1)
Both right and left arm	7.1 (3.6-14.2)
Chest pain most important symptom	2.0
Nausea or vomiting	1.9 (1.7-2.3)
Diaphoresis	2.0 (1.9-2.2)
History of myocardial infarction	1.5-3.0

Source: Panju AA, Hemmelgarn BR, Guyatt GH, et al. The rational clinical examination. Is this patient having a myocardial infarction? *JAMA* 1998 Oct 14;280(14):1256-1263.

Table 4. Analysis of clinical predictors of AMI or ACS in intermediate-risk patients.

	AMI	ACS
Clinical feature	Odds ratio (CI)	Odds ratio (CI)
Chest pain radiation		
Left arm	1.5 (0.6-4.0)	1.7 (0.9-3.1)
Right arm	3.2 (0.4-27.4)	2.5 (0.5-11.9)
Both left and right arm	7.7 (2.7-21.9)	6.0 (2.8-12.8)
Nausea or vomiting	1.8 (0.9-3.6)	1.0 (0.6-1.7)
Diaphoresis	1.4 (0.7-2.9)	1.2 (0.8-1.9)
Exertional pain	3.1 (1.5-6.4)	2.5 (1.5-4.2)
Burning/indigestion pain	4.0 (0.8-20.1)	1.5 (0.5-4.5)
Crushing/squeezing pain	2.1 (0.4-10.9)	0.9 (0.4-2.9)
Relief with nitroglycerin	0.9 (0.1-6.5)	2.0 (0.6-4.9)
Pleuritic pain	0.5 (0.1-2.5)	0.5 (0.2-1.3)
Tender chest wall	0.2 (0.1-1.0)	0.6 (0.3-1.2)
Sharp /stabbing pain	0.5 (0.1-2.8)	0.8 (0.3-2.1)

Source: Goodacre S, Locker T, Morris F, et al. How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? *Acad Emerg Med* 2002 Mar;9(3):203-208.

Aortic dissection and AMI may coexist in the same patient; pathological studies show that nearly 8% of dissections involve the coronary arteries.[80] ECG changes such as acute ST and T wave abnormalities are present in half of all patients with aortic dissection—often confounding the initial diagnosis.[81]

Pulmonary Embolism

The clinical diagnosis of PE is often difficult because symptoms of PE can be highly variable and nonspecific, ranging from dyspnea and fatigue to severe pleuritic chest pain and syncope. The classic description of pleuritic pain, dyspnea, and hemoptysis represents embolic pulmonary infarction and is much more common in hospitalized than ambulatory patients. It is important to note that ED patients (i.e., ambulatory patients) with PE often present with painless dyspnea.[82] The physician should not be led astray by several weeks' worth of intermittent symptoms. The classic description of pleuritic pain, dyspnea, and hemoptysis represents embolic pulmonary infarction and is much more common in hospitalized than ambulatory patients.[83,84] Careful interview and analysis of imaging from ED patients diagnosed with PE reveals that many have had multiple emboli of various ages. The physical examination is rarely diagnostic in PE, and the presence of reproducible chest wall tenderness does not exclude the diagnosis.[26]

Patients with PE describe a wide spectrum of pain quality and location. Pain that is peripheral, increases with a deep breath, and is not reproducible with palpation should raise suspicion. On the other hand, data suggest that isolated substernal chest pain is less likely to represent PE, even if the pain seems "pleuritic."[85] Substernal, anginal-type chest pain occurs in only 4% of PE, and radiation to the arms or jaw is distinctly unusual. In the PIOPED study, no patient with PE had radiation of pain to the arms.[86]

Hemoptysis, though not frequent, is strongly predictive of PE.[26] Sudden onset of symptoms occurs in fewer than half of patients with confirmed PE and has no predictive value.[26] Pleuritic chest pain and leg symptoms are more commonly found in patients with confirmed PE than those with other diagnoses.[27,28]

Other Conditions

Classic Boerhaave's syndrome presents as spontaneous esophageal rupture after severe vomiting. Boerhaave gave the initial description in the case of Baron Jan van Wassenaer, grand admiral of the Holland fleet, in whom severe pain developed after regurgitating an intemperate feast of roast duck. Patients may complain of pain on swallowing, and a significant number may be acutely or recently intoxicated.

The pain associated with pericarditis typically refers to the neck and acromial region and worsens with inspiration, swallowing, and lying supine.

Physical Examination

The physical examination is of limited use in identifying stable patients with ACS or AMI since abnormal findings are rare. The physical examination does, however, assist in the identification of non-coronary causes of chest pain (and occasionally coronary causes in the unstable patient). Several findings that correlate with an increased relative risk (RR) of AMI relate to poor left ventricular function: hypotension (RR, 3.1), S3 gallop (RR, 3.2), and rales (RR, 2.1).[72]

Vital Signs

As their name implies, vital signs are critically important in the evaluation of patients with chest pain. While the combination of chest pain and hypotension does not necessarily differentiate between the various etiologies, it does portend an ominous condition. Eight percent of patients presenting with PE and 15% of those with aortic dissection are hypotensive on arrival.[33,87] Patients presenting with chest pain and hypotension are three times more likely to have AMI than normotensive patients.[72]

Fever should lead to the consideration of noncardiac sources of chest pain, especially pneumonia or mediastinitis with or without esophageal rupture. In the PIOPED study, although low-grade fever occurred in 14% of patients with PE, only 2% had a temperature of 38.9°C (102°F) or higher.[88] While tachypnea is the most common sign associated with PE, 15% of patients with PE have a respiratory rate of fewer than 20 breaths per minute.[87,89]

Tachycardia is a nonspecific sign, but it may be the only clue to early pericarditis or myocarditis. Bradycardia, especially that caused by conduction defects, may be seen in right coronary artery occlusions.

Attend to the fifth vital sign, pulse oximetry, as well. Hypoxia can be present in a wide variety of conditions and may or may not be related to the chest pain. Patients with low oxygen saturations will require supplemental oxygen, although those with a significant shunt from PE may not show improvement. *Oxygen saturation is normal in one-quarter of patients with PE.*[87]

Head And Neck Examination

Evaluate the neck for Kussmaul's sign (a paradoxical increase in jugular venous distention with inspiration), which is seen with pericardial tamponade, right heart failure or infarction, PE, or tension pneumothorax. The presence of subcutaneous air at the root of the neck suggests pneumomediastinum or pneumothorax. While carotid or aortic bruits increases the likelihood of CAD, their absence has no predictive value.

Pulmonary Examination

Evaluate the patient for evidence of respiratory distress, including nasal flaring, intercostal retractions, and accessory muscle use.

Percussion can detect infiltrates, pulmonary effusions, and pneumothorax. While the technique is generally not sensitive for any of these findings, it is fairly specific.

The most important finding to identify on lung auscultation is the unilateral absence of breath sounds; this should prompt consideration of pneumothorax or massive pleural effusion. Wheezing and rales can be important signs of pathology but are not specific for certain diseases. Asthma, foreign body, pneumonia, congestive heart failure,

or PE may all cause wheezing. Rales are rare in patients with MI but their presence, associated with left heart failure, raises the likelihood of MI by twofold.[72]

Cardiac Examination

Auscultation of the heart can reveal several etiologies for chest pain. A new murmur may signal papillary muscle rupture from ischemia or valvular incompetence from retrograde aortic dissection. The murmur of aortic insufficiency is an important finding associated with aortic dissection. An S3 gallop secondary to congestive heart failure raises the likelihood of MI threefold.[72] Hamman's crunch is a rhythmic crunching sound made as the heart beats against mediastinal air. A pericardial rub (sometimes compared to the creaking of new leather) should prompt consideration of pericarditis, while Beck's triad (distant heart sounds, jugular venous distention, and pulsus paradoxus) suggests proximal aortic dissection with impending pericardial tamponade.

Chest Wall Examination

Even in the presence of chest wall tenderness, the clinician must consider life-threatening causes of chest pain. Reproducible chest wall pain is frequently reported in patients with PE or ACS, especially in the case of repeated examination or overly vigorous palpation. Panju et al identified a likelihood ratio of 0.2-0.3 for MI with pain that is positional, pleuritic, or reproduced with palpation, and other studies have shown that patients with MI may have a tender chest.[72]

Costochondritis is inflammation of the costal cartilages and may result in pain that is intermittently sharp, dull, or pleuritic, but it is rarely associated with swelling of the soft tissues. Tietze's syndrome is associated with fusiform swelling of the upper costal cartilages and is usually limited to one rib.

Compression of the cervical or thoracic ventral nerve roots may produce dull chest pain mimicking angina (cervico-precordial angina). This pain usually worsens with neck movement, coughing, sneezing, or with axial loading of the vertebrae by applying moderate pressure to the top of the head (Spurling's maneuver).

Failure to examine the skin of a patient with chest pain can be an embarrassing oversight. Herpes zoster typically causes unilateral pain that is isolated to one or two contiguous dermatomes.

Examination Of The Extremities

Examination of the extremities involves searching for evidence of edema, thrombosis, or pulse deficit. Peripheral edema is frequently found in association with right-sided or biventricular failure; however, it is usually absent in patients with acute left ventricular dysfunction.[90] Unilateral edema or palpable venous thrombosis (cords) suggests DVT and hence PE; however, most patients with PE have normal extremity exams.[91]

Examination Of The Pulses

Examine the pulses for symmetry and quality. A pulse deficit is evidenced by asymmetrical amplitude between the right and left carotids or the right vs. left peripheral pulses. Pulse deficits are most common in type A dissections (ascending aorta). A measured blood pressure differential between arms occurs in only 15% of patients with dissection (although it has previously been described in over half of patients with acute aortic dissection).[33,92,93] However, one well-designed prospective, observational study found that a blood pressure differential of greater than 20 mmHg between arms was an independent predictor of dissection.[93]

Neurologic Examination

Altered mental status is a nonspecific finding that could be associated with any cause of chest pain that leads to hemodynamic instability and cerebral hypoperfusion. More specifically, as many as 17% of patients with aortic dissection may have a focal neurologic deficit secondary to occlusion of the carotid or vertebral arteries.[94] Distal aortic dissections may also cause spinal cord ischemia or ischemic peripheral neuropathies.

Diagnostic Studies

Electrocardiography

The ECG is the single most important diagnostic test in the evaluation of patients with chest pain.[95] It is easily performed, relatively inexpensive, and can be repeated quickly. It is useful in disease processes ranging from PE to AMI. Many critical clinical decisions are based on the emergency physician's interpretation of ECGs. In one study, as many as half of the MIs that were not initially recognized could have been diagnosed through improved ECG reading skills.[96,97] Access to previous ECG tracings can expedite detection of AMI and prevent unnecessary hospital admissions in patients with baseline ECG abnormalities.[98,99]

The initial ECG is insensitive in identifying acute coronary syndromes. Only 20%-50% of patients presenting with MI have diagnostic changes on the initial ECG.[70,100-102] The definition of "diagnostic changes" differs among authorities. In a prospective study of 1190 subjects, the optimum ST elevation model consisted of at least 1 mm of elevation in one or more inferior/lateral leads, or at least 2 mm of elevation in one or more anteroseptal leads. This definition provided a sensitivity and specificity of 56% and 94%, respectively, for AMI.[103] Up to 10% of patients with AMI present with left ventricular hypertrophy with repolarization changes.[104] Tall and narrow (peaked) T waves may be the earliest sign of AMI.[105]

While acute ST segment elevation mandates an aggressive diagnostic and therapeutic approach, its absence should not reassure. However, a *completely* normal ECG can be useful. The negative predictive value of a "completely, absolutely, stone-cold normal" ECG is roughly 99% for excluding AMI.[70] The referenced study required "normal" to mean that there were no ST/T-wave changes (nonspecific or otherwise), strain, ischemia, old infarcts, or pseudonormalization. Further, five patients of the 114 with "normal" ECGs were ultimately diagnosed with unstable angina.[70] Thus, a "normal" ECG is useful to exclude AMI; however, it does not exclude unstable angina.

Pitfalls In Interpretation

Several factors can make the ECG diagnosis of ischemia difficult. Early repolarization, bundle branch blocks, paced rhythms, ventricular aneurysms, intracranial hemorrhage, and left ventricular hypertrophy with repolarization changes may all produce ST elevation.[106,107] Other mimics of ACS on ECG include pericarditis, hypothermia, and electrolyte disorders. One study demonstrated that emergency physicians were particularly likely to misinterpret ST elevation syndromes that showed left ventricular aneurysm, AMI with atypical ST elevation, benign early repolarization, pericarditis, left ventricular hypertrophy, and left bundle branch block with or without AMI.[108]

The ECG detection of AMI in patients with a left bundle branch block is especially troublesome. Sgarbossa et al developed criteria for diagnosing acute ischemia in the presence of bundle branch block.[109] Their criteria include ST elevation of 1 mm or greater concordant (same direction) with the QRS complex; ST depression of 1 mm or greater in leads V_1, V_2, or V_3; and ST elevation of 5 mm or greater discordant (opposite direction) with QRS. (See **Figure 2** and **Figure 3**.) Yet Shlipak et al later found that only 10% of patients presenting with AMI and left bundle branch block would have been detected using these criteria.[110] However, they found the Sgarbossa criteria to be very specific. Therefore, if the Sgarbossa criteria occur, even in the presence of atypical chest pain, consider emergent reperfusion therapy.

Access to a previous ECG and or continuous ST segment monitoring may be of particular benefit in identifying dynamic ECG changes representing myocardial injury in left bundle branch block.[111]

Additional Leads

The ECG provides a geographic reference to the location of injury. The standard 12-lead array is relatively unfocused on the high lateral and posterior aspects of the myocardium. Right-sided leads, specifically 1 mm or greater ST elevation in V_4R or V_5R, increase both the sensitivity (90%) and specificity (91%) of detecting right ventricular infarcts.[112] Posterior leads may help identify posterior wall infarcts. A V_9 Q wave of greater than 40 ms in duration is more sensitive and specific than a V_2 R-wave to S-wave ratio greater than 1.[113] However, Brady et al found that while routine 15-lead ECGs "provided a more complete anatomic picture," they did not improve sensitivity or change the course of therapy.[114] Additional leads, either right-sided or posterior, may be most valuable when the standard 12-lead tracing is suggestive but not diagnostic of an injury to a particular area of the heart. (See **Figure 4**.)

Serial ECGs

The ECG typically reflects only 10 seconds of data collection, yet ACSs are dynamic in nature. Repeat a normal ECG if the patient has persistent ischemic-type pain or a change in symptoms. Fewer than half of ED patients with AMI have diagnostic ECGs on presentation, but up to 20% more will develop injury patterns that meet fibrinolytic criteria early in their hospital course; half of these changes will be detected within 12 hours of presentation.[101,115]

The recommended interval between serial ECGs is not well-established, but obtaining an ECG 15-30 minutes after presentation in a patient still having symptoms is not unreasonable. Unfortunately, scheduling repeat ECGs at intervals may not capture transient electrical changes that accompany ischemia. Hedges et al evaluated the utility of

Figure 2. 12-lead ECG showing left bundle branch block.

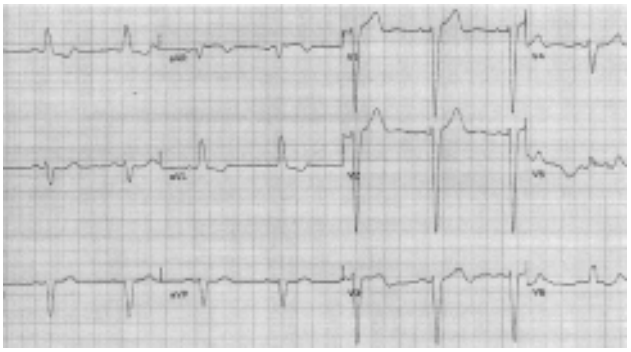


Figure 3. 12-lead ECG showing left bundle branch block with ST segment changes diagnostic of AMI.

The solid arrow shows greater than 1 mm of ST elevation concordant with the QRS in lead V_4. The dashed arrow shows greater than 5 mm of ST elevation discordant with the QRS in lead V_2.

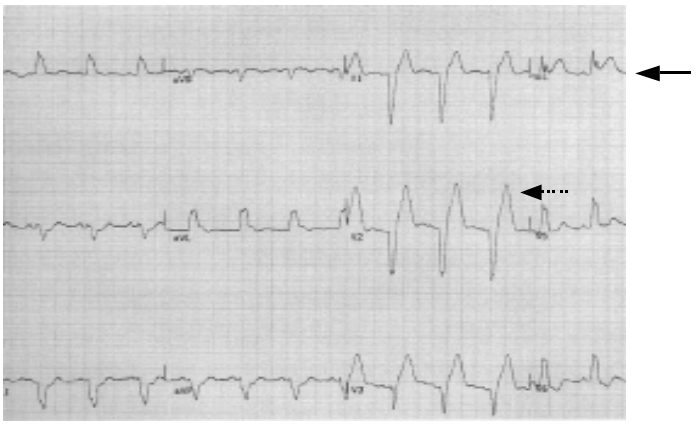


Figure 4. Right ventricular infarct with right-sided leads.

scheduled serial ECGs in patients with suspected AMI and found the sensitivity to be only 39%, though patients with active intermittent symptoms were not evaluated.[116]

The ECG And Pulmonary Embolism

While ECG findings in PE are insensitive, they can be specific in the setting of massive PE, reflecting severe pulmonary hypertension. As the severity of clot burden increases, the ECG may reflect acute pulmonary hypertension and right heart strain. Studies of patients with angiographically confirmed PE demonstrate that T-wave inversion in the anterior precordial leads is the earliest change in patients with pulmonary hypertension from PE.[117] Beware the return visit to the ED of a 30- to 40-year-old patient with persistent chest complaints who had a "normal cath" last week and has an ECG with flipped T-waves in V_1-V_3!

Incomplete right bundle branch block and sinus tachycardia are found more commonly in patients with PE. The supposedly classic finding of an S1, Q3, T3 pattern (an S wave in lead I, Q wave in lead III, and T wave in lead III) is neither sensitive nor specific for PE.[118]

Radiographic Tests

Chest Radiograph

The chest radiograph is another useful and accessible test. About 14%- 23% of chest radiographs of ED patients with chest pain influence management.[119,120]

Pneumothorax And Pneumomediastinum

Pneumothorax and pneumomediastinum are both readily identified by chest radiography. Make the diagnosis of tension pneumothorax clinically, based on hypotension combined with either tracheal deviation or unilateral breath sounds. Waiting for confirmatory radiography can be deadly.

Figure 5. Hampton's hump.

Hampton's hump is a wedge-shaped pleural-based infiltrate that is occasionally seen with PE. Note the density at the right costophrenic angle in this film.

Pulmonary Embolism

The chest x-ray rarely reveals the supposedly classic findings of massive PE: Hampton's hump (a wedge-shaped infarct downstream from the emboli—see **Figure 5**), Westermark's sign (prominent pulmonary hilum with peripheral oligemia), or Fleischner's sign (dilated sausage-shaped pulmonary artery). While these signs are occasionally useful, none is sensitive or specific.[121]

The most common radiographic findings include a blunted costophrenic angle, atelectasis, and/or parenchymal areas of increased opacity.[121]

"There is no disease more conducive to clinical humility than aneurysm of the aorta."—William Osler, circa 1900[122]

Aortic Dissection

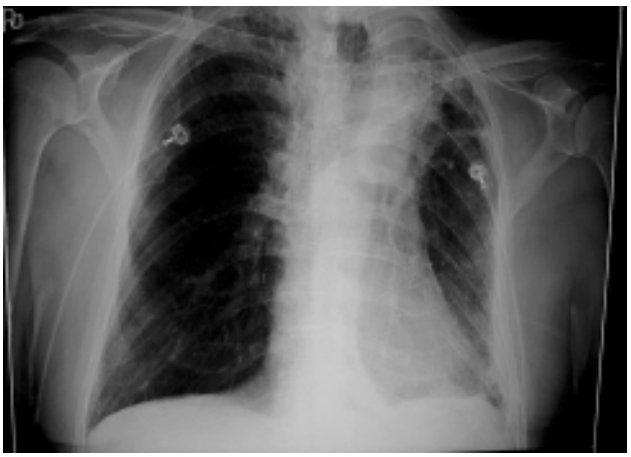
The chest radiograph (see **Figure 6**) is often helpful in case of aortic dissection, as normal chest films occur in only 11% of patients.[33] However, a normal aortic contour and mediastinum are seen in 20% of patients. The egg-shell sign (defined as a greater than 5 mm interval between the calcification along the aortic arch and lateral [adventitial] margin of the aorta) on chest radiograph is fairly specific for dissection but is reported in only 14% of patients.[33] (See **Figure 7** on page 12.)

Echocardiography

Echocardiography is very useful in the bedside evaluation of unstable patients in whom the differential diagnosis includes aortic dissection, PE, and AMI. In regards to transthoracic echocardiography, the accurate detection of wall motion abnormalities, valvular dysfunction, stigmata of PE, and evidence of dissection (apart from tamponade) generally requires advanced echocardiographic skills.

Transesophageal echocardiography is very sensitive in the identification of aortic dissection. Though it provides less-than-perfect images of the ascending aorta, it accurately detects aortic regurgitation and pericardial tamponade.[123,124]

Figure 6. Chest x-ray showing aortic dissection.



In the case of PE, ultrasound can detect signs of right heart strain and pulmonary hypertension, and it may visualize the presence of a clot in the right pulmonary artery.[125] The sensitivity of echocardiography associated with PE ranges from 75% to 80%.[27] However, in patients with a large clot burden and hemodynamic instability, the finding of significant right heart strain may assist the emergency physician in the decision to administer fibrinolytics.[27]

Contrast-Enhanced Computed Tomography For Acute Coronary Syndrome

The refinement of noninvasive imaging technologies—specifically, electron beam computed tomography (EBCT)—has changed the way medicine is practiced. Recently, EBCT has been studied as a means of noninvasive coronary angiography and to quantify the overall calcium "load" in the coronary arteries. However, it cannot accurately localize critical coronary stenosis.[126]

When compared to coronary angiography, EBCT was only 33%-69% sensitive for detecting critical coronary artery stenosis.[127-129] However, in patients with minimal coronary calcium scores, the negative predictive value for significant CAD is 91%-98%.[126,127,129] EBCT is only useful in excluding patients with CAD (i.e., it has a high negative predictive value). It is only 50% specific for ACS, as presence of calcium in an artery does not equate to the presence of coronary ischemia.

CT Angiography For Aortic Dissection

Given its sensitivity, rapidity, and availability, the diagnostic modality of choice in suspected aortic dissection is helical CT with intravascular contrast.[130,131] (See **Figure 8**.) Angiography is now viewed as excessively invasive, slow, and expensive for a screening test. However, for patients too unstable to travel to the CT scanner, bedside transesophageal echocardiography is both sensitive and specific in making the diagnosis and localizing the intimal tear.[132]

CT Angiography For Pulmonary Embolism

In many centers, spiral CT angiography has emerged as the diagnostic modality of choice to evaluate possible PE due to its availability, safety, and ability to elucidate alternative diagnoses such as aortic dissection, malignancy, and pneumonia.[133-136] Spiral CT performs exceptionally well in detecting emboli in the main pulmonary artery and first segmental branches—with a sensitivity and specificity over 94%.[137,138] In early studies, CT scans had difficulty detecting subsegmental pulmonary thrombosis (which accounts for up to one-third of patients with PE), with sensitivities falling to 50%-70%.[26] However, the latest-generation CT scanners employing a multi-detector row spiral technique use 1-2 mm image reconstruction to visualize subsegmental PE. Preliminary studies suggest that these new-generation CT scanners will have an even higher sensitivity and specificity for the detection of PE.[139-141] Importantly, outcome studies (i.e., studies that focus on the risk of death or recurrent PE) demonstrate that CT scan is reliable in identifying and excluding clinically significant PE.[142-146]

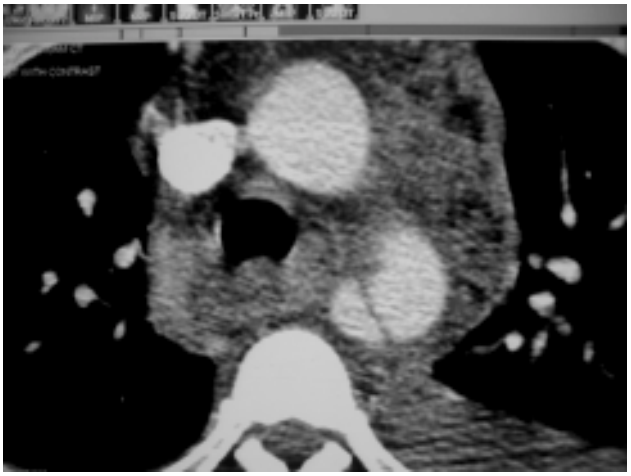
Including CT venography markedly improves sensitivity. In this technique, delayed venous images are obtained through the deep venous system of the pelvis and proximal lower extremities. Cham et al reported that CT venography in conjunction with CT angiography identified an additional 18% of patients deserving treatment (16 patients with negative CT angiography had positive CT venography).[147]

It is unclear whether V/Q scans perform better in detecting subsegmental emboli. Ultimately, the choice between V/Q and CT angiography should involve the risk of dye load to the patient, the availability of the imaging modalities, and which study the attending radiologist is most confident interpreting. The PIOPED-2 trial will study these two modalities head-to-head.[248]

Figure 7. The egg-shell sign.

The egg shell sign, defined as a greater than 5 mm interval between the calcification along the aortic arch and lateral (adventitial) margin of the aorta, is specific but insensitive for dissection. Note the calcific line on the aortic knob.

Figure 8. CT scan showing aortic dissection.



Ventilation/Perfusion Scans

For over 30 years, V/Q lung scans have been favored as the initial test in suspected PE.[26] Though a high-probability V/Q scan has a 90% positive predictive value for PE and a normal V/Q scan can exclude PE, most scans (78%) fall into the non-diagnostic category (intermediate, indeterminate, or low probability), where the incidence of PE ranges from 10%-30%.[27] V/Q scans are especially likely to be non-diagnostic in patients with an abnormal chest x-ray.[148]

Laboratory Tests

Complete Blood Count And Electrolyte Panels

Although some physicians routinely order an electrolyte panel and CBC in patients complaining of chest pain, these studies rarely affect clinical decision-making. A baseline creatinine level is useful in the older or compromised patient who requires a contrast-enhanced study; the renal transplant patient suspected of PE who has a creatinine of 3.0 may be better served by a V/Q scan than a contrast-enhanced spiral CT. Routine screening with chemistry panels in low-risk patients is insensitive, cost-ineffective, rarely alters clinical decision-making, and is not recommended.[149] However, the interpretation of cardiac stress testing may be influenced by electrolyte abnormalities, particularly potassium and magnesium. For this reason, in some institutions, physicians routinely obtain and correct electrolytes in patients undergoing cardiac stress testing.

While the CBC is the most frequently ordered test in EDs, routine CBCs are cost-ineffective and are not recommended in patients complaining of chest pain.[149] However, when clinical signs (pale skin or mucosa, heme-positivestool, etc.) suggest anemia, a bedside hemoglobin can immediately direct clinical interventions. A baseline CBC is also warranted in patients who will undergo reperfusion therapy. One recent study of 153,213 patients 65 years or older showed that the white blood cell count within 24 hours of admission strongly predicts short-term mortality and morbidity in patients with AMI.[150]

Arterial Blood Gas

Alveolar-arterial oxygen gradient, once thought to be a sensitive indicator of pulmonary shunt, performs no better than a coin toss in predicting PE. Further, a normal alveolar-arterial gradient does not exclude the diagnosis of PE.[27,151] However, in one study, the combination of a normal gradient plus a PCO_2 of greater than 36 mmHg had a 98% negative predictive value for PE.[152] Still, in the vast majority of cases, the arterial blood gas has no diagnostic utility for PE.

D-dimer

Several trials have evaluated the utility of bedside D-dimer assays in conjunction with either clinical criteria or indices of gas exchange in the evaluation of suspected PE.[26-28] For the bedside evaluation to be most useful, patients must be categorized as non-high-risk for PE using a clinical scoring system.

If a bedside D-dimer such as the SimpliRED assay is used, then the best-validated diagnostic option is to use the Canadian low-risk criteria, also known as the Wells score. (See **Table 5** on page 14.) In a prospective study of 930 patients with suspected PE, a combination of a negative SimpliRED D-dimer plus a low-risk Canadian rules score had a negative predictive value of 99.5%.[29]

Kline and Wells have proposed point-of care testing for PE using a D-dimer assay combined with measurement of end-tidal CO_2. The details of the data collection procedure are described in an upcoming study.[30] The first step in their algorithm involves a clinical decision rule (a simplified version is shown in **Table 6** on page 14) to determine which patients have an acceptable or safe pretest probability. Patients declared high-risk by this rule should proceed directly to the CT or ventilation/perfusion (V/Q) scanner. Non-high-risk patients are evaluated by the combination of a bedside D-dimer (SimpliFY) and the alveolar dead space measurement computed from a deep-exhaled CO_2 measurement coupled with an arterial $PaCO_2$ measurement. These data are entered into the following equation to estimate the percentage of alveolar dead space (< 20% is normal):

$$\mathbf{100\% \times (PaCO_2 - etCO_2) / PaCO_2}$$

Patients with a positive D-dimer or an alveolar dead space of greater than 20% require CT angiography of the lungs or V/Q scanning. The authors have studied over 1700 patients with this protocol. The protocol has been negative in 60% of patients (thus obviating the need for CT or V/Q scanning in this 60%) and has had an overall false-negative rate less than 1% (using a 90-day outcome of PE, deep venous thrombosis [DVT], or unexpected death). Moreover, the protocol has not led to an increase in the net rate of imaging and was associated with a reduced length of stay for patients evaluated for PE.[31] (See also "Clinical Pathway: Probability Of Pulmonary Embolism" on page 18.)
D-dimer assays may be useful in excluding PE in low-risk patients. There are several different types of assays. The ELISA is a sensitive quantitative test, available in a rapid format, that takes 30 minutes to complete. (It is produced by VIDAS, in Biomerieux, France, which is now owned by Roche.) However, the number of published studies that systematically examine outcome after a normal rapid ELISA D-dimer in outpatients is too small to permit conclusions about its utility.[153,154] The turbidimetric assay also provides accurate, rapid quantitative results available within 15 minutes. In a meta-analysis, Brown et al found the diagnostic sensitivity of the turbidimetric-based D-dimer to be 93% and the specificity to be 51%—performing similar to the standard ELISA assay.[153]

At least three different qualitative D-dimer assays are available, and several can be used at the bedside. The latex assay is commonly used but has marginal sensitivity.[27] Second-generation D-dimer assays are both sensitive and specific, and they can be performed in real time at the bedside.[27,155,156] These tests include the red blood cell agglutination assay, SimpliRED or SimpliFY (Agen Biomedical, Ltd., Brisbane, Australia), Instant IA (Stago, Asnieres, France), and immunofiltration assays such as NycoCard D-dimer (NycoMed Pharma AS, Norway).[27] Sensitivities of

these tests range from 75%-98% in the detection of PE, with specificities of 30%-60%.[27]

Cardiac-Specific Markers

Cardiac biomarkers, including myoglobin, CK-MB, and troponin T and I, are proteins released into the circulation as a result of myocardial cell necrosis. Any process causing myocardial cell death (including myocarditis, toxins, trauma, AMI, and sepsis) can elevate these markers.

The old World Health Organization definition of AMI involved any two of the following criteria: a clinical history suggestive of cardiac ischemia, ECG findings characteristic of myocardial injury pattern, and/or diagnostic elevation in serum biomarkers.[157] In clinical practice, this definition can be difficult as only 40%-60% of patients have a diagnostic ECG on presentation.[157-159] Thus, in the old scheme, for roughly half of patients presenting with AMI, the diagnosis rested on the shoulders of serum biomarkers.[157-159] Under the new guidelines, this number will dramatically increase.

The new European Society of Cardiology/American College of Cardiology guidelines define AMI as a typical rise and gradual fall of troponin or a more rapid rise and fall of CK-MB with at least one of the following:

- ischemic symptoms;
- development of pathologic Q-waves on the ECG;
- ECG changes indicative of ischemia (ST segment elevation or depression); or
- coronary artery intervention (e.g., coronary angioplasty).[160]

One prospective study of 80 patients admitted with suspected ischemic chest pain (excluding those with diagnostic ECG changes) compared the old vs. new criteria for AMI. Among patients with ACS but non-diagnostic ECG changes, 40% (32/80) fulfilled the new criteria for myocardial infarction using high-sensitivity cardiac troponin I measurement, compared with only 29% (23/80) using the World Health Organization diagnostic criteria.[161]

For the emergency physician, the questions are clear even if the answers are not: Which biomarkers drawn at what time intervals can rapidly and reliably diagnose AMI? Because the holy grail of serum biomarkers has yet to be identified, combinations of assays are commonly employed.[157,159]

Creatine Kinase And CK-MB

Creatine kinase (CK) is cardiac serum marker found in both cardiac and skeletal muscle. Abnormal levels of CK can be detected as early as three hours following the onset of AMI and peak at 12-24 hours; they normalize by 3-4 days.[162] The sensitivity and specificity of CK (not CK-MB) in the diagnosis of AMI, even for serial measurements, is roughly 50%.[163]

Elevated CK-MB levels are highly suggestive of myocardial necrosis.[157] However, trauma, rhabdomyolysis, myositis, muscular dystrophies, and exercise can all elevate levels.[162] CK-MB levels 5% or greater of the total CK are more specific for myocardial necrosis.[162] CK-MB release follows kinetics similar to CK.

Various types of CK assays include CK subforms, CK activity, and CK mass. The activity and mass are closely related, the activity being measured in international units per milliliter while the mass is measured in nanograms per milliliter. In one prospective, double-blind, multicenter

Table 5. Canadian or Wells criteria to determine patient pretest probability for pulmonary embolism.

Variable	Score
Clinical signs and symptoms of DVT	3.0 points
PE as or more likely than an alternative diagnosis	3.0 points
Heart rate greater than 100 bpm	1.5 points
Immobilization or surgery in the previous four weeks	1.5 points
Previous DVT/PE	1.5 points
Hemoptysis	1.0 points
Malignancy (on treatment, or treated in the past six months)	1.0 points

Total score: _____

Score less than 2: Low probability of PE
Score 2.0-6.0: Intermediate probability of PE
Score greater than 6: High probability of PE

**Low probability (score < 2)
+ quantitative D-dimer < 500 mcg/L
safely excludes the diagnosis of PE**

Adapted from: Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med* 2001 Jul 17;135(2):98-107.

Table 6. Kline criteria for rapid rule-out of pulmonary embolism using D-dimer and alveolar dead space.

If any two boxes are checked, patient is unsafe for rule-out of pulmonary embolism:

- [ ] Age greater than 50 years or heart rate greater than systolic blood pressure
- [ ] Recent surgery (requiring general anesthesia in past four weeks)
- [ ] Unilateral leg swelling (asymmetry on visual examination)
- [ ] Hemoptysis
- [ ] Unexplained room air pulse oximetry less than 95% (nonsmoker, no asthma, no chronic obstructive pulmonary disease)

If any two boxes are checked, the patient is classified as high-risk (40% pretest probability) for PE and unsafe for bedside rule-out with D-dimer and alveolar dead space. Such patients require an imaging study (V/Q scan or CT angiography).[26-28]

Source: Kline JA,Wells PS. Methodology for a rapid protocol to rule out pulmonary embolism in the emergency department. *Ann Emerg Med* 2003. (In press) (To see the originally described Kline rule, go to: Kline JA, Israel EG, Michelson EA, et al. Diagnostic accuracy of a bedside D-dimer assay and alveolar dead-space measurement for rapid exclusion of pulmonary embolism: a multicenter study. *JAMA* 2001 Feb 14;285(6):761-768.)

study of nearly 1000 patients, CK-MB subforms were the most reliable early markers (within six hours after symptom onset) of AMI, and total CK-MB activity was the most reliable later marker.[164] The subforms (MB_1 and MB_2) had a sensitivity, specificity, and negative predictive value of 92%, 89%, and 97%, respectively, at six hours.

The sensitivity of CK-MB in diagnosing AMI is time-dependent. Levels drawn less than four hours from symptom onset are only 25%-50% sensitive, increasing to 50%-70% at four hours and 60%-100% at 8-12 hours.[157,165-169]

Rapid serial CK-MB sampling, where levels are drawn every hour for the first 2-3 hours, can expedite the diagnosis of AMI. Fesmire evaluated 578 patients admitted for chest pain with non-diagnostic ECGs.[170] He found that a rise in CK-MB (delta CK-MB ≥ +1.5) or a rise in troponin over two hours was nearly 90% sensitive in detecting AMI, compared to only 75% when using absolute CK-MB values.[170] Further, an unchanged two-hour delta CK-MB carried a 99% negative predictive value for AMI.

Troponins: A New Gold Standard

Cardiac troponins are contractile proteins found in both skeletal and cardiac myocytes. There are three types of troponins: troponin I, troponin T, and troponin C. The troponins I and T found in cardiac myocytes are structurally distinct from those in skeletal muscle, making them specific for myocardial necrosis. Troponins are first detected in serum 3-6 hours following myocardial cellular necrosis, and they remain elevated for 4-8 days.[157-159] Troponin I and troponin T have sensitivities of 50% within the first four hours of symptoms but are positive in greater than 95% of AMI patients eight hours following symptom onset.[157,171-176]

There is a clear relationship between the level of troponin release and the amount of myocardial necrosis, which is not necessarily true for CK-MB.[158,177-180] A mounting body of evidence suggests that even mild elevations in troponins represent myocyte cell death and not reversible injury.[158] Patients diagnosed with "unstable angina with positive troponin" are probably more accurately described as having sustained a small NSTEMI.[157-159,175,181] Such patients demonstrate the same risk for complications as those with AMI.[157]

In short, because of their exquisite sensitivity and reasonable specificity, troponins represent the new gold standard for the diagnosis of AMI. A meta-analysis that included over 11,000 patients showed that in those with non-ST-segment elevation ACS, an abnormal troponin increases the short-term odds of death three- to eightfold.[182]

Despite their high specificity, troponins have their limitations. Spurious or sporadic troponin elevations may be a common occurrence as the number of tests ordered increases. In a study of 1000 patients with chest pain presenting to a large urban hospital emergency room, nearly half of the positive troponins (> 0.6 ng/mL) were isolated elevations not secondary to MI.[183]

Continued on page 20

Cost- And Time-Effective Strategies For Chest Pain

1. Use a sensitive D-dimer assay in conjunction with a clinical scoring system (or end-tidal CO_2, if available) to evaluate patients with PE.

A sensitive D-dimer combined with a low clinical probability score or a normal dead space analysis can safely rule out PE rapidly and inexpensively in many patients.

Caveat: A D-dimer assay alone is not sufficiently sensitive to exclude PE in those with a high pretest probability of disease. If using the Kline approach of dead space analysis plus D-dimer, be sure that the patient does not have any high-risk features. (See **Table 6** on page 14.)

2. If you do not have a chest pain center, consider outpatient provocative testing rather than admission.

Low-risk patients with a normal ECG and a negative six-hour troponin level may not require admission but instead may be scheduled for outpatient stress testing.

Caveat: Patients must be low-risk, not have continuing pain, should have a normal or nearly normal ECG, and should have a negative troponin drawn at least six hours after the onset of pain. Follow-up must be ensured.

3. Consider a shortened rule-out protocol prior to stress testing for low-risk patients with chest pain.

While many centers continue to use an eight- to 12-hour interval in which patients receive serial cardiac markers with or without continuous ST segment monitoring, a shorter evaluation period may be safe and effective. Six-hour protocols are becoming common, and several studies have demonstrated the safety of a 90-minute protocol.[195,196,211]

Caveat: Not only do 90-minute protocols rely on bedside triple markers (CK-MB, troponin, and myoglobin), but they also incorporate the change in markers over time to achieve high sensitivity. Many authorities still consider 90-minute rule-outs excessively short.

4. Consider immediate stress testing in low-risk patients.

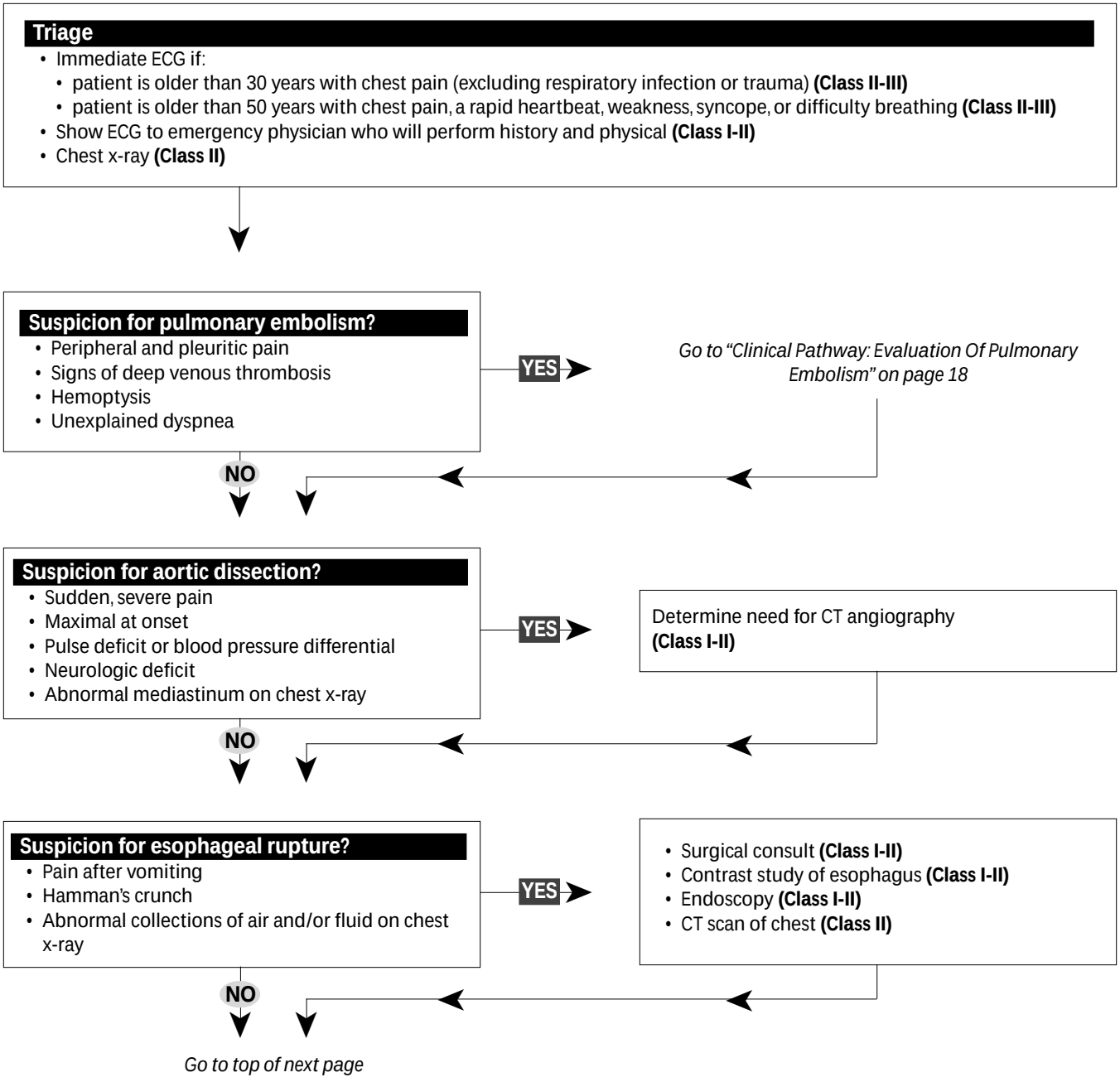
Instead of prolonged observation including serial testing of cardiac markers, some centers immediately stress low-risk patients to evaluate for cardiac disease. Trained emergency physicians can accurately interpret graded exercise stress tests performed on site.

Caveat: To safely employ this strategy, the patient must be pain-free and have a normal ECG (including no evidence of Wellens' syndrome). While immediate stress testing has been studied even in patients with known CAD, most centers would perform serial markers on this population.

5. Employ bedside cardiac markers.

The use of point-of-care technology can speed decisions in patients with chest pain. Those with positive troponins can be consulted to cardiology minutes after arrival despite a normal ECG. The accuracy of these tests is comparable to standard laboratory assays. ▲

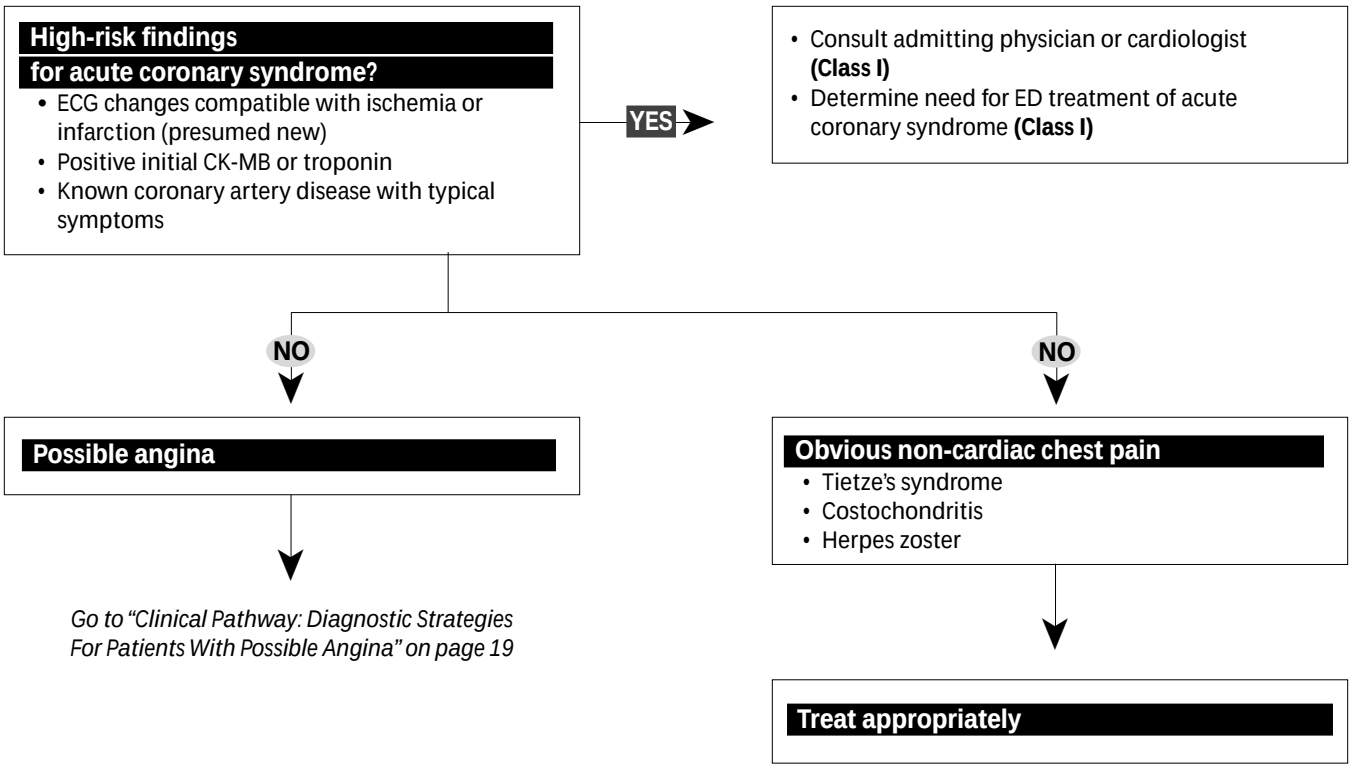
Clinical Pathway: Diagnostic Algorithm For Stable Patients With Chest Pain



The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Clinical Pathway: Diagnostic Algorithm For Stable Patients With Chest Pain (continued)



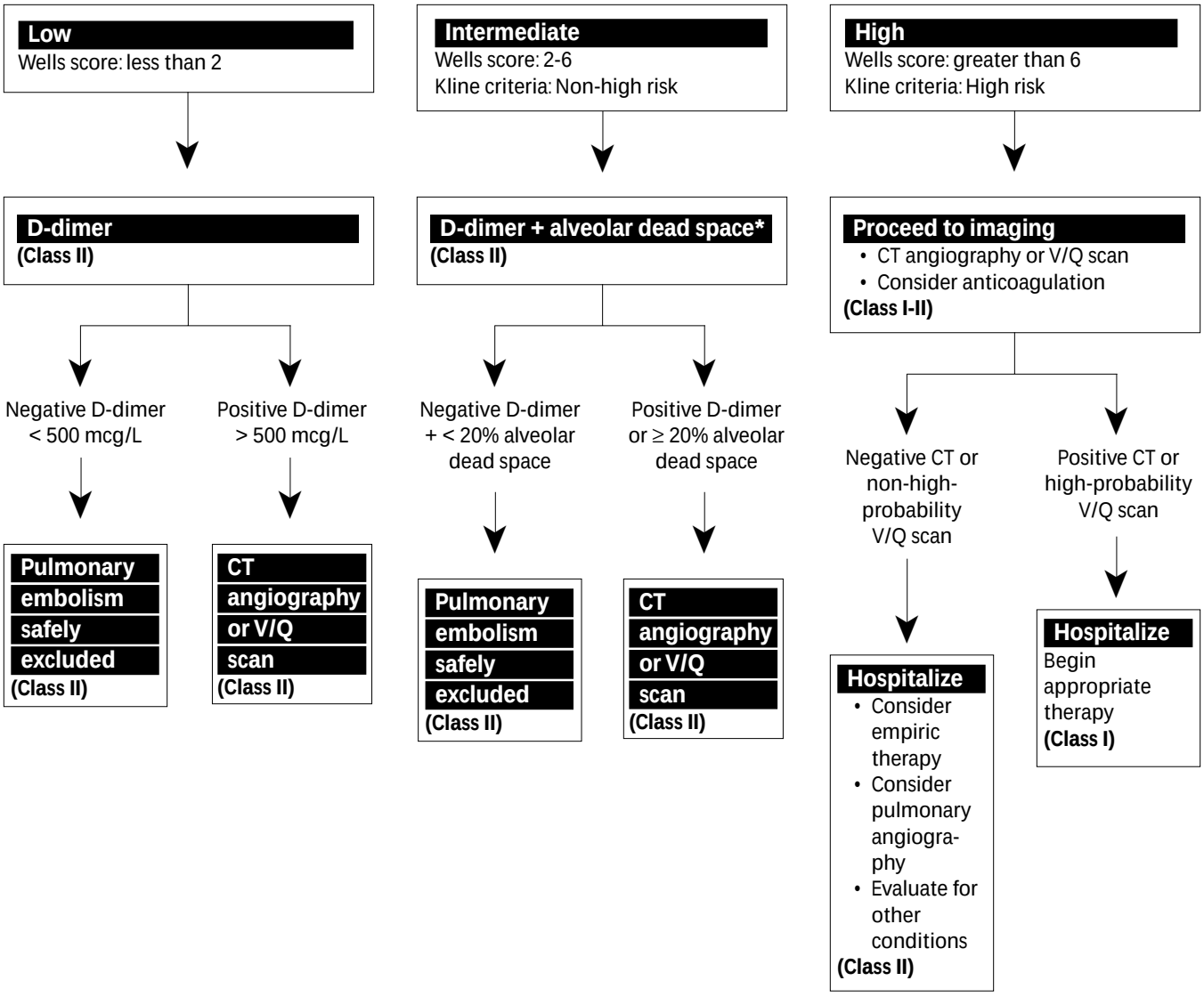
Go to "Clinical Pathway: Diagnostic Strategies For Patients With Possible Angina" on page 19

The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Clinical Pathway: Evaluation For Pulmonary Embolism

Note: See Wells criteria and Kline criteria for assessing probability of pulmonary embolism in Table 5 and Table 6 on page 14.



* The Wells algorithm uses only D-dimer and a clinical score (not dead space analysis). The Kline criteria use clinical criteria, D-dimer, and dead space analysis.

The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Clinical Pathway: Diagnostic Strategies For Patients With Possible Angina

Note: Patients who develop ECG changes, positive cardiac markers, arrhythmias, clinical deterioration, or recurrent ischemic pain during the chest pain protocol should be admitted to the hospital

No ECG evidence of ischemia or infarction and negative initial cardiac markers

Option 1

Immediate provocative testing
(Class II-III)
Low-risk patients with normal ECGs and resolved pain may undergo immediate stress testing

Cocaine chest pain
(Class II-III)
- Serial troponins over 6-12 hours
- Outpatient stress testing

If markers negative, then outpatient stress testing (2-6 weeks). If markers positive, admit to hospital. **(Class I)**

Option 2

Chest pain protocol

90-minute chest pain protocol
(Class III)
- Cardiac markers at 0, 30, 60, and 90 minutes
- Measure change in markers over time
- ± continuous ST segment monitoring
- Provocative testing (see text)

If markers negative, then provocative testing (see text). If markers positive, admit to hospital. **(Class I)**

Option 3

Outpatient provocative testing
(Class II-III)
Low-risk patients with no ST segment abnormalities and a negative troponin measured six hours or more after symptom onset can be scheduled for urgent outpatient testing

6- to 12-hour chest pain protocol
(Class II)
- Cardiac markers over 6-12 hours including markers at beginning and end of protocol
- ± continuous ST segment monitoring
- Provocative testing (see text)

If markers negative, then provocative testing (see text). If markers positive, admit to hospital. **(Class I)**

The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Continued from page 15

Those with renal disease present another conundrum. At least one study suggests that cardiac troponin I cannot predict mortality and hospital admissions in asymptomatic patients with chronic renal failure treated with long-term hemodialysis.[184] Another trial, however, disputes this claim.[185]

More significantly, troponins may be elevated in PE. In a prospective, double-blind study of 36 patients with acute PE, more than one-third had elevated serum troponin I concentrations.[186] Troponins are also elevated in patients with pericarditis/myocarditis.[187]

Myoglobin

While myoglobin is sensitive in detecting AMI, it is not specific to cardiac muscle. For this reason, if measured, myoglobin must be used in conjunction with additional cardiac markers and never alone. Following AMI, myoglobin is first detectable in 1-4 hours, peaking at 6-9 hours, and completely clearing from the serum in 12-24 hours. A single myoglobin level drawn within eight hours of symptom onset is 24%-60% sensitive for AMI.[157,169,173,188,189] However, serial measurements of myoglobin improve the test performance significantly. Within two hours of presentation, a myoglobin value that doubles is greater than 95% sensitive

Ten Pitfalls To Avoid

1. "How could she have had a heart attack? She was only 45 years old, had a normal ECG, and no cardiac risk factors."

The biggest groups of patients with cardiac disease missed in the ED include women under 55 year of age and those with atypical pain. Appropriate use of cardiac markers, close scrutiny of the ECG, and provocative testing may be necessary to secure the diagnosis.

2. "But his pain sounded like reflux and was even relieved by a GI cocktail. I gave him an antacid and a referral to a gastroenterologist."

A burning or indigestion type of pain is often associated with cardiac disease in intermediate-risk patients (more often than a crushing-type pain), and relief of pain with a GI cocktail is *not* diagnostic.

3. "But the left bundle branch block was old—I even got a prior ECG to prove it."

It is very difficult (some say almost impossible) to diagnose AMI in the presence of a left bundle—and individuals with a left bundle branch block have underlying cardiac disease in the first place. Use cardiac markers and be liberal in admission or observation in such patients with chest pain.

4. "I thought she had pleurisy; her pulse ox was normal and her legs weren't swollen."

It was PE. A quarter of all patients with PE have normal oxygen saturation, and most have a normal extremity examination.

5. "He had ECG changes and severe chest pain; why did I need a chest film?"

Because he had an aortic dissection. Nearly half of all patients with dissection have some ECG changes. Almost 10% have dissection involving the coronary arteries, in which case the ECG may show an AMI.[33]

6. "I only did one set of enzymes because his pain was atypical."

One set won't do. If your suspicion is high enough to get enzymes in the first place, it should be high enough to do them right—serial levels over a six- or eight-hour period (or delta levels over a shorter period). One negative set drawn more than six hours after pain onset accompanied by a normal ECG may be an exception to this rule.

7. "The pain wasn't ripping or tearing; it didn't even radiate to his back."

We know from the International Registry of Acute Aortic Dissection that the pain of dissection is sudden and severe and is often maximal at onset, but otherwise it may not fit the "classic" description. Perform a detailed physical examination looking for a pulse deficit or neurologic abnormalities, scrutinize the chest film for mediastinal changes, and order CT angiography when the diagnosis remains in doubt.

8. "He was just another cocaine chest pain case—we see them all the time."

Up to 6% of patients with cocaine associated chest pain may be having an MI.[47,48] Obtain an ECG. (Note that many cocaine users without coronary disease may have chronic elevations of their ST segments.) Serial enzyme testing with outpatient provocative testing is a safe strategy for those with ischemic-sounding pain.

9. "I know she had coughed up some blood, but she had an infiltrate on chest x-ray and a temperature of 101˚F."

She also had lupus (and you forgot to ask her about her prior DVT). Patients with PE frequently have a low-grade fever and may present with an infiltrate on chest x-ray. Be dogged in questioning about risk factors, and obtain necessary studies when the diagnosis remains in doubt.

10. "He had left ventricular hypertrophy with strain and a negative set of enzymes at six hours—that *New England Journal of Medicine* article said it was okay to send them home."

Hamm et al's 1997 article suggested that a patient was low risk if he or she had a negative six-hour troponin level, no ongoing pain, and no significant ST segment abnormalities.[200] Left ventricular hypertrophy with repolarization changes remains a high-risk ECG. ▲

and specific for AMI.[190] Still, frequent false-positive myoglobin elevations due to cocaine use, alcoholism, renal disorders, and muscle trauma limit its use in some settings.

While some believe elevated myoglobin levels may be helpful as an early screening test, the test *cannot* be used to direct treatment, as in giving fibrinolytics without ST elevation or new left bundle branch block.[191]

Which Markers And How Often?

Serial measurement of biomarkers is more accurate than single measurement for the identification of AMI, but the sensitivity for acute cardiac ischemia, even with serial testing, remains extremely low.[192] Kontos found that by combining CK-MB, myoglobin, and serial ECGs at zero and four hours, sensitivity increased to over 90% for the detection of AMI.[193] The CHECKMATE study was a prospective multicenter study of 1005 patients with non-diagnostic initial ECGs admitted to one of six chest pain units. They compared a panel of three bedside markers (myoglobin, CK-MB, and troponin I) to local laboratory testing. The rapid bedside multi-marker testing strategy proved superior to single-marker local laboratory testing in patients with chest pain and without ST segment elevation.[194]

It is traditionally felt that both CK-MB and troponin require at least 6-9 hours following symptom onset before being maximally reliable in identifying AMI (although measuring changes in biomarker concentration rather than absolute value may provide earlier detection of AMI). Yet several recent studies have suggested 90-minute "rule-out" protocols. Recently a study performed at the Veterans Affairs Medical Center evaluated 1285 consecutive patients with signs and symptoms of cardiac ischemia. Physicians used clinical history, ECG findings, and bedside triple cardiac markers (CK-MB, troponin T, and myoglobin) to detect 100% of AMIs within two hours of arrival to the ED.[195] In this study, point-of-care markers were drawn at 0, 30, 60, and 90 minutes, and positive markers were defined as: sustained positive troponin-I (cTnI); sustained positive CK-MB at three or six hours; and increasing myoglobin greater than 25% over 90 minutes with a final value of greater than 150 ng/mL if the patient had chest pain within six hours. Ninety percent of patients with negative cardiac markers and a negative ECG at 90 minutes were discharged home; one patient (0.2%) returned with an MI within the next 30 days.

In another prospective study of 817 patients with possible infarction, a 90-minute bedside assay protocol for myoglobin and cTnI was 97% sensitive (and 53% specific) in detecting AMI.[196] However, this study has been criticized for incorporation bias, post-hoc analysis, wide confidence intervals, and poor discriminative value.[197] Despite these two large trials arguing for a 90-minute protocol, most other studies suggest a longer "rule-out" period.[198]

Bedside point-of-care assays for cardiac markers perform very well, with sensitivities greater than 97% for AMI, and may prove to be time- and cost-effective.[171,199] The National Academy of Clinical Biochemistry advises the implementation of point-of-care test systems if the hospital logistics cannot consistently deliver cardiac marker results within one hour.[159]

Reliance on a single marker taken at the time of presentation to exclude ACS is hazardous. If a patient's condition warrants cardiac biomarkers, he or she is usually committed to serial levels over a period of hours. One exception may be the patient who presents more than six hours after the onset of chest pain. Data indicate that troponins measured six hours or more after pain onset are sensitive predictors of short-term complications (within 30 days).[200]

Decision Support Models

There are a number of decision aids to help the physician determine the likelihood of either acute cardiac ischemia or the risk of complications in patients presenting with chest pain. Some of these are computerized, while others are not.

The Goldman protocol stratifies patients with suspected MI into categories (very low risk, < 1%; low risk, ~4%; intermediate risk, ~8%; and high risk, > 16%) according to the risk of major cardiac events within 72 hours after admission. This algorithm is based on historical features, physical examination, and ECG findings.[69] Historical factors include known unstable ischemic heart disease (which is defined as a worsening of previously stable angina), the new onset of post-infarction angina or angina after a coronary-revascularization procedure, or pain similar to a prior MI. Important physical findings include systolic blood pressure below 110 mmHg and rales heard above the bases bilaterally on physical examination. Important ECG findings include new ST segment elevation of 1 mm or more, pathologic Q waves in two or more leads, ST segment depression of 1 mm or more, or T-wave inversion in two or more leads. In the past, the Goldman criteria have reliably risk-stratified patients as to the level of hospital care (e.g., intensive care unit vs. telemetry) but have not identified any subset safe for ED release. In a trial of nearly 1000 patients who met both the low-risk Goldman criteria and had a single negative troponin I level, almost 5% went on to have an adverse event within 30 days of ED presentation.[201]

ACI-TIPI is a computer-assisted risk-stratification tool to determine the likelihood of symptomatic CAD in patients presenting to EDs complaining of chest pain.[202] This model incorporates age, sex, chief complaint of left arm pain, chest pain or pressure, Q waves, ST segment elevation or depression, and degree of T wave elevation or inversion. In a multicenter trial of over 10,000 patients, the ACI-TIPI model reduced unnecessary hospitalizations while appropriately identifying patients with acute coronary syndromes. If widely applied in throughout the United States, over 200,000 unnecessary admissions might be prevented annually.[202]

The Baxt neural network is another program that may aid in the early diagnosis of cardiac ischemia. In one study, 2204 patients presenting to the ED with chest pain who received an ECG were used to train and test an artificial neural network to recognize the cardiac ischemia. Forty variables, including patient history, physical examination,

ECG, and the first set of chemical cardiac marker determinations, were entered into the network. The network was 88.1% sensitive and 86% specific for cardiac ischemia, outperforming ACI-TIPI and the Goldman algorithm.[203]

Kline et al employed computer-assisted attribute matching to estimate pretest probability of ACS in 15,000 ED patients.[204] They used classification and regression tree analysis to select eight attributes: age, gender, race, history of CAD, chest pain reproduced with palpation, diaphoresis, ST segment depression greater than 0.5 mm, and T wave inversion greater than 2 mm. By using an attribute matching method, they classified 2224 of 15,000 patients (15%) as low risk for ACS, and only one of these patients met the 45-day outcome criteria for ACS (MI, revascularization, or death). In this study, computer-assisted attribute matching far outperformed the ACI-TIPI instrument, which only designated 206 of these 15,000 patients (1.3%) as low risk (and also had one patient meet the 45-day outcome criteria).

Disposition

Of the 6 million annual visits to EDs for chest pain, over 70% have a non-cardiac source of their pain.[205] While the combination of cardiac biomarkers and serial ECG monitoring is very effective in the detection of AMI, unstable angina is a much more difficult diagnostic challenge. Timely diagnosis is critical, as many patients with unstable angina will have AMI or death within one year, most within the first two weeks of presenting symptoms.[206,207] Only one-third of patients with unstable angina will have positive biomarkers during their first 24 hours, leaving the majority dependent on provocative testing.[205,208,209]

The choice of which stress test, its timing, and whether it needs to be performed as an inpatient procedure vs. through the ED confronts emergency physicians on every shift. The answer to these questions begins with effective risk stratification. The Medical College of Virginia designed a practical approach to risk stratification of acute coronary syndromes, using a five-level approach.[9] Level 1 patients include those with ST segment elevation mandating emergent reperfusion. Level 2 (high-risk) patients have positive biomarkers, transient ST segment elevation, ST depression, or known CAD with typical symptoms. These patients require intensive care admission with aggressive medical management. Level 3 (intermediate-risk) patients have a moderate probability for unstable angina, are pain-free, and have a non-diagnostic ECG. Level 4 (low-risk) patients have a low probability for unstable angina and a normal or non-diagnostic ECG. Level 5 patients have clinically apparent non-cardiac chest pain. It is the intermediate- and low-risk patients—level 3 and level 4—who benefit most from an ED-based chest pain protocol.

In addition to patient factors, the personality of the attending physician plays an important role in the disposition of chest pain patients. In one study, emergency physicians were designated as "risk seekers," "risk avoiders," and "medium risk," based on a series of psychological tests.[210] The "risk-avoiding" physicians admitted four times the number of patients who complained of chest pain than the "risk-seeking" physicians. Interestingly, the only known death at the six-month follow-up occurred in the "risk-avoiding" group.

Chest Pain Observation Units

ED-based chest pain evaluation centers are becoming commonplace in hospitals across the country. They are usually geographically linked with the ED and rely on relatively strict protocols to rapidly rule out cardiac ischemia. Protocols generally involve ECG monitoring (sometimes serial ECGs and continuous ST segment monitoring), evaluation of serial cardiac markers, and provocative testing. While many protocols involve 6-12 hours of serial testing of biomarkers, others, like the Erlanger chest pain evaluation protocol, are quite compressed. This protocol includes two-hour delta serum marker determinations, automated serial 12-lead ECG monitoring, and selective dual nuclear scanning for category 3 patients (those with possible ACS). Dual nuclear scans involve a resting scans performed with thallium-201 and stress scanning with technetium-99m sestamibi.[211]

A number of authors trumpet the value of continuous ST segment monitoring. Audible and visual alarms alert staff to often asymptomatic changes in ST segment amplitude. Fesmire et al evaluated continuous ST segment monitoring in 1000 ED patients and found that such ischemia monitoring increased the sensitivity in detecting ACS by 16% and, more importantly, expedited reperfusion therapy.[13] High-risk patients with a non-diagnostic initial ECG benefited most from ST segment monitoring.[8,13,212] A recent study by Decker et al found that continuous 12-lead serial ECG monitoring was of limited value in the diagnostic evaluation of intermediate-risk patients managed in the chest pain unit. However, when ST segment changes were present, there was an increased likelihood for an adverse cardiac event.[249] Further prospective, multicenter trials are required before continuous ST segment analysis can be considered the standard of care.

Do these observation units improve patient care, and are they cost-effective? Shesser and Smith published a critical cost analysis in 1994, estimating that chest pain evaluation centers would cost between $378,000 and $3.78 million per life saved.[213] However, several subsequent studies have found otherwise. In these studies, ED chest pain evaluation reduced hospital charges by over 60% (at a savings of $500-$1500 per patient) and decreased the total time spent in the hospital by 10-40 hours per patient.[10,205,214-216] Graff et al reported a reduction in the rate of missed AMI from 4% to 0.4% with the use of ED-based provocative testing.[5]

The economic issue at hand involves the cost-effective evaluation of patients at low-to-moderate risk of cardiac disease vs. the routine evaluation of nearly all patients with chest pain, even those with minuscule or no risk. While chest pain centers are cost-effective for this first category of patient, they may be an extravagant waste of resources for the second.

"*They…are seized while they are walking (more especially if it be*

up a hill and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all this uneasiness vanishes."—William Heberden[217]

Provocative Testing

The most common provocative tests for ACS include graded exercise testing, echocardiography, and nuclear medicine studies (most frequently sestamibi). Graded exercise testing is relatively inexpensive, and a normal test has a strong negative predictive value for adverse cardiac outcomes in one year. Ioannidis et al performed an excellent meta-analysis that demonstrated that echocardiography and technetium-99m sestamibi scanning have good diagnostic accuracy for acute cardiac ischemia and AMI in low- to moderate-risk patients in the ED.[218]

Graded Exercise Testing

Graded exercise testing is the simplest and least expensive form of provocative testing. It requires that patients obtain 70%-85% of predicted maximal heart rate, usually achieved by treadmill or bicycle ergometer. Sensitivities for detecting significant CAD have been reported as low as 70% for graded exercise testing alone.[219,220] However, the prognostic value of a normal graded exercise test (GXT) is very helpful. Several studies have shown that low-risk patients with a normal GXT have extremely low subsequent risk of cardiac events over the next two weeks to six months.[205] Mikhail et al evaluated over 500 patients with serial markers followed by stress testing and reported 100% sensitivity for AMI through a five-month follow-up. Of those patients diagnosed with ACS, over half were diagnosed with graded exercise testing.[221] Zalenski et al evaluated over 300 low-risk patients with serial markers and exercise testing and reported a negative predictive value of 97%.[222] Similarly, Polanczyk et al prospectively evaluated 276 low-risk patients and found that two-thirds had a normal GXT. Of these patients, none had any "hard" complications (death or AMI) at six months.[223] Even a non-diagnostic GXT has a favorable prognostic value, as no patient with a non-diagnostic GXT had subsequent death or AMI at 30-day follow-up.

To be eligible for a GXT, the patient must be symptom-free, have a normal ECG, and be able either to walk on a treadmill or ride a bicycle to achieve 70%-85% predicted maximal heart rate (220 – age). Common excluding factors include significant ST and T wave changes, left ventricular hypertrophy, left bundle branch block, digoxin effect, poor exercise reserve, and, possibly, the use of beta-blockers. Pay special attention to excluding Wellens' syndrome, which is symmetric inverted or biphasic T wave in V_2 and/or V_3 reflective of a proximal left anterior descending coronary artery lesion. (See **Figure 9**.) This finding is an absolute contraindication to stress testing.[224] Although there has been much discussion regarding the increased number of false-positive GXTs in women,[216] several recent small studies show equal utility between the sexes.[205,225] Graded exercise testing remains a valuable tool in evaluating low-risk patients who are able to exercise.

Immediate Stress Testing

Immediate stress testing in the ED, rather than after a prolonged chest pain protocol, may be time- and cost-effective—and especially useful in EDs that do not have chest pain centers. With special training, emergency physicians can accurately interpret exercise tests, and over-reading by cardiologists for quality assurance may be unnecessary.[226]

Kirk et al evaluated immediate stress testing in low-risk patients, *without evaluating biomarkers*.[225] In their group of 212 patients, 59% had negative tests and 28% had non-diagnostic tests. All of the patients with a negative GXT were discharged home, as were 93% of those patients with a non-diagnostic GXT. None of the patients discharged from the ED had any adverse events or mortality at 30-day follow-up. A larger study by Amsterdam et al examined the safety and accuracy of immediate exercise testing in 1000 low-risk patients presenting to the ED with chest pain suggestive of a cardiac etiology.[227] Low-risk patients with no evidence of hemodynamic instability, arrhythmias, or ECG signs of ischemia underwent immediate exercise treadmill testing without serial measurements of cardiac markers. They found that immediate exercise testing is safe and accurate. Several other studies confirm these results.[228-230]

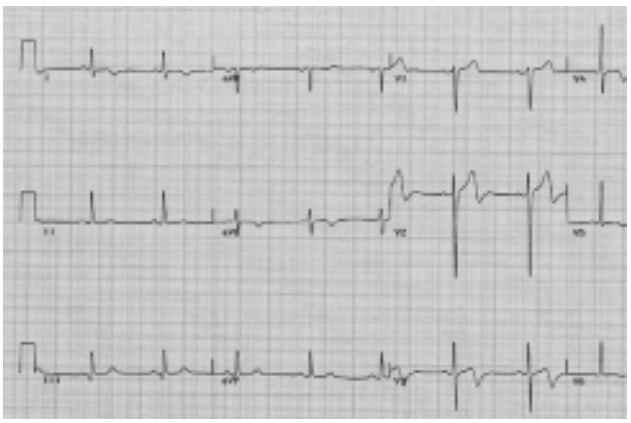
Immediate exercise treadmill testing may be safe even in patients with known CAD. Lewis et al evaluated 100 patients with CAD and a low-risk clinical assessment (hemodynamically stable with non-diagnostic ECG) and found that immediate stress testing was safe and effective in determining which patients required hospitalization.[231]

Echocardiography

Stress echocardiography is commonly used to evaluate patients with chest pain. It provides real-time anatomic and physiologic information during rest and exercise. For patients with poor exercise tolerance, dobutamine will chemically drive the heart rate into the target range. Inducible wall motion abnormalities are the hallmark of critical CAD, though discerning pre-existing wall motion

Figure 9. Wellens' syndrome.

Wellens' syndrome is a symmetric inverted or biphasic T wave in V_2 and/or V_3 that is reflective of a proximal left anterior descending coronary artery lesion.



deficits may be difficult without prior baseline studies.[205] Echocardiography also provides important information regarding valvular function, pericardial disease, right heart strain (found with large pulmonary emboli), and existing myocardial defects such as ventricular aneurysms. For those patients who have ACS with normal or non-diagnostic ECGs, the sensitivity of stress echocardiography is over 85%.[206,232-235] More importantly, low-risk patients with a negative stress echocardiogram have a less than 1% rate for AMI and cardiac death in the subsequent year.[236,237] For those with an abnormal stress echocardiogram, adverse event rates range from 7% to 23%.[236,238] Patients with left ventricular dysfunction (ejection fractions of < 40%) comprise an especially high-risk group, with one-year event rates as high as 20%-25%.[234,236,238]

The limitations of echocardiography include cost, operator dependence in both imaging and interpretation, and occasional difficulty in obtaining quality images in patients who are obese or who have chronic obstructive pulmonary disease.

Myocardial Perfusion Imaging

Technetium 99m sestamibi, tetrofosmin, and thallium 201 provide physiological evidence of myocardial perfusion. Compounds are administered intravenously and are rapidly taken up by viable myocardial tissue. The isotopes are not absorbed by dead or lethally injured myocardium, and ischemic myocardium typically demonstrates a delay in tracer uptake. Images are obtained in two phases—at rest and followed by exercise or chemical stress—which requires up to six hours to obtain both sets of images.

Nuclear perfusion imaging studies report sensitivities for ACS greater than 90%, quantify infarct size, and predict the need for revascularization.[205,206,219,239,240] Tatum et al evaluated over 1000 patients with chest pain presenting to the ED without a history of coronary disease and who had a non-diagnostic ECG.[9] Immediate sestamibi imaging was 100% sensitive for AMI and predicted the need for revascularization in greater than 80% of patients. Other advantages to nuclear imaging lie in the prognostic value. Iskander et al reviewed 14 studies, including over 12,000 patients, and found a hard-event (death or AMI) rate at one year after a normal nuclear scan of 0%-1.8%.[241] Those patients with abnormal perfusion images had a one-year hard-event rate of 7%-30%.[9,241] Scans accurately predicted both infarct size and likelihood of left ventricular dysfunction.

In one study of 1775 low-risk patients with chest pain who had intermediate- and high-risk ACS ruled out by means of a two-hour protocol, stress nuclear scanning was more sensitive and specific than resting nuclear scanning for identification of ACS.[242] When compared to stress echocardiography, nuclear perfusion imaging has similar sensitivity and prognostic value in identifying future cardiac events.[243]

There are significant drawbacks to nuclear imaging. The radioisotopes must be stored in special facilities. Once the patient has been injected with the isotope, he or she must be moved to a radioisotope-approved area for the duration of the scan. The second major drawback is cost. Patient charges range from $1000-$1600 per study.[206] Still, the net effect can be a cost savings, because widespread use of this technology reduces unnecessary hospital admissions by 20%-30%.[244,245] Scanning all low-risk patients, however, would likely be associated with increased costs.[246]

What If You Do Not Have A Chest Pain Center?

Despite the proliferation of chest pain centers, not all emergency physicians have access to these units. How can such emergency physicians make safe and cost-effective decisions in low-risk patients presenting with chest pain? An important study published by Hamm et al in the *New England Journal of Medicine* may help.[200]

In this study, 773 consecutive patients who had had acute chest pain for less than 12 hours without ST segment elevation on their ECGs had bedside measurements of troponin T and troponin I with at least one sample taken at least six hours after the onset of pain. In patients with negative test results, the risk of short-term major cardiac events was very low—1.1% of patients with negative troponin T and 0.3% of patients with negative troponin I results had nonfatal MIs or died during the 30-day follow-up period. Only one patient with a negative troponin T result had a cardiac event within two weeks after discharge.[200] These data suggest that by using the ECG and a troponin level at least six hours after pain, the emergency physician can safely discharge certain patients home for urgent outpatient stress testing. Another alternative is immediate stress testing in the ED as discussed above.

Cutting-Edge Technology

With the expanded pace of cardiovascular research, yesterday's cutting-edge technology is today's orthodox practice. Technologies such as dead space analysis for PE and electron beam CT for CAD are no longer exotic. An interesting new blood assay for ACS is called ischemia-modified albumin. The test is based on the fact that albumin is modified by exposure to ischemic tissue, decreasing its binding to certain metals. In a clinical trial of 256 ACS patients at four medical centers, ischemia-modified albumin on presentation was significantly more sensitive to cardiac ischemia than the initial troponin.[247] Recent data indicate that high-dose dobutamine cardiovascular magnetic resonance with myocardial tagging is extremely accurate in detecting coronary artery disease.[254]

Conclusion

The emergency physician is expert at rapidly identifying life threats and reducing unnecessary use of healthcare resources. Nowhere is this balance so precarious as in the patient with chest pain. Contrary to the expectations of our patients, our charge is not to make a specific diagnosis but instead to rule out life threats. Focus specifically on acute cardiac ischemia or infarction, aortic dissection, PE, and, to a lesser extent, esophageal rupture.

Since clinical features alone can rarely predict which patients may be discharged without further testing, liberal

use of diagnostic tests, including chest x-ray, ECG, and cardiac markers, is often necessary. The use of chest pain protocols involving serial cardiac markers and provocative testing can decrease the likelihood of misdiagnosis.

Acknowledgment

The authors wish to thank Dr. Jeff Kline for his assistance in preparing this manuscript. ▲

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in the paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

1. Amsterdam EA, Lewis WR, Yadlapalli S. Evaluation of low-risk patients with chest pain in the emergency department: value and limitations of recent methods. *Cardiol Rev* 1999 Jan-Feb;7(1):17-26. **(Review)**
2. Barish RA, Doherty RJ, Browne BJ. Reengineering the emergency evaluation of chest pain. *J Healthcare Qual* 1997;19(5):6-12. **(Review)**
3.* Lau J, Ioannidis JP, Balk EM, et al. Diagnosing acute cardiac ischemia in the emergency department: a systematic review of the accuracy and clinical effect of current technologies. *Ann Emerg Med* 2001 May;37(5):453-460. **(Meta-analysis; 106 articles)**
4.* Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000 Apr 20;342(16):1163-70. **(Prospective, multicenter; 10,689 patients)**
5. Graff LG, Dallara J, Ross MA, et al. Impact on the care of the emergency department chest pain patient from the chest pain evaluation registry (CHEPER) study. *Am J Cardiol* 1997 Sep 1;80(5):563-8. **(Retrospective, multicenter; 2229 patients)**
6. Murata GH. Evaluating chest pain in the emergency department. *West J Med* 1993 Jul;159(1):61-68. **(Review)**
7. Karcz A, Korn R, Burke MC, et al. Malpractice claims against emergency physicians in Massachusetts: 1975-1993. *Am J Emerg Med* 1996 Jul;14(4):341-345. **(Retrospective analysis; 549 claims)**
8. Gibler WB, Runyon JP, Levy RC, et al. A rapid diagnostic and treatment center for patients with chest pain in the emergency department. *Ann Emerg Med* 1995 Jan;25(1):1-8. **(Retrospective; 1010 patients)**
9. Tatum JL, Jesse RL, Kontos MC, et al. Comprehensive strategy for the evaluation and triage of the chest pain patient. *Ann Emerg Med* 1997 Jan;29(1):116-125. **(Observational; 1187 patients)**
10. Farkouh ME, Smars PA, Reeder GS, et al. A clinical trial of a chest-pain observation unit for patients with unstable angina. Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. *N Engl J Med* 1998 Dec 24;339(26):1882-1888. **(Prospective, randomized, controlled trial; 212 patients)**
11. *Evaluation of Technologies for Identifying Acute Cardiac Ischemia in Emergency Departments.* Summary, Evidence Report/Technology Assessment: Number 26. AHRQ Publication No. 00-E031, September 2000. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/clinic/epcsums/cardsum.htm. **(Review)**
12.* Goldman L, Weinberg M, Weisberg M, et al. A computer-derived protocol to aid in the diagnosis of emergency room patients with acute chest pain. *N Engl J Med* 1982 Sep 2;307(10):588-596. **(Follow-up study; 482 patients)**
13.* Fesmire FM, Percy RF, Bardoner JB, et al. Usefulness of automated serial 12-lead ECG monitoring during the initial emergency department evaluation of patients with chest pain. *Ann Emerg Med* 1998 Jan;31(1):3-11. **(Prospective, observational; 1000 patients)**
14.* Fruergaard P, Launbjerg J, Hesse B, et al. The diagnoses of patients admitted with acute chest pain but without myocardial infarction. *Eur Heart J* 1996 Jul;17(7):1028-1034. **(Prospective; 204 patients)**
15. Fruergaard P, Launbjerg J, Hesse B. Frequency of pulmonary embolism in patients admitted with chest pain and suspicion of acute myocardial infarction but in whom this diagnosis is ruled out. *Cardiology* 1996 Jul-Aug;87(4):331-4. **(Retrospective; 175 patients)**
16. Wulsin L, Liu T, Storrow A, et al. A randomized, controlled trial of panic disorder treatment initiation in an emergency department chest pain center. *Ann Emerg Med* 2002 Feb;39(2):139-143. **(Randomized, controlled trial; 156 patients)**
17. McNulty PH, Ettinger SM, Gascho J, et al. Comparison of subjective perception of myocardial ischemia produced by coronary balloon occlusion in patients with versus those without type 2 diabetes mellitus. *Am J Cardiol* 2003 Apr 15;91(8):965-968. **(Prospective; 200 patients)**
18. Milner KA, Funk M, Richards S, et al. Gender differences in symptom presentation associated with coronary heart disease. *Am J Cardiol* 1999 Aug 15;84(4):396-9. **(Prospective; 550 patients)**
19. Ghaemmaghami CA, Brady WJ Jr. Pitfalls in the emergency department diagnosis of acute myocardial infarction. *Emerg Med Clin North Am* 2001 May;19(2):351-69. **(Review)**
20.* Then KL, Rankin JA, Fofonoff DA. Atypical presentation of acute myocardial infarction in 3 age groups. *Heart Lung* 2001 Jul-Aug;30(4):285-93. **(Prospective, comparative; 231 patients)**
21. Camargo CA, Lloyd-Jones DM, Giugliano RP, et al. Characteristics and prognosis of patients with acute myocardial infarction who present with atypical symptoms. *Ann Emerg Med* 1998 September;32(3);supplement. **(Retrospective cohort; 584 patients)**
22. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. *Thromb Haemost* 2001 Jul;86(1):452-463. **(Retrospective)**
23. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998 Mar 23;158(6):585-593. **(Retrospective; 2218 patients)**
24. Dalen JE, Alpert JS. Natural history of pulmonary embolism. *Prog Cardiovasc Dis* 1975 Jan-Feb;17(4):259-270. **(Review)**
25. Alpert JS, Smith R, Carlson J, et al. Mortality in patients treated for pulmonary embolism. *JAMA* 1976 Sep 27;236(13):1477-1480. **(Retrospective; 144 patients)**
26. Rodger M, Wells PS. Diagnosis of pulmonary embolism. *Thromb Res* 2001 Sep 15;103(6):V225-238. **(Review)**
27.* Kline JA, Johns KL, Colucciello SA, et al. New diagnostic tests for pulmonary embolism. *Ann Emerg Med* 2000 Feb;35(2):168-180. **(Meta-analysis)**
28.* Kline JA, Israel EG, Michelson EA, et al. Diagnostic accuracy of a bedside D-dimer assay and alveolar dead-space measurement for rapid exclusion of pulmonary embolism: a multicenter study. *JAMA* 2001 Feb 14;285(6):761-768. **(Prospective; 380 patients suspected of having PE)**
29.* Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med* 2001 Jul 17;135(2):98-107. **(Prospective; 930 patients)**
30.* Kline JA, Wells PS. Methodology for a rapid protocol to rule out pulmonary embolism in the emergency department. *Ann Emerg Med* 2003. **(In press)**
31.* Kline JA, Webb WB, Jones AE, et al. Impact of a clinical decision rule and a D-dimer plus alveolar deadspace measurement to rule out pulmonary embolism in an urban emergency department. *Acad Emerg Med* 2003;10:502. **(Prospective, observational; 1905 patients)**
32. Leonard JC. Thomas Bevill Peacock and the early history of dissecting aneurysm. *Br Med J* 1979 Jul 28;2(6184):260-262. **(Historical article)**
33.* Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA* 2000 Feb 16;283(7):897-903. **(Multicenter; 464 patients)**
34. Lemke T, Jagminas L. Spontaneous esophageal rupture: a frequently missed diagnosis. *Am Surg* 1999 May;65(5):449-452. **(Retrospective)**
35. Walker WS, Cameron EW, Walbaum PR. Diagnosis and management of spontaneous transmural rupture of the oesophagus (Boerhaave's syndrome). *Br J Surg* 1985 Mar;72(3):204-207. **(Retrospective; 14 cases)**
36. Curci JJ, Horman MJ. Boerhaave's syndrome: The importance of early diagnosis and treatment. *Ann Surg* 1976 Apr;183(4):401-408. **(Review, case report)**
37. Triggiani E, Belsey R. Oesophageal trauma: incidence, diagnosis, and

management. *Thorax* 1977 Jun;32(3):241-249. **(Retrospective; 110 cases)**
38.* Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 2000 Jun 22;342(25):1855-1865. **(Multicenter; 671 episodes in 538 patients)**
39.* Vichinsky EP, Styles LA, Colangelo LH, et al. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative Study of Sickle Cell Disease. *Blood* 1997 Mar 1;89(5):1787-1792. **(Prospective; 3751 patients)**
40. Bonadio WA. Clinical features of abdominal painful crisis in sickle cell anemia. *J Pediatr Surg* 1990 Mar;25(3):301-302. **(Retrospective; 106 cases in 43 children)**
41. Martin L, Buonomo C. Acute chest syndrome of sickle cell disease: radiographic and clinical analysis of 70 cases. *Pediatr Radiol* 1997 Aug;27(8):637-641. **(Retrospective; 70 cases in 41 patients)**
42. As cited in: Auden WH. *The Oxford Book of Light Verse*. London: Oxford University Press; 1938.
43. Hahn IH, Hoffman RS. Cocaine use and acute myocardial infarction. *Emerg Med Clin North Am* 2001 May;19(2):493-510. **(Review)**
44. Cregler LL. Protracted elimination of cocaine metabolites. *Am J Med* 1989 May;86(5):632-633. **(Letter)**
45.* Hollander JE, Todd KH, Green G, et al. Chest pain associated with cocaine: an assessment of prevalence in suburban and urban emergency departments. *Ann Emerg Med* 1995 Dec;26(6):671-676. **(Prospective, multicenter; 349 patients)**
46. Hollander JE, Hoffman RS, Gennis P, et al. Cocaine-associated chest pain: one-year follow-up. *Acad Emerg Med* 1995 Mar;2(3):179-184. **(Prospective, observational; 203 patients)**
47. Hollander JE, Hoffman RS, Burstein JL, et al. Cocaine-associated myocardial infarction. Mortality and complications. Cocaine-Associated Myocardial Infarction Study Group. *Arch Intern Med* 1995 May 22;155(10):1081-1086. **(Retrospective, multicenter; 136 cases in 130 patients)**
48.* Hollander JE, Hoffman RS, Gennis P, et al. Prospective multicenter evaluation of cocaine-associated chest pain. Cocaine Associated Chest Pain (COCHPA) Study Group. *Acad Emerg Med* 1994 Jul-Aug;1(4):330-339. **(Prospective, multicenter; 246 patients)**
49. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995 Nov 9;333(19):1267-1272. **(Review)**
50. Minor RL Jr, Scott BD, Brown DD, et al. Cocaine-induced myocardial infarction in patients with normal coronary arteries. *Ann Intern Med* 1991 Nov 15;115(10):797-806. **(Review)**
51.* Hollander JE, Vignona L, Burstein J. Predictors of underlying coronary artery disease in cocaine associated myocardial infarction: a meta-analysis of case reports. *Vet Hum Toxicol* 1997 Oct;39(5):276-280. **(Meta-analysis)**
52. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med* 2001 Aug 2;345(5):351-358. **(Review)**
53. Gitter MJ, Goldsmith SR, Dunbar DN, et al. Cocaine and chest pain: clinical features and outcome of patients hospitalized to rule out myocardial infarction. *Ann Intern Med* 1991 Aug 15;115(4):277-282. **(Retrospective; 101 patients)**
54. Weber JE, Shofer FS, Larkin GL, et al. Validation of a brief observation period for patients with cocaine-associated chest pain. *N Engl J Med* 2003 Feb 6;348(6):510-517. **(Prospective; 344 patients)**
55. Marques-Magallanes JA, Koyal SN, Cooper CB, et al. Impact of habitual cocaine smoking on the physiologic response to maximum exercise. *Chest* 1997 Oct;112(4):1008-1016. **(Comparative; 64 patients)**
56. Cigarroa CG, Boehrer JD, Brickner ME, et al. Exaggerated pressor response to treadmill exercise in chronic cocaine abusers with left ventricular hypertrophy. *Circulation* 1992 Jul;86(1):226-231. **(49 patients)**
57. Dribben WH, Kirk MA, Trippi JA, et al. A pilot study to assess the safety of dobutamine stress echocardiography in the emergency department evaluation of cocaine-associated chest pain. *Ann Emerg Med* 2001 Jul;38(1):42-48. **(Prospective; 24 patients)**
58. Aufderheide TP, Hendley GE, Thakur RK, et al. The diagnostic impact of prehospital 12-lead electrocardiography. *Ann Emerg Med* 1990 Nov;19(11):1280-1287. **(Prospective; 151 ECGs)**
59. Purvis GM, Weiss SJ, Gaffney FA. Prehospital ECG monitoring of chest pain patients. *Am J Emerg Med* 1999 Oct;17(6):604-607. **(Case report)**
60.* Ioannidis JP, Salem D, Chew PW, et al. Accuracy and clinical effect of out-of-hospital electrocardiography in the diagnosis of acute cardiac ischemia: a meta-analysis. *Ann Emerg Med* 2001 May;37(5):461-470. **(Meta-analysis; 11 studies, 7508 patients)**
61. Rogers WJ, Bowlby LJ, Chandra NC, et al. Treatment of myocardial infarction in the United States (1990 to 1993). Observations from the National Registry of Myocardial Infarction. *Circulation* 1994 Oct;90(4):2103-2114. **(Retrospective)**
62. Higgins GL 3rd, Lambrew CT, Hunt E, et al. Expediting the early hospital care of the adult patient with nontraumatic chest pain: impact of a modified ED triage protocol. *Am J Emerg Med* 1993 Nov;11(6):576-582. **(Prospective; 382 patients)**
63.* Graff L, Palmer AC, Lamonica P, et al. Triage of patients for a rapid (5-minute) electrocardiogram: A rule based on presenting chief complaints. *Ann Emerg Med* 2000 Dec;36(6):554-560. **(Prospective; 18,759 patients)**
64. Speake D, Terry P. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. First ECG in chest pain. *Emerg Med J* 2001 Jan;18(1):61-62. **(Case report)**
65. Roberts R, Kleiman NS. Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a "new diagnostic mind-set." *Circulation* 1994 Feb;89(2):872-881. **(Review)**
66. Buzzard F. Preparation for medical practice. *Lancet* 1933;2:820. **(Historical reference)**
67. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979 Jun 14;300(24):1350-1358. **(Review)**
68.* Braunwald E, Jones RH, Mark DB, et al. Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. *Circulation* 1994 Jul;90(1):613-622. **(Practice guideline)**
69.* Goldman L, Cook EF, Johnson PA, et al. Prediction of the need for intensive care in patients who come to the emergency departments with acute chest pain. *N Engl J Med* 1996 Jun 6;334(23):1498-1504. **(Multicenter; 10,682 patients [derivation set], 4676 patients [validation set])**
70. Lee TH, Cook EF, Weisberg M, et al. Acute chest pain in the emergency room. Identification and examination of low-risk patients. *Arch Intern Med* 1985 Jan;145(1):65-69. **(596 patients)**
71. Gupta M, Tabas JA, Kohn MA. Presenting complaint among patients with myocardial infarction who present to an urban, public hospital emergency department. *Ann Emerg Med* 2002 Aug;40(2):180-186. **(Retrospective; 721 cases)**
72.* Panju AA, Hemmelgarn BR, Guyatt GH, et al. The rational clinical examination. Is this patient having a myocardial infarction? *JAMA* 1998 Oct 14;280(14):1256-1263. **(Review)**
73.* Goodacre S, Locker T, Morris F, et al. How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? *Acad Emerg Med* 2002 Mar;9(3):203-208. **(Prospective; 893 patients)**
74. McCurren RH, Mikhail MG, Ensign LD, et al. Does time of onset and duration of chest pain reliably exclude the diagnosis of acute myocardial infarction in chest pain observation patients? *Acad Emerg Med* 2001;8:540. **(Prospective cohort; 8723 patients)**
75. Shry EA, Dacus J, Van De Graaff E, et al. Usefulness of the response to sublingual nitroglycerin as a predictor of ischemic chest pain in the emergency department. *Am J Cardiol* 2002 Dec 1;90(11):1264-1266. **(Evaluation study)**
76. Wrenn K, Slovis CM, Gongaware J. Using the "GI cocktail": a descriptive study. *Ann Emerg Med* 1995 Dec;26(6):687-690. **(Retrospective; 97 patients)**
77.* Jayes RL Jr, Beshansky JR, D'Agostino RB, et al. Do patients' coronary risk factor reports predict acute cardiac ischemia in the emergency department? A multicenter study. *J Clin Epidemiol* 1992 Jun;45(6):621-626. **(Prospective, multicenter; 1743 patients)**
78. Singh R, Tiffany B, Bay C, et al. The utility of the traditional coronary artery disease risk factors in risk-stratifying patients presenting to the emergency department with chest pain. *Acad Emerg Med* 2002;9:398-a. **(Prospective, multicenter; 5043 patients)**
79. Rosman HS, Patel S, Borzak S, et al. Quality of history taking in patients with aortic dissection. *Chest* 1998 Sep;114(3):793-795. **(Retrospective; 83 patients)**
80. Hirst AE Jr, Johns VJ Jr, Kime SW Jr. Dissecting aneurysm of the aorta: a review of 505 cases. *Medicine (Balt.)* 1958 Sept;37(3):217-279. **(Review)**
81. Hirata K, Kyushima M, Asato H. Electrocardiographic abnormalities in patients with acute aortic dissection. *Am J Cardiol* 1995 Dec 1;76(16):1207-1212. **(Retrospective; 89 patients)**
82. Susec O Jr, Boudrow D, Kline JA. The clinical features of acute pulmonary embolism in ambulatory patients. *Acad Emerg Med* 1997 Sep;4(9):891-897. **(Prospective, observational; 170 patients)**
83. Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. *Chest* 1997 Oct;112(4):974-979. **(Multicenter; 119 patients)**
84. Bell WR, Simon TL, DeMets DL. The clinical features of submassive and massive pulmonary emboli. *Am J Med* 1977 Mar;62(3):355-360. **(167 patients)**
85. Jeff Kline, personal communication.

86.* No authors listed. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. *JAMA* 1990 May 23-30;263(20):2753-2759. **(Prospective; 933 patients)**

87. Stein PD, Saltzman HA, Weg JG. Clinical characteristics of patients with acute pulmonary embolism. *Am J Cardiol* 1991 Dec 15;68(17):1723-1724. **(Prospective; 155 patients in this arm)**

88. Stein PD, Afzal A, Henry JW, et al. Fever in acute pulmonary embolism. *Chest* 2000 Jan;117(1):39-42. **(Randomized, controlled trial; fever present in 43 of 311 patients)**

89. Stein PD, Willis PW 3rd, DeMets DL. History and physical examination in acute pulmonary embolism in patients without preexisting cardiac or pulmonary disease. *Am J Cardiol* 1981 Feb;47(2):218-223. **(215 patients)**

90. Badgett RG, Lucey CR, Mulrow CD. Can the clinical examination diagnose left-sided heart failure in adults? *JAMA* 1997 Jun 4;277(21):1712-1719. **(Meta-analysis)**

91. Stein PD, Henry JW, Gopalakrishnan D, et al. Asymmetry of the calves in the assessment of patients with suspected acute pulmonary embolism. *Chest* 1995 Apr;107(4):936-939. **(Prospective evaluation of PIOPED data; 232 patients with angiographically diagnosed PE, 446 patients with no PE by angiography, 101 healthy subjects)**

92. Wooley CF, Sparks EH, Boudoulas H. Aortic pain. *Prog Cardiovasc Dis* 1998 May-Jun;40(6):563-589. **(Review)**

93. von Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. *Arch Intern Med* 2000 Oct 23;160(19):2977-2982. **(Prospective; 250 patients)**

94.* Klompas M. Does this patient have an acute thoracic aortic dissection? *JAMA* 2002 May 1;287(17):2262-2272. **(Meta-analysis)**

95. Lee TH. Chest pain in the emergency department: uncertainty and the test of time. *Mayo Clin Proc* 1991 Sep;66(9):963-965. **(Editorial)**

96.* Lee TH, Rouan GW, Weisberg MC, et al. Clinical characteristics and natural history of patients with acute myocardial infarction sent home from the emergency room. *Am J Cardiol* 1987 Aug 1;60(4):219-224. **(Prospective, multicenter; 400 patients)**

97.* McCarthy BD, Beshansky JR, D'Agostino RB, et al. Missed diagnoses of acute myocardial infarction in the emergency department: results from a multicenter study. *Ann Emerg Med* 1993 Mar;22(3):579-582. **(Observational, case-controlled; 1050 patients)**

98.* Lee TH, Cook EF, Weisberg MC, et al. Impact of the availability of a prior electrocardiogram on the triage of the patient with acute chest pain. *J Gen Intern Med* 1990 Sep-Oct;5(5):381-388. **(Prospective, multicenter; 5673 patients)**

99. Fesmire FM, Percy RF, Wears RL. Diagnostic and prognostic importance of comparing the initial to the previous electrocardiogram in patients admitted for suspected acute myocardial infarction. *South Med J* 1991 Jul;84(7):841-846. **(Retrospective cohort; 258 patients)**

100.* Lao J, Ioannidis JP, Balk EM, et al. Diagnosing acute cardiac ischemia in the emergency department: a systematic review of the accuracy and clinical effect of current technologies. *Ann Emerg Med* 2001 May;37(5):453-460. **(Meta-analysis; 106 articles)**

101. Velez J, Brady WJ, Perron AD, et al. Serial electrocardiography. *Am J Emerg Med* 2002 Jan;20(1):43-49. **(Review, case report)**

102. McQueen MJ, Holder D, El-Maraghi NR. Assessment of the accuracy of serial electrocardiograms in the diagnosis of myocardial infarction. *Am Heart J* 1983 Feb;105(2):258-261. **(Retrospective; 25 patients)**

103. Menown IB, Mackenzie G, Adgey AA. Optimizing the initial 12-lead electrocardiographic diagnosis of acute myocardial infarction. *Eur Heart J* 2000 Feb;21(4):275-283. **(Randomized, controlled trial; 1190 patients)**

104. Fesmire FM, Percy RF, Wears RL, et al. Initial ECG in Q wave and non-Q wave myocardial infarction. *Ann Emerg Med* 1989 Jul;18(7):741-746. **(Retrospective, comparative; 440 patients)**

105. Sagie A, Sclarovsky S, Strasberg B, et al. Acute anterior wall myocardial infarction presenting with positive T waves and without ST segment shift. Electrocardiographic features and angiographic correlation. *Chest* 1989 Jun;95(6):1211-5. **(18 patients)**

106. Brady WJ. Electrocardiographic left ventricular hypertrophy in chest pain patients: differentiation from acute coronary ischemic events. *Am J Emerg Med* 1998 Nov;16(7):692-6. **(Case report, review)**

107. Brady WJ. Benign early repolarization: electrocardiographic manifestations and differentiation from other ST segment elevation syndromes. *Am J Emerg Med* 1998 Oct;16(6):592-597. **(Review, case report)**

108. Brady WJ, Perron AD, Chan T. Electrocardiographic ST-segment elevation: correct identification of acute myocardial infarction (AMI) and non-AMI syndromes by emergency physicians. *Acad Emerg Med* 2001 Apr;8(4):349-360. **(Questionnaire)**

109.* Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. *N Engl J Med* 1996 Feb 22;334(8):481-487. **(Multicenter; 26,003 patients)**

110. Shlipak MG, Lyons WL, Go AS, et al. Should the electrocardiogram be used to guide therapy for patients with left bundle-branch block and suspected myocardial infarction? *JAMA* 1999 Feb 24;281(8):714-719. **(Retrospective; 83 patients)**

111. Fesmire FM. ECG diagnosis of acute myocardial infarction in the presence of left bundle-branch block in patients undergoing continuous ECG monitoring. *Ann Emerg Med* 1995 Jul;26(1):69-82. **(Review, case report)**

112. Croft CH, Nicod P, Corbett JR, et al. Detection of acute right ventricular infarction by right precordial electrocardiography. *Am J Cardiol* 1982 Sep;50(3):421-427. **(Prospective; 43 patients)**

113. Melendez LJ, Jones DT, Salcedo JR. Usefulness of three additional electrocardiographic chest leads (V_7, V_8, and V_9) in the diagnosis of acute myocardial infarction. *Can Med Assoc J* 1978 Oct 7;119(7):745-748. **(Prospective; 117 patients)**

114. Brady WJ, Hwang V, Sullivan R, et al. A comparison of 12- and 15-lead ECGs in ED chest pain patients: impact on diagnosis, therapy, and disposition. *Am J Emerg Med* 2000 May;18(3):239-243. **(Prospective, comparative; 595 patients)**

115. Silber SH, Leo PJ, Katapadi M. Serial electrocardiograms for chest pain patients with initial nondiagnostic electrocardiograms: implications for thrombolytic therapy. *Acad Emerg Med* 1996 Feb;3(2):147-152. **(Retrospective, comparative; 114 patients)**

116. Hedges JR, Young GP, Henkel GF, et al. Serial ECGs are less accurate than serial CK-MB results for emergency department diagnosis of myocardial infarction. *Ann Emerg Med* 1992 Dec;21(12):1445-1450. **(Prospective, observational; 261 patients)**

117. Ferrari E, Imbert A, Chevalier T, et al. The ECG in pulmonary embolism. Predictive value of negative T waves in precordial leads—80 case reports. *Chest* 1997 Mar;111(3):537-543. **(Retrospective; 80 patients)**

118. Stein PD, Dalen JE, McIntyre KM, et al. The electrocardiogram in acute pulmonary embolism. *Prog Cardiovasc Dis* 1975 Jan-Feb;17(4):247-257. **(Retrospective; 90 patients)**

119.* Templeton PA, McCallion WA, McKinney LA, et al. Chest pain in the accident and emergency department: is chest radiography worthwhile? *Arch Emerg Med* 1991 Jun;8(2):97-101. **(Prospective; 297 patients)**

120. Russell NJ, Pantin CF, Emerson PA, et al. The role of chest radiography in patients presenting with anterior chest pain to the Accident & Emergency Department. *J R Soc Med* 1988 Nov;81(11):626-628. **(Prospective; 120 patients)**

121.* Worsley DF, Alavi A, Aronchick JM, et al. Chest radiographic findings in patients with acute pulmonary embolism: observations from the PIOPED Study. *Radiology* 1993 Oct;189(1):133-136. **(Prospective, multicenter; 1063 radiographs)**

122. Bean RB, Bean WB, eds. *Sir William Osler: Aphorisms From His Bedside Teachings and Writings.* Springfield, IL: Charles C. Thomas; 1961:138.

123. Nienaber CA, von Kodolitsch Y, Nicolas V, et al. The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. *N Engl J Med* 1993 Jan 7;328(1):1-9. **(Comparative; 133 patients)**

124. Keren A, Kim CB, Hu BS, et al. Accuracy of biplane and multiplane transesophageal echocardiography in diagnosis of typical acute aortic dissection and intramural hematoma. *J Am Coll Cardiol* 1996 Sep;28(3):627-636. **(Retrospective; 112 patients)**

125. Vieillard-Baron A, Qanadli SD, Antakly Y, et al. Transesophageal echocardiography for the diagnosis of pulmonary embolism with acute cor pulmonale: a comparison with radiological procedures. *Intensive Care Med* 1998 May;24(5):429-433. **(Prospective; 44 patients)**

126. Gerber TC, Kuzo RS, Karstaedt N, et al. Current results and new developments of coronary angiography with use of contrast-enhanced computed tomography of the heart. *Mayo Clin Proc* 2002 Jan;77(1):55-71. **(Meta-analysis; 1924 patients)**

127. Salazar HP, Raggi P. Usefulness of electron-beam computed tomography. *Am J Cardiol* 2002 Feb 21;89(4A):17B-22B; discussion 22B-23B. **(Review)**

128. Budoff MJ, Oudiz RJ, Zalace CP, et al. Intravenous three dimension coronary arteriography using contrast enhanced electron-beam computed tomography. *Am J Cardiol* 1999;83(6):840-845. **(Prospective; 52 patients)**

129. Achenbach S, Moshage W, Ropers D, et al. Value of electron-beam computed tomography for the noninvasive detection of high-grade

coronary-artery stenoses and occlusions. *N Engl J Med* 1998 Dec 31;339(27):1964-1971. **(Prospective; 125 patients)**
130. Small JH, Dixon AK, Coulden RA, et al. Fast CT for aortic dissection. *Br J Radiol* 1996 Oct;69(826):900-905. **(81 patients)**
131. Sebastia C, Pallisa E, Quiroga S, et al. Aortic dissection: diagnosis and follow-up with helical CT. *Radiographics* 1999 Jan-Feb;19(1):45-60; quiz 149-150. **(Review)**
132. Penco M, Paparoni S, Dagianti A, et al. Usefulness of transesophageal echocardiography in the assessment of aortic dissection. *Am J Cardiol* 2000 Aug 17;86(4A):53G-56G. **(Comparative; 80 cases)**
133. Greaves SM, Hart EM, Aberle DR. CT of pulmonary thromboembolism. *Semin Ultrasound CT MR* 1997 Oct;18(5):323-337. **(Review)**
134. Goodman LR. Helical CT for initial imaging of pulmonary embolus. *AJR Am J Roentgenol* 1998 Oct;171(4):1153-1154. **(Review)**
135. Goodman LR. CT of acute pulmonary emboli: where does it fit? *Radiographics* 1997 Jul-Aug;17(4):1037-1042. **(Review)**
136. Remy-Jardin M, Remy J, Artaud D, et al. Spiral CT of pulmonary embolism: diagnostic approach, interpretive pitfalls and current indications. *Eur Radiol* 1998;8(8):1376-1390. **(Review)**
137. Van Rossum AB, Treurniet FE, Kieft GJ, et al. Role of spiral volumetric computed tomographic scanning in the assessment of patients with clinical suspicion of pulmonary embolism and an abnormal ventilation/perfusion lung scan. *Thorax* 1996,51;23-28 **(Prospective; 249 patients)**
138. Mayo JR, Remy-Jardin M, Muller NL, et al. Pulmonary embolism: prospective comparison of spiral CT with ventilation-perfusion scintigraphy. *Radiology* 1997;205:447-452. **(Prospective; 142 patients)**
139. Qanadli SD, Hajjam ME, Mesurolle B, et al. Pulmonary embolism detection: prospective evaluation of dual-section helical CT versus selective pulmonary arteriography in 157 patients. *Radiology* 2000 Nov;217(2):447-455. **(Prospective; 204 patients)**
140. Schoepf UJ, Holzknecht N, Helmberger TK, et al. Subsegmental pulmonary emboli: improved detection with thin-collimation multidetector row spiral CT. *Radiology* 2002 Feb;222(2):483-490. **(Comparative; 17 patients)**
141. Raptopoulos V, Boiselle PM. Multi-detector row spiral CT pulmonary angiography: comparison with single-detector row spiral CT. *Radiology* 2001 Dec;221(3):606-613. **(Comparative; 93 patients)**
142. Goodman LR, Lipchik RJ, Kuzo RS, et al. Subsequent pulmonary embolism: risk after a negative helical CT pulmonary angiogram—prospective comparison with scintigraphy. *Radiology* 2000 May;215(2):535-542. **(Prospective; 1015 patients)**
143. Ost D, Rozenshtein A, Saffran L, et al. The negative predictive value of spiral computed tomography for the diagnosis of pulmonary embolism in patients with nondiagnostic ventilation-perfusion scans. *Am J Med* 2001 Jan;110(1):16-21. **(Prospective; 103 patients)**
144. Gottsater A, Berg A, Centergard J, et al. Clinically suspected pulmonary embolism: is it safe to withhold anticoagulation after a negative spiral CT? *Eur Radiol* 2001;11(1):65-72. **(Follow-up study; 305 patients)**
145. Perrier A, Howarth N, Didier D, et al. Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. *Ann Intern Med* 2001 Jul 17;135(2):88-97. **(Observational; 299 patients)**
146. Swensen SJ, Sheedy PF 2nd, Ryu JH, et al. Outcomes after withholding anticoagulation from patients with suspected acute pulmonary embolism and negative computed tomographic findings: a cohort study. *Mayo Clin Proc* 2002 Feb;77(2):130-138. **(Retrospective; 1512 patients)**
147. Cham MD, Yankelevitz DF, Shaham D, et al. Deep venous thrombosis: detection by using indirect CT venography. The Pulmonary Angiography-Indirect CT Venography Cooperative Group. *Radiology* 2000 Sep;216(3):744-751. **(Prospective; 541 patients)**
148. Goldberg SN, Palmer EL, Scott JA, et al. Pulmonary embolism: prediction of the usefulness of initial ventilation-perfusion scanning with chest radiographic findings. *Radiology* 1994 Dec;193(3):801-805. **(Retrospective; 951 patients)**
149. Desai B, Seaberg DC. The utility of routine electrolytes and blood cell counts in patients with chest pain. *Am J Emerg Med* 2001 May;19(3):196-198. **(Retrospective; 191 patients)**
150. Barron HV, Harr SD, Radford MJ, et al. The association between white blood cell count and acute myocardial infarction mortality in patients ≥ 65 years of age: findings from the cooperative cardiovascular project. *J Am Coll Cardiol* 2001 Nov 15;38(6):1654-1661. **(Retrospective; 153,213 patients)**
151. Stein PD, Goldhaber SZ, Henry JW. Alveolar-arterial oxygen gradient in the assessment of acute pulmonary embolism. *Chest* 1995 Jan;107(1):139-143. **(Prospective, multicenter; 779 PIOPED patients)**
152. McFarlane MJ, Imperiale TF. Use of the alveolar-arterial oxygen gradient in the diagnosis of pulmonary embolism. *Am J Med* 1994 Jan;96(1):57-62. **(Retrospective; 873 patients)**
153. Brown MD, Rowe BH, Reeves MJ, et al. The accuracy of the enzyme-linked immunosorbent assay D-dimer test in the diagnosis of pulmonary embolism: a meta-analysis. *Ann Emerg Med* 2002 Aug;40(2):133-144. **(Meta-analysis)**
154. Dunn KL, Wolf JP, Dorfman DM, et al. Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. *J Am Coll Cardiol* 2002 Oct 16;40(8):1475-1478. **(Prospective; 1106 assays)**
155. Daniel KR, Courtney DM, Kline JA. Assessment of cardiac stress from massive pulmonary embolism with 12-lead ECG. *Chest* 2001 Aug;120(2):474-481. **(Retrospective; 60 patients)**
156. Kline JA. Sensitivity of the simpliRED D-dimer assay. *Ann Emerg Med* 2001 May;37(5):549-550. **(Letter)**
157. Karras DJ, Kane DL. Serum markers in the emergency department diagnosis of acute myocardial infarction. *Emerg Med Clin North Am* 2001 May;19(2):321-337. **(Review)**
158. Jaffe AS, Ravkilde J, Roberts R, et al. It's time for a change to a troponin standard. *Circulation* 2000 Sep 12;102(11):1216-1220. **(Editorial)**
159. Wu AH, Apple FS, Gibler WB, et al. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. *Clin Chem* 1999 Jul;45(7):1104-1121. **(Practice guideline)**
160. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000 Sep;36(3):959-969. **(Practice guideline)**
161. Ferguson JL, Beckett GJ, Stoddart M, et al. Myocardial infarction redefined: the new ACC/ESC definition, based on cardiac troponin, increases the apparent incidence of infarction. *Heart* 2002 Oct;88(4):343-347. **(Prospective; 80 patients)**
162. Lee TH, Goldman L. Serum enzyme assays in the diagnosis of acute myocardial infarction. Recommendations based on a quantitative analysis. *Ann Intern Med* 1986 Aug;105(2):221-233. **(Review)**
163. Lee TH, Weisberg MC, Cook EF, et al. Evaluation of creatine kinase and creatine kinase-MB for diagnosing myocardial infarction. Clinical impact in the emergency room. *Arch Intern Med* 1987 Jan;147(1):115-121. **(Prospective; 639 patients)**
164. Zimmerman J, Fromm R, Meyer D, et al. Diagnostic marker cooperative study for the diagnosis of myocardial infarction. *Circulation* 1999 Apr 6;99(13):1671-1677. **(Prospective, multicenter; 955 patients)**
165. Bakker AJ, Gorgels JP, van Vlies B, et al. The mass concentrations of serum troponin T and creatine kinase-MB are elevated before creatine kinase and creatine kinase-MB activities in acute myocardial infarction. *Eur J Clin Chem Clin Biochem* 1993 Nov;31(11):715-724. **(Prospective, comparative; 322 patients)**
166. Bakker AJ, Gorgels JP, van Vlies B, et al. Contribution of creatine kinase MB mass concentration at admission to early diagnosis of acute myocardial infarction. *Br Heart J* 1994 Aug;72(2):112-118. **(Prospective; 297 patients)**
167. Collinson PO, Rosalki SB, Kuwana T, et al. Early diagnosis of acute myocardial infarction by CK-MB mass measurements. *Ann Clin Biochem* 1992 Jan;29(Pt 1):43-47. **(Prospective; 73 patients)**
168. Mair J, Artner-Dworzak E, Dienstl A, et al. Early detection of acute myocardial infarction by measurement of mass concentration of creatine kinase-MB. *Am J Cardiol* 1991 Dec 15;68(17):1545-1550. **(Prospective; 126 patients)**
169. Van Blerk M, Maes V, Huyghens L, et al. Analytical and clinical evaluation of creatine kinase MB mass assay by IMx: comparison with MB isoenzyme activity and serum myoglobin for early diagnosis of myocardial infarction. *Clin Chem* 1992 Dec;38(12):2380-2386. **(Retrospective, comparative; 39 patients)**
170. Fesmire FM. Delta CK-MB outperforms delta troponin I at 2 hours during the ED rule out of acute myocardial infarction. *Am J Emerg Med* 2000 Jan;18(1):1-8. **(Retrospective; 578 patients)**
171. Antman EM, Grudzien C, Sacks DB. Evaluation of a rapid bedside assay for detection of serum cardiac troponin T. *JAMA* 1995 Apr 26;273(16):1279-1282. **(Prospective, comparative; 100 patients)**
172. Bakker AJ, Koelemay MJ, Gorgels JP, et al. Troponin T and myoglobin at admission: value of early diagnosis of acute myocardial infarction. *Eur Heart J* 1994 Jan;15(1):45-53. **(Prospective, comparative; 290 patients)**
173. Bakker AJ, Koelemay MJ, Gorgels JP, et al. Failure of new biochemical markers to exclude acute myocardial infarction at admission. *Lancet* 1993 Nov 13;342(8881):1220-1222. **(Prospective, comparative; 290 patients)**

174. Mair J, Artner-Dworzak E, Lechleitner P, et al. Cardiac troponin T in diagnosis of acute myocardial infarction. *Clin Chem* 1991 Jun;37(6):845-852. **(Prospective; 72 patients)**
175. Mair J, Dienstl F, Puschendorf B. Cardiac troponin T in the diagnosis of myocardial injury. *Crit Rev Clin Lab Sci* 1992;29(1):31-57. **(Review)**
176. Wu AH, Valdes R Jr, Apple FS, et al. Cardiac troponin-T immunoassay for diagnosis of acute myocardial infarction. *Clin Chem* 1994 Jun;40(6):900-907. **(Comparative; 49 patients)**
177. Hartmann F, Kampmann M, Frey N, et al. Biochemical markers in the diagnosis of coronary artery disease. *Eur Heart J* 1998 Nov;19 Suppl N:N2-7. **(Review)**
178.* Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med* 1996 Oct 31;335(18):1333-1341. **(Multicenter, randomized, controlled trial; 855 patients)**
179.* Lindahl B, Venge P, Wallentin L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. *Circulation* 1996 May 1;93(9):1651-1657. **(Randomized, controlled trial; 976 patients)**
180. Stubbs P, Collinson P, Moseley D, et al. Prospective study of the role of cardiac troponin T in patients admitted with unstable angina. *BMJ* 1996 Aug 3;313(7052):262-264. **(Randomized, controlled trial; 460 patients)**
181. Tanasijevic MJ, Antman EM. Diagnostic performance of cardiac troponin I in suspected acute myocardial infarction: implications for clinicians. *Am Heart J* 1999 Feb;137(2):203-206. **(Editorial)**
182.* Heidenreich PA, Alloggiamento T, Melsop K, et al. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. *J Am Coll Cardiol* 2001 Aug;38(2):478-485. **(Meta-analysis)**
183. Ng SM, Krishnaswamy P, Morrisey R, et al. Mitigation of the clinical significance of spurious elevations of cardiac troponin I in settings of coronary ischemia using serial testing of multiple cardiac markers. *Am J Cardiol* 2001 Apr 15;87(8):994-999; A4. **(Retrospective; 1000 patients)**
184. Khan IA, Wattanasuwan N, Mehta NJ, et al. Prognostic value of serum cardiac troponin I in ambulatory patients with chronic renal failure undergoing long-term hemodialysis: a two-year outcome analysis. *J Am Coll Cardiol* 2001 Oct;38(4):991-998. **(126 patients)**
185. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med* 2002 Jun 27;346(26):2047-2052. **(7033 patients)**
186. Meyer T, Binder L, Hruska N, et al. Cardiac troponin I elevation in acute pulmonary embolism is associated with right ventricular dysfunction. *J Am Coll Cardiol* 2000 Nov 1;36(5):1632-1636. **(Prospective)**
187. Bonnefoy E, Godon P, Kirkorian G, et al. Serum cardiac troponin I and ST-segment elevation in patients with acute pericarditis. *Eur Heart J* 2000 May;21(10):832-836. **(Retrospective; 69 patients)**
188. Gibler WB, Gibler CD, Weinshenker E, et al. Myoglobin as an early indicator of acute myocardial infarction. *Ann Emerg Med* 1987 Aug;16(8):851-856. **(Prospective, comparative; 59 patients)**
189. Kallner A, Sylven C, Brodin U, et al. Early diagnosis of acute myocardial infarction. A comparison between chemical predictors. *Scand J Clin Lab Invest* 1989 Nov;49(7):633-639. **(Prospective, comparative; 155 patients)**
190.* Tucker JF, Collins RA, Anderson AJ, et al. Value of serial myoglobin levels in the early diagnosis of patients admitted for acute myocardial infarction. *Ann Emerg Med* 1994 Oct;24(4):704-708. **(Prospective; 133 patients)**
191. No authors listed. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994 Feb 5;343(8893):311-322. **(Review)**
192.* Balk EM, Ioannidis JP, Salem D, et al. Accuracy of biomarkers to diagnose acute cardiac ischemia in the emergency department: a meta-analysis. *Ann Emerg Med* 2001 May;37(5):478-494. **(Meta-analysis)**
193.* Kontos MC, Anderson FP, Hanbury CM, et al. Use of combination myoglobin and CK-MB mass for the rapid diagnosis of acute myocardial infarction. *Am J Emerg Med* 1997 Jan;15(1):14-19. **(Prospective; 101 patients)**
194.* Newby LK, Storrow AB, Gibler WB, et al. Bedside multimarker testing for risk stratification in chest pain units: The chest pain evaluation by creatine kinase-MB, myoglobin, and troponin I (CHECKMATE) study. *Circulation* 2001 Apr 10;103(14):1832-1837. **(Prospective; 1005 patients)**
195.* Ng SM, Krishnaswamy P, Morissey R, et al. Ninety-minute accelerated critical pathway for chest pain evaluation. *Am J Cardiol* 2001 Sep 15;88(6):611-617. **(Prospective, observational; 1285 patients)**
196.* McCord J, Nowak RM, McCullough PA, et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. *Circulation* 2001 Sep 25;104(13):1483-1488. **(Prospective; 817 patients)**
197. Hoffman JR, Bukata R. *Emergency Medicine Abstracts* March 2002.
198. Hamm CW. Cardiac biomarkers for rapid evaluation of chest pain. *Circulation* 2001 Sep 25;104(13):1454-1456. **(Editorial)**
199. Luscher MS, Ravkilde J, Thygesen K. Clinical application of two novel rapid bedside tests for the detection of cardiac troponin T and creatine kinase-MB mass/myoglobin in whole blood in acute myocardial infarction. *Cardiology* 1998 Mar;89(3):222-228. **(Follow-up study; 92 patients)**
200.* Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 1997 Dec 4;337(23):1648-1653. **(Prospective; 773 patients)**
201.* Limkakeng A Jr, Gibler WB, Pollack C, et al. Combination of Goldman risk and initial cardiac troponin I for emergency department chest pain patient risk stratification. *Acad Emerg Med* 2001 Jul;8(7):696-702. **(Prospective; 2322 patients)**
202.* Pozen MW, D'Agostino RB, Selker HP, et al. A predictive instrument to improve coronary-care-unit admission practices in acute ischemic heart disease. A prospective multicenter clinical trial. *N Engl J Med* 1984 May 17;310(20):1273-1278. **(Prospective, multicenter; 2320 patients)**
203.* Baxt WG, Shofer FS, Sites FD, et al. A neural network aid for the early diagnosis of cardiac ischemia in patients presenting to the emergency department with chest pain. *Ann Emerg Med* 2002 Dec;40(6):575-583. **(2204 patients)**
204.* Kline JA, Johnson CL, Newgard CD, et al. Use of computer-assisted attribute matching to estimate pretest probability. *Acad Emerg Med* 2003 May;10(5):509. **(Prospective; database analysis of 15,000 patients)**
205. Chandra A, Rudraiah L, Zalenski RJ. Stress testing for risk stratification of patients with low to moderate probability of acute cardiac ischemia. *Emerg Med Clin North Am* 2001 Feb;19(1):87-103. **(Review)**
206. Wilkinson K, Severance H. Identification of chest pain patients appropriate for an emergency department observation unit. *Emerg Med Clin North Am* 2001 Feb;19(1):35-66. **(Review)**
207. Karlson BW, Herlitz J, Hallgren P, et al. Emergency room prediction of mortality and severe complications in patients with suspected acute myocardial infarction. *Eur Heart J* 1994 Nov;15(11):1558-1565. **(Prospective; 7157 patients)**
208. Green GB, Beaudreau RW, Chan DW, et al. Use of troponin T and creatine kinase-MB subunit levels for risk stratification of emergency department patients with possible myocardial ischemia. *Ann Emerg Med* 1998 Jan;31(1):19-29. **(Prospective, observational; 292 patients)**
209. Hilton TC, Fulmer H, Abuan T, et al. Ninety-day follow-up of patients in the emergency department with chest pain who undergo initial single-photon emission computed tomographic perfusion scintigraphy with technetium 99m-labeled sestamibi. *J Nucl Cardiol* 1996 Jul-Aug;3(4):308-311. **(Retrospective; 150 patients)**
210. Pearson SD, Goldman L, Orav EJ, et al. Triage decisions for emergency department patients with chest pain: do physicians' risk attitudes make the difference? *J Gen Intern Med* 1995 Oct;10(10):557-564. **(Retrospective)**
211.* Fesmire FM, Hughes AD, Fody EP, et al. The Erlanger chest pain evaluation protocol: a one-year experience with serial 12-lead ECG monitoring, two-hour delta serum marker measurements, and selective nuclear stress testing to identify and exclude acute coronary syndromes. *Ann Emerg Med* 2002 Dec;40(6):584-594. **(Prospective, observational; 2074 patients)**
212. Fesmire FM. Which chest pain patients potentially benefit from continuous 12-lead ST-segment monitoring with automated serial ECG? *Am J Emerg Med* 2000 Nov;18(7):773-778. **(Prospective, observational; 678 patients)**
213. Shesser R, Smith M. The chest pain emergency department and the outpatient chest pain evaluation center: revolution or evolution? *Ann Emerg Med* 1994 Feb;23(2):334-341. **(Cost-benefit analysis)**
214.* Gomez MA, Anderson JL, Karagounis LA, et al. An emergency department-based protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: results of a randomized study (ROMIO). *J Am Coll Cardiol* 1996 Jul;28(1):25-33. **(Randomized, controlled trial; 100 patients)**
215.* Pope JH, Ruthazer R, Beshansky JR, et al. Clinical features of emergency department patients presenting with symptoms suggestive of acute cardiac ischemia: a multicenter study. *J Thromb Thrombolysis* 1998 Jul;6(1):63-74. **(Prospective; 10,689 patients)**
216.* Zalenski RJ, Rydman RJ, McCarren M, et al. Feasibility of a rapid diagnostic protocol for an emergency department chest pain unit. *Ann Emerg Med* 1997 Jan;29(1):99-108. **(Observational, comparative; 446**

patients)
217. Heberden W. Some account of a disorder of the breast. *Med Trans Coll Phys Lond*. 1772;2:59-67. As cited in: Heberden W. *Commentaries on the History and Cure of Diseases.* Birmingham, AL: Classics of Medicine Library; 1982:363-365. **(Historical reference)**
218.* Ioannidis JP, Salem D, Chew PW, et al. Accuracy of imaging technologies in the diagnosis of acute cardiac ischemia in the emergency department: a meta-analysis. *Ann Emerg Med* 2001 May;37(5):471-477. **(Meta-analysis)**
219. Roberts R, Graff LG 4th. Economic issues in observation unit medicine. *Emerg Med Clin North Am* 2001 Feb;19(1):19-33. **(Review)**
220. Patterson RE, Eisner RL, Horowitz SF. Comparison of cost-effectiveness and utility of exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease. *Circulation* 1995 Jan 1;91(1):54-65. **(Review)**
221. Mikhail MG, Smith FA, Gray M, et al. Cost-effectiveness of mandatory stress testing in chest pain center patients. *Ann Emerg Med* 1997 Jan;29(1):88-98. **(Prospective, observational; 502 patients)**
222. Zalenski RJ, McCarren M, Roberts R, et al. An evaluation of a chest pain diagnostic protocol to exclude acute cardiac ischemia in the emergency department. *Arch Intern Med* 1997 May 26;157(10):1085-1091. **(Prospective; 317 patients)**
223.* Polanczyk CA, Johnson PA, Hartley LH, et al. Clinical correlates and prognostic significance of early negative exercise tolerance test in patients with acute chest pain seen in the hospital emergency department. *Am J Cardiol* 1998 Feb 1;81(3):288-292. **(Prospective; 276 patients)**
224.* Tandy TK, Bottomy DP, Lewis JG. Wellens' syndrome. *Ann Emerg Med* 1999 Mar;33(3):347-351. **(Review)**
225. Kirk JD, Turnipseed S, Lewis WR, et al. Evaluation of chest pain in low-risk patients presenting to the emergency department: the role of immediate exercise testing. *Ann Emerg Med* 1998 Jul;32(1):1-7. **(Prospective; 212 patients)**
226. Kirk JD, Turnipseed SD, Diercks DB, et al. Interpretation of immediate exercise treadmill test: interreader reliability between cardiologist and noncardiologist in a chest pain evaluation unit. *Ann Emerg Med* 2000 Jul;36(1):10-14. **(Prospective; 645 patients)**
227.* Amsterdam EA, Kirk JD, Diercks DB, et al. Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain. *J Am Coll Cardiol* 2002 Jul 17;40(2):251-256. **(Retrospective; 1000 patients)**
228. Sarullo FM, Di Pasquale P, Orlando G, et al. Utility and safety of immediate exercise testing of low-risk patients admitted to the hospital with acute chest pain. *Int J Cardiol* 2000 Sep 15;75(2-3):239-243. **(Comparative; 190 patients)**
229. Lewis WR, Amsterdam EA. Utility and safety of immediate exercise testing of low-risk patients admitted to the hospital for suspected acute myocardial infarction. *Am J Cardiol* 1994 Nov 15;74(10):987-990. **(93 patients)**
230. Tsakonis JS, Shesser R, Rosenthal R, et al. Safety of immediate treadmill testing in selected emergency department patients with chest pain: a preliminary report. *Am J Emerg Med* 1991 Nov;9(6):557-559. **(28 patients)**
231. Lewis WR, Amsterdam EA, Turnipseed S, et al. Immediate exercise testing of low risk patients with known coronary artery disease presenting to the emergency department with chest pain. *J Am Coll Cardiol* 1999 Jun;33(7):1843-1847. **(Retrospective; 100 patients)**
232. Kontos MC, Arrowood JA, Paulsen WH, et al. Early echocardiography can predict cardiac events in emergency department patients with chest pain. *Ann Emerg Med* 1998 May;31(5):550-557. **(Prospective; 260 patients)**
233. Peels CH, Visser CA, Kupper AJ, et al. Usefulness of two-dimensional echocardiography for immediate detection of myocardial ischemia in the emergency room. *Am J Cardiol* 1990 Mar 15;65(11):687-691. **(Prospective; 43 patients)**
234. Berning J, Launbjerg J, Appleyard M. Echocardiographic algorithms for admission and predischarge prediction of mortality in acute myocardial infarction. *Am J Cardiol* 1992 Jun 15;69(19):1538-1544. **(Prospective; 201 patients)**
235.* Selker HP, Zalenski RJ, Antman EM, et al. An evaluation of technologies for identifying acute cardiac ischemia in the emergency department: executive summary of a National Heart Attack Alert Program Working Group Report. *Ann Emerg Med* 1997 Jan;29(1):1-12. **(Review)**
236. Mather PJ, Shah R. Echocardiography, nuclear scintigraphy, and stress testing in the emergency department evaluation of acute coronary syndrome. *Emerg Med Clin North Am* 2001 May;19(2):339-349. **(Review)**
237.* Marwick TH, Mehta R, Arheart K, et al. Use of exercise echocardiography for prognostic evaluation of patients with known or suspected coronary artery disease. *J Am Coll Cardiol* 1997 Jul;30(1):83-90. **(Prospective; 500 patients)**
238.* Cherng WJ, Wang CH, Hung MJ, et al. Dobutamine stress echocardiography in the prediction of acute or chronic myocardial infarction. *Am Heart J* 1998 Dec;136(6):1021-1029. **(Prospective; 266 patients)**
239. Go RT, Marwick TH, MacIntyre WJ, et al. A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. *J Nucl Med* 1990 Dec;31(12):1899-1905. **(Prospective; 202 patients)**
240. Van Train KF, Maddahi J, Berman DS, et al. Quantitative analysis of tomographic stress thallium-201 myocardial scintigrams: a multicenter trial. *J Nucl Med* 1990 Jul;31(7):1168-1179. **(Prospective, multicenter; 318 patients)**
241. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol* 1998 Jul;32(1):57-62. **(Review)**
242.* Fesmire FM, Hughes AD, Stout PK, et al. Selective dual nuclear scanning in low-risk patients with chest pain to reliably identify and exclude acute coronary syndromes. *Ann Emerg Med* 2001 Sep;38(3):207-215. **(Prospective, observational; 1775 patients)**
243.* Fleischmann KE, Hunink MG, Kuntz KM, et al. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA* 1998 Sep 9;280(10):913-920. **(Meta-analysis)**
244. Tatum JL. Cost effective nuclear scanning in a comprehensive and systematic approach to the evaluation of chest pain in the emergency department. *Md Med J* 1997;Suppl:25-29. **(Cost-benefit analysis)**
245.* Udelson JE, Beshansky JR, Ballin DS, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA* 2002 Dec 4;288(21):2693-2700. **(Multicenter, randomized, controlled trial; 2475 patients)**
246. Kosnik JW, Zalenski RJ, Grzybowski M, et al. Impact of technetium-99m sestamibi imaging on the emergency department management and costs in the evaluation of low-risk chest pain. *Acad Emerg Med* 2001 Apr;8(4):315-323. **(Prospective; 69 patients)**
247. Christenson RH, Duh SH, Sanhai WR, et al. Characteristics of an Albumin Cobalt Binding Test for assessment of acute coronary syndrome patients: a multicenter study. *Clin Chem* 2001 Mar;47(3):464-470. **(Multicenter, evaluation; 256 patients)**
248. Gottschalk A, Stein PD, Goodman LR, et al. Overview of Prospective Investigation of Pulmonary Embolism Diagnosis II. *Semin Nucl Med* 2002 Jul;32(3):173-182. **(Multicenter)**
249. Decker WW, Prina LD, Smars PA, et al. Continuous 12-lead electrocardiographic monitoring in an emergency department chest pain unit: an assessment of potential clinical effect. *Ann Emerg Med* 2003 Mar;41(3):342-351. **(Randomized, controlled trial; 119 patients)**
250. No authors listed. Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected acute myocardial infarction or unstable angina. American College of Emergency Physicians. *Ann Emerg Med* 2000 May;35(5):521-525. **(Practice guideline)**
251. No authors listed. Clinical policy for the initial approach to adults presenting with a chief complaint of chest pain, with no history of trauma. American College of Emergency Physicians. *Ann Emerg Med* 1995 February;25(2):274-299. **(Practice guideline)**
252. Braunwald E, Antman EM, Beasley JW, et al. American College of Cardiology. American Heart Association. Committee on the Management of Patients With Unstable Angina. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2002 Oct. 2;40(7):1366-1374. **(Practice guideline)**
253. Archibald N, Jones RH. Guidelines for treatment of unstable angina. In: Califf RM, ed. *Acute Myocardial Infarction and Ather Acute Ischemic Syndromes.* Philadelphia: Current Medicine; 1996:14.1–14.22. **(Textbook chapter)**
254. Kuijpers D, Ho KY, van Dijkman PR, et al. Dobutamine cardiovascular magnetic resonance for the detection of myocardial ischemia with the use of myocardial tagging. *Circulation* 2003 April 1;107(12):1592-1597. **(Evaluation study)**

Physician CME Questions

81. Most cases of chest pain:
a. are due to myocardial infraction.
b. are not the result of an acute coronary event.
c. are due to pulmonary embolism.
d. are due to aortic dissection.

82. The most important task for the emergency physician treating a patient with chest pain is:
a. to rule out life threats.
b. to diagnose the cause.
c. to admit all patients into the ICU for further work-up.
d. to admit all patients into observation units for further work-up.

83. Prehospital 12-lead ECG:
a. has moderate sensitivity (76%) and specificity (88%) for the diagnosis of acute cardiac ischemia.
b. has demonstrated a reduction of the mean time to thrombolysis by 33 minutes.
c. has demonstrated a reduction in short-term overall mortality in randomized trials.
d. all of the above.

84. In the general ED setting, which of the following has demonstrated, in a large, multicenter clinical trial, a reduction in unnecessary hospitalizations without decreasing the rate of appropriate admission for patients with acute cardiac ischemia?
a. The Goldman chest pain protocol
b. ACI-TIPI
c. serial serum markers
d. selective stress testing

85. Biomarkers cannot identify most patients with unstable angina.
a. True
b. False

86. Potentially life-threatening cause of chest pain include all of the following *except:*
a. Gastroesophageal reflux
b. Acute coronary syndromes
c. Pulmonary embolism
d. Aortic dissection
e. Tension pneumothorax

87. Risk factors for pulmonary embolism include:
a. increasing age.
b. immobilization or recent surgery/trauma.
c. previous history of thromboembolic disease.
d. active malignancy.
e. all of the above.

88. Oxygen saturation is normal in one-quarter of patients with PE.
a. True
b. False

89. No single set of markers can exclude AMI within six hours of symptom onset.
a. True
b. False

90. A missed diagnosis of AMI is more likely to occur in all of the following *except:*
a. younger patients.
b. those with atypical symptoms.
c. those with less experienced physicians, who order fewer screening ECGs.
d. white men.

91. Risk factors for aortic dissection include:
a. male sex.
b. older age (i.e., seventh decade of life).
c. history of hypertension.
d. none of the above.
e. all of the above.

92. All of the following are true about the initial ECG *except*:
a. It is very sensitive in identifying acute coronary syndromes.
b. It may show diagnostic changes in only 20%-50% of patients presenting with MI.
c. It may have a very high negative predictive value for excluding MI if there are no ST/T-wave changes (nonspecific or otherwise), strain, ischemia, old infarcts, or pseudonormalization.
d. Interpretation can be enhanced by access to previous ECG tracings, which can expedite detection of AMI and prevent unnecessary hospital admissions in patients with baseline ECG abnormalities.

93. The most useful laboratory test in detecting PE is:
a. the CBC.
b. electrolyte panels.
c. D-dimer.
d. arterial blood gas.

94. The new European Society of Cardiology/American College of Cardiology guidelines define AMI as a typical rise and gradual fall of troponin or a more rapid rise and fall of CK-MB with at least one of the following: ischemic symptoms; development of pathologic Q-waves on the ECG; ECG changes indicative of ischemia; or coronary artery intervention.
a. True
b. False

95. Chest pain observation units:
a. rely on relatively strict protocols to rapidly rule out cardiac ischemia.
b. sometimes employ the more compressed Erlanger chest pain evaluation protocol for category 3 patients (those with possible ACS).
c. may involve continuous ST segment analysis once further studies are done.
d. are generally most cost-effective for the evaluation of patients at low-to-moderate risk of cardiac disease vs. the routine evaluation of all patients with chest pain, including those with minuscule or no risk.
e. all of the above.

96. Historical factors that may help discriminate the etiology of chest pain include all of the following *except:*

a. radiation of pain to both arms.
b. tender chest wall.
c. relief of pain with a GI cocktail.
d. history of prior MI.

This test concludes the January through June 2003 semester testing period of *Emergency Medicine Practice.* The answer form for this semester and a return envelope have been included with this issue. Please refer to the instructions printed on the answer form. All paid subscribers are eligible to take this test.

Monthly online CME testing is available for subscribers at no extra charge at http://www.empractice.net.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives an alpha-numerical score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA* 1992;268(16):2289-2295.

Physician CME Information

This CME enduring material is sponsored by Mount Sinai School of Medicine and has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education. Credit may be obtained by reading each issue and completing the printed post-tests administered in December and June or online single-issue post-tests administered at www.empractice.net.

Target Audience: This enduring material is designed for emergency medicine physicians.

Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Date of Original Release: This issue of *Emergency Medicine Practice* was published June 1, 2003. **This activity is eligible for CME credit through June 1, 2006.** The latest review of this material was May 9, 2003.

Discussion of Investigational Information: As part of the newsletter, faculty may be presenting investigational information about pharmaceutical products that is outside Food and Drug Administration approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product. *Disclosure of Off-Label Usage:* This issue of *Emergency Medicine Practice* discusses no off-label use of any pharmaceutical product.

Faculty Disclosure: In compliance with all ACCME Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Dr. Ornato is on the speaker bureau for Genentech and Wyeth-Ayerst and receives research funding from Meridian Medical. Dr. Bean, Dr. Roshon, Dr. Garvey, and Dr. Fesmire report no significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation.

Accreditation: Mount Sinai School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Credit Designation: Mount Sinai School of Medicine designates this educational activity for up to 4 hours of Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit actually spent in the educational activity. *Emergency Medicine Practice* is approved by the American College of Emergency Physicians for 48 hours of ACEP Category 1 credit (per annual subscription). *Emergency Medicine Practice* has been reviewed and is acceptable for up to 48 Prescribed credit hours by the American Academy of Family Physicians. *Emergency Medicine Practice* has been approved for 48 Category 2-B credit hours by the American Osteopathic Association.

Earning Credit: Two Convenient Methods

- **Print Subscription Semester Program:** Paid subscribers with current and valid licenses in the United States who read all CME articles during each *Emergency Medicine Practice* six-month testing period, complete the post-test and the CME Evaluation Form distributed with the December and June issues, and return it according to the published instructions are eligible for up to 4 hours of Category 1 credit toward the AMA Physician's Recognition Award (PRA) for each issue. You must complete both the post-test and CME Evaluation Form to receive credit. Results will be kept confidential. CME certificates will be delivered to each participant scoring higher than 70%.
- **Online Single-Issue Program:** Paid subscribers with current and valid licenses in the United States who read this *Emergency Medicine Practice* CME article and complete the online post-test and CME Evaluation Form at www.empractice.net are eligible for up to 4 hours of Category 1 credit toward the AMA Physician's Recognition Award (PRA). You must complete both the post-test and CME Evaluation Form to receive credit. Results will be kept confidential. CME certificates may be printed directly from the Web site to each participant scoring higher than 70%.

***Emergency Medicine Practice* is not affiliated with any pharmaceutical firm or medical device manufacturer.**

Publisher: Robert Williford. **Executive Editor**: Heidi Frost.

Direct all editorial or subscription-related questions to EB Practice, LLC: **1-800-249-5770** • Fax: 1-770-500-1316 • Non-U.S. subscribers, call: 1-678-366-7933
EB Practice, LLC • 305 Windlake Court • Alpharetta, GA 30022
E-mail: **emp@empractice.net** • Web Site: **http://www.empractice.net**

Emergency Medicine Practice (ISSN 1524-1971) is published monthly (12 times per year) by EB Practice, LLC, 305 Windlake Court, Alpharetta, GA 30022.