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Initial Approach to the Patient who has Chest Pain

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Scope of the problem

According to Center for Disease Control 2001–2002 National Hospital Ambulatory Medical Care Survey, an estimated 107 to 110 million visits were made to hospital emergency departments. Of these, approximately 3.5 to 5.4 million visits (3.4% to 5.3%) were patients who presented with chest pain as their chief complaint [1]. In 2001, first-listed and secondary hospital discharge data from the National Registry of Myocardial Infarction-4 (NRMI-4) indicate there were 1,680,000 unique discharges for acute coronary syndrome (ACS) [2].

In evaluating acute chest pain, the immediate goal is to determine the accurate diagnosis and to initiate the appropriate life-saving therapies as quickly as possible. It is particularly important to identify as quickly as possible those patients presenting with ST-segment elevation myocardial infarction (STEMI) so that the appropriate reperfusion therapies can be initiated with as little delay as possible. Recent work estimates that at least 500,000 patients each year qualify for acute reperfusion therapy for STEMI [3].

The particular challenge facing today's practitioners of emergency medicine is to evaluate every patient who presents with acute chest pain for a variety of life-threatening causes of chest pain, such as ACS, acute aortic dissection (AD), pulmonary embolism (PE), pericardial disease with tamponade physiology, penetrating ulcer, and tension pneumothorax (Box 1). Once these entities are excluded, other benign causes of chest pain are considered. Most of the cases presenting with acute chest pain are of benign origin.

This article focuses on assessment; diagnosis, and management within the first 2 to 3 hours of emergency department presentation of patients who have a chief complain of chest pain and whose clinical status or diagnosis merits admission to the coronary care unit or medical ICU.

Prehospital evaluation and interventions

A patient complaining of chest pain who is at risk for ACS should be transported from home or the outpatient clinic to the emergency department by an ambulance with advanced life-support (ALS) capabilities. Only ALS ambulance personnel can obtain intravenous access, provide sublingual nitroglycerin and morphine, and provide advanced cardiac life support if the patient's condition deteriorates in route.

Advanced emergency medical services (EMS) can also perform and transmit prehospital ECGs (PH-ECGs), stabilize a compromised airway including endotracheal intubation and initiation of mechanical ventilation, and initiate pharmacologic support in situations of hemodynamic compromise before arrival at the emergency department.

Many patients who have acute myocardial infarction (AMI) suffer cardiac arrest in the first few hours of the event. Many of these patients die at home suddenly. The use of an ALS-based EMS offers the best option for early, rapid management of cardiac arrhythmias and sudden cardiac death. Lives are saved by having excellent prehospital

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Box 1. Differential diagnosis of chest pain

Life-threatening causes
Acute coronary syndrome
Aortic dissection
Pulmonary embolus
Tension pneumothorax

Other cardiovascular and nonischemic causes
Pericarditis
Atypical angina
Hypertrophic cardiomyopathy
Vasospastic angina

Other noncardiac causes
Boerhaave's syndrome (esophageal rupture with mediastinitis)
Gastroesophageal reflux and spasm
Chest-wall pain
Pleurisy
Peptic ulcer disease
Panic attack
Biliary or pancreatic pain
Cervical disc or neuropathic pain
Somatization and psychogenic pain disorder

care for patients who are in ventricular fibrillation arrest, for whom survival rates to hospital discharge with acceptable neurologic function can reach 40% [4].

Unfortunately, ambulance services are not always requested. Despite many national education campaigns, patients continue to bypass the EMS systems and arrive by other means. In NRMI-2, 53% of patients who had STEMI arrived by private means [5]. In other studies, the average percentage of patients who had a confirmed coronary event and used EMS was 23%, with a range of 10% to 48%. It is a matter of concern that 16% drove themselves to the emergency department [6], especially considering that approximately 1 in every 300 patients transported to the emergency department by private vehicle goes into cardiac arrest in route [7]. When they do call an ambulance, the average patient who has STEMI does not seek medical care for approximately 2 hours after symptom onset, and this pattern seems to be unchanged during the last decade [8–10]. Average and median delays in obtaining treatment for patients who had STEMI were 4.7 and 2.3 hours, respectively, from the 14-country Global Registry of Acute Coronary Events project [11].

The reasons given by patients in the United States for delay in seeking care have been studied in the REACT project. The investigators conducted focus groups ($N = 34{,}207$ participants) in major regions of the United States. Target groups included adults who had had previous heart attacks, those at higher risk for heart attack, and bystanders to heart attacks. Reasons given by the target groups for delaying seeking help were (1) they expected heart attack symptoms to be more dramatic; (2) they unrealistically judged their personal risk as low; (3) they understood little about the benefits of rapid interventions; (4) they were unaware of the benefits of using EMS instead of alternative transport; and (5) they seemed to need the "permission" or advice of health care providers or family to act [9,12,13].

Prehospital ECGs

PH-ECGs are an underused component in modern ACS care. In most places in the United States they can be obtained easily by advanced EMS personnel and transmitted en route to an emergency department control center. If transmission is a problem, delays in the emergency department can be avoided, because the computer readout is highly accurate and can be called in to the receiving emergency department. Doing so allows emergency department personnel to alert the coronary care unit and be ready for fibrinolysis or primary percutaneous intervention (PPCI). The use of PH-ECGs reduces door-to-needle time for in-hospital fibrinolysis by a mean of 10 minutes; NRMI-2 found the use of PH-ECGs reduced the door-to-balloon- time for primary PCI by a mean of 23 minutes [5].

Prehospital triage

The use of PH-ECGs can also help EMS triage more efficiently. In general, patients who have STEMI should be transported to the nearest facility that best handles the situation. For example, a patient who has an uncomplicated STEMI can be transported to the nearest facility that offers acute reperfusion therapy. The patient who has STEMI and who is also in cardiogenic shock should be transported preferentially to a facility capable of performing PPCI or coronary artery bypass graft surgery rather than being transported

to a facility that has only intravenous fibrinolysis available, if the transport times are not significantly different. The Should We Emergently Revascularize Occluded Arteries in Cardiogenic Shock (SHOCK) trial demonstrated that emergency revascularization improved 1-year survival, achieving an absolute 12.8% reduction in 6-month mortality in patients treated with early revascularization ($P = .027$) [14]. Because much of the mortality in patients in cardiogenic shock occurs early in the time course, it is prudent to transport patients rapidly to the nearest center of excellence that is best equipped to provide the optimal cardiovascular care.

Initiation of prehospital fibrinolysis

Recent work has suggested that time to reperfusion remains one of the most important determinants of the degree of salvaged myocardium [15,16]. Fig. 1 suggests that the earlier reperfusion is initiated, the more myocardium one can salvage. Fig. 1 also reveals that a strategy that significantly delays primary reperfusion therapy may result in little myocardial salvage. Such data have inspired clinical trails to perform prehospital fibrinolysis (PHF). A meta-analysis of PHF trials showed time to treatment was reduced by a mean of 58 minutes, with a range of 33 minutes (Seattle, WA) to 130 minutes (rural Scotland). The pooled data demonstrated a 17% relative risk (RR) reduction in early mortality [17]. A more real-world contemporary analysis of PHF versus other reperfusion therapies has been provided by the French nationwide Unité de Soins Intensifs Coronaires 2000 registry [18]. In November 2000 in France use of PHF was used for 9% of the patients who had STEMI (range, 7%–26%; N = 180). This therapy seemed to offer the best survival benefit (Fig. 2). One-year survival was 94% for patients treated with PHF, 89% for patients treated with in-hospital fibrinolysis or PPCI, and 79% for patients who did not receive reperfusion therapy.

The American College of Cardiology (ACC) and the American Heart Association (AHA) recommend establishment of a PHF protocol in systems where the prehospital transport times are more than 20 minutes and ALS-EMS units have high volume (>25,000) runs per year [3]. It also recommended that the PHF team include full-time paramedics, have available PH-ECG technology with physician support, and be overseen by a medical director committed to developing and maintaining a quality PHF program. Unfortunately, no single study in the United States has demonstrated a reduction in short-term mortality risks compared with hospital-based fibrinolysis. (An in-depth discussion of options for reperfusion is given elsewhere in this issue.)

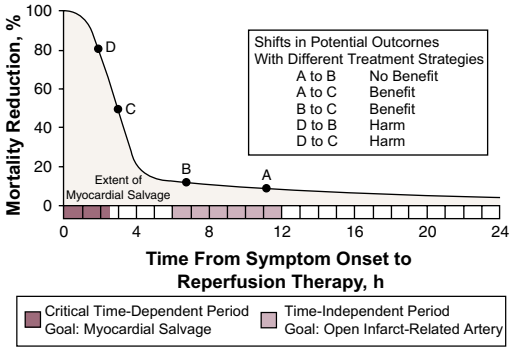

Fig. 1. Hypothetical construct of the relationship among the duration of symptoms of acute myocardial infarction before reperfusion therapy, mortality reduction and extent of myocardial salvage. (*From* Gersh JB, Stone WG, White DH, et al. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction. JAMA 2005;293(8):980; with permission.)

Emergency department evaluation

Once a patient arrives at the emergency department, the initial nursing triage of patients who have chest pain and are at risk for ACS must be to a telemetry bed staffed with nurses and physicians capable of performing an immediate assessment and delivering advanced cardiac life support.

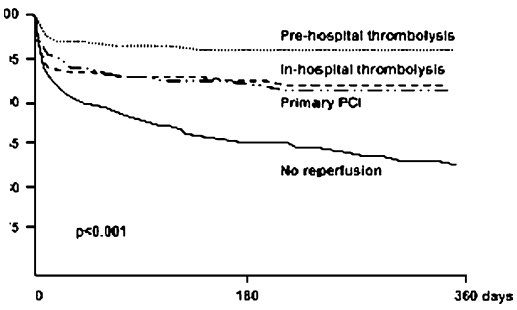

Fig. 2. Age-adjusted Kaplan-Meier 1-year survival according to reperfusion strategy. PCI, percutaneous primary intervention. (*From* Danchin N, Blanchard D, Steg GP, et al. Impact of prehospital thrombolysis for acute myocardial infarction on 1-yr outcome. Circulation 2004;110:1913; with permission.)

Placement on a monitor, intravenous access, oxygen administration, and administration of aspirin (ASA) or clopidogrel (if the patient is allergic to ASA) should be done within 5 minutes of patient arrival. These actions should be driven by nursing care to minimize the time to initiation of therapy. In the critically ill patient whose vitals signs are compromised (ie, cardiac arrest, tachyarrhythmias, severe bradycardia, shock, or hypotension), the advanced cardiac life support guidelines developed by the AHA should be followed. (Detailed management of particular arrhythmias is discussed elsewhere in this issue.)

If the patient is stable, and if no PH-ECG is available, an ECG should be obtained within 10 minutes of arrival at the emergency department, according to the ACC/AHA guidelines [3]. No study to date has shown that this can be done consistently, however. Barriers to optimizing early care for patients who have chest pain are relatively trivial but are common in busy emergency departments. Such barriers include large or demanding clinical volumes and time spent undressing the patient (especially the elderly), in monitor placement, in obtaining intravenous access, and in administering ASA and oxygen. These are important and necessary tasks, but they should not delay the acquisition of an ECG. The authors encourage all emergency department personnel to create a systems-based approach that intentionally works to minimize door-to-ECG-acquisition time in a way that facilitates clinical decision making and improves patient outcomes. To evaluate better the patient presenting with chest pain, they advocate using a standard 12-lead ECG and additional ECG techniques including right-sided leads (V_3R through V_6R), posterior leads (V_7, V_8, and V_9), and continuous ST-segment monitoring in selected patients who have ongoing chest pain and high pretest probability of ACS. Approximately 20% of patients who present to the emergency department with chest pain have a completely normal 12-lead ECG. The use of these additional techniques helps uncover a significant number of patients who have AMI but whose 12-lead ECG is not diagnostic. The rate of AMI in patients who have chest pain and a totally normal ECG remains around 1% to 4% [19].

Patient history and examination

The initial history and physical examination optimally should be performed within 10 minutes of patient arrival. The initial encounter should be focused and is done to identify best those who have life-threatening cardiac and noncardiac situations.

The pain characteristics in ACS are frequently substernal and are characterized as crushing, aching, vise-like, or pressure. The pain commonly radiates to the neck, jaw, and left arm. Associated symptoms include dyspnea, nausea, vomiting, diaphoresis, and presyncope. Pain often begins abruptly, lasting 15 minutes or longer and taking several minutes to reach maximal intensity. The pain is worse with activity and improves with rest. Although sharp, stabbing, or fleeting pain is regarded as atypical for ischemic pain, such pain is seen in 5% of patients who have AMI [20]. Elderly patients who have ACS can present with a range of complaints including generalized weakness, altered mental status, syncope, atypical chest pain, and dyspnea. Dyspnea is the single most common presenting symptom of angina in patients who are more than 85 years old [21]. Women presenting with ACS tend to be older on average than their male counterparts, to have more comorbid disease (eg, diabetes and hypertension), and to have a longer delay from symptom onset to presentation in the emergency department [22].

Assessment of cardiac risk factors is traditionally considered a routine element of the patient history, but its value in the emergency department has been disputed. Patient age, sex, body habitus, family history of coronary artery disease, and comorbid illness including diabetes mellitus, hypertension, hypercholesterolemia, and tobacco abuse are all classic coronary risk factors. Aside from age, sex, and family history of premature coronary artery disease, the actual role of risk factors in predicting ACS or AMI in patients presenting to the emergency department with chest pain seems minimal [23]. Risk factors are based on population studies and thus are more predictive of development of coronary artery disease over a lifetime, not of whether a patient experiencing chest pain in the emergency department is likely to have ACS [21]. One should not dwell on this component of the history.

The initial physical examination should focus on the cardiovascular system. The clinician should evaluate the jugular venous pressure, looking for elevation, the presence of a Kussmaul's sign, and the presence of hepato-jugular reflux. The lung fields should be examined for signs of congestion and wheezing. The heart and peripheral vasculature should be examined for abnormalities. The abdomen should also be examined for signs

of hepatic congestion and abdominal aortic pathology.

Cardiac biomarker and laboratory assessment

The use of cardiac biomarkers is well established in patients who have ACS. These biomarkers provide the most accurate diagnosis of acute myocardial injury and are considered the reference standard for the diagnosis of AMI [3,24,25]. In addition to diagnostic accuracy, the troponins provide prognostic data [26].

Additional cardiac biomarkers that provide prognostic data in STEMI and non-STEMI patients include B-type natriuretic peptide (BNP) and C-reactive protein [27] Patients who had elevations of several of these biomarkers faced the greatest risks. In the Orbofiban in Patients with Unstable Coronary Syndromes Trial 16 study, baseline measurements of troponin I, C-reactive protein, and BNP were performed in 450 patients. Elevations in troponin I, C-reactive protein, and BNP were independent predictors of the composite of death, myocardial infarction (MI), or congestive heart failure. When patients were categorized on the basis of the number of elevated biomarkers at presentation, there was a near doubling of the mortality risk for each additional biomarker that was elevated ($P = .01$) [28].

Recent work suggests a prognostic role for soluble CD-40 ligand and myeloperoxidase in patients who have AMI, but additional work is needed to confirm the long-term prognostic role of these newer markers and what value they add when combined with troponin, BNP, and C-reactive protein in patients who have AMI.

The authors recommend additional laboratory testing in patients presenting with chest pain. Glucose, creatinine, and electrolyte levels and a complete blood cell count should be obtained. In patients in whom acute pulmonary embolism is suspected, a D-dimer should be obtained. All these laboratory measures should be obtained as soon as possible.

Reperfusion strategies in ST-segment elevation myocardial infarction

A detailed discussion of reperfusion strategies in STEMI is given elsewhere in this issue. Following is a brief discussion of initial considerations.

When faced with a patient whose ECG demonstrates STEMI or new left bundle branch block, it is important to have pre-established multidisciplinary guidelines in place to indicate the best and the most expeditious reperfusion management. The authors recommend the use of intravenous fibrinolytic therapy (IFT) in hospitals without onsite and experienced catheterization laboratories. The use of IFT should be restricted to patients who present within 6 hours of symptom onset and have clear-cut ST segment elevation or new left bundle branch block. IFT should not be used in asymptomatic patients whose symptoms began more than 24 hours previously [3]. This therapy is most useful in the first 3 hours after symptom onset and restores coronary flow completely in about half the patients treated with it. The success rate, defined as Thrombolysis in Myocardial Infarction (TIMI)-3 flow at 90 minutes after the start of treatment, varies between 32% and 55%. The great risk of IFT is hemorrhage, including a 0.5% to 1.2% risk of intracranial hemorrhage and a 3% to 6% risk of other major bleeding complications (gastrointestinal bleeding, retroperitoneal bleeding, a $\geq$ 4-g drop in hemoglobin) [29]. PPCI can be performed in nearly all patients who have STEMI and is more successful than IFT at restoring TIMI-3 flow [30,31]. PPCI has a lower risk of intracranial hemorrhage and reinfarction compared with IFT [3,18]. PPCI must be done promptly. Several groups have reported increased mortality with increased door-to-balloon time [32,33,34]. De Luca and colleagues [35,36], in a study population of 1791 patients who had STEMI treated with emergent PCI, demonstrated that for every 30-minute delay in reperfusion therapy with PPCI, there was an increased 1-year mortality of 7.5%. ACC/AHA guidelines stipulate, that after adjusting for baseline characteristics, time from symptom onset to balloon inflation is significantly correlated with 1-year mortality (RR, 1.08 for each 30-minute delay; $P = .04$). The ACC recommends a door-to-balloon time of 60 to 120 minutes [3]. This goal can be achieved only if specific intradepartmental time goals are reached for the critical emergency department actions:

1. The diagnosis: door-to-ECG (preferably less than 10 minutes)
2. The decision to treat: door-to-catheterization team activation (preferably within 15–25 minutes and preferably performed by the emergency physician on call to minimize delays in consultation)
3. The transition in care: door-to-emergency department departure (preferably within 45–60 minutes)

This flow allows a 30-minute response time for the catheterization team members to respond after hours. Most invasive cardiologists are able to perform the first balloon inflation within 45 minutes after the patient's arrival at the catheterization laboratory. This flow would allow a door-to-balloon time of 90 to 120 minutes. Although it is impossible to achieve this flow for 100% of patients, maintaining these goals and making efforts to achieve such timelines are essential steps in achieving consistency in care and making health care more reliable. Future quality-assurance efforts in emergency medicine and cardiology will be to study, publish, and advise on best practice models that can serve as blueprints to achieve such goals.

High-risk ST-segment elevation myocardial infarction

In certain situations, slightly delayed PPCI is preferable to immediate IFT. Patients who present in cardiogenic shock have a high mortality risk, and the data from the SHOCK trial suggested that immediate revascularization is superior to delayed revascularization [14]. In practice, for such patients it is preferable to initiate reperfusion therapy with PPCI, even delayed PPCI, rather than immediate IFT if one can activate a team for PPCI reasonably quickly. Additionally, observational data from the NRMI registry have suggested that patients who have more advanced CHF (Killip class $\geq$ II) have better outcomes with PPCI than with IFT [5].

Risk of bleeding

A rare but important clinical conundrum is the patient who does not have a high risk of STEMI and who has a perceived high risk for bleeding from IFT. What should one do? Delay treatment with IFT and transfer the patient to a facility with PPCI, accept the risk and administer IFT anyway, or withhold all reperfusion therapies? One potential decision is to withhold IFT in any patient who has a greater than 4% risk for life-threatening bleeding and to transfer the patient to another facility for PPCI. To assess risk of bleeding, the ACC/AHA has defined contraindications and cautions for fibrinolysis use [3]. Risk scores (based on points for bleeding risks) are better predictors, and among these the best are those derived from observational studies [37]. In centers where immediate PPCI is not available, the use of such risk scores is highly recommended.

Delayed primary percutaneous coronary revascularization

In the United States the balance of risk–benefit between the expedited transfer of patients for PPCI and more immediate treatment with IFT remains an uncertain science. The decision regarding transfer must be based on multiple factors, and transfer should be made only when there is a clear-cut benefit for the patient. Although there is little consensus in the United States regarding a role for delayed PPCI in patients presenting to community hospitals without PPCI capability, the data from Danish Acute Myocardial Infarction-2 trial are provocative. The investigators demonstrated that patients transferred for PPCI within 2 hours of presentation had a better composite outcome (death, stoke, and recurrent nonfatal MI) than if treated with fibrinolysis at the local hospital [33,35,38]. No consensus has emerged in the United States regarding this issue, and ongoing randomized clinical trials are testing this strategy along with a strategy of facilitated PPCI using upstream administration of IFT before PPCI.

From the current literature, it is not possible to state that a particular reperfusion strategy is applicable to all STEMI, in all clinical settings, and in all hours of the day. It is most important to choose the appropriate reperfusion strategy based on the patient's clinical presentation and symptom onset and to provide the therapy in a timely fashion.

Early therapy for acute cardiac syndromes

Oxygen

Supplemental oxygen administration has become routine for all patients presenting with chest pain. Experimental results indicate that breathing oxygen might limit ischemic myocardial injury, and there is evidence that it reduces ST-segment elevation. Therefore, the use of oxygen is recommended for all AMI patients during in the first 6 hours and longer if the AMI is complicated by congestive heart failure, PE, or other significant underlying disease causing hypoxemia.

Aspirin

Aspirin (162–325 mg) should be chewed immediately at arrival if no ASA allergy exists. ASA produces a rapid antithrombotic effect by near-total inhibition of thromboxane A_2. The second International Study of Infarct Survival Collaborative (ISIS-2) demonstrated an absolute risk difference in 35-day mortality of 2.4% (RR,

23%) [39]. When combined with IFT, the absolute difference in mortality was 5.2% (RR, 25%) [40]. In patients who are allergic to ASA, clopidogrel should be substituted.

Unfractionated heparin

The authors recommend the routine use of unfractionated heparin (UFH) in all patients who have AMI, and it is essential for those undergoing IFT. UFH administration should precede IFT in all circumstances. The authors recommend weight-adjusted UFH administration including a bolus of 60 U/kg (maximum of 4000 U) followed by a 12-U/kg/hour infusion (maximum of 1000 U/hour) adjusted to a partial thromboplastin time at 1.5 to 2.0 times control. If a nonselective fibrinolytic (streptokinase, urokinase, or anistreplase) is used, UFH can be given only to patients who have a high risk of systemic emboli, such as large or anterior MI, atrial fibrillation, or known left ventricular thrombus. For patients who will receive PPCI, the authors recommend a weight-adjusted bolus dose of UFH of 50 to 70 U/kg accompanied by a 12-U/kg/hour infusion (maximum of 1000 U/hour).

Low molecular weight heparin

Low molecular weight heparin is an acceptable alterative to UFH for patients younger than 75 years, provided that serum creatinine is not greater than 2.5 mg/dL in men or 2.0 mg/dL in women.

The authors recommend the use of enoxaparin as a 30-mg intravenous bolus followed by 1.0 mg/kg injected subcutaneously every 12 hours for 48 to 72 hours. In the United States, the Food and Drug Administration has not yet approved enoxaparin for treatment of IFT, but ongoing studies are testing the efficacy of this combination.

Nitroglycerin

Patients who have ongoing chest discomfort should receive sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of three doses, after which the need for intravenous infusion is assessed. Nitrates reduce preload and afterload through peripheral arterial and venous dilatation, relax the epicardial coronary arteries to improve coronary flow, and dilate collateral vessels, potentially creating a favorable subendocardial-to-epicardial flow ratio. Nitrates are harmful in patients who have hypotension, bradycardia, or a suspected right ventricular infarction and in those who have taken a phosphodiesterase inhibitor-5 for erectile dysfunction within the last 24 hours.

Morphine sulfate

Pain increases sympathetic activity, and surges in catecholamine levels have been implicated as having a role in plaque fissuring and thrombus propagation in AMI, as well as reducing the threshold for ventricular fibrillation. Morphine is useful in controlling the pain of AMI but should be used judiciously. When necessary, morphine sulfate should be given in 2 to 4 mg doses intravenously with increments 2 to 8 mg at 5- to 15-minute intervals. Recent data from Can Rapid Risk Stratification Of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation Of The ACC/AHA Guidelines study [41] suggest that the use of morphine, alone or in combination with nitroglycerin for patients presenting with non-STEMI, is associated with adverse outcomes. The rate of AMI increased from 3.0% in the group of patients not receiving morphine (n = 40,036) to 3.8% in the group of patients receiving morphine (n = 17,003). Death increased from 4.7% to 5.5%, respectively, and the composite endpoint of death and AMI increased from 7.1% to 8.5%, respectively. There might be a selection bias, because the morphine group had higher incidence of ST-segment depression, transient ST-segment elevation, and positive cardiac markers and was more likely to receive an ECG within 10 minutes of arrival and to be cared for by a cardiologist. The authors address this potential by providing a risk adjustment and a propensity score matched-pair analysis for 33,972 of the patients. They conclude that the use of morphine is associated with a higher mortality and raise concerns regarding the safety of using morphine for this selected population. They hypothesize that common side effects such as hypotension, bradycardia, and respiratory depression result in decreased myocardial oxygen delivery, increased arterial carbon dioxide, and perhaps even decreased cerebral perfusion. Unfortunately, these parameters were not evaluated in this observational study. The authors' observation and conclusions are interesting and deserve future study. To date the ACC/AHA recommendations support the use of morphine as a class I indication (conditions for which there is evidence or general agreement that a given procedure or treatment is beneficial, useful, and effective), level of evidence C (only consensus opinion of experts, case studies, or standard of care exists). It is possible that this

classification will change to a class IIB (usefulness/efficacy less well established by evidence/opinion).

Beta-blockers

Intravenous or oral beta-blockers should be given promptly to patients who have AMI and who do not have a contraindication. Immediate beta-blocker therapy seems to reduce the magnitude of infarction and the incidence of associated complications in patients not receiving fibrinolysis, to reduce the rate of reinfarction in those receiving fibrinolysis, and to reduce the frequency of life-threatening arrhythmias. During the first few hours of STEMI, beta-blockers diminish myocardial oxygen demand by reducing heart rate, systemic arterial pressure, and myocardial contractility. In addition, prolongation of diastole may augment perfusion to ischemic myocardium, particularly the subendocardium. In the ISIS-1 trial, immediate oral atenolol, 5 to 10 mg, followed by atenolol, 100 mg daily, reduced 7-day mortality from 4.3% to 3.7% ($P < .02$; 6 lives saved per 1000 treated). In the Metoprolol in Acute Myocardial Infarction trial [42], metoprolol, 15 mg administered intravenously in three divided doses followed by 50 mg orally every 6 hours for 48 hours and then 100 mg daily, reduced 15-day mortality from 4.9% to 4.3% as compared with placebo. The benefits of routine early intravenous use of beta-blockers in the fibrinolytic era have been challenged by two later randomized trials and by a post hoc analysis of the use of atenolol in the Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries (GUSTO-1) trial [43,45].

Beta-blocker therapy is contraindicated in patients who have STEMI and moderate left ventricular failure until compensated and in patients who have bradycardia, hypotension, shock, a PR interval greater than 0.24 second, second- or third-degree atrioventricular block, active asthma, or reactive airway disease. Beta-blockers are also contraindicated in cocaine-induced chest pain because of the risk of inducing coronary spasm.

Glycoprotein IIb/IIIa inhibitors

Antagonism of glycoprotein (Gp) IIb/IIIa receptor blocks the final common pathway of platelet aggregation. Three such agents are available in the United States: abciximab, tirofiban, and eptifibatide. The use of these agents with IFT is not proven despite two large trials (GUSTO-V and Assessment of the Safety and Efficacy of a New Thrombolytic-3), which tested the efficacy of combined therapy. It is reasonable to start an intravenous Gp IIB/IIIA antagonist before initiation of PPCI in selected patients. In STEMI, the evidence favors abciximab for patients receiving immediate PPCI, but there are no direct comparisons of abciximab and eptifibatide. Decisions regarding upstream use of a Gp IIb/IIIa agent should be made in consultation with the consulting interventional cardiologist.

The use of Gp IIb/IIIa inhibitors in unstable angina and non-STEMI was best evaluated by Boersma and colleagues [45] who published a comprehensive meta-analysis that included six investigations (PARAGON A, Platelet Receptor Inhibition in Ischemic Syndrome Management, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited By Unstable Signs And Symptoms, GUSTO IV-ACS, Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network B (PARAGON B), and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) The primary endpoint was death or nonfatal MI. The meta-analysis included 31,402 patients. Patients who received the Gp inhibitor had a 1.2% risk reduction in the odds of death or MI after randomization (5.7% versus 6.9%; $P = .0003$). Recently, the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-TIMI 18 trial combined early PCI with a Gp IIb/IIIa antagonist and demonstrated a benefit from the use of the combination [46]. The authors believe that initiation of these agents in the emergency department is reasonable and may facilitate successful early PCI. (A detailed discussion of early management of non-ST-segment elevation ACS appears later in this issue).

Undifferentiated chest pain: the threats to life

If the ECG obtained has no significant ST-segment abnormalities, the evaluation of acute chest pain continues with an in-depth clinical history taking that focuses on the characteristics of pain, the time of onset, and the duration of symptoms, associated symptoms, risk assessment for ACS, PE, AD, and pericardial disease with tamponade physiology, and an examination that emphasizes vital signs and cardiovascular, pulmonary, and neurologic status. Most physicians do

a mental exercise; others use an algorithmic approach; but the focus of the evaluation *is* not on determining the most likely cause of chest pain. Instead, the question is: What life threatening entity could cause this patients chest pain (even if the possibility is less than 5%), and how will I make sure that I exclude it? As with missed AMI, the medical community, patients, and certainly the judicial system have no tolerance for missed life-threatening entities. The discussion that follows is based on the two most important threats to life, AD and PE.

Acute aortic dissection

Epidemiology

AD is the most common and most lethal aortic emergency [45,47,48]. The true incidence has been difficult to determine, because many incorrectly diagnosed cases escape notice. The occurrence of AD was reported to be between 5 and 20 per million population [49]. The incidence of hospital admission for AD ranged between 1 in 5335 to 1 in 16,550 [50]. Among the life-threatening causes of chest pain, AD has the highest mortality—an estimated 1% to 2% per hour for the first 48 hours [44]. Unfortunately, when initially evaluating patients who have AD, physicians correctly suspect the diagnosis in as few as 15% to 43% of cases [51–53]. Diagnostic delays of more than 24 hours after hospitalization are common and occur in up to 39% of the cases (31% for proximal AD and 53% for distal AD) [54]. Finally, when the diagnosis is made, it is often an incidental discovery made during an advanced imaging procedures requested to assess for other diagnoses. Several factors drive this poor performance. The most frustrating combination for a physician to face when evaluating a patient is a chief complaint (ie, chest pain) that has no typical presentation and is life threatening. Unfortunately, that combination is the rule in AD: classic findings such as ripping interscapular back pain, diastolic murmur, and a wide mediastinum are present less than one third of the cases [51,53,55].

During the last decade a substantial number of studies have evaluated the predictive value of several historical clues and physical examination findings in AD. Particularly useful is Klompas' [53] comprehensive review of the literature and the International Registry of Aortic Dissection (the IRAD database) whose inception and structure is based on 18 large referral centers in six countries [55]. Following are some of the most recent advances in understanding the clinical presentation of AD, based on these and other studies.

Clinical manifestations of aortic dissection

Traditionally, AD occurs in patients in the later decades of life: 95% of these patients are older than 40 years, and the mean age at presentation is 65 years [51,53,55]. Risk factors for AD include hypertension, male sex, non-white race, connective tissue disease (ie, Ehlers-Danlos syndrome or Marfan's syndrome), bicuspid aortic valve, coarctation of the aorta, and drug use including methamphetamine and cocaine. Januzzi and colleagues [56] evaluated patients younger than 40 years who had AD. Of 1078 patients in IRAD who had AD, 69 (6.4%) were younger than 40 years old. In these 69 patients, traditional risk factors such as hypertension and atherosclerosis were significantly lower than in the overall population of patients who had AD. The incidence of Marfan's syndrome, bicuspid aortic valve, and prior aortic valve surgery was significantly higher in these patients ($P < .0001$).

Clinical manifestations of AD are often dominated by the pathoanatomic characteristics of a malperfusion syndrome from a dissection-related side branch obstruction [57]. Severe pain is the most common presenting symptom; 74% to 84% of the patients recall an abrupt onset [51,53,55]. This symptom alone should trigger suspicion of an AD. Anterior chest pain is more frequent in patients who have AD involving the aortic arch, whereas patients who have AD distal to the left subclavian more often experience back pain and abdominal pain (29% of all patients who have AD; 42% of the patients who have distal AD) [55]. Contrary to common belief, pain is described as sharp more often than tearing or ripping. Pain that migrates throughout the chest is present in only 28% of the patients, with no difference between type A or type B.

Less frequent presentations of AD are stroke (carotid occlusion), heart failure (aortic valve insufficiency), syncope (tamponade, central nervous system ischemia), buttock and leg pain with or without lower extremity weakness (femoral artery occlusion), back and flank pain (renal artery occlusion), abdominal pain (mesenteric ischemia or celiac trunk involvement), and of course the infamous painless AD.

Of particular importance is the presence of syncope as a symptom of AD. In 2001, IRAD had identified 728 patients who had AD. Syncope was found in 96 patients (13%), including 24 (3%)

who described it in isolation without any symptoms of chest or back pain [56]. Syncope is more frequent in proximal AD than in distal AD (19% versus 3%; $P > .001$). Those who had syncope were more likely to have cardiac tamponade (28% versus 8%; $P > .001$), stroke (18% versus 4%; $P > .001$), and other neurologic deficits such as decreased level of consciousness, coma, and spinal cord ischemia (25% versus 14%; $P > .005$). In 46% of patients, a cause was not found.

Other symptoms that require particular attention are transient ischemic attack and other focal neurologic complaints. These findings are documented in 4.7% to 17% of the cases [51,53,55]. A complaint of focal deficits paired with chest pain has one of the highest likelihood ratios of being AD (positive likelihood ratio, 6.6–33) [53].

Findings on physical examination

Physical examination findings associated with AD are typically present in less than half the cases [53]. Among the most useful signs able to predict AD is a pulse deficit. A pulse deficit between the carotid, radial, or femoral arteries is relatively infrequent (25%–30%) but when present is strongly suggestive of AD in the setting of chest or back pain (positive likelihood ratio, 5.7; 95% CI, 1.4–23.0) [53]. This finding can predict in-hospital complications and mortality. Bossone and colleagues [58] noted that in-hospital mortality is higher when pulses absent (41% versus 25%). The more absent pulses the higher mortality. Blood pressure on presentation does not seem to be helpful in predicting who might have AD. Although approximately half the patients present with elevated blood pressure, an equal proportion are either hypertensive or normotensive [52,53,55]. A history of chronic hypertension as a risk factor is helpful, however, because it is the most frequent risk factor. Other physical findings are murmur of aortic insufficiency (detected in one third of the cases) and muffled heart tones and jugular venous distention that point toward cardiac tamponade.

Biomarkers in the workup of aortic dissection

The lack of symptoms or signs that have a good negative predictive value has forced investigators to look at serologic means to diagnose AD. This concept is particularly attractive because a serum test with a good negative predictive value would obviate the need for imaging. In the last decade several efforts have been made toward achieving this goal. Investigators have looked at soluble elastic compounds, D-dimer, and smooth muscle myosin heavy chain (SMMHC).

SMMHC is a major component of smooth muscle. Katoh and Suzuki [59] first described the use of SMMHC in AD in Japan in 1995. SMMHC was tested in serum of healthy subjects with levels of 0.9 ± 0.9 ng/mL and in four patients who had AD confirmed by surgery, all four of whom demonstrated elevated levels at presentation (> 7 ng/mL) that dropped to normal values after 24 hours. The immunoassay showed a sensitivity of 90% in the first 12 hours after onset of symptoms with a specificity of 97%. Most recently, Suzuki and colleagues [60] documented 25 patients enrolled in the IRAD whose measured SMMHC showed elevated levels of 19.6 ± 56.6 ng/mL (normal < 2.5 ng/mL) with a presentation time of 6.1 hours $\pm$ 4.5 hours. This study showed superior diagnostic performance in the early hours after onset ($> 90\%$ sensitivity in the first 3 hours after onset). The sensitivity decreased to 44% after 3 hours, however, and decreased most significantly after 6 hours [60].

Elastin is one of the major components of the arterial wall. An ELISA to measure soluble elastin fragments, a product of human aortic elastin, was developed by Shinohara and colleagues [61]. They reported that 16 of 25 patients who had AD had elevated soluble elastin fragments; unfortunately, all patients who did not have a patent false lumen had normal levels. Although the authors conclude that the test might be helpful in the diagnosis and screening of AD, one patient who had AMI had elevated levels, the study was retrospective, and the negative predictive value was poor and therefore not useful to exclude AD.

D-dimer is frequently used to exclude thromboembolic disease in low-risk patients. It is a cross-linked fiber degradation product formed by plasmin, which serves as a marker of clot lysis. Weber and colleagues [62] prospectively tested D-dimer levels in 10 patients suspected of having AD. In addition, they retrospectively reviewed 14 patients who had proven AD; 35 patients served as a control group. D-dimer was elevated in all patients who had AD. No patients who did not have AD had elevated D-dimer. The authors concluded that the presence of AD is unlikely in the setting of a negative D-dimer [62]. This conclusion is thought provoking and currently is being evaluated in a multicenter study along with soluble elastin fragments and SMMHC (L.H. Haro, personal communication, 2004).

ECG findings suggesting ST-segment elevation myocardial infarction

Emergency physicians and cardiologists are frequently challenged by a patient who presents with chest pain that radiates to the back and an ECG with ST-segment elevation suggestive of an AMI. In these cases, therapy is frequently delayed, because patients often go to CT or transfer without fibrinolytic therapy to rule out dissection. The frequency of ST-segment elevation and Q waves suggestive of an AMI in AD are well documented in the literature. In the initial IRAD publication, the finding was documented in 4.6% of type A and in 0.7% of type B [55]. In Komplas' review [53], new MI on ECG was present in 7% of the cases (95% CI, 4–14). Coronary artery involvement (CAI) in AD and ST abnormalities in the ECG do not go hand-in-hand, however. Bossone and colleagues [63] evaluated the clinical characteristics and outcomes of 475 patients who had AD, of whom 64 (13.5%) had CAI. When they reviewed the ECGs, patients who had CAI were more likely to show new Q wave or ST-segment elevation (16.7% versus 4.3%; $P = .000l$). Thus, these ECG findings were present in only one of six patients who had CAI. Therefore, ST-segment elevation in AD seems to be uncommon, and the ECG often is not diagnostic even when AD with CAI is present. The low frequency of AD with ST-segment elevation compared with actual STEMI would argue for selected and infrequent need for imaging. (The US Census Bureau projected a 296,042,501 population for May 2005. The best estimate of the occurrence of AD is between 5 and 20 per million population, or approximately 1400 to 6000 new dissections per year, 62% of which would be type A. Five percent to 7% of those type A dissections would have ST-segment abnormalities suggestive of a STEMI, representing less than 300 cases in the United States each year. Approximately 500,000 patients in the United States have STEMI each year.)

In general, when a patient presents with chest pain and ST-segment elevation in the ECG, one should assume STEMI and treat accordingly. The authors believe that reperfusion therapy with PPCI is the safest way to proceed. If no culprit artery is found, arteriography or intraoperative transesophageal echocardiography (TEE) can be performed. If PPCI is not available, and symptom onset occurred more than 3 hours previously, the benefit of fibrinolysis is low. Obtaining a CT emergently or transferring the patient for PPCI is the best option. Heparin can be withheld. In a patient who demonstrates ST-segment elevation in the ECG, an anterior distribution, and more than 3 hours of pain with no findings highly suggestive of AD (severe abrupt pain, focal deficit, pulse deficit), and a completely normal chest radiograph, the likelihood of AD is low (likelihood ratio, 0.07%; 95% CI, 0.03–0.17) [18], and the morbidity and mortality of STEMI are high. The authors recommend fibrinolysis while awaiting transfer or further imaging such as CT or TEE.

Imaging

The choice of imaging modality is usually based on availability and the patient's stability. CT and TEE are frequent choices [55]. CT is the most readily available, widely used, noninvasive technique for the diagnosis of AD. The sensitivity and specificity of CT approaches 100% for the diagnosis of AD [64]. Aortography was the traditional method for making the diagnosis of AD, with an accuracy of 95% to 99% [65]. Aortography, however, is highly invasive, requires the patient be out of the emergency department for an extended period of time, and exposes the patient to a significant contrast load [47]. TEE is being used with increasing frequency and has been shown to be safe, even in critically ill patients [58,66,67]. The sensitivity of TEE for detecting both proximal and distal dissections is 100% [59]. The main limitations to the use of the TEE is a lack of widespread, 24-hour availability. Finally, MRI is the newest imaging method for the diagnosis of AD. It is highly sensitive and specific and does not require exposing the patient to contrast material. It is not ideal in ventilated or monitored patients and is not widely available.

Treatment of aortic dissection

Treatment of AD is aimed at eliminating the forces that favor progression of the dissection. Prompt production of blood pressures can be accomplished through use of sodium nitroprusside with a rate adjusted to achieve a systolic blood pressure between 100 and 120 mm Hg [44,47,57]. Concomitant use of a beta-blocker to avoid reflex tachycardia secondary to the nitroprusside use is desirable to decrease further the shear forces that promote propagation. A target heart rate of 60 to 80 beats per minute is desirable [44,57].

Patients who have acute dissection involving the ascending aorta should receive rapid surgical

consultation. An exception might be isolated arch dissection; most physicians consider this a surgical entity. Richartz and colleagues [68] published the international experience with isolated arch dissections. Of 989 patients, 92 (9%) had isolated arch dissection. Of these, 39 (42%) were treated surgically, and 53 (58%) were treated medically. Thirty-day mortality was 17% (23% with surgery and 13% with medical management) and therefore was much lower than typical for type A dissections (35% with surgery and 65% with medical management). Complications were the same. The conclusion was that isolated arch dissections are best managed conservatively. Distal ADs are in general traditionally treated medically. Surgery is indicated in distal dissections when there is evidence of lower extremity or visceral ischemia, renal failure, or paraplegia [47].

Percutaneous management of aortic dissection

Complicated type B dissections have been subject to novel percutaneous therapies such as percutaneous fenestration (restoring flow to the true lumen by creating a tear in the dissection flap between the true and false lumen) and percutaneous stent–graft placement. With these techniques compromised flow can be restored in 90% of the cases (range, 70%–100%). If a patient survives the intervention, postoperative average 30-day mortality is 10% (range, 0%–25%), and additional surgical intervention is rarely needed [69].

Pulmonary embolism

Missed PE is a major source of malpractice litigation in emergency medicine [70]. It is estimated that the diagnosis of PE is missed 400,000 times annually, leading to 100,000 preventable deaths [71]. Other studies have estimated that only 30% of PE is diagnosed ante mortem [72]. The mortality rate for untreated PE is 18.4%—seven times greater than that of appropriately treated PE [73]. Certainly, failure to be diagnosed is the greatest threat to the patient who has PE [74]. The challenges faced in the diagnosis of PE are similar to those discussed for ACS and AD.

In general, the presentation of PE is nonspecific. Young patients who have excellent cardiac reserve tend to have mild, transient, or no symptoms at all [74]. Patients may complain of chest pain which is typically sudden in onset and pleuritic in nature. Dyspnea, palpitations, presyncope, or syncope may also be presenting complaints. Accurate diagnosis is clouded when clinical presentations coexist with underlying obstructive lung disease, pneumonia, or underlying congestive heart failure. In such cases, PE can present with the symptoms of any of these entities [75].

The clinical likelihood of a patient's having PE has long been estimated by implicit means. Physician judgment is based on the patient's clinical presentation, history and physical evaluation, and risk factor assessment. Studies, however, have shown poor agreement among physicians in estimating pretest probability of disease [76]. Physician experience affects pretest probability assessment, with less experienced clinicians demonstrating less ability to assign pretest probability accurately [77]. Implicit assessment results in a large group of patients being placed in the moderate-risk category. Thus, clinical judgment has yielded disappointing results in accurately determining the pretest probability of disease.

Therefore, clinical scoring systems have been developed. Wells and colleagues [78] and Anderson and others [79] have created a seven-feature bedside assessment tool to categorize patients as having low, moderate, or high pretest probability of PE. Even with Wells' criteria, studies have shown poor agreement among physicians on the assignment of pretest probability and poor accuracy for the same [80]. Until a reliable, validated clinical scoring system can be developed, the assignment of pretest probability of PE will remain a challenge.

History and physical examination

As in the entities previously described, history taking in a patient presenting with chest pain suspicious for PE should focus on features of the pain and associated symptoms. Particularly important in patients suspected of having PE is risk factor assessment. Box 2 lists the many of risk factors that need to be considered in a patient who has possible PE [74]. The physical examination in a patient suspected of having PE should focus on vital signs and pulmonary findings. Tachycardia and tachypnea are classically described, but the former is often absent in younger patients, and the later is absent in up to 13% of patients who have documented PE [74]. The physical examination may show pleural rub, rales, or findings consistent with pulmonary consolidation. In summary, no physical finding is sensitive or specific for the diagnosis of PE. Physical examination offers no clues to the diagnosis in 28% to 58% of cases [74].

Box 2. Risk factors for pulmonary embolism

Inherited disorders (thrombophilias)
Elevated individual clotting factor levels (VIII, IX, XI)
Factor V_{Leiden} mutation
Hyperhomocystinemia
Protein C, protein S, or antithrombin III deficiency
Prothrombin G20210A mutation

Acquired—persistent
Age
Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody)
History of pulmonary embolism/deep venous thrombosis
History of superficial thrombophlebitis
Hyperviscosity syndrome (polycythemia vera, malignant melanoma)
Immobilization (bedridden, paresis, or paralysis)
Malignancy
Medical conditions

Congestive heart failure
Obesity
Nephrotic syndrome

Tobacco abuse
Acute myocardial infarction
Varicose veins

Acquired—transient
Central venous catheter/pacemaker placement
Hormone replacement therapy
Immobilization—isolated extremity
Long distance travel/air travel
Oral contraceptive pills
Pregnancy and puerperium
Surgery
Trauma

From Sadosty AT, Boie ET, Stead LG. Pulmonary embolism. Emerg Med Clin North Am 2003;21(2):363–84; with permission.

D-dimer assays

The advent of quantitative ELISA has improved the sensitivity of D-dimer assays tremendously [81]. D-dimer assays as a whole have poor specificity, with numerous conditions resulting in false-positive results. They are most useful when combined with other noninvasive imaging or clinical probability assessment scoring systems. In this way, a negative D-dimer can be incorporated into diagnostic algorithms to withhold anticoagulation safely in patients who have a low pretest probability for PE [81]. Recent studies report the negative likelihood ratios for a negative result on a quantitative rapid ELISA D-dimer make them as predictive as a normal V/Q scan or negative duplex ultrasound [82].

Eleven prospective clinical studies have evaluated the role of D-dimer in excluding venous thromboembolic disease. In patients who have a high clinical pretest probability of PE but a negative D-dimer, there is not enough evidence to support stopping an investigation for PE [73]. In contrast, it has become increasingly accepted that the diagnosis of PE is effectively ruled out in patients who have a low clinical pretest probability of disease and a negative quantitative rapid ELISA D-dimer [82]. Controversy still exists over the extent of workup necessary in patients who have a moderate pretest clinical probability and a negative D-dimer assay.

One significant limitation affecting widespread use of D-dimer is the numerous commercially available assays that are not interchangeable, differing significantly in sensitivity and negative likelihood ratios [81]. Latex glutination assays and whole-blood qualitative assays do not demonstrate the same negative predictive value as quantitative ELISA assays and should not be incorporated in diagnostic algorithms similarly.

V/Q scanning

The Prospective Investigation of Pulmonary Embolism Diagnosis investigators employed V/Q scanning as the primary advanced imaging diagnostic modality for patients suspected of having PE [83]. Ventilation/perfusion scans are most helpful when they are read as either normal or high probability. Results of V/Q scans, however, fail to provide definitive indications for withholding or administering anticoagulation in up to 70% of patients on whom the test is performed [74].

CT scanning

CT is widely available, noninvasive, increasingly sensitive, and has the advantage of revealing

alternative diagnoses when PE is not found [84]. CT can miss subsegmental PE. Some authors have argued that this finding is insignificant and that outcome studies of rate of subsequent or recurrent PE and death would be more a appropriate reference standard than comparisons to the standard of angiographic subsegmental PE detection rates [85]. Eleven such studies exist, both prospective and retrospective, which demonstrate patient outcome is not adversely affected when anticoagulation is withheld based on a negative spiral CT [86].

Diagnostic evaluation summary

A review by Fedullo and Tapson [87] provides rational guidance to the approach to the patient suspected of having PE, using a combination of pretest probability assessment, D-dimer assays, and advanced imaging modalities to rule in or rule out effectively the diagnosis of PE.

Patients who have a low pretest probability of PE account for 25% to 65% of all patients evaluated for PE, with subsequent diagnosis of PE in 5% to 10% of cases [78,88–90]. For these patients at low clinical probability, a negative quantitative ELISA D-dimer effectively rules out the diagnosis of PE.

Patients who have a high pretest probability for PE comprise 10% to 30% of all patients evaluated for PE, with subsequent diagnosis of PE in 70% to 90% [78,88–90]. D-dimer has no significant role in this patient population, because a negative result does not rule out the presence of PE. Spiral CT should be performed in these patients. If CT is negative, duplex ultrasound or CT venography of the lower extremities may be indicated. If lower extremity studies are also negative in this high-risk patient population, pulmonary angiogram is indicated to rule out the presence of PE.

Intermediate-risk patients comprise 25% to 65% of all patients examined for PE, with subsequent diagnosis of PE in 25% to 45% [78,88–90].

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