The clinical spectrum of acute coronary syndromes

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More than 5 million Americans visit hospital emergency departments each year with the complaint of chest pain. Two million patients are admitted to hospitals because of chest pain, but the diagnosis of coronary heart disease is confirmed in only one fourth of them. Acute coronary syndrome represents a clinical syndrome that includes unstable angina, non-Q-wave myocardial infarction and Q-wave myocardial infarction. The goal of management of patients with acute coronary syndrome is to rapidly recognize and manage their cardiac ischemic event, define the risk of myocardial ischemia and recurrent cardiac events, and minimize unnecessary risk to the patient. These decisions can all be made by the use of standard clinical descriptors that include chest pain, the electrocardiogram, and biochemical markers of myocardial injury during and after an acute ischemic episode.

(Key words: unstable angina, acute coronary syndrome, non-Q-wave myocardial infarction)

Acute coronary syndromes (ACS) include the spectrum of conditions of unstable angina pectoris, non–Q-wave myocardial infarction (MI), and Q-wave acute myocardial infarction (AMI). The cardinal symptom of patients who present with ACS is chest pain. Patients with chest pain are commonly classified by the use of standard clinical descriptors that include chest pain as well as electrocardiogram (ECG) changes and biochemical markers of myocardial injury during and after an ischemic episode. Typically, patients who are subsequently shown to have Q-wave MI present with prolonged chest pain and ST-segment elevation. Patients with non–Q-wave MI have prolonged chest pain without ST-segment elevation. Their ECGs may be normal, show ST-segment depression, or T-wave inversion. In this group of patients, the diagnosis of non–Q-wave MI is established by cardiac enzymes. The distinction between unstable angina and non–Q-wave MI may not be made until hours, or even days, after the initial presentation.

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Vascular biology of acute coronary syndromes

The ACS represent a spectrum of conditions that hold in common the presence of plaque fissuring, which has been described as the cause of AMI and unstable angina, as well as sudden ischemic death. The disruption of a formed plaque is a complex process that is the central feature of the initiation of the ACS. The sudden total or near-total occlusion of a coronary artery usually occurs at the site of stenosis that was previously not hemodynamically significant, or at least not critical. The arterial lesion of unstable angina and MI is a complex eccentric plaque angiographically, which histologically represents a ruptured plaque with superimposed thrombus.

There are two main components to the vulnerable atherosclerotic plaque: the lipid-rich core, and the meshwork of extracellular-matrix proteins that forms the fibrous cap. The vulnerable atherosclerotic lesion, although not necessarily stenotic at angiography, may be prone to disruption because of its softness resulting from a high lipid content and macrophage-dependant chemical properties.

Chronic minimal injury to the arterial endothelium is physiologic and is often the result of a disturbance in the pattern of the blood flow at bending points and near bifurcations in the arterial tree. In addition to these local shear forces, endothelial dysfunction occurs because of hypertension, hypercholesterolemia, advanced glycation end products from diabetes, chemical irritants in tobacco, circulating vasoactive amines, immune complexes, and perhaps infections.

Passive plaque disruption occurs most frequently where the fibrous cap is the thinnest, where it is most heavily infiltrated by foam cells and at sites of mechanical stress. Active disruption of atherosclerotic plaques may be initiated by proteinases that are secreted by macrophages, which then enzymatically degrade the fibrous cap by phagocytosis or secretion of proteolytic enzymes. These enzymes include plasminogen activators and matrix metalloproteinases. In addition to degradation of the matrix of the fibrous cap, shedding of membrane microparticles leads to a potent procoagulant activity. These shed particles account for almost all the tissue factor activity present in plaque and may be a major contributor in the initiation of the coagulation cascade after plaque disruption.

Following plaque disruption, local thrombosis results from complex interactions between the lipid core, smooth muscle cells, macrophages, and collagen. The lipid core itself is the most potent substrate for platelet-thrombus formation. (This effect on the coagulation cascade of the exposure of the lipid core to circulating blood has been vividly compared to the analogy of throwing gasoline on a fire.) Both smooth muscle cells and foam cells correlate with expression of tissue factor in unstable plaques. Once exposed to blood, tissue factor interacts with factor VIIa to initiate a cascade of enzymatic reactions that results in the local generation of thrombin and the deposition of fibrin. Because of the balance between thrombosis and endogenous thrombolysis, some acute lesions resolve when plaque fissures are repaired.

As part of the response to the disruption of the endothelial wall, platelets aggregate and then release their granular contents. This release further promotes platelet aggregation and may lead to coronary vasoconstriction and thrombus formation. Various agonists trigger platelet activation by multiple pathways, including thrombin, collagen, adenosine diphosphate, and epinephrine. The final common path is the expression of the fibrinogen receptor function of the platelet glycoprotein IIb/IIIa. This integrin, which is present only on the surface of platelets, undergoes a conformational change, which enables it to bind to a specific sequence on the fibrinogen molecule.

During the past 35 years, the view has evolved that the ACS are caused by plaque rupture and formation of a platelet thrombus. Greater platelet stability and transmural infarction has been attributed to more severe or extensive plaque rupture. Unstable angina and non-Q-wave infarction were thought to be due to less extensive and less stable platelet thrombi that caused less severe, less extensive ischemia or infarction or both; however, more recent clinical findings have refined this viewpoint. The occlusive thrombi causing Q-wave MI contain more fibrin than the thrombi found in other ACS that are characterized by more platelets and less fibrin. The higher fibrin content of thrombi causing Q-wave infarction explains their higher stability. Further, this higher fibrin content suggests that the coagulation cascade is activated to a greater degree during Q-wave infarction than during non-Q-wave infarction, in which platelets play a more dominant role. This pathophysiologic feature defines the therapeutic role of thrombolytic agents for patients with ST-segment-elevation MI and the use of antiplatelet agents (aspirin, heparin, platelet GP IIb/IIIa receptor blocking agents) in non-Q-Wave MI.

In about one third of patients with ACS, and particularly in acute sudden coronary death, there was no disruption of a fairly small lipid-rich plaque, but just a superficial erosion of a markedly stenotic and fibrotic plaque. Thus, complicated thrombosis may well be dependant on a hypercoagulable state triggered by systemic factors. There is evolving evidence that circulating monocytes and white blood cells may be involved in tissue factor expression and thrombogenicity. Further, the predictive value for coronary events of high titers of C-reactive protein may be a manifestation of such systemic phenomena. Hypercholesterolemia, a high catecholamine drive, and perhaps infection may also be triggers of such hypercoagulable phenomena.

Dynamic obstruction may represent a further complicating feature of the pathophysiologic events of ACS. Vasoconstriction may occur as a response to a mildly dysfunctional endothelium near the culprit lesion, or more likely, may be a response to deep arterial damage or plaque disruption of the culprit lesion itself. Platelet-dependent vasoconstriction, mediated by serotonin and thromboxane A2, and thrombin-dependent vasoconstriction occur if the vascular wall has been damaged substantially with denuding of the endothelium, which suggests the direct interaction of these substances with the vascular smooth muscle cells.

Until recently, the embolization of plaque content and of platelet-thrombus into the distal microvasculature had been thought to be uncommon. Recent studies, however, indicate that microvascular embolization is not only common, but it also carries an adverse prognosis. Histologic studies have confirmed platelet-thrombus as part of occlusive material in the downstream microvasculature, and atherosclerotic particulate material has been identified as well. In addition, endothelial cells have been found to be present in the circulation with a higher frequency in patients with ACS compared with control patients or those who have stable effort angina. The benefits of short-
term platelet glycoprotein IIIa receptor blocking agents appear to be related to a decrease in microvascular obstruction from embolization, with a subsequent decrease in myocardial necrosis and decrease in risk for malignant arrhythmias. These agents do not decrease the embolization of atherosclerotic lipid and matrix constituents. The embolic events may also reflect significant inflammation in the diseased artery.

For patients with chronic stable coronary artery disease (CAD), angina or silent ischemia commonly results from increases in myocardial oxygen demand that outstrips the ability of stenosed coronary arteries to supply the needed blood flow. In contrast, in ACS, there is an abrupt reduction in coronary flow. In unstable angina, a relatively small erosion or fissuring of an atherosclerotic plaque may lead to an acute change in plaque structure and a reduction in coronary blood flow, resulting in exacerbation of angina. Transient episodes of thrombotic vessel occlusion at the site of plaque injury may occur, leading to angina at rest. This thrombus is usually labile and results in temporary vascular occlusion, perhaps lasting only 10 to 20 minutes. In non-Q-wave MI, more severe plaque damage would result in more persistent thrombotic occlusion, perhaps lasting up to 1 hour. Resolution of vasoconstriction may also be pathologically important in non-Q-wave MI. Therefore, spontaneous thrombolysis, vasoconstriction resolution and the presence of collateral circulation are important in preventing the development of Q-wave infarction by limiting the duration of myocardial ischemia. In Q-wave MI, larger plaque fissures may result in the formation of a fixed and persistent thrombus, which is rich in fibrin.

Clinical presentation of acute coronary syndromes

The evaluation of patients presenting with chest pain continues to be challenging despite new advances in our understanding of the pathophysiology of ACS, new biochemical markers for cardiac injury, and insights from large randomized controlled trials that provide important data on risk stratification and appropriate algorithms for patient management. The assessment of chest pain represents the starting point for evaluating the possibility that a person might have an ACS (Figure 1). The pertinent features of this evaluation are equally important for the primary care physician, emergency department physician, cardiologist, and house officer. The critical components of the evaluation include the history, physical examination, and ECG. Several implications arise from this apparently simple precept. Evaluation of the patient for chest pain cannot be conducted by telephone. Individuals who phone their primary care physician with a description of chest pain must be referred to a clinical setting where electrocardiography can be performed. Some of these patients will be shown to have AMI, when it is appropriate for immediate restoration of flow through thrombolytic agents or direct angioplasty. Because the only hint that would describe the urgency for this action is the description of chest pain, quality assurance programs for the evaluation of patients with ACS should not look just at the door-to-needle time for thrombolysis. Rather, an assessment needs to include door-to-ECG-interpretation time, door-to-cardiac-enzyme-result time, and door-to-initiation-of-general-treatment time.

Once the initial evaluation of the patient is completed, the physician then needs to determine the care environment. For low-risk individuals, the entire evaluation can be conducted on an outpatient basis and hospitalization is not necessary. Individuals at high risk should be hospitalized in a telemetry cardiac unit. Patients at intermediate risk represent the majority of patients, and they include a broad range between the low- and high-risk designations. These individuals may be evaluated in an emergency department holding area, a chest pain observation unit, a general hospital telemetry bed, or an acute-care setting. Several algorithms have been developed for the assessment of the patient with chest pain who presents to the hospital emergency department. Despite the effectiveness of these protocols, there is continuing concern about the ability to establish a definite diagnosis in the hospital emergency department. Emergency department physicians are typically even more averse to taking a risk than the general physician population and are prone to err on the side of hospitalization of patients with chest pain. Even though the percentage of patients who are discharged from the hospital who are subsequently shown to have unstable angina or MI is low, the discharge of these individuals may be associated with an increase in mortality. Ongoing concern exists about the risk of discharging patients from the hospital who are subsequently shown to have unstable angina or MI.

The central feature for the diagnosis of unstable angina is the determination of underlying CAD (Figure 2). In the initial assessment of the patient, the single most important component is the physicians’ determination of the characteristic of chest pain. The other features of the clinical presentation that help to define the presence of CAD include the ECG, the patient’s age, gender, and history of previous cardiac event (MI, resuscitation from sudden cardiac death, or Q waves on ECG). With the exception of diabetes mellitus, the presence of cardiovascular risk factors are of little help in the diagnosis of unstable angina. At the conclusion of this initial assessment, the physician should be able to classify the patient with chest pain as having:

- unstable angina,
- probably unstable angina,
- probably not unstable angina, or
- noncardiac chest pain.11

House officers and other physicians are especially encouraged to avoid completing their assessment with the vague term “chest pain, rule out MI.” After all, the triage person in the hospital emergency department has already provided that diagnosis. The evaluating physician should be able to advance this process further!

The first phase of risk stratification of the patient with chest pain is to determine the care environment in which an additional evaluation is to take place. Patients at low risk can be evaluated in the physician’s office or discharged directly from the hospital emergency department. In general, more definitive testing such as stress tests should be completed within 72 hours.11,15

The assessment of clinical symptoms alone is insufficient for risk stratification because symptoms may be difficult to assess objectively, and they can easily be subject to misinterpretation. Therefore, it is often necessary for patients to be held for observation while cardiac enzyme levels are determined. Cardiac enzymes should not be measured in the primary care physician’s office. If the physician suspects that a patient has a significant risk of MI, the place to draw blood for serum enzyme studies and to observe the patient until serial enzyme studies prove the presence or absence of myocardial necrosis is a hospital setting, not an outpatient environment.
**EVALUATION FOR CHEST PAIN**

<table>
<thead>
<tr>
<th>Electrocardiogram with ST-segment elevation</th>
<th>Yes</th>
<th>Acute infarction</th>
<th>Restore blood flow immediately</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-segment depression on electrocardiogram or T-wave changes</td>
<td>Yes</td>
<td>Evolving infarction or unstable angina</td>
<td></td>
</tr>
<tr>
<td>Cardiac enzymes elevated</td>
<td>Yes</td>
<td>Evolving infarction</td>
<td></td>
</tr>
<tr>
<td>Repeated measurements of cardiac enzymes (at 3, 6, and 9 hours) are elevated</td>
<td>Yes</td>
<td>Evolving infarction</td>
<td></td>
</tr>
<tr>
<td>Consider in-hospital or outpatient stress test</td>
<td></td>
<td>Discharge</td>
<td></td>
</tr>
</tbody>
</table>

**ADMISSION**

For patients held for clinical evaluation of chest pain, initial therapy should include aspirin, heparin, and sublingual nitroglycerin for episodes of recurrent chest pain. β-Blocking drugs represent the agent of first choice for the treatment of unstable angina.

A second step in the risk stratification of patients presenting with chest pain is the determination of prognosis, which is initially based on the history, electrocardiographic changes, and cardiac enzyme levels at the time of presentation. Additional prognostic information is subsequently gained from exercise testing, myocardial perfusion imaging, and cardiac catheterization.

**Diagnosis of acute coronary syndromes**

The cardinal symptom of patients with ACS is chest pain. The Braunwald classification was introduced to allow identification of subgroups of patients with unstable angina who were at different levels of cardiac risk. This classification is based on pain severity and duration as well as the pathogenesis of myocardial ischemia. Patients with unstable angina at rest have been shown to be at the highest risk of an adverse cardiac event (11% in-hospital event rate). The Braunwald classification, an accepted standard for evaluating patients, has been supplemented by evidence-based guidelines for the categorization of patients into low, intermediate, and high risk. However, the assessment of clinical symptoms alone is insufficient for risk stratification, and physicians often need to rely on electrocardiography and cardiac enzyme levels for the appropriate assessment of patients presenting with chest pain.

**Electrocardiography**

Approximately 5 million patients present to hospitals with chest pain each year in the United States. A confirmed acute infarction develops in only a minority of these patients. The ECG provides a specific diagnosis in 40% of those patients subsequently shown to have AMI. Of all patients presenting with chest pain, the ECG is diagnostic in only 5%. The ECG represents the definitive test to define the patient with an ACS who would benefit from thrombolysis. In the TIMI IIIb Trial, thrombolysis provided significant benefit for patients with ST-segment-elevation MI. In contrast, patients with non-Q-wave MI had no benefit from thrombolytic therapy; for patients with unstable angina, there was an increase in the incidence of death and MI.

The admission ECG has significant prognostic value in patients presenting with symptoms consistent with ACS. A retrospective analysis of the presenting ECG in 12,142 patients in the GUSTO-IIb (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Trial assessed the 30-day incidence of death or MI in patients who presented with symptoms of cardiac ischemia at rest within 12 hours of admission and had signs of myocardial ischemia confirmed by ECG. On the presenting ECG, 23% of the patients had T-wave inversion, 28% had ST-segment elevation, 35% had ST-segment depression, and 15% had a combination of ST-segment elevation and depression. The 30-day incidence of death or MI was 5.5% in patients with T-wave inversion, 9.4% in those with ST-segment elevation, 10.5% in those with ST-segment depression, and 12.4% in those with ST-segment elevation and depression (Table). An elevated serum creatine kinase level at admission also correlated with a higher risk of death. The ECG category and creatine kinase level at admission remained highly predictive of death and MI after multivariate adjustment for significant baseline predictors of events.

Because the benefit of reperfusion is greatest when it is initiated early in the course of an MI, the ECG remains the single immediately available and universally used diagnostic test on which the critical decision to attempt to restore flow to jeopardized myocardium is based. According to current guidelines of the American College of Cardiology and the American Heart Association, ST-segment elevation of at least 0.1 mV in contiguous ECG leads provides strong evidence of thrombotic occlusion of the coronary artery and makes the patient with chest pain a candidate for immediate reperfusion.
Figure 2. Likelihood of significant coronary artery disease (CAD) in a patient with symptoms suggesting unstable angina. Note: Estimation of the likelihood of significant coronary artery disease is a complex, multivariable problem that cannot be fully specified in a flow chart such as this. Therefore, the flow chart is meant to illustrate major relationships rather than rigid algorithms. (Source: Braunwald E, et al, eds. Unstable Angina: Diagnosis and Management. Clinical Practice Guideline 10. Rockville, Md: Agency for Health Care Policy and Research, National Heart, Lung and Blood Institute. AHCPR publication No. 94-0602; March 1994; p 22.)
A clinical problem involves the patient who presents with left bundle branch block (LBBB). Sgarbossa and colleagues\textsuperscript{18} recommended an algorithm based on 131 patients with LBBB in the cohort of 26,003 patients enrolled in the GUSTO-I trial. In a large community-based group of patients presenting with prolonged chest pain, the value of this algorithm was compared with empiric treatment with reperfusion. Reperfusion therapy should be immediately instituted for all those patients who have chest pain consistent with ischemia and LBBB, new or old, and in whom no contraindications exist.\textsuperscript{19}

Cardiac enzymes

During the past two decades, most of the emphasis for prompt diagnosis and treatment of ACS has been focused on the patient with ST-segment-elevation AMI. It is recommended that these patients receive thrombolytic therapy with a door-to-needle-time of less than 30 minutes. If direct angioplasty is done, the door-to-balloon time should be less than 90 minutes.

For patients with non–Q-wave MI or unstable angina, prompt diagnosis and immediate treatment is equally important. Further, the proportion of patients presenting to the hospital with non–Q-wave MI is increasing, and now more than half of all patients with infarction have non-ST-segment elevation MI. As previously described, the ECG is the definitive test to decide to initiate reperfusion therapy, and it provides useful prognostic information for patients with ACS. As previously stated, however, only about 5% of patients who present to the emergency department with chest pain have a specific ECG abnormality. Cardiac enzyme levels provide critical diagnostic and prognostic information for the majority of patients with chest pain.

The markers of cardiac injury are influenced by a number of factors. Proteins from the cytosol such as myoglobin and creatine kinase are released more rapidly, within 2 to 4 hours. Because myoglobin has such a small molecular weight of 17,000 d, its release could reflect ischemia as well as myonecrosis. Structural proteins such as troponin are released more slowly, over 12 to 16 hours, and their release typically reflects myonecrosis. The greatest utility for cardiac enzymes is to provide information that allows for the initiation of prompt treatment. For optimal triage in the emergency department, myoglobin or creatine kinase MB (CK-MB) subforms have advantages. The patient who is identified as high risk would therefore benefit from more aggressive therapy, and the low-risk patient should receive less expensive diagnostic and treatment approaches.

In the GUSTO-IIa substudy of 801 patients,\textsuperscript{20} elevation of the troponin T level on presentation to the hospital occurred in 36% of patients and is associated with a 30-day mortality of 11.8%. In contrast, if the troponin T level was not elevated on admission, the 30-day mortality was 3.9%.

In the same study, the baseline troponin T level was positive in 35% of 734 patients who presented within 12 hours of the onset of chest pain. In an additional 44% of patients, troponin T became positive at 8 hours or 16 hours, with a 30-day mortality rate of 5%. In the remaining 21% of patients, the troponin T was negative over 16 hours, and the 30-day mortality in this group of patients was zero. A positive troponin test first developed at the 16-hour sample in only 8 of 675 patients who had results for all three samples obtained at 0, 8, and 16 hours. Therefore, for nearly all patients presenting to the emergency department within 12 hours of the onset of chest discomfort, sampling of cardiac enzyme levels for 8 hours is sufficient to exclude MI.

Hamm and coworkers\textsuperscript{21} also described the low risk associated with negative troponin T or troponin I test results. These patients should be able to be discharged safely after a brief period of observation. A retrospective review of the patients who tested negative for troponin T in the GUSTO-IIa study group revealed that their median length of stay was 5 days!

Even minor elevations of CK-MB are associated with an increase in mortality at 30 days and 6 months.\textsuperscript{22} In 8250 patients enrolled in the PURSUIT (Platelet Glycoprotein IIb/IIIa Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial of patients with unstable angina, patients with mild elevation of CK-MB to one to two times normal had a significant increase in risk of mortality when compared with patients with normal peak CK-MB. If the total CK is normal, but the MB is increased (“MB leak”), patients are at high risk for cardiovascular events in the hospital and for death by 1 year. They may benefit from early aggressive therapy and risk stratification.\textsuperscript{23}

**Clinical implication**

The initial evaluation of the patient with chest pain should incorporate a focused history, physical examination, and 12-

<table>
<thead>
<tr>
<th>Variable</th>
<th>ST-segment elevation and ST-segment depression</th>
<th>ST-segment elevation</th>
<th>ST-segment depression</th>
<th>T-wave inversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, %</td>
<td>15</td>
<td>28</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td>Acute myocardial infarction on admission, %</td>
<td>87</td>
<td>81</td>
<td>47</td>
<td>31</td>
</tr>
<tr>
<td>Incidence of death, %</td>
<td>6.8</td>
<td>5.0</td>
<td>5.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Incidence of reinfarction, %</td>
<td>6.9</td>
<td>5.1</td>
<td>6.7</td>
<td>4.3</td>
</tr>
</tbody>
</table>

lead ECG. All patients should immediately receive aspirin, unless compelling reasons dictate otherwise. If the 12-lead ECG is not diagnostic for ST-segment elevation MI, the patient then needs to be evaluated for the presence of myocardial necrosis (non–Q-wave MI), for rest ischemia, and for exercise-induced ischemia. Comprehensive, protocol-driven approaches are necessary because they minimize the variation in the diagnosis and treatment of ACS and promote optimal management. Several widely accepted treatment approaches have been published.11-13,24

Of equal importance to the algorithm for admission of patients to the hospital are the discharge instructions for patients after diagnosis of AMI. Patients need to be counseled about signs and symptoms of heart disease, cardiac rehabilitation, modification of cardiac risk factors, and medications.11 An accumulating body of evidence would suggest that all patients with ACS should be placed on cholesterol-lowering therapy because it rapidly improves endothelial function after ACS.25

References

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