Acute Coronary Syndrome Clinical Presentations and Diagnostic Approaches in the Emergency Department

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KEYWORDS

• Acute coronary syndrome • Chest pain
• Cardiac biomarkers • Cardiac ischemia

A 47-year-old woman with a history of gastroesophageal reflux disease, hypertension, and hyperlipidemia arrives in the emergency department complaining of shortness of breath for 4 hours. It began abruptly and is accompanied by nausea and vomiting. She has had these symptoms before, but they resolved with Maalox and were never this uncomfortable. Her vital signs are normal, she is given a lidocaine and Maalox suspension and zofran, which alleviates her discomfort. Her electrocardiogram, basic laboratory studies, and troponin sent on arrival are normal. Two hours later she looks and feels well. She is discharged home with a diagnosis of noncardiac chest pain and reflux disease exacerbation. Seven hours later, she returns to the emergency department poorly responsive with an electrocardiogram diagnostic of a ST-elevation myocardial infarction. In the coronary catheterization laboratory she is found to have a fully occlusive lesion in her left anterior descending artery.

Many discussions of cardiac ischemia start with chest pain. It is a chief complaint that captures attention because it is one of the most common emergency department (ED) patient presenting complaints, and is associated with potential life-threatening diagnoses, such as acute coronary syndrome (ACS), pulmonary embolism, and aortic dissection. However, the identification of cardiac ischemia, as is captured within the spectrum of ACS, requires one to cast a broader net. There are now years of research showing that nonclassic ACS symptoms (eg, shortness of breath, fatigue, and nausea)

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are common and do not reflect less severe disease.[1–4] These are the patients in whom a diagnosis of ACS is likely to be missed,[5] and the biggest medicolegal risk as a specialty.[6,7] There were 124 million United States ED visits in 2010.[8] It is challenging to identify the 16% that will have ACS, particularly when the symptoms are more subtle.[9]

ACS CONTINUUM

ACS is a specific physiology that results in myocardial injury where a thrombus forms on an acutely ruptured acute coronary artery wall to heal the defect. If this clot obstructs the artery's lumen, it can diminish blood flow to tissues beyond the lesion. Diminished flow leads myocardial ischemia, or the process of cells starving for oxygen and other nutrients delivered by the blood.[10] When this process leads to cells starving to death, myocardial infarction occurs and myocardial cell components are released into the blood. The experience of injury from this physiology is represented by three clinical entities: (1) ST-elevation myocardial infarction (STEMI), (2) non-ST elevation myocardial infarction (NSTEMI), and (3) unstable angina (UA). Acute myocardial infarction (AMI) is a subset of ACS that includes both STEMI and NSTEMI.

STEMI is the most urgent and severe condition within ACS. It represents a complete occlusion of a coronary artery leading to full-thickness myocardial infarction, and its diagnosis is based solely on the presence of ST segment elevation on the electrocardiogram (ECG) that meets specific STEMI criteria.[11,12] NSTEMI represents myocardial cell loss and can be identified either by ECG changes or a positive biomarker evaluation, which typically consists of two samples of cardiac enzymes where one is drawn on arrival and the other hours later.[13] The diagnosis of UA is a clinical diagnosis made based on the report of symptom quality and duration. It represents a patient with known coronary disease (CAD) causing a coronary flow limitation who reports a recent history of symptoms that are accelerating or induced with less activity. Also included in this category are patients without a history of angina or CAD who are presenting with a report of symptoms concerning for ischemia without evidence of myocardial cell infarction. These patients are at risk for AMI and can evolve to have a NSTEMI or STEMI. The diagnosis of UA can only be confirmed in the setting of normal or unchanged ECGs, and a negative biomarker evaluation. Until this occurs NSTEMI should be included as the potential diagnosis.[14]

Cardiac biomarkers, typically troponin and creatine kinase-MB (CKMB) levels, serve as tests for myocardial injury. When ACS is suspected, signs of acute myocardial injury are assumed to be from ischemia-caused infarction, or primary (Type I) ACS.[15] However, this is not always a direct relationship. Myocardial injury may be the consequence of another medical condition stressing the heart. This is often referred to as "demand ischemia" (Type II ACS). In addition, other myocardial injury mechanisms, such as direct trauma and surgical manipulation, can elevate serum troponin levels. False elevations can occur because of poor serum troponin clearance, as often seen in end-stage renal disease patients.

Early treatment of ACS is the essential element in reducing morbidity and mortality. Because cardiac biomarker results have become available within the time frame of an ED evaluation, the burden of diagnosis, treatment, and mobilization of definitive therapy is a focus of emergency medical care. One approach to reducing the frequency of missed AMI is to test patients more liberally. However, this poses two problems. First, any test's negative predictive value and positive predictive value are dependent on the prevalence of disease in the test population. If those without concerning symptoms receive the test, its usefulness is reduced.[16] Second, this

approach does not take into account the need for appropriate resource use in an era where cost containment is a priority and value-added diagnostics are encouraged and increasingly monitored.

There are robust guidelines providing evidence-based recommendations for the management of patients with ACS and their care. The most widely endorsed are those of the American Heart Association and European Cardiology Associations joint recommendations for STEMI[11] and NSTEM/UA.[13] However, the hardest parts of ACS diagnosis and treatments in the ED are the least informed with clinical evidence. Specifically these challenges are identifying patients whose symptoms may be caused by ACS, and deciding which patients are safe to send home from the ED after what type and extent of testing. The data supporting such decision making are growing, and are discussed in this article.

PATIENT SCREENING FOR POTENTIAL ACS

The ECG is often described as the front-line screening tool for ACS. Altered ion channel function in ischemic tissue can change the electrical conduction pattern, and ECGs can often detect these electrical abnormalities. The ECG is one of the earliest cardiac diagnostic technologies,[17] and this history has made it a hallmark tool in the identification of ACS. However, the criteria for a good screening test or examination is that it has high sensitivity and high specificity,[18] and the ECG has very poor sensitivity, being normal in more than 5% to 10% of all patients eventually diagnosed with AMI, and normal or nondiagnostic (nonspecific ST or T-wave changes) in more than 50% in those with a missed MI.[2]

The Clinical History

The true screening tool is the clinical history. The patient's prior medical history helps gauge their demographic risk. Because CAD is a predisposing condition for ACS, considering a patient's Framingham risk factors (age >55, male gender, diabetic, hypertension, hyperlipidemia, smoker, or family history of an early CAD in a first-degree relative)[19] or TIMI score[20] is helpful in assessing the likelihood that the patient falls into a population of patients with a higher incidence of CAD. However, presenting to an ED with chest pain or other ACS-associated symptoms is more predictive of disease than demographic risk factors.[21] Demographic risk is a reflection of population risk, which is helpful for general risk stratification. It is important to note that in the rare cases of missed ACS these patients are more often non-white, female, or less than 45 years of age. However, it is less important when assessing the incident risk, or whether a particular presentation in a patient is likely to be ACS. A better assessment of risk for ACS is the story behind the patient's arrival in the ED.

The first clinical decision point is whether one believes the complex of symptoms leading up to the clinical encounter could be accounted for by ACS. This is an assessment of the patient's incident risk. Conventional teaching differentiates between classic or typical symptoms (chest pain or crushing pressure, radiating discomfort to the right shoulder and arm [highly specific], the left shoulder and arm, with jaw or neck pain) from atypical symptoms (pricking or stabbing chest pain, shortness of breath, fatigue, dizziness, nausea, upper abdominal pain). Classic symptoms are more specific of ACS, whereas atypical symptoms are less specific given that they have more significant overlap with other diagnoses.[2] However, atypical symptoms are not infrequent or a sign of less severe disease. They account for anywhere between 20% and 30% of all patients with ACS.[2,5] Certain populations, such as women, the elderly, and diabetics, are more likely to present with atypical symptoms

and may never have chest pain.[2,20,22] Many patients who end up with coronary revascularization never experienced chest pain.

The ECG

Once the decision is made to evaluate the patient for potential ACS, the ECG is the first, oldest, and fastest test. It is recommended that any patient with symptoms concerning for potential ACS have an ECG performed within 10 minutes to evaluate for potential STEMI, which requires rapid identification and management. The reality of ED patient flow is that patients rarely make it through registration and triage within 10 minutes. Individual EDs need to devise ways to meet this goal in parallel with patient check-in procedures. Methods have included nursing triage protocols identifying patients who should have an early ECGs performed, performing an EKG on arrival for every patient who has a chief complaint involving an organ system from the clavicle to the umbilicus, and direct-to-room triage of all patients for early provider evaluation.

ECGs have limited sensitivity and specificity, so they cannot be used to rule out ACS alone. In addition, they are a single snapshot of a dynamic process.[23] A patient with a normal ECG may evolve into an NSTEMI or STEMI, and some NSTEMIs can become a STEMI with time. Repeating ECG within reasonable intervals to assess for change provides a more longitudinal data. In addition, dynamic ST segment and T-wave changes should increase one's concern for AMI.[24]

The Physical Examination

Signs of heart failure can be a consequence of ischemia. However, the physical examination adds little to the identification of ACS directly. It is helpful in exploring the likelihood of conditions within the differential diagnosis for ACS symptoms. These include pneumonia, aortic dissection, pulmonary embolism, pneumothorax, musculoskeletal pain, pericardial effusion, and reflux disease.

Cardiac Biomarkers

In light of the limited diagnostic capabilities of the ECG, biomarker testing is an essential part of making the diagnosis. There are many biomarkers available with which to detect ischemia. These include myoglobin, CKMB, and cardiac troponins T or I.[14] In the 1990s, CKMB and the associated CKMB/total CK ratio were the gold standard for AMI diagnosis. They are still widely used, but have been replaced by cardiac-specific troponin T and I as the gold standard. Troponins are more sensitive tests for myocardial ischemia, but early generation troponins were found to have levels detectable in serum 4 to 12 hours after symptom onset (**Fig. 1**).

As a result CKMB, which is present in serum and reaches peak levels earlier than troponin, is still used in many facilities as an early warning test.[25] However, it is not recommended for making a final diagnosis of AMI if troponin testing is available.[12] Data from two recent studies indicate that this early warning value for CKMB testing may not be needed with new third- and fourth-generation troponin assays: ultrasensitive troponin I and troponin T. Troponins were elevated much earlier using these highly sensitive assays, obviating any need for CK measurements.[26,27]

Cardiac biomarkers are a direct test for myocardial injury, and ACS is one of many processes that lead to myocardial injury; thus, elevated troponin level does not always indicate AMI. In the absence of an alternative diagnosis a positive troponin should be assumed to be evidence of myocardial infarction until proved otherwise. A recent study noted that most troponin elevations in ED patients are from noncardiac causes and that a hospital discharge diagnosis of primary AMI was assigned to only 11% of patients admitted with positive troponin values.[28] If an alternative diagnosis exists, the

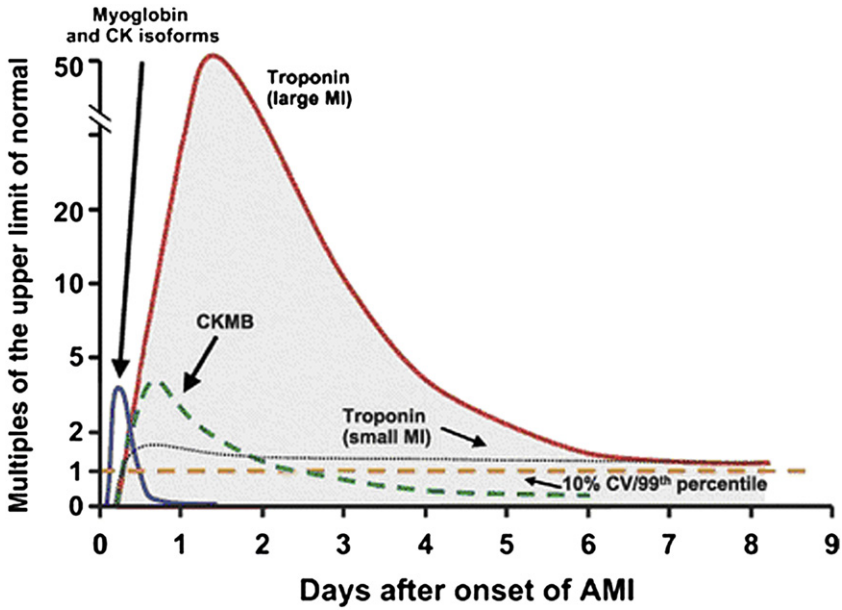

Fig. 1. Time to release of various biomarkers after acute ischemic myocardial infarction. (*From* Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-Elevation myocardial infarction. J Am Coll Cardiol 2007;50(7):e26; with permission.)

possibility of AMI as a cause or consequence of that condition should be considered against a troponin elevation from an alternative mechanism of myocardial injury. If it is unclear, AMI should be treated and the course re-evaluated with time, repeat biomarkers, and consideration of a cardiology consultation. Examples of the latter case include atrial fibrillation with a rapid ventricular response that could be a consequence of primary ischemia or the cause of secondary ischemia because of the excessive cardiac demand of the tachycardia. Also, patients with an abnormal troponin level caused by a non-AMI source often have a worse prognosis than if they had had an AMI, and therefore should be admitted.

EXTENT OF TESTING

No test or work-up is perfect. This makes missed cases an expectation. However, there is no acceptable miss rate for ACS. Recent studies have demonstrated rates of 2% to 3%. But most were done before the era of ultrasensitive troponins. It is expected that the more sensitive assays have improved case capture, but the miss rate with current practice is still unclear. Similarly, it is not known what degree of investment and additional testing will reduce this number. The impact of observation medicine and emergent stress testing on miss rates is not directly known. Despite this data void, figuring out how much testing to do for which patients is an active clinical question faced multiple times a day by emergency and family medicine physicians, internists, and cardiologists.

It is encouraged to use the clinical history (demographic risk and incident risk) and ECG to risk stratify patients for the likelihood of ACS. One should use caution when using these three items to rule out cardiac chest pain in moderate- and high-risk

patients. When the history and ECG alone are used to formulate a diagnostic impression of noncardiac chest pain, 2% to 5% of ACS cases are missed.[29,30] Having a higher demographic risk profile (CAD, prior myocardial infarction, multiple CAD risk factors, and so forth) was correlated with missed events (**Table 1**).[31]

For patients with lower-risk profiles, most specifically those who have had a limited lifetime to acquire CAD, ACS is less prevalent. Mason and colleagues[32] found that missed ACS rates were less than 0.14% among non–cocaine using patients with symptoms concerning for ACS who have no CAD history, are less than 40 years of age, without CAD risk factors or a normal ECG, and a negative initial set of biomarkers. This work-up can be considered in these lower demographic risk patients when their incident risk is believe to be low.

In cases of missed AMI, the usefulness of ECG in diagnosing AMI is limited by physician ECG interpretation. Key pitfalls include interpreting ST depressions as a strain rather than evidence of NSTEMI, failure to identify subtle ST segment elevations, not recognizing nonspecific ST and T-wave abnormalities as signs of potential ischemia, and not pursuing ischemia as a cause of new bundle branch blocks.[1,6,7]

If the decision is made to further pursue potential ACS, there are several tools available. First is to extend the evaluation for AMI by repeating the cardiac biomarkers after a time interval. When to repeat the biomarkers is highly dependent on the onset of symptoms, the biomarkers positive and negative predictive value, the kinetics of release, and clearance in the serum. The sensitivity, positive productive values of troponin, is greater than CKMB, and CKMB's performance in these areas is greater than myoglobin. It is generally accepted to repeat an older-generation troponin within 8 to 12 hours and a newer-generation troponin within 6 to 9 hours.[33,34] Current international guidelines recommend testing at presentation and at 6 hours. However, new data suggest that newer troponin assays may be reliable at as few as 3 hours, although there is no study that supports making disposition decisions using these new assays at any interval.[26,27]

Table 1
Screening and early diagnostic tools for acute coronary syndrome

	Pretest Probability		ACS Early Diagnostic Tools	
Tools	**Demographic Risk**	**Incident Risk**	**ECG**	**Cardiac Enzyme**
	CAD risk factors Diabetes Hypertension Hyperlipidemia Smoking Family history of early CAD in a first-degree relative Age >45 for men or >55 for women Male gender	Typical Symptoms Chest pain, pressure or discomfort Arm pain Neck/jaw pain Atypical symptoms Shortness of breath Fatigue Nausea Vomiting Dizziness Upper abdominal pain	ST segment elevations that meet STEMI criteria or a new LBBB ST elevations that do not meet STEMI criteria New ST depressions New T-wave inversion in a coronary distribution ST and T-wave abnormalities in a nonspecific (noncoronary) distribution Normal ECG	Elevated troponin Normal troponin but an elevated CKMB ratio Normal troponin and normal CKMB ratio Elevated CKMB with a Normal CKMB ratio only

If this testing is negative, the next step is to consider potential UA, by testing for reproducible ischemia with exercise testing or nuclear stress testing. The most common modalities are exercise treadmill testing, sestamibi scanning, and stress echocardiography. These tests were not initially developed for UA evaluations in patients without a history of prior CAD or myocardial infarction, but their use is becoming common in hospitals, chest pain units, and directly from many EDs. Their positive predictive value, as with most tests, is dependent on the prevalence of disease in the risk population, so when a test is positive in a low-risk patient it is more likely to be a false-positive. However, their negative predictive value for 30-day adverse events approaches 100% when a structured interpretation (eg, the Duke score) is used. The reverse is true in high-risk patients.[35] For the low-risk ED patient, the clinical yield of these provocative tests on reducing missed ACS has not yet been demonstrated. Evolving literature in this area is sure to comment in coming years.

Another method of extending the ACS evaluation is to look for the presence or absence of a flow-limiting lesion or CAD. This is a well-established approach used in higher-risk patients when they can be admitted for coronary catheterization. In very-low-risk patients coronary CT angiography is emerging as a noninvasive means of ruling out ACS by demonstrating the lack of a flow-limiting lesion or CAD. Whether the goal of an ED visit should be to evaluate for CAD in this population is up for debate. However, in patients with a low likelihood for coronary disease, ruling out CAD can help clinicians to pursue other etiologies of pain, if the presenting story is concerning and the ECGs and biomarker testing are negative. The radiation involved is approximately 50% to 75% less than an abdominal CT scan.

All patients evaluated for CAD with negative testing should be given very clear discharge instructions with details on when to return for re-evaluation. Setting up a very specific primary care or cardiology follow-up plan creates a safety net for potentially missed disease.

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