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Emergency Department Assessment of Acute-Onset Chest Pain: Contemporary Approaches and Their Consequences

Acute-onset chest pain is one of the most worrisome and anxiety-producing symptoms experienced by adults in industrialized nations. Although its origins can be obscure, recent research, and communications from organizations dedicated to lessening the impact of cardiovascular disease on public health (eg, the American Heart Association), have well informed the public on the importance of chest pain as a sentinel symptom of acute coronary syndromes (ACSs) and the role of underlying coronary artery disease (CAD) as the most frequent cause of death in the United States.[1] Not surprisingly, patients are increasingly likely to urgently seek hospitals' emergency department (ED) services for evaluation of acute-onset chest pain. The rapid disposition and management of chest pain made possible by contemporary algorithms and pathways in emergency medicine and cardiology are credited with dramatic improvements in outcomes of patients with ACS.[1] The Symposium on Cardiovascular Diseases article in the March 2010 issue of *Mayo Clinic Proceedings* provided an overview of the diagnosis and management of chest pain.[2] Three articles in the current issue of *Mayo Clinic Proceedings* expand on several of the themes addressed in that part of the Symposium: recent advances in the ED diagnosis of ACS and the subsequent evaluation of patients who are discharged directly from the ED after ACS has been "ruled out" as a cause of acute-onset chest pain.[3-5]

The prompt and accurate evaluation of acute chest pain has immense implications for patient morbidity and mortality and health care economics. Chest pain or other symptoms consistent with myocardial ischemia are a common presentation in the ED. They account for 5% to 10% (or approximately 8-10 million) of the estimated 109 to 116 million ED visits per year.[6] Importantly, the number of ED visits for chest pain is increasing yearly. The cumulative cost associated with the initial evaluation and triage of chest pain in the ED was estimated to be in excess of 8 billion dollars in 1982[7] and is almost certainly higher now.

Most patients with chest pain in the ED (55%-60%) have no worrisome electrocardiographic abnormalities and no history of CAD. Identifying the small number of patients who actually have ACS within this "low-risk" category[8] presents a challenge to ED physicians. Although current evaluation strategies tend to err on the side of caution, a small number of patients with unrecognized ACS are discharged home. The subsequent morbidity and mortality of these patients is 2 to 3 times that of patients who were admitted to the hospital.[9] Although one multicenter study reported that 2% of ACS in the ED may be "missed,"[9] other studies have found higher rates of "missed" ACS.[10] Missed ACS represents greater than 20% of malpractice awards against ED physicians and thus is a substantial medicolegal liability.[11] Although some of these patients may have had ongoing myocardial infarction (MI) at the time of discharge, most of them likely had unstable angina that subsequently evolved into MI. This concept underscores the importance of identifying among ED chest pain patients not only those with MI but also those with ischemia.

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The primary goal of the evaluation of patients with chest pain in the ED is accurate risk stratification and identification or exclusion of ACS, rather than the detection of CAD. "Traditional" risk stratification in chest pain patients incorporates elements from the patient's history, electrocardiographic findings, and initial clinical presentation. The simplest criteria rely on one set of cardiac injury markers, electrocardiographic findings, and a history of

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CAD. If none of these are present or abnormal, the patient can be considered at low risk, with a probability of MI in progress of less than 6%.[8] More complex risk stratification schemes[12,13] have been developed for high- and low-risk patients with chest pain; however, even the lowest scores may indicate a level of risk that is not low enough to comfortably discharge patients without further testing.[14] A recent systematic review that compared the diagnostic accuracy of 8 clinical prediction rules for excluding ACS in ED patients concluded that all risk prediction rules had important shortcomings that limit their value as the sole tool for the evaluation of patients experiencing chest pain.[15] Therefore, additional diagnostic testing is usually performed.

Efforts to improve the efficacy of the evaluation of chest pain patients in the ED have included incorporation of newer diagnostic strategies and modalities, such as new cardiac biomarkers and noninvasive imaging.[16] These approaches are typically used in various combinations as part of "accelerated" diagnostic protocols for patients admitted to chest pain units. If the initial evaluation shows no evidence of MI or ischemia, a confirmatory study is performed to further exclude ischemia. If findings on the confirmatory study are negative, the patient can be discharged. Although plain exercise treadmill testing is most widely used as a confirmatory test, imaging stress tests with echocardiography or myocardial perfusion imaging are increasingly common. In some centers, this process is further accelerated by skipping serial biomarker sampling and instead using "front-loading" testing with acute myocardial perfusion imaging,[17] or echocardiography[19] at rest, early exercise treadmill testing,[18] and, more recently, cardiac computed tomography (CT).[20]

The article by Laudon et al[3] in the current issue of *Mayo Clinic Proceedings* addresses a specific approach to cardiac CT for the evaluation of possible ACS: the quantification of coronary artery calcium (CAC). The relationship between CAC and biologically "unstable" coronary artery plaque prone to rupture, thereby causing ACS, is not well understood.[21] According to various theories, CAC may "stabilize" plaque, may signify areas of shear stress within plaque, or may simply colocalize with unstable plaque. This last concept provides a simple rationale for using CAC scanning in patients with acute chest pain. According to this line of reasoning, the higher the CAC score, the higher the probability of an unstable plaque somewhere in the coronary artery tree that may relate to a patient's chest pain.

A recent study of more than 1000 ED patients[22] with symptomatic chest pain found that the absence of CAC identifies a low-risk population with a very low event rate, both in-hospital and during a median 3.3-month follow-up period, and a rate of abnormal stress myocardial perfusion imaging of less than 1%. The article by Laudon et al[3] adds the new information that absence of CAC in symptomatic ED patients also indicates low risk in the *long-term* (5 years). Do these studies in comparatively small numbers of relatively young, predominantly white, male patients suggest that CAC scanning is a preferable means of stratifying the risk of patients with acute chest pain? As another important piece of information, the current study by Laudon et al confirms previous reports that the specificity and positive predictive value of CAC scanning in symptomatic patients are not optimal.[21] Receiver operating characteristic analysis suggested that using a CAC score of 36 as a cutoff point gave the best overall diagnostic accuracy. At this level, specificity was 85%, and the positive predictive value was 44%. Clearly, being highly sensitive is preferable to being highly specific in the detection of possible ACS in ED patients with acute chest pain. On the basis of the data reported by Laudon et al,[3] patients with no CAC can be safely discharged. However, the disposition of patients with CAC is less clear. Might other contemporary cardiac imaging modalities offer higher value?

The review by Winchester et al[4] in the current issue of *Mayo Clinic Proceedings* provides a useful update on contrast-enhanced CT for noninvasive, angiographic visualization of the coronary arteries (cardiac CT angiography), which, in its brief history,[23] has met with considerable enthusiasm. Establishing or excluding high-grade coronary artery stenoses as the cause of acute chest pain in ED patients is a conceptually promising use of cardiac CT angiography for 2 reasons. First, in contrast to patients with chronic stable angina, patients with ACS can have high-grade stenoses with no CAC.[24,25] In this setting, CT angiography might detect noncalcified coronary stenoses, thus avoiding "false-negative" results. Second, cardiac CT angiography might authoritatively demonstrate the absence of high-grade stenoses in patients with some CAC, thus avoiding "false-positive" results, and help refine the disposition of ED patients with mild to moderate CAD. For these reasons, the number of studies of cardiac CT angiography in the ED has in recent years greatly exceeded the number of studies with CAC scanning.

The current evidence base for cardiac CT angiography in evaluating chest pain in the ED consists of several relatively small (N=197-586) single-center studies in low- to intermediate-risk patients with short follow-up.[26-30] Such studies typically use combinations of expert clinical assessment, information from other noninvasive imaging or biomarker studies, and patient follow-up as reference standards to establish the presence or absence of ACS. In some studies, cardiac CT angiography with contemporary scanners in the ED allowed discharge of patients earlier and at lower cost than usual standard evaluation algorithms.[26,27] In another study, the sensitivity for detecting ACS was

100% and the specificity 54% if *any* degree of coronary atherosclerosis was used as the diagnostic criterion.[28] Use of the more stringent criterion of greater than 50% stenosis on cardiac CT angiography had a sensitivity of 77% and a specificity of 87%. In the largest study to date, 476 (84%) of 568 patients with suspected ACS who were at low risk as indicated by their Thrombolysis in Myocardial Infarction score were discharged from the ED after cardiac CT angiography, and none had adverse cardiac events at 30 days.[30] On the basis of current data, cardiac CT angiography in the ED will likely be most useful in patients without known CAD who have low to intermediate risk of ACS after initial risk stratification.

The high spatial resolution and large field of view in CT reveal incidental noncardiac findings that could relate to the etiology of chest pain in approximately 20% to 60% of patients.[31-33] The clinical relevance of these incidental findings and even the need for routinely reporting them are currently controversial. In approximately 10% to 20% of patients, follow-up with further tests and observation may be necessary.[31-33] These additional costs have not been routinely factored into studies of the cost-effectiveness of cardiac CT angiography in the ED. Similarly, the logistical and medicolegal question of who is responsible for the follow-up testing in patients with incidental extracardiac findings on cardiac CT angiography in the ED (especially those who have no documented primary care physician) is also currently unresolved. Information on the negative predictive value of cardiac CT angiography and on the relevance and appropriate follow-up of incidental findings is needed, preferably in the form of randomized trials of patient outcomes.

Some imaging techniques used to assess acute chest pain use ionizing radiation, and the potential cancer risk is a frequently cited concern. First, it must be understood that this risk is unproved at the levels of radiation used in medical imaging.[34] Second, even if the age- and sex-averaged lifetime risks of fatal cancer that are extrapolated mainly from follow-up studies in atomic bomb explosion survivors were true, this risk would be small (0.05%) for standard cardiac CT angiography (effective dose, 10 mSv) compared with the population-averaged lifetime intrinsic risk of dying of cancer (21%) and similar to that from a conventional 1-day myocardial perfusion stress test with technetium Tc 99m sestamibi (12 mSv).[34] Third, the potential health risks of a cardiac imaging test with ionizing radiation should be considered relative to the earlier discussed risks of disabling MI or sudden cardiac death in a patient with acute chest pain and low to intermediate probability of CAD in whom an ACS is missed.[34] However, the fact that some ED chest pain patients may undergo serial testing with more than one imaging modality that uses ionizing radiation is frequently overlooked, and the cumulative radiation dose in these patients has not been well characterized to date.

The frequency and outcomes for noncardiac etiologies of chest pain syndromes evaluated in the ED are also not well established. Most studies are based on clinical discharge diagnoses, and few studies report outcomes in patients in whom a noncardiac etiology of chest pain was established with certainty. In some series, gastrointestinal (GI) etiologies were most common. In the current issue of *Mayo Clinic Proceedings*, Leise et al[5] report that in 26% of patients with an ED discharge diagnosis of noncardiac chest pain, the pain was thought to have a GI etiology, whereas no specific etiology was listed for the remaining 64% of patients. Interestingly, referral for a subsequent GI evaluation was less frequent in patients in whom a GI etiology of chest pain was suspected than in those with no specific diagnoses. Empiric treatment with receptor-specific drugs aimed at altering gastric acidity (eg, histamine H_2-receptor blockers and proton pump inhibitors) and eventual referral for GI evaluation of only those patients whose symptoms did not improve with this management may explain the observations of Leise et al.[5] Among the patients referred for GI evaluation, diagnostic GI procedures (pH testing and manometry) were used in a minority of patients (<10%). Therefore, the low proportion diagnosed as having esophageal disease as an etiology of chest pain in this study is likely an underestimation.

In other studies of noncardiac chest pain, a musculoskeletal etiology was the most common (approximately 25%), and a GI etiology was present in 7% to 9% of patients.[35,36] These proportions are consistent with the current study by Leise et al.[5] However, in one study that performed a systematic GI evaluation, more than 25% of patients in whom CAD had been excluded had esophageal dysmotility.[37] Another study of 214 patients with chest pain used myocardial stress perfusion imaging, Holter monitoring, echocardiography, pulmonary scintigraphy, abdominal ultrasonography, upper endoscopy with pH monitoring and manometry, and physical examination of the chest wall and thoracic spine for a comprehensive evaluation.[38] A GI etiology was identified in 42% of patients, more than in any other study. As an important concept, the investigators identified more than one potential cause for chest pain in 9% of patients. This finding highlights the potential difficulty of determining a single, "accurate" etiology for chest pain in the ED population.

Given the 22% prevalence of prior MI, the cohort in the current study by Leise et al[5] was clearly not a low-risk group, and the frequency of subsequent referral for cardiology evaluation is not unexpected. Importantly, at the time the study was performed, biomarkers highly specific for myocardial compromise were not widely available. There-

fore, it is conceivable that some of the patients with a clinical diagnosis of noncardiac chest pain in fact had an ACS. This would be entirely consistent with the 3% readmission rate for ACS of patients initially discharged from the ED with a diagnosis of noncardiac chest pain.[36]

What should our readers take away from the cluster of articles about evaluation of chest pain in the ED in the current issue of *Mayo Clinic Proceedings*? First, further rigorous studies are needed to establish the relative frequencies of noncardiac etiologies for chest pain and to define the most reliable means of exluding ACS as a high-risk cause of acute chest pain. Second, new diagnostic imaging modalities may improve the proportion of patients in whom ACS can be ruled out with a certainty high enough to comfortably permit timely discharge from the ED. Among the cardiac CT modalities, the benefits of CAC scoring include low radiation dose and excellent negative predictive value. However, the possibility of noncalcified high-grade coronary artery stenoses in patients with ACS suggests that CAC should be used in combination with other means of risk stratification such as biomarkers for myocardial compromise. Cardiac CT angiography is promising for the evaluation of ED patients with acute chest pain. However, cardiac CT angiography with most scanners currently in wide use is not consistently reliable in patients with heart rates greater than 60 to 70 beats/min and is not possible in patients with a documented allergy to iodinated contrast agents or significant renal insufficiency. Finally, given the wide variety of different diagnostic modalities that are currently available for evaluation of patients with chest pain, training specialized teams to provide opinions on the optimal choice of diagnostic testing after initial evaluation and on the proper course of action when the results of initial testing are not entirely normal might be a safe and cost-effective addition to standardized chest pain evaluation pathways.

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