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EDITORIAL COMMENT

Ischemic Versus Nonischemic Chest Pain in the Emergency Room

Echoes of Contrast*

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More than six million patients present with chest pain and suspected acute coronary syndrome (ACS) to emergency departments (EDs) across the U.S. annually (1,2). These patients require rapid and efficient triage to hospitalization versus discharge to maximize appropriate allocation of resources to the highest-risk patients who require timely life-saving therapy. The 12-lead electrocardiogram (ECG) and serial cardiac enzymes, which are the cornerstone of decision-making in the ED, have significant shortcomings. As many as 50% of patients have a nondiagnostic ECG, and cardiac injury markers frequently are normal in the early hours of ACS (3). These findings, when combined with inadvertent discharge of 2% to 4% of patients with ACS and the fact that missed ACS is one of the leading causes of litigation against EDs, has meant that the threshold of hospitalization has remained suboptimal (4).

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Therefore, it is imperative that we continue to find algorithms that may help to reliably identify the lowest-risk patients who may not even have coronary artery disease (CAD) because the economic burden of hospitalization of these patients is enormous. During the last decade, chest pain units (CPUs) in the ED were born out of such an effort to triage patients with intermediate- and low-risk for ACS (5). Typically, these units hold patients for as long as 12 h for clinical observation, during which time serial ECGs and cardiac enzymes are performed. A positive evaluation leads to hospitalization, whereas a negative evaluation leads to stress testing or discharge without stress testing.

The role of exercise electrocardiography (ExECG) in the ED among patients with intermediate or low risk for ACS has been tested in a number of studies (6,7). On the basis of the collective data, it can be surmised that ExECG is a good and cost-effective test to triage patients with intermediate risk. There are, however, several limitations to ExECG: the percentage of patients who present to the ED and are unable to exercise has been reported to be as high as 35%, the rate of suboptimal exercise is largely unaccounted for in the published studies, the rate of false-positive tests is unacceptably high especially among women. Furthermore, stress imaging testing has been shown to have excellent accuracy and cost-benefit in stratifying patients in the ED (8).

Multiple imaging studies have been performed in the ED and CPU settings in patients with suspected ACS or those who were admitted with the diagnosis of acute myocardial infarction. Resting echocardiograms have been reported to be ~90% sensitive and ~65% specific for the diagnosis of ACS or acute myocardial infarction (9). A large randomized study of rest nuclear imaging in the ED showed that there was a 10% absolute reduction in hospitalization in patients with chest pain and nondiagnostic ECG when perfusion data was included in the decision-making (8). The study by Tong et al. (10) in this issue of the *Journal* is an important addition to the accumulating evidence for using imaging in CPUs for efficient assignment of patients to admission versus discharge. They studied contrast echocardiography (CE) compared with a modified Thrombolysis In Myocardial Infarction (TIMI) score for triage of nearly 1,000 patients presenting with chest pain and nondiagnostic ECG. Both regional myocardial function and perfusion were analyzed by rest CE and related to early (in the first 24 h), intermediate (at 30 days), and late (1 year) events. The comparison of CE was performed with the modified TIMI (mTIMI) score, which initially did not include serum troponin levels. Troponin levels became available during the CPU stay after CE was performed. The presence of normal regional function (RF) was most efficient in predicting lowest risk in the first 24 h.

The lowest mTIMI score failed to identify approximately 4% of ACS (myocardial infarction), which is consistent with previous data. Further, CE also was able to classify patients with an intermediate mTIMI score into low risk (normal RF) and high risk (abnormal RF) for ACS. For a given RF finding, the presence of perfusion abnormality by CE was indicative of the highest risk whereas normal perfusion identified a very low risk (0.4%) for ACS. Even the subsequent complete TIMI score (which included the troponin level) failed to predict up to 5% of early events. These findings are a confirmation that clinical variable plus cardiac enzymes alone are insufficient to adequately triage low- and intermediate-risk patients in the CPU, and the reliable discrimination would need the aid of an imaging test.

Which imaging test does one choose? In the case of nuclear imaging, the wealth of experience with myocardial perfusion imaging, the safety of adenosine or stress imaging, and the recent approach of using fatty acid imaging to identify ischemic memory offer tremendous advantages in the ED (11). However, the ability to readily obtain information on left ventricular regional function and perfusion by rest CE at the bedside is a significant advantage from a practical standpoint and universal applicability. Previous

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echocardiographic studies in the ED were performed at a time when a significant proportion of transthoracic echocardiograms were suboptimal, thus limiting the clinical applicability of the approach. The advent of CE and new transducer technology has had a tremendous positive impact on image quality, making transthoracic echocardiography interpretable in ~90% of studies. Current transducer and equipment technology also allow myocardial perfusion imaging with little additional operator interaction.

The limitations of CE have to do with the traditional arguments of image quality and operator dependency of echocardiography. Contrast echocardiography has made the former problem a rarity and, with CE wall motion and thickening, can be appreciated even by a modestly trained eye. Interpretation of perfusion may be more challenging for the untrained eye. However, the growth of telemedicine means that the expert can both guide the acquisition and read the information in real time. These issues are not prohibitory to the application of CE or, for that matter, any imaging modality in the ED. Recent experimental data from work on targeted imaging using either radioisotopes or microbubbles add another exciting dimension to imaging in the ED. For example, annexin-A5 can be bound to polymer microbubbles, which can then be insonated with ultrasound to image myocyte apoptosis in the infarcted myocardium (12). It is also possible that the endothelial alterations during ischemic injury will also offer a convenient target for CE in the ED in the future (13).

There are challenges to contend with implementation of imaging in the CPU protocol for triage. Patients with chest pain who present after-hours to the ED require additional resources that have to be specifically allocated, readily available, and carefully monitored (e.g., the quality of the data obtained during "after hours"). The economics of imaging, whether it be rest or stress imaging in the CPU, is uncertain. Contrast echocardiography will certainly have more resource-based relative value units than standard noncontrast two-dimensional echocardiography but this would still favorably compare with resting or stress nuclear testing. There is a burgeoning interest in studying the role of multislice computed tomography imaging of coronary anatomy in patients presenting to the CPU in the ED. Whether multislice computed tomography will cut into or complement CE or nuclear imaging remains to be seen. Cardiac magnetic resonance seems to be least practical because of the time it takes to obtain an image. Finally, the adverse clinical outcome and the fear of litigation of missed ACS in <1% of patients have been strong deterrents to the implementation of any of the early diagnostic protocols in the ED. This issue has been amplified by the uncertainty of marginal elevations of troponin in the setting of atypical symptoms and suspected ACS. All of this has further fueled the practice of watchful waiting in the CPU, with its attendant enormous cost burden. Imaging stress testing may alleviate some of this burden and arguably improve the efficiency and effectiveness of triage of patients in the CPU by bringing the cardiologist into play early in the process of clinical decision-making.

Echocardiography may be uniquely placed in the CPU as a practical and efficient imaging modality for rest or stress imaging. However, CE will have to be tested widely for differentiating ischemic from nonischemic origin of chest pain in the ED.

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