The Diagnosis of Acute Myocardial Infarction*

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Changes in the economic and therapeutic environment have altered the time frame in which an accurate diagnosis of acute myocardial infarction (AMI) must be made. The advent of effective reperfusion therapies and the increasing emphasis on reducing cost produce an environment in which rapid diagnosis can reduce morbidity and mortality while simultaneously reducing overall cost by avoiding unnecessary hospitalization and intervention. The first element of a diagnostic strategy remains a brief, directed history and physical examination. The orientation of this phase is to identify important causes of symptoms other than AMI, while rapidly leading to more definitive evaluation for myocardial ischemia when another diagnosis is not found. The ECG provides the most rapid definitive diagnosis, but the diagnosis remains equivocal in many patients with nondiagnostic ECGs. In this group, the use of cardiac enzyme measurements early in the course holds promise in directing intensive care at high-risk patients while avoiding unnecessary intervention in low-risk patients. A protocolized approach to patient evaluation should become a part of standard practice patterns in every hospital.

Paul Dudley White once said, "Small heart attacks are so common, they are almost within the normal range." In the past, the early diagnosis of acute myocardial infarction (AMI) was of limited utility to the clinician. After the acute phase of the AMI, the "retrospective" diagnosis has been important in making decisions about length of stay, further diagnostic testing, and postdischarge activity. However, in the acute phase, because of the limited sensitivity of early clinical and enzyme markers, patients with suspected AMI were admitted to the coronary care unit (CCU) for observation and treatment of complications. Legal concerns and lack of emphasis on cost led to a strategy designed to minimize the probability of an event occurring outside the intensive care unit. From this perspective, early diagnosis did not change the treatment plan.

Recent advances in pharmacologic and mechanical means of reperfusion have changed the situation so that early detection of myocardial infarction (MI) has become a critical component of an overall strategy to reduce the morbidity and mortality attributable to coronary artery disease. Furthermore, increasing concern about the cost of medical care has heightened the awareness that early diagnosis of ongoing infarction or elimination of infarction as a viable diagnosis could reduce medical care costs by leading to more effective triage of patients with suspected ischemic syndromes to appropriate medical care settings. In this article, we will review the current status of methods of evaluating patients with suspected infarction, and we will suggest two algorithms for clinical use: one based on technology that is currently universally available, and one based on evolving technology coupled with quantitative risk stratification.

**BACKGROUND**

In the past decade, substantial progress has been made in the understanding of the pathophysiology of AMI. In most cases, disruption of the endothelial surface of an atherosclerotic plaque leads to platelet activation and thrombin formation, culminating in complete occlusion of the epicardial coronary vessel by a thrombus. When complete occlusion occurs, unless substantial coronary collaterals are present, myocardial necrosis begins within approximately 30 min. The cornerstone of pharmacologic therapy for AMI has become reperfusion with thrombolytic agents. This therapy reduces mortality by 25% to 50%, improves left ventricular function, and reduces symptoms of congestive heart failure. Importantly, although thrombolysis reduces mortality when started within about 12 h from symptom onset, the magnitude of the mortality reduction is directly related to the time from symptom onset to treatment. For this reason, early identification of the patient with ongoing myocardial necrosis leads to a greater probability of survival.

Although thrombolysis may be contraindicated in many patients with AMI, especially when ST-segment elevation is not present, recent evidence indicates that percutaneous transluminal coronary angioplasty can also achieve a high reperfusion rate with equivalent mortality. Thus, in the majority of patients with AMI, some form of reperfusion therapy could be offered in most centers if the diagnosis could be made in a timely fashion. Furthermore, the likelihood of patient benefit is directly related to the time between coronary occlusion and institution of therapy.

Multiple recent trials have demonstrated that other

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therapies beside thrombolysis are effective in the acute phase of MI. In particular, aspirin reduces mortality by 25% and beta-blockers reduce the rates of mortality, reinfarction, and cardiac arrest. More recent data suggest that angiotensin-converting enzyme inhibitors, nitrates, and perhaps acute magnesium administration are beneficial. The sum total of acute interventions could lead to a marked reduction in early-phase mortality from AMI if patients were identified accurately and early.

The cost of intensive care unit hospitalization continues to escalate, particularly in the United States. In most major medical centers, the daily room charge exceeds $1,000 per day. As long ago as 1983 it was estimated that admitting patients to the intensive care unit with a low (<5%) probability of an AMI would cost $2.04 million per life saved compared with admission of these patients to "step-down" units. A strategy that could defer CCU admission based on diagnostic and prognostic algorithms could save substantial resources for the national health care budget.

Because of these changes in therapeutics and economics, the early and accurate diagnosis of AMI must receive a high priority for the benefit of the individual patient and society. For some purposes, such as thrombolytic therapy, the use of diagnostic tests with high specificity is required, since exposure to the risk of intracranial hemorrhage in a patient without the chance for benefit is not desired. For other purposes, such as CCU triage, a high sensitivity is needed, since all patients with AMI leading to complications should be in the CCU. Thus, a flexible approach to diagnostic testing is essential for the overall strategy, in which over time, as the patient is evaluated, a probabilistic approach is used to lead to the most accurate and efficient acute clinical decision making.

A critical factor in the United States is the preeminence of medical-legal concerns in the evaluation of acute ischemic heart disease. Between 1974 and 1985, missed AMI claims subsumed almost 20% of the malpractice-related losses of emergency departments in the United States. In an analysis of 65 successfully prosecuted cases, inexperienced physicians without specialty board certification who failed to order an ECG or document the findings of their physical examinations were most likely to be successfully sued, especially if the patient was young. Reading an abnormal ECG as normal and discharging a patient because of negative cardiac enzyme studies on the initial evaluation were also associated with a successful suit. Thus, both a theoretical and an empirical framework support the need for physicians to be apprised of the most recent information on this topic.

**THE HISTORY**

Several recent prospective studies have emphasized the difficulty of relying on the history to make a definitive diagnosis of AMI, yet in most clinical circumstances the history is critical to selection of further diagnostic testing. The majority of "chest pain" calls to emergency medical services systems are eventually classified as noncardiac, and among the cardiac diagnoses, the majority are not AMI. Thus, the history should be used as a rapid screening process to identify patients with possible myocardial ischemia so that additional diagnostic testing can be initiated as rapidly as possible.

Two large projects with extensive data bases have evaluated the history as a diagnostic test in the evaluation of patients with symptoms leading to some suspicion of an acute ischemic syndrome. Both of these data bases have found specific elements of the history to be useful in screening patients and, in combination with the ECG, in estimating the probability of acute ischemic heart disease for the individual patient. In one case, a randomized study demonstrated that prospective use of the predictive instrument improved the diagnostic specificity without compromising sensitivity, thus reducing "unnecessary" intensive care unit admissions.

In the Multicenter Chest Pain Study, an effort was made to predict the probability of AMI by using features from the history and physical examination findings. In a series of studies, over 6,000 patients evaluated in emergency departments underwent a standardized history, physical examination, and ECG acquisition. As shown in Figure 1, the following

![Figure 1: Prospectively validated algorithm for emergency department evaluation of patients with symptoms of AMI to determine probability of AMI.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest//chest/21643/ on 06/21/2017)
features were found to be associated with a higher probability of AMI: start of symptoms <48 h before emergency department visit, previous history of angina or AMI, longest pain episode ≥1 h if worse than previous angina or AMI symptoms, age ≥40 years, and radiation of pain to neck, left shoulder, or left arm. Features helpful in reducing the probability of AMI included radiation of pain to back, abdomen, or legs; "stabbing" character of pain; and reproduction of pain by palpation. When these features are combined by using recursive partitioning, a series of 14 subgroups are produced with a probability of AMI ranging from 1% to 77%. These results have been reproduced in a number of independent populations. It is important to note that, regardless of the history, patients who have ST-segment elevation or Q waves in ≥2 leads not known to be old have a probability of AMI of over 70%.

An alternative approach was developed in a study of 2,320 patients reporting to emergency departments in which the investigators used logistic regression modeling to develop a predictive algorithm for the probability of either AMI or unstable angina. The critical factors in this algorithm are listed in Table 1. As in the recursive partitioning model, the location and radiation of the symptoms, as well as the past history of heart disease, were critical factors. This approach has now also been validated in a number of studies in different populations.

Several critical alternative diagnoses must be considered early in the history (Table 2). Aortic dissection is suggested by the presence of a "tearing" or "ripping" pain down the back, especially in the presence of a history of severe hypertension. Pulmonary embolus is associated with pleuritic pain and severe dyspnea. Acute pericarditis should be suspected when the patient has pleuritic and/or positional chest pain. These diagnoses are especially important in the era of intervention, since incorrect therapy could lead to catastrophic iatrogenic consequences.

The difficulty with the use of the history in the diagnosis of AMI was underscored by reports from two recent studies. The Myocardial Infarction Triage and Intervention trial (MITI) is a study evaluating the use of emergency medical services to provide rapid thrombolytic therapy. In a recent report of the data on 2,472 patients calling an emergency number with a history suggesting possible acute myocardial ischemia, only 453 (18%) developed evidence of AMI subsequently. In the total population, the history was unreliable in 106 (4%) because they were disoriented or comatose.

The Thrombolysis Early in Acute Heart Attack Trial in Sweden did not require enzymatic or ECG evidence of AMI prior to randomization to treatment with tissue plasminogen activators. Cardiologists on the ambu-

Table 1—Critical Characteristics from Emergency Department Evaluation in Diagnosis of Acute Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Feature</th>
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<tr>
<td>Pain in chest or left arm</td>
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<tr>
<td>Pressure, pain, or discomfort in chest as main symptom</td>
</tr>
<tr>
<td>History of AMI</td>
</tr>
<tr>
<td>History of nitroglycerin prescription</td>
</tr>
<tr>
<td>ST elevation or depression ≥1 mm on ECG</td>
</tr>
<tr>
<td>T waves inverted ≥1 mm or peaked on ECG</td>
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</table>

lance enrolled patients based on “typicality” of symptoms of a duration >15 min and <165 min. Acute MI was confirmed in 59% of the patients enrolled.

Despite these drawbacks, the history remains the cornerstone of MI diagnosis, and no patient should be dismissed without ECG investigation and other appropriate assessment if the history is suggestive. An exhaustive history is unnecessary, however, and a directed history usually should take less than 5 min.

Physical Examination

As the history is being taken and an ECG is being obtained, an abbreviated, but carefully directed, physical examination should be performed. Although almost any physical examination findings could be compatible with a diagnosis of AMI, specific findings could lead to alternative diagnoses or evidence for increased risk or benefit of pharmacologic or mechanical intervention. Vital signs, which are often forgotten, are critically important. The presence of either tachycardia or bradycardia should lead the clinician to act more rapidly because of heightened risk to the patient without intervention. The blood pressure should be taken in both arms, since a difference of >20 mm Hg should raise suspicion of aortic dissection, although lesser differences are extremely common and should not lead to a change in therapy. In the MITI experience, 12% of patients with chest pain had a difference in blood pressure from left arm to right arm of >20 mm Hg, as did 6% of patients with AMI. None of these patients was diagnosed as having aortic dissection. The presence of hypotension is obviously a critical factor, but detecting acute hypertension has become more important now that the increased risk of intracranial hemorrhage with thrombolytic therapy has been documented.

Cardiac and chest auscultation remains a critical part of the evaluation of the patient with chest pain. The presence of rales may signify left ventricular decompensation, although the clinician should refrain from reacting to basilar rales in the absence of other evidence of heart failure, as they are frequently present without left ventricular failure due to atelectasis. However, more reliable signs of cardiac decompensation, such as a ventricular gallop in association with both hypoperfusion and rales, should lead to rapid treatment for heart failure. Furthermore, the
Table 2—Clinical Syndromes That May Simulate AMI*

<table>
<thead>
<tr>
<th>Data</th>
<th>Aortic Dissection</th>
<th>Pericarditis</th>
<th>Pulmonary Embolus</th>
<th>Pneumothorax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Back pain, but can be variable</td>
<td>Variable, but usually pleuritic, positional chest pain</td>
<td>Pleuritic chest pain</td>
<td>Pleuritic chest pain</td>
</tr>
<tr>
<td>ECG</td>
<td>LVH, ST elevation if associated with coronary occlusion</td>
<td>Widespread ST electrical alternans</td>
<td>Sinus tachycardia, rightward shift of QRS, RBBB, nonspecific T waves, nonspecific ST-segment changes</td>
<td>Rightward shift of QRS amplitude, precordial wave inversion</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Widening of mediastinum and aortic knob &quot;double shadow,&quot; blunting of costophrenic angles</td>
<td>Enlarged cardiac silhouette; may be normal</td>
<td>Pleural effusion, infiltrate; usually normal</td>
<td>Air in pleural space</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Unequal or absent pulses, focal neurologic deficits, hypertension, aortic regurgitation</td>
<td>Friction rub, pulsus paradoxicus, narrow pulse pressure, distended neck veins</td>
<td>May be normal, right heart gallop, venous V wave, tricuspid regurgitation</td>
<td>Decreased blood pressure, hyperresonance to percussion on affected side</td>
</tr>
</tbody>
</table>

*LVH = left ventricular hypertrophy; RBBB = right bundle branch block. (Adapted from reference 83.)

Auscultation of a new systolic murmur heralding ventricular septal rupture or acute mitral valvular regurgitation is critical to achievement of improved outcome. The absence of breath sounds on one side can signify acute pneumothorax, a rare but critical diagnosis in patients with chest pain, particularly in the intensive care unit. The finding of a pericardial friction rub could signify acute pericarditis. The clinician should be cautious, however, since patients with recent AMI can develop pericarditis as a complication of the MI.20 When a murmur of aortic regurgitation is heard, the diagnosis of aortic dissection should be suspected, especially if the murmur is known to be new.

A brief neurologic examination has taken on new importance in the thrombolytic era.30 The presence of an acute or recent stroke is an absolute contraindication to administration of thrombolytic therapy. At a minimum, mental status and gross cranial nerve and peripheral motor function should be documented on the initial examination.

Chest Radiography

The routine chest x-ray film is generally not a critical part of the initial diagnostic evaluation. In the majority of cases of AMI the initial chest radiograph is normal, since the heart has not had time to dilate and hemodynamic changes continue to evolve in the early hours. When aortic dissection is suspected, the chest x-ray film can provide critical evidence that the aortic silhouette is enlarged, sometimes with a pleural effusion from extravasated blood. The importance of the chest x-ray film in suspected pneumothorax is obvious. Although the chest radiograph is not otherwise generally useful in diagnosis, an initial portable film is useful in detecting early cardiac decompensation, so that appropriate supportive hemodynamic treatment can be instituted.

Electrocardiography

The standard 12-lead ECG remains the most definitive early test to document AMI. Unfortunately, although the test is highly sensitive, the specificity remains poor. When two or more precordial leads demonstrate ST-segment elevation in the presence of a compatible history, the likelihood of acute myocardial necrosis has ranged between 70% and 90%. However, in the absence of ST-segment elevation, the diagnosis of acute MI cannot be excluded.

A number of studies have evaluated the operating characteristics of the ECG as a diagnostic test for acute MI.31-33 Most recently, the MITI group found that the sensitivity of cardiologists was superior to that of emergency room physicians, but that a computerized interpretation had the best operating characteristics.32

Recent data have demonstrated that most hospitals in the United States have a significant delay between the time the patient enters the medical care system and the time of ECG acquisition. Sharkey and colleagues34 demonstrated a delay of 20 min, while the average delay time in Seattle was 18 min.18 The total time from admission to the hospital until administration of definitive therapy to patients with AMI has been over 1 h in most studies.

One approach to this problem has been to develop rapid application systems that can be applied in the field to diagnose AMI. Several investigators have demonstrated that an ECG can be obtained within minutes in the field.18,19,35 This approach appears not only to make ECG acquisition more efficient but also
to lead to more rapid administration of thrombolytic therapy.\textsuperscript{18,19,35}

Common ECG findings that can be confused with those of AMI should be recognized by the clinician (Table 3). Early repolarization is a normal variant that is characterized by diffuse J-point elevation in multiple leads. The ECG of early repolarization usually has generalized ECG changes with an elevated J point, upward concave ST segments, and a normal corrected QT interval. Acute pericarditis most frequently involves multiple lead groups simultaneously. Patients with previous MI, especially when associated with a left ventricular aneurysm, may have persistent ST-segment elevation that is not distinguishable from AMI. The presence of left ventricular hypertrophy on the ECG is frequently associated with precordial ST-segment elevation.

A critical point in ECG interpretation is that the absence of ST-segment elevation cannot be used to exclude the diagnosis of AMI. In a recent multicenter emergency department study,\textsuperscript{36} only 39 of 108 patients with AMI had a diagnostic ECG. In fact, several studies\textsuperscript{37-39} have documented the outcomes in series of patients with normal initial ECGs in association with AMI. Although these patients have extremely low risk, careful monitoring for change in status is needed.

Serial electrocardiography is a promising method for evaluating the patient with suggestive symptoms but with a nondiagnostic initial ECG. Development of ischemic changes with an initially normal ECG or resolution of ST abnormalities over a brief time provides substantial evidence of ongoing ischemia meritng hospital admission. Several studies have now documented that intermittent ST-segment elevation is common in the early phases of AMI both with\textsuperscript{40,41} and without\textsuperscript{42} thrombolytic therapy. Furthermore, the first ECG is not the ECG with the most pronounced ST-segment deviation in many patients.\textsuperscript{43}

The advent of computerized technology for serial comparisons of ECG tracings using digital data acquisition\textsuperscript{44} has raised the possibility of a "new" method of electrocardiography in patients with symptoms suggesting acute ischemic heart disease. In this method, a 12-lead system could be applied to the patient at the point of first contact, and serial tracings could be automatically triggered at regular intervals or when changes in the ECG occurred as detected in a surveillance mode.

**Enzymatic Methods**

The release of cardiac enzymes from irreversibly damaged myocardium has become the cornerstone of objective evidence of MI. In 1979, the World Health Organization published a set of criteria regarding diagnosis of AMI and the detection of serum enzyme changes.\textsuperscript{45} Since that time, the enzymes used for the diagnosis of myocardial necrosis have changed. The markers that have been used for diagnostic purposes and the time to peak levels are listed in Table 4.

Myocardial tissue contains a variety of macromolecules, many of which coexist in skeletal muscle. However, myocardial tissue is rich in creatine kinase (CK) MB isoenzyme (CK-MB), troponin B, and myosin light chains, making these markers ideal for use as a diagnostic test. During MI, the cardiac macromolecules are released by two mechanisms.\textsuperscript{46,47} Prolonged cellular acidosis gradually causes the sarcolemma to lose its integrity and to become permeable to the concentration gradient of macromolecules. Finally, frank breakdown of the sarcolemma and other cytoplasmic structures occurs, leading to complete release of cytoplasmic constituents. The lymphatic circulation and local capillaries provide a pathway to the serum, with the rate of uptake predominantly determined by: (1) the amount of free components versus components bound to structures in the cytosolic compartments, (2) regional myocardial perfusion, and (3) the molecular weight of the macromolecule.

The use of serum aspartate aminotransferase and lactate dehydrogenase (LDH) as markers of myocardial necrosis is now mostly of historical interest. Lactate dehydrogenase can occasionally still be of value for diagnosis in patients admitted more than 48 h after the onset of symptoms. The late peak of

<table>
<thead>
<tr>
<th>ECG Pattern</th>
<th>AMI</th>
<th>Pericarditis</th>
<th>LV Aneurysm</th>
<th>Vasospasm</th>
<th>Early</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG evolution</td>
<td>Slow</td>
<td>Rapid</td>
<td>None</td>
<td>Rapid</td>
<td>Variable</td>
</tr>
<tr>
<td>Distribution of changes</td>
<td>Localized</td>
<td>Generalized</td>
<td>Localized</td>
<td>Generalized</td>
<td></td>
</tr>
<tr>
<td>&quot;Reciprocal&quot; changes</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>Q waves</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>Chronic ECG changes</td>
<td>±</td>
<td>+</td>
<td>Concave down</td>
<td>Variable</td>
<td>J point elevated, concave up</td>
</tr>
<tr>
<td>ST segments</td>
<td>Concave down</td>
<td>Usually elevated &lt;5 mm; concave up</td>
<td>Concave down</td>
<td>Variable</td>
<td>Can be tall</td>
</tr>
<tr>
<td>T waves</td>
<td>Inversion before ST</td>
<td>Inversion after ST</td>
<td>Variable ST</td>
<td>Variable</td>
<td>Normal</td>
</tr>
<tr>
<td>QTC</td>
<td>Often prolonged</td>
<td>Normal</td>
<td>Often prolonged</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*LV = left ventricular; + = present; - = absent; QTC = corrected QT interval. (Adapted from reference 81.)
Table 4—Serum Tests for Diagnosis of AMI

<table>
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<tr>
<th>Serum Marker</th>
<th>Time to Peak</th>
<th>Suggested Frequency of Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoglobin</td>
<td>6-12 h</td>
<td>Q4 h for 1 day</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>12-24 h</td>
<td>Q8 h for 2 days</td>
</tr>
<tr>
<td>MB isoenzyme</td>
<td>10-18 h</td>
<td>Q8 h for 2 days</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>18-26 h</td>
<td>Q12 h for 3 days</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>3-6 days</td>
<td>Q24 h for 7 days</td>
</tr>
<tr>
<td>Myosin light chains</td>
<td>4-5 days</td>
<td>Q24 h for 7 days</td>
</tr>
<tr>
<td>Troponin T</td>
<td>12-24 h (late peak: 2-3 days)</td>
<td>Q12 h for 5 days</td>
</tr>
</tbody>
</table>

LDH can then be used to confirm the diagnosis, when other markers may be equivocal. If LDH isoenzymes are used, a ratio of LDH-1 to LDH-2 of greater than 1 is considered to be diagnostic. The LDH-1 subform is the predominant cardiac form, but it is also found in red blood cells, so that hemolysis can cloud the issue. In the future, late diagnosis will be made more accurately on the basis of myosin light chains or troponin T, since both are cardiac-specific and have a late peak at 3 to 6 days after AMI. Unfortunately, few laboratories currently perform these assays routinely.

Myoglobin appears to be the most sensitive early marker of MI, but its specificity is low because myoglobinemia is found in a variety of conditions, such as skeletal muscle or surgical trauma and renal failure. Even small intramuscular injections have been reported to stimulate the release pattern of AMI; nevertheless, uncomplicated cardiac catheterization has not been associated with release of myoglobin. Although the high sensitivity of myoglobin has been known for many years, the low specificity has kept it from being used commonly for diagnosis.

The assay of CK and CK-MB has become the most widely used serum test for the diagnosis of AMI. Both CK and CK-MB concentrations appear above the threshold level in serum within approximately 4 to 6 h after the onset of symptoms. Both reach a peak in the nonreperfused patient between 14 and 18 h, with a return to baseline value within 2 to 3 days. Total CK is found in both skeletal and cardiac muscle, while CK-MB is found predominantly in cardiac tissue. Using total CK alone as a diagnostic test must now be regarded as obsolete with the availability of sensitive and standardized assays of CK-MB. Total CK measurement has a false-positive rate of approximately 15% depending on the population studied, while the sensitivity and specificity of CK-MB measurement approach 100%. A number of conditions can cause false elevation of both CK and CK-MB in the absence of myocardial necrosis (Table 5). In the presence of these confounding conditions, obtaining both a total CK value and a CK-MB value can help in judging whether a true AMI has occurred. Furthermore, serial sampling will also aid the diagnostic effort, since the values should rise and fall at different rates depending on the condition. In cases of surgery, trauma, or strenuous exercise, CK-MB release may be similar to that occurring during AMI. In these situations, where there is a clinical suspicion of MI and possible CK-MB release from other sources, appropriate scintigraphy techniques to confirm or refute the diagnosis should be used. In particular, new antimyosin antibody scanning may have a role.

The specific criteria used to define a "diagnostic" level of CK-MB remain controversial. For each specific assay, an upper level of normality has been defined based on sampling of normal populations and patient populations without cardiac disease. However, using one cutoff value has significant limitations. Several patient characteristics can affect the expected normal values. For example, women have lower levels of both CK and CK-MB than men have. The degree of daily physical activity can also affect the enzyme levels. A final reason for being concerned about the use of diagnostic cutoff values is the important overlap that exists between the upper range of normal and the values seen in patients with small amounts of myocardial necrosis.

Our preference is to take into account the relative changes in both CK and CK-MB. A pattern of a rise, a fall, and transient doubling in total CK-MB levels, with at least one CK-MB value more than 5% of the total CK value during the sampling period, has been proposed as a criterion. In this scheme, patients with normal CK levels but with alterations in CK-MB could be considered to have AMI. In one study, patients with these small peaks in CK-MB were described as having an excellent prognosis; in other studies, however, the in-hospital mortality was low, but the late cardiac event rate was similar to that in patients with "classic" MI.

The need to deliver thrombolytic therapy rapidly to appropriate patients and to determine whether it has
resulted in successful reperfusion has placed a renewed emphasis on the early use of diagnostic enzymes. Most patients arrive at the hospital within 4 h of the onset of symptoms of AMI. Ideally, the serum marker should at this early stage already have reached an abnormally high level to be useful. In addition, the particular assay used for the serum marker needs to be simple and rapid in its application.

Serum myoglobin is the only currently available serum marker that becomes elevated as early as 1 h after coronary occlusion in humans.64 Newer semi-quantitative assays that can be performed at the bedside make the use of rapid myoglobin determinations feasible.65 In one study, serum myoglobin was the serum marker that was most closely associated with M1.90 It also added significant diagnostic information, even after the ECG findings had been accounted for. As previously noted, the serum myoglobin assay lacks specificity, which prevents it from being an ideal test in the early phase of AMI on its own.

Total CK and CK-MB become elevated between 4 and 6 h after symptom onset; therefore, a single CK-MB or CK level within the normal range shortly after admission is not adequate to rule out AMI. However, studies by Gbler et al96 have shown that CK-MB determined by a mass assay can achieve very high (>90%) sensitivity and specificity within 6 h after the onset of symptoms. Similarly, Lee et al99 have shown that with traditional CK-MB assays, similar test characteristics can be achieved within 12 h after the onset of symptoms.

The mass assay used by Gbler et al96 and others96,97 represents a significant advance since the measurement of the amount of CK-MB mass in serum is quick (10-20 min assay time) compared with the traditional activity assays, which generally take 1 to 2 h to perform. Several studies have documented the reliability of the method.96,97 Development of a whole-blood mass assay would greatly enhance the value of early enzyme testing, since it could be used at the bedside.

The specific tissue forms of CK and CK-MB have drawn the most attention in the quest for early markers of AMI. Total CK exists in three isoenzyme forms, which are defined by the configuration of the M and B subunits of the CK molecule. In normal circulating CK, the MM form accounts for the vast majority, while the MB form makes up less than 3% and the BB form less than 1%. The subunits of MM and MB exist in tissue forms MM-3 and MB-2.98 Upon their release into the bloodstream, they undergo conversion of a lysine residue by carboxypeptidase to MM-2 and MB-1, respectively; MM-2 undergoes a further conversion to MM-1 in the blood. Because the tissue forms can be measured by new sensitive assays,96 it has become possible to measure the MB-2 and MM-3 molecules as soon as they occur in the blood. Studies have shown that assays for both MM-3 and MB-2 may be superior to assays for CK or CK-MB in the early diagnosis of AMI. The MB-2 assay is particularly attractive, since it retains a high level of specificity compared with MM-3 assays. In particular, the ratio of MB-2 to MB-1 has been found to be an early marker of AMI.91 Currently, the assay time required for these measurements is relatively long (20 to 40 min), and the test is not available in most laboratories.

In the future, early serum diagnosis should incorporate several markers of myocardial necrosis into a batch of tests. In addition, important clinical variables, such as age, gender, hemodynamic status, and time from onset of symptoms, should be incorporated into a model giving an overall probability of the presence of AMI. This predictive instrument could serve to integrate clinical and laboratory data to aid in rapid decision making in the emergency department.

A logical extension of the early diagnosis of MI is to apply thrombolytic therapy to enhance the clinical outcome. Serial sampling in the prereperfusion era documented that an early peak of CK-MB was associated with non-Q wave infarction and a high likelihood of reinfarction.73 Similarly, patients with good collateral flow to the infarct zone have been noted to have an early peak, suggesting evidence of partial reperfusion through collateral blood supply.74 Several studies have found that an early peak of CK-MB has been associated with successful reperfusion after thrombolytic therapy.75-78 We have used such an approach to develop a computer model for predicting reperfusion in the first 3 h after starting thrombolytic therapy.79,80 Such an approach could be used to select specific therapies, including rescue angioplasty, for patients with a high likelihood of failing to reperfuse.

NONINVASIVE IMAGING TECHNIQUES

When the ECG and enzyme levels are not diagnostic but a high suspicion for AMI persists, especially when the clinical status of the patient is marginal, echocardiography can be used to document wall motion abnormalities consistent with AMI. This test will be most useful in patients with bundle branch block or nonspecific ST-segment changes in the absence of Q waves. The echocardiogram cannot distinguish new from old wall motion abnormalities, so that the test will not be particularly useful in patients with Q waves on the ECG. Several recent reports have documented a high sensitivity and specificity for echocardiography in the evaluation of suspected AMI.81,82 However, the clinician should be aware of the subjectivity of wall motion analysis, and the experience of the echocardiographer should be considered in the assessment of the information content of the test.

Thallium scintigraphy is a method that allows imaging of the myocardium in areas where perfusion is
adequate and cellular metabolism is sufficient to allow extraction of thallium from the circulation into the tissue. Unfortunately, ischemic tissue cannot be distinguished from scar in real time, since a delay is imposed by the need to allow the tracer to redistribute to ischemic but not infarcting tissue. Similarly, old and new MIs cannot be distinguished by this method.

**Current Suggestions**

A reasonable approach to the patient with suspected acute ischemic heart disease is depicted in Figure 2. Unless the history and physical examination demonstrate an alternative diagnosis, an ECG and cardiac enzyme assay should be obtained immediately. If a characteristic pattern of ST-segment elevation is found on the ECG, the clinician should presume that the patient is having an AMI. A trial of sublingual nitroglycerin with repeat ECG may document transient reversible ischemia with resolution of ECG changes in some patients.

In the absence of a diagnostic ECG, the clinician should base decision making on the other clinical findings. If the patient is in hemodynamic distress, a decision may be made to proceed with reperfusion therapy or with emergency coronary angiography if the other signs and symptoms are classic. If time and circumstances allow, an echocardiogram may be useful. If the patient has recurrent or persistent symptoms in the absence of definitive ECG or enzyme findings, echocardiography or angiography should again be considered. The patient who is asymptomatic at this point should be observed for 12 h, at which time the ECG and enzyme measurements should be repeated. If the findings are not diagnostic, the patient should be evaluated carefully for noncardiac diagnoses or unstable angina, with its appropriate therapy.

The algorithm recently proposed by Lee et al provides an empirical basis for the strategy described above. When their algorithm was used on patients with a low probability of AMI (≤7%) based on the initial history, physical examination findings, and ECG, 80% did not have further symptoms or abnormal enzyme levels over the next 12 h. These patients had a 0.5% rate of AMI, and all MIs were nonfatal. Accordingly, the vast majority of patients with chest pain can be treated by applying a simple algorithm with monitoring, symptomatic evaluation, and monitoring of enzyme levels over 12 h.

**Future Approach**

Given the technologic advancements in both electrocardiography and enzymatic analysis methods, an exciting era for the early diagnosis and appropriate triage of patients with suspected acute ischemic heart disease symptoms will soon be feasible. With this future approach, when a patient is identified, whether in the emergency department or in the field, a quick, guided history and physical examination can lead to application of continuous ECG acquisition with computer-assisted diagnostic algorithms, and enzymes can be rapidly sampled. When a patient with ongoing necrosis is identified by either method, maximum surveillance and pharmacologic or mechanical intervention can be initiated rapidly. Patients with negative findings through 9 to 12 h can be admitted to a routine hospital ward or discharged, depending on other findings. In heavily populated areas, the most efficient place for such evaluation would be in a specially designated section of the emergency department. This new approach will require a much more proactive attitude by physicians, who must realize the therapeutic and economic benefits to be gained by rapid intervention in patients with acute ischemic heart disease and the avoidance of unnecessary monitoring and procedures in patients with signs and symptoms caused by other factors.

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