Editorial Comment

Is Diagnostic Certainty Essential for the Use of Thrombolytic Therapy During Myocardial Infarction in the 1990s?

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Traditionally, the diagnosis of acute myocardial infarction has been based on the presence of signs and symptoms suggestive of myocardial infarction associated with changes on the 12-lead electrocardiogram compatible with myocardial damage and evidence of myocardial necrosis detected by measurement of leakage of components of myocardial tissue into the circulation. The time frame in which this diagnosis could be made was not critical because of the cautious approach to hospitalization (admit and observe all patients with suspected infarction) and the lack of intervention that could alter the course of infarction during its early hours. Major changes in therapy and in the structure of the healthcare system have led to the need for a change in this time frame for diagnosis. With the advent of a more interventional approach to the management of acute coronary syndromes and the need to conserve resources by rapid triage of patients through the intensive care system, we should no longer diagnose myocardial infarction by looking back at the evolution of the electrocardiographic and enzymatic evidence over the first 24 hours. Instead, a premium must be placed on diagnostic tests that can be used in the initial patient evaluation as an indication for intervention or triage. The study by Puleo and colleagues in this issue of Circulation provides important new information about the potential for cardiac enzymes to be used in this manner.

When the patient is first seen in the emergency medical care setting, the physician has limited information: the history, the physical exam and the electrocardiogram. Carefully performed prospective studies have documented that relatively simple algorithms incorporating clinical data can stratify patients into very high and very low risk populations with suspected myocardial infarction. The presence of ST elevation has such a high positive predictive value for the diagnosis of myocardial infarction that little further information is needed when this electrocardiographic finding is present, especially in concert with appropriate symptoms. Unfortunately, a large proportion of patients with myocardial infarction will have other initial findings on the electrocardiogram, including bundle branch block, ST depression or T wave inversion. Many patients presenting with suggestive symptoms and without ST segment elevation will have unstable angina or noncardiac diagnosis, while many others, especially those with circumflex occlusion or previous infarction, will have acute myocardial infarction. Thus, the major clinical role for rapid assessment of cardiac enzymes will be in patients with nondiagnostic initial electrocardiograms.

The potential for reperfusion therapy to benefit patients with nondiagnostic electrocardiograms remains to be definitively demonstrated. Those with an initially normal electrocardiogram are unlikely to die with conservative care whereas the presence of bundle branch block or previous myocardial infarction connotes a poor prognosis without intervention. Two large studies have randomized patients to thrombolytic therapy or placebo in suspected myocardial infarction without ST segment elevation. In the Anglo-Scandinavian Study of Early Thrombolysis, a 25% reduction in mortality was observed in patients without a confirmed myocardial infarction. Patients with a normal electrocardiogram had a 3% mortality with placebo compared with 1.6% with t-PA, which was a nonsignificant difference given the sample size. All five patients with aortic dissection in the t-PA arm diagnosed within 24 hours of therapy died before 30 days. In the International Study of Infarct Survival (ISIS-2) Trial, ST elevation was recorded in 56%, bundle branch block in 6%, ST depression in 8%, “normal” in 2%, and other abnormalities in 27%. A marked reduction in mortality was noted with streptokinase and aspirin therapy compared with placebo for patients with bundle branch block (49% reduction), “other” abnormalities (38% reduction), and “normal” (50% reduction). Interest-

The opinions expressed in this editorial comment are not necessarily those of the editors or of the American Heart Association.

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ingly, in both ASSET and ISIS-2, patients with ST depression had a very high mortality with placebo (18%) and a slightly higher mortality with thrombolytic therapy (20%). This high mortality rate with ST segment depression is not consistent with clinical experience with otherwise uncomplicated patients with ST depression, raising the possibility that patients with ST depression admitted into ASSET and ISIS-2 represented only the severely ill patient with ST depression. The ongoing TIMI 3 and ISIS-3 trials will further examine the role of thrombolytic therapy in patients with nondiagnostic electrocardiograms, but the potential for a more accurate diagnostic test to identify patients likely to benefit in the early hours is self evident.

Defining the capability of the MB isoform of creatine kinase (CK-MB) and MB-2 assay to provide useful information in patient management will require a careful series of steps. Puleo and colleagues4 have made the critical initial observation that the assays are reproducible and that a clear separation of values exists between patients with documented myocardial infarction and healthy adult volunteers or patients with noncardiac disease. When 95% confidence limits are applied to the values obtained for the control groups (CK-MB, 1.1–1.4 IU/l; MB-2, 0.5–0.7 IU/l), no overlap occurs with values obtained 4–6 hours after symptom onset in patients with myocardial infarction (CK-MB, 12.7–35.7 IU/l; MB-2, 10.0–26.8 IU/l). Two concerns need to be addressed by subsequent studies concerning these particular molecules before the values from this study should be used in practice. The specific “cutoff” values developed in this study (MB activity >1.0 IU/l and MB-2/MB-1 ratio >1.5) yielded a moderately high sensitivity and a very high specificity in this small population. Validation of these results in larger populations will almost certainly result in deterioration of these values.18 In fact, the 95% confidence intervals for the point estimates of sensitivity in the myocardial infarction population on the first available sample range from 54% to 80% and from 82% to 100% on the 4–6 hour sample. The 95% confidence intervals for the specificity in the normal controls have a lower boundary of 95%, and in the hospitalized controls the lower boundary is 92%. Accordingly, from available information in this report, the use of the given enzymatic criteria could lead to inappropriate treatment of 8% of patients. Second, when applied to patients coming to the emergency department with symptoms suggesting myocardial ischemia, a substantial number of patients with unstable angina will blur the diagnostic capability of the measurement. A proportion of these patients will bridge the continuum between unstable angina and myocardial necrosis and will leak a small amount of enzyme producing an “infarctlet.”

Because no test will be perfect in this setting, we believe that as a proposed assay is moved toward the clinical arena, its potential use can best be understood by plotting the data in a cumulative distribution function (displaying the proportion of patients with and without MI with each value for the enzyme test) so that the test characteristics (sensitivity, specificity, positive and negative predictive value) can be calculated for a range of diagnostic thresholds. In this setting, a high specificity is preferable, even if the sensitivity is sacrificed, because false diagnosis of myocardial infarction could lead to inappropriate intervention (for example, thrombolytic therapy).19 Similarly, a positive predictive value close to 100% is desirable and should be explicitly examined because some subgroups with an abnormal electrocardiogram will have a low pretest probability for infarction. When the results are presented in final form, the use of regression modeling techniques to produce an estimate of the probability of myocardial infarction for each enzyme value could lead to the best use of the information in practice.

The ideal serologic marker for early diagnosis should be cardiac specific and released rapidly into the circulation with an early peak. Furthermore, it should be easily measured in whole blood within a few minutes. Other alternatives besides those investigated by Puleo and colleagues4 have been considered. CK-MM subunits have been evaluated by Abendschein and colleagues,20 who found a sensitivity of 92% with an MM-3 to MM-1 ratio of >0.5. However, CK-MM lacks cardiac specificity and assay times are approximately 40 minutes in a dedicated laboratory. Myoglobin possesses many desirable characteristics with a rapid release21 and the presence of a rapid latex agglutination test that takes 10 minutes to perform.22 We found myoglobin to be superior to both ST elevation and CK-MB for identifying the largest number of patients with acute myocardial infarction in a prospective study.23 The combination of diagnostic criteria of ST elevation and a rapid test for serum myoglobin in patients without ST elevation gave a sensitivity of 82% within 1 hour of admission. Thus, CK-MB, MB-2, MM-3 to MM-1 ratio, and myoglobin all provide high diagnostic sensitivity within the first few hours after symptom onset. CK-MB and MB-2 provide a high level of specificity but the time to elevation is protracted, whereas CK-MM subunits and myoglobin rise somewhat more rapidly but lack specificity for myocardial damage.

The goal of this research as applied to patient care is to provide a process by which the diagnosis of acute ischemic heart disease can be made rapidly and reliably, leading to appropriate intervention in a time frame that will maximize myocardial salvage. This process will almost certainly include a directed history and examination24 and application of a continuous monitor to acquire information from the electrocardiogram that can be used to alter diagnosis and therapy during the course of the event.25 Once a diagnosis has been made, intervention to establish and maintain coronary arterial patency can be monitored by the same procedures.26,27 Central to this concept is the development of rapid, whole-blood,
bedside assays for serologic markers of myocardial necrosis in concert with further studies, such as the approach described by Puleo and colleagues in this issue, to determine which markers are most desirable.

Acknowledgment

The authors wish to acknowledge the valuable assistance of Donna Olson in the preparation of this manuscript.

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(Circulation 1990;82:1073–1075)
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Circulation. 1990;82:1073-1075
doi: 10.1161/01.CIR.82.3.1073

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