Earlier Diagnosis and Treatment of Acute Myocardial Infarction Necessitates the Need for a ‘New Diagnostic Mind-set’

Robert Roberts, MD; Neal S. Kleiman, MD

Abstract  Triaging patients suspected of myocardial infarction is performed primarily in the coronary care unit, with infarction determined within 12 to 24 hours, and only about 20% are subsequently shown to have myocardial infarction. Plasma MB CK is not elevated until 8 to 10 hours after onset, and the ECG is unreliable; thus, the need has arisen for a new “diagnostic mind-set.” The need is threefold: (1) more effective triaging in the emergency room to prevent unnecessary use of hospital beds, particularly those in the intensive care units, (2) to administer thrombolytic therapy in the early hours, and (3) earlier detection of coronary reocclusion and reinfarction. Diagnostic imaging techniques such as pyrophosphate, thallium-201 technetium septamibi, or positron emitting agents lack the necessary early diagnostic specificity, but echocardiography has potential although its specificity is limited. Plasma CK isoforms provide diagnostic sensitivity and specificity of 96% and 94%, respectively, within the initial 4 to 6 hours of onset and can be assayed within minutes. In a prospective study of 1100 patients suspected of infarction, with conventional MB CK, 22% of the patients admitted to the coronary care unit would have had infarction, whereas using the CK isoforms, 75% had infarction and about 50% were discharged home. A scenario for the future might be to initiate thrombolytic therapy outside the hospital (eg, recombinant tissue-type plasminogen activator [r-TPA] 20 mg bolus) and upon arrival, confirm or exclude infarction by the MB CK isoform which can be performed in the emergency room in 20 minutes to determine whether thrombolytic therapy and heparin should be continued. (Circulation. 1994;89:872-881.)

Key Words • thrombolyis • myocardial infarction

The Dilemma
Clinical and experimental studies show that thrombolytic therapy administered within the first hour of onset of symptoms is associated with a marked reduction in mortality and morbidity. The process of infarction may be completely aborted if reperfusion is initiated within 30 to 40 minutes. The major limitation is the unreliability of conventional markers (pain, ECG, and enzymes) in diagnosing myocardial infarction in the initial hours. Thus, the need has arisen for a new “diagnostic mind-set.”

Historical Perspective
Given that cardiovascular disease is the number-one killer in the Western world, it is surprising that the entity we now call myocardial infarction (coronary thrombosis) was widely recognized clinically only about 50 years ago.1 Despite Dr Herrick’s classic article of 1912,2 medical students and house staff in 1923 in Chicago, Herrick’s hometown, had still not heard of the diagnosis of coronary thrombosis (myocardial infarction). The full impact of the ECG was felt only after the introduction of the precordial and augmented limb leads, which led to the documentation of the Q wave and by the late 1940s widespread appreciation of its specificity for myocardial infarction.3 Diagnostic objectivity was greatly aided by the introduction of plasma enzymes in 1954,4 and the specificity significantly improved after the introduction of LDH isoenzymes in 1957 and of CK isoenzymes in 1966.6

The rationale for the coronary care unit (CCU) introduced more than 30 years ago was primarily to provide better treatment for arrhythmias in patients with myocardial infarction; however, it also ushered in a new era in the diagnosis and assessment of myocardial infarction.7-9 The public and the medical profession became wedded to the concept that patients with chest pain suspected to be of cardiac origin required admission to the CCU. Patients underwent daily enzyme analysis for 3 days consisting of LDH, SGOT, and CK, together with daily ECGs. Those in whom infarction was confirmed remained in the CCU for 5 to 7 days. In the 1970s, a decade of intense research was spearheaded by the goal of cardioprotection and myocardial salvage, which shifted the focus of the CCU to limitation of infarct size and its sequelae.10,11 The development of enzymatic assays and diagnostic imaging techniques thus became necessary. The first quantitative assay for plasma MB CK was developed in 197412 and was soon followed by other assays13,14 with greater specificity, sensitivity, and convenience. Similarly, improved assays were developed for LDH isoenzymes.15 Ultimately, overcrowding of the CCU necessitated that patients who did not have infarction be transferred within hours. This requirement provided the impetus for a change in the enzymatic diagnostic routine to serial analysis every 4 to 6 hours for 24 hours. Isoenzyme analysis is now restricted primarily to MB CK, with analysis of LDH isoenzymes usually reserved for patients admitted late after onset (48 to 72 hours), and SGOT has been virtually removed from the diagnostic armamentar-
The recent introduction of troponin-T as a specific diagnostic tool appears promising, but it is too early to assess its potential as an early marker. This marker is being studied in the GUSTO-2 Trial.

The Need for a 'New Diagnostic Mind-set'

We have entered an era in which most patients suspected of having chest pain caused by myocardial ischemia are admitted to the CCU. Of those admitted, more than 70% are subsequently shown not to have myocardial infarction. There is, thus, a great need to develop an objective means to triage patients before admission to the CCU. Several factors have developed that are likely once again to accelerate the course of definitive diagnosis from 12 to 24 hours to 1 to 2 hours, and ideally minutes if possible. The pressure to establish an accurate method of early diagnosis is now greatly increased because of the availability of potentially lifesaving therapies that need be applied very early in the course of infarction and because of the economic need to run our CCUs more effectively.

Given that reperfusion within the first 1 or 2 hours as opposed to 4 to 6 hours can preserve ventricular function and reduce mortality by nearly 50%, and given that studies of prehospital thrombolysis have demonstrated that most detectable myocardial salvage occurs within the first hour after the onset of symptoms and that a reduction of 90 minutes in time to treatment is needed to effect a significant reduction in cardiac mortality, it is time to develop a "new diagnostic mind-set" in our approach to the diagnosis and treatment of acute myocardial infarction. The challenge with which we are faced is twofold: first, to develop a diagnostic technique that rapidly and accurately allows identification of patients in the early hours of acute myocardial infarction, and second, to allow rapid identification of patients in whom reperfusion is not successful. The reasons to provide an earlier diagnosis are compelling: (1) only about 15% of patients presenting to the emergency room with chest pain and suspected acute myocardial infarction are ultimately found to have myocardial infarction as subsequently documented by objective means, (2) conventional markers do not as yet provide a reliable diagnosis during the first 1 or 2 hours of an evolving infarction when thrombolytic therapy is most likely to be effective, (3) even a 0.5% incidence of intracranial bleeding complicating thrombolytic therapy is unacceptable in individuals without acute myocardial infarction, and (4) early detection of coronary reocclusion and reinfarction might prevent as many as one fifth of the hospital deaths among patients who have received thrombolysis.

Limitations of Chest Pain and the ECG: A Critical Diagnostic Problem

The ECG has been the mainstay, together with chest pain, in the screening of patients for myocardial infarction and ischemia. The critical issue, however, in patients screened for suspected myocardial infarction is that the ECG is diagnostic only in a minority. The early signs of myocardial infarction are ST segment changes that also occur with transient reversible ischemia; however, ST-T segment elevation of ≥1 mm is highly likely to evolve into myocardial infarction, whereas ST-T segment depression is very nonspecific. Although the presence of new, even nonspecific ECG changes will markedly increase the likelihood that the chest pain is due to myocardial ischemia, the predictive value of this finding is <50%. The magnitude of this dilemma appears to be increasing. In 1981, it was reported that 43% of infarctions occurring were non-Q-wave, up from 31% in 1972, while today, based on statistics from the state of Massachusetts, it is estimated that 53% are classified as non-Q-wave.

In most recent studies of patients presenting to the emergency room with chest pain suspicious for myocardial infarction, between 40% and 60% of patients ultimately proven to have infarction have nondiagnostic ECGs, whereas only a minority of patients with ST segment depression have infarction. For example, in the Western Washington Emergency Department Tissue Plasminogen Activator Treatment Trial, of 391 patients with myocardial infarction aged <75 years, presenting within 6 hours, and having no contraindications to thrombolysis, only 221 (57%) patients were eligible to receive recombinant tissue-type plasminogen activator (r-TPA) while 170 (43%) patients were excluded for nondiagnostic ECGs alone.

For these reasons, most studies assessing thrombolytic therapy have included only patients with ST segment elevation >1 mm. In the TIMI I Trial using this criteria, 80% of the patients evolved Q waves, and on coronary angiography, a similar percentage had complete coronary artery occlusion.

On the other hand, of patients with non-Q-wave infarction, 70% to 80% present with ST segment depression, and about 80% have incomplete coronary artery occlusion. In a large, prospective study, 75% of patients with non-Q-wave infarction presented with ST-T segment depression. Recent thrombolytic trials that have included patients with ST segment depression have consistently shown no effect from thrombolytic therapy in this subgroup. Results of a recent prospective trial (TIMI-3B) performed specifically to assess the effect of thrombolytic therapy in patients presenting with chest pain and ECG changes other than persistent ST-T elevation again confirmed the lack of benefit of thrombolytic therapy in this subgroup. In TIMI-3B, 11% of patients had transient ST-T elevation, whereas the remainder had either ST-T segment depression or T-wave inversion. About one third were subsequently documented to have non-Q-wave infarction.

The lack of benefit in patients with non-Q-wave infarction is somewhat perplexing. It is well recognized, for example, that of patients with lateral infarction due to sustained circumflex occlusion, more than two thirds will present with ST-T segment depression. The implication of this lack of benefit might be that patients with circumflex occlusion and ST-T segment depression (rather than elevation) do not respond to reperfusion therapy. On the other hand, these negative findings may reflect a dilution of the benefit. Since most patients with ST-T depression do not have infarction, the benefit in the minority (approximately one third) who do have infarction may be counterbalanced, the result being that no effect is seen in the general population. An alternative mechanism may relate to the nature of coronary arterial thrombosis in patients with ST-T segment depression that evolves into non-Q-wave infarction. Several studies suggest that patients with non-Q-wave
infarction undergo early spontaneous reperfusion.\textsuperscript{34-36} Thus, pharmacologically induced thrombolysis after 2 to 3 hours may be redundant, since reperfusion has already occurred. For example, in TIMI-3, therapy was given an average of 9 hours from onset of symptoms.\textsuperscript{32} Although timing is the best that can be attained with current conventional technology, the benefit of treatment this late after the onset of symptoms may be limited even in patients with ST segment elevation. Resolution of this dilemma is thus likely to require large studies in which therapy is given more promptly and is based on earlier diagnosis.

Even among patients in whom the indications for thrombolysis are conventional based on clinical findings, successful thrombolysis followed by optimal adjunctive therapy is still less than adequate, since 10\% to 15\% of patients undergo coronary reocclusion and 5\% to 10\% develop reinfarction. Mortality for patients with reocclusion is at least twofold that of those without,\textsuperscript{37} and reinfarction accounts for about 20\% of the hospital deaths occurring after thrombolytic therapy.\textsuperscript{37} The immediate readministration of a thrombolytic agent or implementation of mechanical revascularization upon development of reinfarction appears pivotal. On the basis of symptoms alone, early detection is not feasible, since 30\% to 40\% of all patients will have chest pain after thrombolytic therapy, and early ECG findings, particularly in this setting of evolving ECG changes, are usually nondiagnostic. Thus, the need for an objective diagnostic marker to detect early reinfarction is clear.

**Limitation in Conventional Enzymatic Diagnosis of Infarction**

The established enzymatic criteria for myocardial infarction, namely, serial quantitative analysis of plasma MB CK every 4 to 6 hours, is regarded as the most specific, sensitive, and cost-effective means\textsuperscript{38,39} of diagnosis. Release of plasma MB CK after irreversible myocardial injury occurs probably within 40 to 60 minutes of sustained coronary occlusion, but the extent and rate of release is minimal such that the plasma MB CK levels often remain within the normal range of up to 13 IU/L for the first 8 to 10 hours. Without knowing the individual's baseline, it is not feasible to diagnose infarction reliably, even though there may have been a doubling or tripling of the baseline level. Experience to date with the most sensitive and reliable quantitative assays such as radioimmunoassay\textsuperscript{14} have shown that plasma levels of MB CK can reliably exclude infarction only after a minimum of 6 to 8 hours have expired after the onset of chest pain. To this interval must be added the time required for the assay to be performed.\textsuperscript{13} The sensitivity of plasma MB CK for diagnosing acute myocardial infarction within the first 4 hours of onset of chest pain using conventional electrophoretic techniques is reported to be around 25\%.\textsuperscript{13} Other markers such as LDH require even longer for the plasma activity to be elevated to reliable diagnostic levels.

**Plasma CK Isoforms**

Since a period of 8 to 10 hours is required for plasma levels of MB CK to be elevated in the range that provides a reliable diagnosis of myocardial infarction, the potential for MB CK to be an early diagnostic marker appeared bleak until the recent exploitation of an observation made in 1977 by Wevers et al,\textsuperscript{40,41} namely, the existence of plasma CK isoforms (or "subforms"). While the CK isoenzymes MM and MB are present in tissues in a single form, several isoforms can be identified in the plasma. Cytosolic CK is composed of two subunits, M and B, each with a molecular weight of about 41 000. MM CK predominates in skeletal muscle, BB CK in brain, and the hybrid MB CK, having one subunit of each, is relatively specific for heart. MB CK comprises 15\% of the total myocardial CK activity, the remainder being MM CK.\textsuperscript{42} In 1981,\textsuperscript{43} we purified the isoforms of MB CK from plasma and showed the mechanism of conversion to be the loss of an amino acid, lysine, from the C-terminus of the M-subunit,\textsuperscript{44,45} catalyzed by the enzyme carboxypeptidase. We have since cloned and sequenced the cDNA for both the human M and B subunits and shown that lysine is the C-terminal amino acid of the M- and B-subunits as it is in all species examined to date.\textsuperscript{46-48} Electrophoresis shows the tissue form of MM CK near the origin, with plasma forms MM\textsubscript{2} and MM\textsubscript{3} exhibiting anodal migration in proportion to their degree of negative charge (Fig 1). Removal of lysine, a positively charged amino acid, from the tissue form (referred to as MM\textsubscript{3}) imparts a net negative charge to the M-subunit so that it moves toward the anode (MM\textsubscript{2}), and subsequent hydrolysis of the second M-subunit causes the molecule to move even further toward the anode (MM\textsubscript{1}). Loss of one amino acid from the M-subunit is not associated with any change in molecular weight or catalytic enzymatic activity; however, it does induce a unique isoelectric point characteristic for each isoform. The B-subunit also has lysine as its C-terminus, but for reasons as yet unclear, isoforms in which lysine is cleared from the B-subunit have been observed (but not consistently) in plasma. However, the M-subunit of MB CK undergoes hydrolysis, so the plasma exhibits two isoforms of MB CK as shown in Fig 2. The rationale for using the CK isoforms for early diagnosis of myocardial infarction is as follows.

The various CK isoforms are present in the plasma in equilibrium. In the case of MB CK, the activity is evenly divided between MB\textsubscript{2} (tissue form) and MB\textsubscript{1} (created in plasma) and amounts to only 0.5 to 1 IU/L of each form present at baseline activity in most individuals (Fig 3). However, to provide a reliable diagnosis of infarction, it has been found that total MB CK must exceed 12 to 14 IU/L. Thus, based on total MB CK, a severalfold increase is necessary for a reliable diagnosis. In contrast, if the diagnosis were based on a change in percentage of the isoforms, a release of minute amounts of the MB\textsubscript{2} into the plasma immediately after myocyte necrosis could lead to a 50\% to 100\% change in the percentage. A similar rationale may be used for the use of MM CK isoforms to make an earlier diagnosis. Initial studies were performed with MM CK isoforms, since they are present in greater amounts and easier to detect.\textsuperscript{49} Results in animal\textsuperscript{50,51} and in humans showed MM CK isoforms, using an increase in ratio of MM\textsubscript{1} (tissue form) to the plasma isoforms, provided an earlier diagnosis of infarction than total MB CK. The initial assay\textsuperscript{44} used to detect the CK isoforms consisted of chromatofocusing. While very sensitive it was tedious, time consuming, and thus not applicable to clinical use, as was true for the subsequent assays of isoelectric
Development of assays for plasma MB CK isoforms were further delayed because of the increased sensitivity required to detect such low plasma levels. Nevertheless, conventional electrophoresis performed at 90 to 150 V using high-resolution agarose under conditions optimized for MB CK provided reliable sensitivity, but the analysis required 2 hours. This barrier was overcome by regional dynamic cooling of the agarose gel, which protected the enzyme from denaturing even at voltages of 1800 V (as opposed to the conventional 90 V). Under these conditions, the plasma MB CK isoforms were separated in 6 to 8 minutes as opposed to 60 to 90 minutes. The results of the initial studies using this assay in normal subjects and patients with myocardial infarction demonstrated sensitivity for the plasma MB CK isoforms at 0.5 IU/L with high reproducibility and showed a reliable diagnosis within 4 to 6 hours, based on a ratio of MB₂ to MB₁ of ≥1.5. The overall diagnostic sensitivity and specificity were in the 90% range. In contrast, the conventional assay for total MB CK had a sensitivity of only 57% in the initial 4 to 6 hours.

In a more recent study designed to determine its potential use as a means of triaging patients for admission, the electrophoretic isofrom assay was applied in the emergency room to all consecutive patients with chest pain. In this prospective study of 1110 consecutive patients with chest pain of diverse etiologies, the overall diagnostic sensitivity and specificity were 96% and 93%, respectively. The test produced results that were quite significant in that 539 patients were able to be discharged from the emergency room. The mean time after which a definitive diagnosis was available was based on samples obtained 2 ± 1.8 hours after arrival in the emergency room. Using this approach to triaging, the proportion of patients admitted to the CCU with myocardial infarction was 75% rather than the 22% who would have been admitted using conventional triaging. The CK isoforms recently have been used in the prospective trials of Thrombolyis in Myocardial Infarction (TIMI). In these trials, TIMI 4, 5, and 6, the blood samples collected at 48 medical centers were analyzed for MB CK isoforms at Washington University and for MB CK isoforms at Baylor College of Medicine, with neither center having any knowledge of the clinical data. In the pilot study, both the diagnostic sensitivity and specificity of the CK MB isoforms performed on the first available sample were >90%. The mean time of the initial sample from onset of symptoms on which the diagnosis was based in this study was 2.5 hours. These findings are also concordant with those reported in smaller series of patients by Kanemitsu and Okigaki and Bhayana et al. The electrophoresis unit with which these assays were performed is readily available. Thus, plasma MB CK isoforms appear to be likely candidates to meet the challenge required for early triaging of acute myocardial infarction.
Utilization of CK Isoforms for Administering Early Thrombolytic Therapy

Currently, based on data from the GISSI-1, ISIS-2, and TIMI-3 trials, the indication for early intravenous thrombolysis in patients with suspected acute myocardial infarction is the presence of ST segment elevation or bundle-branch block. As previously indicated, these guidelines are based on the diagnostic predictive value of the ECG and the pathophysiology of infarction. A major thrust for the 1990s is the challenge to determine whether improvement of our diagnostic regimens will allow the administration of thrombolytic agents to a broader spectrum of patients early in the course of myocardial infarction. Administration of thrombolytics in the field has been shown to be feasible and saves 45 to 90 minutes in beginning thrombolysis.22,58 A novel approach is to have paramedics administer the agent upon seeing the patient and then confirm or exclude the diagnosis upon arrival in the emergency room. Such a trial is now ongoing in which the ECG is transmitted to a physician. In this trial, if ST-T segment elevation or depression or T-wave inversion is present in combination with typical ischemic chest pain, 20 mg of r-TPA is given as a bolus together with an aspirin and heparin (5000 U) bolus. Upon arrival in the emergency room, if ST-T segment elevation is present, thrombolytic therapy is continued as usual (80 mg over 2 hours). In patients without ST-T segment depression, whether or not to continue thrombolytic therapy is based on the results of the MB CK isof orm. An initial blood sample is taken by the paramedic when the patient is first seen and again on arrival in the emergency room and every 30 minutes up to 5 hours after onset or until the diagnosis is determined. We have shown that patients having normal plasma CK isof orm ratios up to 5 hours after onset of symptoms can be excluded from having myocardial infarction at the 95% confidence level. The approach is, of course, experimental, and any such approach has to be approved by the Food and Drug Administration and the local institutional review boards. The results of this trial should help address the issues referred to earlier, namely, the feasibility, safety, and benefit to risk ratio of early thrombolytic therapy in patients with acute myocardial infarction who do not have ST segment elevation.

Another important potential application of the CK isoforms is in the early diagnosis of reinfarction. Coronary reocclusion and reinfarction still account for about one quarter of all of the hospital deaths in the initial
hours after thrombolytic therapy. It should be quite feasible in this setting of chest pain to use CK isoforms to determine rapidly whether reinfarction is occurring. However, if the reinfarction occurs within 24 hours of the previous infarction, definitively detecting release of new MB CK when there is continuing release from the previous infarction is not possible with total MB CK. It is conceivable that reinfarction occurring after 24 hours can be detected within 1 to 2 hours using the CK isoform assay. A change in the ratio of the MB2 to MB1 may provide a reliable diagnosis; however, such studies have not yet been performed. If the MB CK isoform ratio proves to be reliable, readministration of a thrombolytic agent or revascularization using angioplasty or surgery could be initiated in time to effect significant myocardial salvage.

Other Diagnostic Techniques for Early Diagnosis

The diagnostic imaging techniques that have greatly enhanced our assessment of myocardial infarction and continue to be very important in its management are unlikely to help in the early diagnosis of infarction in the immediate future because of either expense, practical feasibility, or difficulty of interpretation. Technetium-99m pyrophosphate is most reliable 24 to 72 hours after the onset of infarction and is extremely insensitive in the initial hours. Myocardial images obtained with thallium-201, as well as technetium sestamibi, detect ischemia but do not distinguish it from necrosis, are not clinically applicable for widespread screening, are very expensive, and do not distinguish between old and new injury. Positron imaging again remains a research tool and is not likely to be available for widespread clinical screening. Radionuclide ventriculography using technetium-99m for regional wall motion abnormalities offers some potential, has the limitations of thallium imaging, but is less sensitive and less specific. The most recent imaging technique, namely, nuclear magnetic resonance, is still far too insensitive to detect early changes with either ischemia or infarction, and since it is extremely expensive as well as time consuming, it is unlikely to be applicable in the near future.

Another imaging modality that has received extensive application both in the diagnosis and assessment of heart disease is echocardiography. This technique can be performed at the bedside or in the emergency room in essentially all hospitals, and results are immediately available and relatively easy to interpret. Although echocardiography offers considerable promise to date, it has not been properly tested for its diagnostic sensitivity and specificity in the emergency room; such studies are now warranted. It has been recognized experimentally and also in humans that immediately after coronary occlusion, the myocardium ceases to function in the area of the infarct-related vessel. One observes on echocardiography the failure of the myocardium to contract and thicken during systole, and, in fact, regions of ischemic myocardium may thin with systolic bulging.

It is said that regional wall motion abnormalities can be detected in patients with acute myocardial infarction with approximately 90% sensitivity on the two-dimensional echocardiogram. An experienced technician can differentiate between normal and abnormal wall contraction by the subjective appreciation of the endocardium and the absence of wall thickening. Oh et al reported their experience with the use of a portable two-dimensional system in 26 patients presenting to the emergency room with acute chest pain. Regional impairment of wall motion was observed in 5 patients and diffuse hypokinesis in another. Each of the 5 patients was shown subsequently to have myocardial infarction, yet, none of them had a typical diagnostic pattern on the ECG. Two of 20 patients without abnormalities of wall motion eventually evolved non-Q-wave infarction. In another study, Horowitz and colleagues showed that 31 of 33 patients with acute infarction had documented regional wall motion abnormalities. Loh and associates in a group of 30 patients with chest pain and nondiagnostic ECG changes showed 10 of the 12 patients who subsequently evolved infarction had regional wall motion abnormalities on echocardiography. It is not surprising that regional wall motion abnormalities would provide a sensitive index, since it is well recognized that the lack of function associated with myocardial ischemia occurs within seconds.

While this technique holds promise, certain limitations must be considered. First, the lack of automation of analysis means interpretation still depends on the subjective skills of the experienced technician. The second is inadequate images that occur in 5% to 10% of patients. Third is the lack of precise quantitative assessment of regional wall function. Fourth and perhaps most important is the inability to distinguish between old and new injury, which greatly increases the likelihood of false-positive results. ECG, however, does appear applicable and is likely to play a major role as a supplement in determining the diagnosis in the emergency room. The presence of chest pain with changes on the ECG, together with abnormal wall motion in the area expected, may significantly improve our chances of diagnosing infarction.

CK Isoforms in the Assessment of Reperfusion

It is well established that thrombolytic therapy, whether given intravenously or by intracoronary infusion, is unsuccessful in inducing lysis in about 20% to 30% of patients. Routine cardiac catheterization is not recommended, detection of patients in whom thrombolytic therapy is unsuccessful is at present not feasible, but several noninvasive techniques have been attempted. It would be preferable that lysis be determined while it is still feasible to salvage ischemic myocardium using other means such as rescue angioplasty. While the time window for limiting infarct size and preserving ventricular function is 4 to 6 hours, there are now data to indicate that reperfusion confers a beneficial effect on mortality even when administered as many as 12 hours from the onset of symptoms. In early studies of reperfusion relief of chest pain, decrease in ST segment elevation and the sudden appearance of arrhythmias have been used and found not to be reliable indices of reperfusion. Since it is well documented that CK is more rapidly released with reperfusion, the time to peak plasma CK activity was evaluated in several studies, but when tested prospectively in a large number of patients, the overlap prohibited separation between successful and unsuccessful reperfusion.
Most recently, there have been three studies showing the initial rate of increase of plasma MB or total CK as a means of detecting reperfusion.\textsuperscript{73-75} Samples were taken at baseline and every 15 to 30 minutes thereafter in patients undergoing early reperfusion within the first 2 to 4 hours. Coronary patency as determined by coronary angiography showed that a rapid rise in MB or total CK corresponded with restoration of flow and provided separation between those patients undergoing successful reperfusion and those in whom the therapy was unsuccessful. Since total or MB CK activity is minimally elevated in the first 4 hours, the occurrence of a dramatic increase most likely signals reperfusion. In view of these results, prospective studies in a large number of patients may be warranted to determine the frequency with which such a dramatic increase occurs, its specificity, and its overall accuracy.

There is a rational basis for expecting that the CK isoforms would provide a more reliable index of reperfusion. The washout of CK from reperfused infarcted myocardium is more rapid than from myocardium that is not adequately perfused. MM\textsubscript{1} (tissue isoform) is converted to the other isoforms in vivo by carboxypeptidase-N\textsuperscript{44}; this conversion is much more rapid than clearance from the plasma.\textsuperscript{76} Consequently, with reperfusion, there is a relatively rapid cessation of release with rapid decline caused by conversion to the isoforms.

In contrast, sustained occlusion is associated with prolonged ongoing release for 24 to 48 hours, with MM\textsubscript{1} remaining predominant through most of this interval, so the decline of MM\textsubscript{1} is much more gradual. To test this hypothesis, a prospective study\textsuperscript{46} was performed in 103 patients, 30 treated conventionally, 39 in whom thrombolytic therapy was unsuccessful as documented on coronary angiography, and 55 in whom thrombolytic therapy was documented to be successful. The rate of decline in MM\textsubscript{1} averaged 4.8±1.25%/h in patients with successful reperfusion, 2.37±1.1%/h in those in whom thrombolytic therapy was unsuccessful compared with 1.77±1.4%/h in patients undergoing conventional treatment without thrombolysis. The overall accuracy was 82%. A major limitation to this method is the requirement of a minimal sampling interval of 10 to 14 hours. An analysis was undertaken using MB CK isoforms\textsuperscript{77} to determine the rate of change of the MB\textsubscript{2} to MB\textsubscript{1} ratio, and the separation was accurate at the 80% level, as confirmed by angiography. Patients undergoing thrombolytic therapy increased their MB\textsubscript{2}/MB\textsubscript{1} ratio from 2.4±1.6 to 4.6±2.0 in 60 minutes compared with a peak value of 3.1±1.2 in the nonreperfused group, and the difference was highly significant. A ratio exceeding 3.8 was able to identify 90% of patients with a patent vessel and 89.5% of patients with an occluded vessel. This study was performed in only 56 patients and will obviously have to be assessed in a larger number of patients. The accuracy of the MB\textsubscript{2}/MB\textsubscript{1} ratio is undergoing prospective assessment along with MM CK isoforms to determine accuracy in detecting reperfusion following thrombolytic therapy in the TIMI trials. Until these results are available, it is premature to judge the accuracy of this technique for evaluating the presence of reperfusion.

We also compared the rate of increase of MM isoforms with or without reperfusion but were unable to find adequate separation, since in 56% of the patients the percentage of MM\textsubscript{3} in the initial sample was already maximal. The results of a study by Jaffe et al\textsuperscript{50} also showed in patients with acute myocardial infarction without reperfusion that the baseline ratio of MM\textsubscript{3}/MM\textsubscript{1} was already 14.4:1 by 3.9 hours after onset; thus, sensitivity would be blunted by being superimposed on an already increased plasma elevation of MM\textsubscript{2}. In animal studies, it was shown that the rate of rise of MM\textsubscript{2} was more promising than using the rate of rise of the ratio.\textsuperscript{78} Several studies have been performed in humans assessing the time of appearance of MM\textsubscript{2},\textsuperscript{79} rate of increase,\textsuperscript{79-82} time to peak plasma activity,\textsuperscript{49,78,82} and the rate of change in the ratio of MM\textsubscript{3} to MM\textsubscript{1}.\textsuperscript{78,82,83} These studies suggest the rate of increase in MM\textsubscript{2} as a percentage of total CK is the most promising.\textsuperscript{80} The rate of increase over the first 60 to 120 minutes separates most patients as to whether they underwent reperfusion as detected by coronary angiography. Further studies are now being performed in the TIMI trials. Promising results have also been observed using the MM isoforms to delineate patency in the PRIMI Trial.\textsuperscript{84}

**Myoglobin for Detecting Reperfusion**

Another potential marker for detecting reperfusion is myoglobin. Myoglobin is a small molecule (17 000 d mol wt) that is rapidly released from myocytes after injury. Plasma concentrations of myoglobin also increase after skeletal muscle trauma, in shock, and in both acute and chronic renal failure (clearance appears to be through renal catabolism). While this lack of specificity may not pose a problem in the otherwise healthy patient with suspected infarction, patients with nondiagnostic ECGs are often older and are more likely to have comorbid disease,\textsuperscript{27} and myoglobin determinations may be less helpful in them. Although myoglobin lacks specificity for early diagnosis, its kinetics make it appear promising for distinguishing patients with successful versus unsuccessful reperfusion and for detecting reocclusion. Myoglobin is released into the circulation approximately 1 hour after experimental coronary occlusion,\textsuperscript{85} which is several hours earlier than the release of CK. Clinical comparisons between the two enzymes confirm the earlier appearance of myoglobin.\textsuperscript{86} This release process appears to occur in pulses.\textsuperscript{87,88} Myoglobin undergoes first-order elimination from the circulation, with a half-time of elimination approximately one-tenth that of CK.\textsuperscript{89} Experimentally, plasma myoglobin peaks within 30 minutes of reperfusion.\textsuperscript{90} In patients undergoing reperfusion therapy, myoglobin after documented reperfusion peaks within approximately 2 hours (with a relatively narrow range of dispersion) compared with 4 to 6 hours for patients in whom reperfusion is unsuccessful.\textsuperscript{91} By definition, the time to peak value is a retrospective diagnosis made only after multiple samples have been collected at short time intervals and after the peak has already occurred. Ellis et al\textsuperscript{91} found that a 4.6-fold increase rise of myoglobin concentration over the first 2 hours can be calculated rapidly and has an even greater predictive accuracy for reperfusion than does the time to peak value. In addition, the relatively rapid clearance of myoglobin from the plasma theoretically would facilitate detection of reocclusion after reperfusion, since the background value of myoglobin would decrease quickly, thus allowing new plasma peaks to stand out more clearly. Until the present, a major
factor limiting the use of myoglobin has been the necessity of using a radioimmunoassay determination, which is time consuming. The recent availability of turbidometric assays that can easily be performed in less than 30 minutes make the use of this enzyme seem promising.\(^7\)

**Future Scenarios**

Obviously, the usefulness of the various markers of myocyte necrosis for the early detection of infarction as well as for the noninvasive detection of reinfarction and reperfusion will require that they be validated in large clinical studies. This process is now occurring in the TIMI and GUSTO studies. If and when such validation occurs, it will become incumbent upon us to advance the use of such markers to the maximum. For example, rapid diagnostic techniques could be used to select patients for dedicated trials of thrombolysis early in the course of non-Q-wave infarction. There is scientific evidence and anecdotal clinical experience to indicate that a thrombolytic agent administered within the first 20 to 30 minutes can completely abort the myocardial infarction process. During this time, most patients are either at home or have just arrived at the hospital. Thus, for patients presenting with equivocal ECG findings, we would foresee the administration of short-acting thrombolytic agents in the field, with the ultimate diagnosis made upon or shortly after arrival in the hospital. At this point, thrombolysis could be terminated and anti-coagulation avoided or modified if myocardial infarction is ruled out. Ultimately, the development of bedside diagnostic kits might allow paramedics to begin full-dose thrombolytic infusions in the field. We would also foresee the development of intermediate care units within the emergency department, where patients could be monitored for relatively brief periods (ie, several hours) until triage could be performed based on the definitive rather than suspected diagnosis. Thus, the incremental cost of administering thrombolytic drugs to a larger number of patients might be offset by averting a large number of admissions to the CCU. Similarly, if such determinations could be made available in a matter of minutes, these assays would be useful in deciding whether to perform emergency angiography and revascularization. These ideas are neither new nor original. What is new, however, is that now that we have developed an effective therapy for myocardial infarction, whose benefit is also greatest when used early, we are also on the verge of developing reliable early diagnostic markers of myocardial infarction.

More rapid and accurate triaging of patients for admission to our intensive care units is long overdue. Regardless of what is ultimately decided about thrombolysis in the patient with non-Q-wave infarction, there is financial motivation to establish early diagnosis. We are currently using frequent MB CK isoform determinations to triage patients for admission to our CCU. It is estimated that it costs $13 billion annually to care for “non-myocardial infarction” in the CCU. To ignore the mandate from both government agencies and third-party providers may prove fiscally embarrassing to medical care providers. What is not acceptable is for us not to accept the nudge for a new modus operandi. We must be ready to take advantage of newer therapeutic and diagnostic techniques that are sure to evolve. Such evolution is likely to occur more rapidly if our awareness of the problem is better honed and the desire to improve continues to be our aspiration.

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**References**


46. de Bonf DP, Simoons ML, Tijssen J, Arnold AER, Berti A, Burgerdijs C, Lopez-Beskos L, Mueller E, Pfisterer M. Effect of


Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a 'new diagnostic mind-set'.
R Roberts and N S Kleiman

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