Early Noninvasive Detection of Successful Reperfusion in Patients With Acute Myocardial Infarction

Avery K. Ellis, MD, PhD, Thomas Little, MD, A.R. Zaki Masud, MD, Henry A. Liberman, MD, Douglas C. Morris, MD, and Francis J. Klocke, MD

Myoglobin (Mb) is a protein that enters rapidly and is rapidly cleared from plasma after coronary reperfusion. We sought to determine the accuracy with which a rapid rise in plasma [Mb] could predict successful coronary artery reopening in patients undergoing coronary arteriography in conjunction with attempted reperfusion in acute myocardial infarction. In 42 patients, plasma Mb levels were measured before and for at least 4 hours after attempted reperfusion. Thirty-five patients were successfully reperfused. In each, the plasma Mb level rose rapidly with peak [Mb] occurring at 111±8.1 (±SEM) minutes after application of therapy. In contrast, Mb levels rose more slowly in the seven patients who were not reperfused, with peak [Mb] occurring 360±61.4 minutes after attempted reperfusion. T25–100 (the time required for [Mb] to rise from 25% to 100% of peak value) was shorter in patients successfully reperfused (71±7.9 minutes) and longer (341±35.3 minutes) in patients in whom therapy was unsuccessful. A rapid rise in [Mb] after successful reperfusion was also evident by a more than 4.6-fold rise in [Mb] over the first 2 hours after reperfusion in all but five patients; in contrast, [Mb] rose by less than 4.6-fold over this same interval in every patient not successfully reperfused (sensitivity, 85%; specificity, 100%; predictive accuracy, 88%). We conclude that a rapid rise in plasma Mb level over the initial 2 hours after attempted reperfusion in acute myocardial infarction provides a useful index of successful reperfusion. (Circulation 1988;78:1352–1357)

With the increased use of thrombolytic therapy early in the course of acute myocardial infarction, there is increasing need to determine in individual patients whether reperfusion has been achieved. Myoglobin (Mb) is an intracardiac protein known to be rapidly released into blood after the onset of coronary reperfusion.1 Because it is also rapidly cleared from the circulation, with a half-time of disappearance of less than 10 minutes,2 Mb concentration-time curves appear to reflect patterns of protein entry into the circulation.

This study examines the usefulness of blood myoglobin level determinations in patients undergoing attempted coronary reperfusion early in the course of acute transmural myocardial infarction. In each patient, vessel patency was directly assessed by coronary arteriography and compared with the pattern of myoglobin release determined from the myoglobin concentration-time curve in systemic venous blood. We sought to assess the extent to which a rapid rise in [Mb] soon after the application of therapy could predict the success or failure of attempted reperfusion.

Patients and Methods

Forty-two patients receiving thrombolytic therapy and/or percutaneous transluminal coronary angioplasty (PTCA) within the first 6 hours of acute transmural infarction were enrolled at the Buffalo Veterans Administration Medical Center, the Erie County Medical Center, or Crawford W. Long Hospital between September 1, 1984, and December 31, 1987. All patients had prolonged chest pain when they presented to the emergency department. Entry into the study also required that the pain be less than 6 hours in duration, be unrelieved by sublingual nitroglycerin and/or nifedipine, and be associated with 0.1 mV ST elevation in at least two adjacent electrocardiographic
leads. In addition, cardiogenic shock, renal failure, intramuscular injections, and arrhythmias requiring cardioversion were required to not present. Ten of the patients were included in an earlier study.1

After each patient had given informed consent, a 3-ml venous sample for blood Mb level determination was drawn before the acute intervention. After application of therapy, 3-ml samples were to be drawn every 30 minutes for 4 hours and then every 4 hours for an additional 20 hours; however, because of patient care factors, it was not possible to obtain every sample in each patient. Treatments varied depending on the clinical circumstance but included intravenous streptokinase (IV SK), intracoronary streptokinase (IC SK), PTCA, and intravenous recombinant tissue-type plasminogen activator (IV rt-PA). IV SK was given as 1,500,000 units over 30–45 minutes; rt-PA was administered in either a standard dose (1.25 mg/kg/3 hr) or high dose (2.00 mg/kg/3 hr); IC SK was given as a 62,500-unit bolus into the infarct-related artery followed by an infusion of 4,000–6,000 units/min/40–60 min. Patients receiving IV rt-PA or IC SK underwent immediate cardiac catheterization, and the status of the infarct-related artery was determined; in these patients, PTCA was attempted if it was thought to be clinically indicated (e.g., unsuccessful thrombolysis and/or high-grade residual stenosis). All patients were subsequently anticoagulated with intravenous heparin to maintain the activated partial thromboplastin time at from one and one half to two control; otherwise, patients received routine coronary care, including nitrates, calcium channel blockers, β-blockers, and antiarrhythmic agents as needed.

The patency of the infarct-related artery was assessed by coronary arteriography in all patients. As just noted, patients receiving IC SK, intravenous rt-PA, and/or PTCA underwent arteriography at the time of application of therapy. Patients receiving IV SK underwent coronary arteriography within 2±0.3 (±SEM) days (range, 1–5 days) after attempted thrombolysis; in all but two patients, arteriography was actually performed within 3 days. The arteriograms were reviewed by at least two experienced angiographers who were unaware of the results of the Mb determinations.

Plasma Mb levels were determined in each sample by radioimmunoassay (NMS Radio-pharmaceuticals, Newport Beach, California), and an Mb concentration-time curve plotted for each patient. The coefficient of variation for myoglobin determination by this assay was ~4%. Time 0 was taken as the time of application of therapy; in patients in whom thrombolysis was followed by PTCA, the time of the intervention that resulted in vessel reopening was designated time 0. All values are reported as mean±SEM unless otherwise stated.

<table>
<thead>
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<th>TABLE 1. Patient Characteristics</th>
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<tr>
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<td>Infarct location by electrocardiogram</td>
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<tr>
<td>Inferior</td>
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<td>Anterior</td>
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<td>Lateral</td>
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<td>Infarct-related artery</td>
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<td>Left anterior descending coronary artery</td>
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<td>Left circumflex coronary artery</td>
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<td>Right coronary artery</td>
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<td>Coronary artery bypass graft</td>
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<td>Method of reperfusion</td>
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<td>IC SK</td>
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<tr>
<td>rt-PA</td>
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<tr>
<td>PTCA</td>
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<tr>
<td>IV SK</td>
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<tr>
<td>Not reperfused</td>
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<tr>
<td>IC SK, intracoronary streptokinase; IV SK, intravenous streptokinase; IV rt-PA, intravenous recombinant tissue-type plasminogen activator; PTCA, percutaneous transluminal coronary angioplasty.</td>
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Results

Patient Characteristics

Table 1 summarizes the patient demographics. This study includes 38 men and four women with a mean age of 54±1.4 (±SEM) years (range, 39–71 years). The average time to treatment was 216±10.5 minutes (range, 90–360 minutes) after the onset of chest pain. Arteriography was immediate in patients receiving IC SK, rt-PA, and/or PTCA and was performed within 3 days in all but two patients receiving IV SK (and within 5 days in all patients).

Myoglobin Concentration-Time Curves in Patients Undergoing Thrombolysis

Figure 1 illustrates representative Mb curves in two patients receiving thrombolytic therapy. The left panel represents a patient in whom therapy was successful. The rate of rise in [ Mb] is rapid, and peak [ Mb], which occurred 162 minutes after the onset of therapy, is 1,500 ng/ml. The rapid release of Mb with an early peak in the myoglobin concentration-time curve contrasts with Mb kinetics after unsuccessful thrombolysis (Figure 1, right panel). In this patient, peak [ Mb] of 378 ng/ml occurred 295 minutes after attempted thrombolysis. Table 2 summarizes Mb kinetics for all 42 patients.

Figure 2 contrasts normalized curves for reperfused and nonreperfused patients. All patients successfully reperfused showed a rapid rise in [ Mb]; plasma Mb levels rose by 13.5±2.3 ng/ml/min, and peak [ Mb] occurred 111±8.1 minutes (range, 0–220 minutes) after administration of therapy. In contrast, [ Mb] rose slowly when attempted reperfusion was unsuccessful; the rate of rise was only 1.2±0.3 ng/ml/min, and peak [ Mb] occurred 360±61.4 minutes (range, 230–660 minutes) after administration of therapy.

An early peak in [ Mb] occurred in all 21 patients with known vessel reopening documented by immediate arteriography (IC SK, IV rt-PA, and PTCA
groups) with a time-to-peak of 77±11.9 minutes. In nine of these 21 patients, the infarct-related artery was occluded at the time of initial arteriography; in each case, plasma Mb levels drawn just before arteriography were low and began to rise rapidly after successful reopening of the occluded vessel (Figure 3, left panel). In the other 12 patients, the vessel was patent at the time of the first arteriogram. In each of these patients, a rapid rise in [Mb] had begun before arteriography (Figure 3, right panel). In three of these 12 patients, the rapid rise occurred despite limited reperfusion (TIMI grade 1 flow) and a severe residual stenosis of 99% in each case.

**Prediction of Success or Failure of Reperfusion From Myoglobin Concentration-Time Curves**

Two indexes derived from the Mb concentration-time curves appear useful in predicting vessel patency after attempted reperfusion. The first, illustrated in Figures 1 and 4, is T25-100 (the time required for [Mb] to rise from 25% to 100% of peak value). As summarized in Table 2 and Figure 4, a rapid rise in [Mb] corresponding to a short T25-100 of 71±7.9 minutes) is present in all patients in whom reperfusion was successful. This contrasts with the slow Mb rise (and higher values of T25-100 averaging 341±35.3 minutes) in patients not successfully reperfused.

The second index is the rate of rise of [Mb] over the first 2 hours after attempted reperfusion, [Mb]_{120}/[Mb]_{0}. As shown in Figure 5, a cutoff value of the [Mb]_{120}/[Mb]_{0} ratio of 4.6 was chosen, representing the upper 95% confidence interval (after a logarithmic transformation) for the nonreperfused patients. A 4.6-fold or greater rise in [Mb] over the first 2 hours after onset of therapy is present in all but five of the 34 patients successfully reperfused in whom this index was calculated (sensitivity, 85%). In contrast, the rise in [Mb] is less than 4.6-fold in every patient in whom thrombolysis was unsuccessful and in whom this index was determined (specificity, 100%). The overall predictive accuracy of the index is 88%, with the status of the infarct-related artery correctly assessed in 35 of 40 patients on the

**Figure 1.** Representative myoglobin (Mb) concentration-time curve from one patient successfully reperfused (left panel) and from one who was not (right panel). In each case, time 0 is taken as the time of application of therapy (intravenous recombinant tissue-type plasminogen activator in the patient on the left and intravenous streptokinase in the patient on the right). After successful reperfusion, a rapid rise in [Mb] is noted, and T25-100 (the time required for Mb to rise from 25% to 100% of peak level) is 62 minutes. A noticeably slower rate of rise, with a longer T25-100 of 230 minutes, is observed when attempted reperfusion is unsuccessful.

**Figure 2.** Normalized myoglobin (Mb) curves for reperfused and unreperfused patients. Again, time 0 is taken as the time at which therapy is applied. The actual time at which the samples were drawn varied in individual patients: 0 hours (−8±3.0 minutes), 1 hour (58±3.9 minutes), 2 hours (117±2.2 minutes), 3 hours (177±2.2 minutes), and 4 hours (236±5.2 minutes). [Mb]₀, Mb concentration at time 0; [Mb]₁, Mb concentration at time T. For each patient, plasma Mb levels were normalized in relation to [Mb] at time 0, which was taken as 1.0 (see text for details).

**Table 2.** Summary of Myoglobin Kinetics After Attempted Reperfusion

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Not reperfused</th>
<th>Overall</th>
<th>IC SK; IV rt-PA</th>
<th>PTCA</th>
<th>IV SK</th>
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<td></td>
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<tr>
<td>Time to peak myoglobin (min)</td>
<td>360±61.4</td>
<td>35</td>
<td>111±8.1</td>
<td>109±11.4</td>
<td>94±20.6</td>
</tr>
<tr>
<td>T25-100 (min)</td>
<td>341±35.3</td>
<td>71±7.9</td>
<td>61±11.3</td>
<td>56±15.0</td>
<td>90±13.5</td>
</tr>
</tbody>
</table>

IC SK, intracoronary streptokinase; IV rt-PA, intravenous recombinant tissue-type plasminogen activator; PTCA, percutaneous transluminal coronary angioplasty; IV SK, intravenous streptokinase; T25-100, time required for myoglobin to rise from 25% to 100% of peak value. Values are mean±SEM.
basis of two blood Mb determinations drawn approximately 2 hours apart.

Similar though slightly less-sensitive results were noted using the rise in [Mb] over only the 1st hour after application of therapy ([Mb]_{60}:[Mb]_0). With a cutoff value of the [Mb]_{60}:[Mb]_0 ratio of 2.5 (representing the upper 95% confidence interval of the nonreperfused patients after logarithmic transformation), sensitivity was 79%, specificity was 100%, and predictive accuracy was 83%.

Discussion

This study extends our initial clinical experience with Mb concentration-time curves as an index of successful coronary reperfusion in the setting of acute myocardial infarction. Mb is an intracardiac protein that is rapidly released from injured myocardium after successful reperfusion, with peak plasma levels occurring at 111±8.1 minutes (vs. 360±61.4 minutes in patients in whom therapy is unsuccessful). We have developed two indexes to assess individual patients after attempted reperfusion. The first, T_{25-100}, separates patients on the basis of the rate of rise of the ascending limb of the Mb concentration-time curve. In patients successfully reperfused, the rate of rise is rapid and T_{25-100} is short (71±7.9 minutes); this contrasts with a much slower rate of rise in patients not reperfused (Figure 4). In terms of prospectively assessing individual patients, however, the ratio of [Mb]_{125}:[Mb]_0 has potentially greater clinical use because only two samples need to be collected and knowledge of the entire concentration-time curve is unnecessary (Figure 5). An increase in [Mb] of at least 4.6-fold over the first 2 hours was present in 29 of 34 patients successfully reperfused, whereas this ratio was less than 4.6 in all six patients in whom therapy was unsuccessful. Similar though slightly less-sensitive results were obtained with [Mb]_{60}:[Mb]_0, the better results for [Mb]_{125}:[Mb]_0 probably relate to the occurrence of peak [Mb] at ~2 hours after application of therapy (Table 2). Measurement of plasma Mb levels just before application of thrombolytic therapy and again 1 or 2 hours later may allow the success or failure of therapy to be determined noninvasively with a high degree of accuracy. With the use of a rapid human assay for Mb determination, the success or failure of attempted thrombolysis could potentially be assessed within 1–2 hours.

Our data show that an early peak in [Mb] occurred in all 21 patients with known vessel reopening documented by immediate arteriography (IC SK, IV rt-PA, and PTCA). As illustrated in Figure 3, the rapid rise in [Mb] appeared to begin immediately after vessel reopening. In the nine patients in whom the infarct-related artery was occluded at the time of initial arteriography, initial plasma Mb levels were
Figure 5. Plot of ratio of myoglobin $[\text{Mb}]_{120}:[\text{Mb}]_0$ for successfully and unsuccessfully reperfused patients. $[\text{Mb}]_{120}$ Mb concentration 120 minutes after application of therapy; $[\text{Mb}]_0$, Mb concentration at time 0. The $[\text{Mb}]_{120}:[\text{Mb}]_0$ ratio of 4.6, indicated by the dashed line, represents the upper 95% confidence interval for this ratio (after a logarithmic transformation) among the nonreperfused patients. As noted in Figure 2, there is variability in the time at which samples were actually drawn in individual patients. In two patients (one reperfused and one not reperfused), $[\text{Mb}]_{120}:[\text{Mb}]_0$ could not be calculated because of difficulties in sample collection. (See text for details.)

low and began to rise rapidly only after successful reopening of the occluded vessel. In the other 12 patients in whom the vessel was patent at the time of the first arteriogram, a rapid rise in [Mb] had begun before arteriography; this rapid rise occurred even in three patients with limited reperfusion (TIMI grade 1 flow) and severe residual stenoses. Thus, plasma Mb levels begin to rise just after vessel reopening, whether this occurs spontaneously or with a therapeutic intervention. In addition, the rise in [Mb] appears to occur even in the face of a severe residual stenosis and limited coronary flow.

In our series of IV SK patients, the infarct-related artery was occluded at the time of arteriography in only five of 19 patients. Because arteriography was not performed immediately in these patients, vessel status at the time of application of therapy could not be determined. Nonetheless, a delayed Mb peak was present in each patient in whom the vessel presumably remained totally occluded. Previous work by McComb et al. and Drexel et al. examined detailed Mb curves in acute infarction patients without attempted thrombolysis. Although arteriography was not routinely performed, Mb concentration-time curves showed late peak Mb levels and appeared qualitatively similar to our unreperfused patients.

In each of the 14 patients receiving IV SK in whom the infarct-related artery was noted to be patent at the time of coronary arteriography, there was an early, discrete peak in the Mb concentration-time curve. Because immediate angiography was not performed, this group may include patients in whom the infarct-related artery was never totally occluded and/or patients in whom spontaneous ves-

sel reopening occurred within the first few hours of onset of symptoms. Delayed recanalization within 2–3 days, as evidenced by the lack of an early Mb peak with a patent vessel at arteriography, was not noted in any of our patients.

Several criteria have been suggested to allow noninvasive determination of vessel patency after attempted thrombolysis: relief of chest discomfort, occurrence of reperfusion arrhythmias, normalization of ST-segment elevation, and an early rapid rise and early peak in creatine kinase activity. Although the first three parameters occur commonly after successful thrombolytic therapy, each parameter is relatively insensitive when considered separately. Although the predictive value is 100% if all three findings are present, this occurs in less than 15% of reperfused patients. With regard to creatine kinase curves, successful reperfusion is associated with peak creatine kinase activity at 13 ± 6 hours compared with 22 ± 4 hours in patients in whom thrombolyis is unsuccessful. However, the large coefficients of variation (20–50%) indicate considerable variability and overlap among individual patients in these two groups. In addition to the large scatter and overlap of peak times, the need to collect frequent samples to determine the time of peak activity further limits this approach. More recently, it has been noted that individual creatine kinase isoenzymes are composed of three isoforms based on differences in isoelectric point. From initial reports it appears that the use of creatine kinase isoform analysis may be quite useful in separating successful from unsuccessful reperfusion in the first few hours after application of lytic therapy.

The need to develop a noninvasive marker of reperfusion is important in view of the large number of patients in whom intravenous thrombolysis is now likely to be used and in whom subsequent triage becomes an important issue. Our findings indicate that the determination of blood Mb levels early in the course of attempted coronary reperfusion is a relatively simple test that appears both sensitive and specific in providing information about the patency of the infarct-related artery.

Acknowledgment

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