Clinical Investigations

Rapid Myoglobin Analysis to Assess Coronary Artery Reperfusion after Acute Myocardial Infarction

HAI SHIANG LEE, M.B., B.CH, M.D., MRCP, STEPHEN J. CROSS, M.B., CH.B., M.D., MRCP, KEVIN JENNINGS, M.D., MBBS, FRCP

Department of Cardiology, Aberdeen Royal Infirmary, Scotland

Summary

Background: Coronary artery reperfusion significantly improves outcome in patients with acute myocardial infarction. A noninvasive method for assessing reperfusion in the early stage of infarction should be helpful in patient management.

Hypothesis: We sought to assess whether release pattern of myoglobin is helpful in identifying patients with and without reperfusion following thrombolytic therapy for myocardial infarction.

Methods: Myoglobin was measured before thrombolysis, half hourly for 4 h, then every 2 h for 10 h. Myoglobin was analyzed using a ward-based "rapid" and automated analyzer that yielded quantitative results within 10 min of blood collection.

Results: In the 15 patients with coronary reperfusion, the time from thrombolysis to peak myoglobin levels (mean $\pm$ SD, 2.4 ± 1.5 h) was significantly lower than in nonreperfused patients (5.1 ± 2.9 , $p < 0.01$). As an indicator for reperfusion, a doubling of myoglobin 1 h after streptokinase achieved a sensitivity of 80%, a specificity of 80%, and a predictive accuracy of 80%.

Conclusions: The difference in myoglobin release kinetics is useful in identifying patients without coronary reperfusion and should aid in their management.

Key words: coronary artery disease, myocardial infarction, reperfusion, myoglobin, thrombolytic therapy

Introduction

Thrombolytic therapy significantly reduces the mortality of patients with acute myocardial infarction (AMI).^{1–3} The GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery) angiographic study demonstrates that early restoration of coronary artery perfusion improved clinical outcome and survival.⁴ Despite utilizing an aggressive regime of accelerated tissue plasminogen activator (TPA), only 54% of the patients achieved complete reperfusion at 90 min. Patients who do not achieve coronary reperfusion may benefit from further intervention such as coronary angioplasty or increased doses of thrombolytic agents.

Early coronary arteriography after initiation of thrombolytic therapy would be the standard of reference for assessing reperfusion, but has failed simply because of its impracticality in most clinical settings. ST-segment analysis is helpful and has been shown to have good predictive accuracy in identifying patients with reperfusion.^{5–7} Although the electrocardiogram (ECG) is useful for this purpose, it cannot be applied to all patients because up to 40% of patients with AMI may not develop ST elevation on admission ECG.^{8,9}

Following myocardial cell death, intracellular proteins are released into the circulation. With reperfusion, a washout of these proteins should occur, resulting in high plasma concentration. Myoglobin is known to rise early after AMI.^{10–12} A compact and automated rapid analyzer can now yield quantitative results within 10 min of blood collection. These analyzers give reproducible results and are suitable for placement in the coronary care unit for use by trained clinical staff.¹³ This study determines whether early serial measurement of myoglobin using rapid analyzers is helpful in identifying patients with and without coronary reperfusion.

Methods

Patients

Twenty-five patients admitted with AMI and ST-segment elevation within 6 h of chest pain onset were included in the study. All patients were treated with aspirin and streptokinase at a dosage of 1.5 MU infused over 1 h.

Address for reprints:

Dr. Hai Shiang Lee
Department of Cardiology
Wythenshawe Hospital
Southmoor Road
Manchester M23 9LT, England

Received: April 16, 1997

Accepted with revision: June 20, 1997

Acute Myocardial Infarction

Acute MI was diagnosed by chest pain duration of more than 30 min, ST-segment elevation of at least 0.1 mV in two limb leads or at least 0.2 mV in two contiguous chest leads on the ECG, and a rise of creatine kinase-MB (CK-MB) to at least twice the upper limit of normal.

Electrocardiogram and Biochemical Analysis

Electrocardiograms were recorded just prior to thrombolytic therapy and then every 15 min if possible. The ECGs were recorded using self-adhesive electrodes to ensure that the positions of the leads were exactly the same for each recording. The ECGs were recorded at a speed of 50 mm/s. The ST segment was measured at the J point on each of the ECG leads. The leads showing the greatest ST-segment elevation were used for serial analysis of the ST segment. The ECGs were analyzed without knowledge of the myoglobin measurements. Myoglobin was measured before thrombolysis, every half h for 4 h, then every 2 h for 10 h.

Definitions and Statistical Analysis

Reperfusion was defined as a 50% reduction of maximum ST segment at 3 h after initiation of streptokinase. The paired *t*-test was used to compare the enzyme readings of two specific timings. The chi-square test with Yate's correction was used to calculate the difference between the two groups of patients.

Results

Patient Characteristics

Of the 25 patients, 15 achieved coronary artery reperfusion. The time from chest pain onset to administration of streptokinase was significantly lower in the reperfused patients [mean $\pm$ standard deviation (SD) 2.8 ± 1.0 h] than in nonreperfused patients (4.2 ± 0.9 h, $p < 0.01$). Clinical characteristics are summarized in Table I.

Myoglobin

In patients with reperfusion, the time from thrombolysis to peak myoglobin was significantly lower than in nonreperfused patients (Table II). Peak myoglobin level was higher in reperfused than in nonreperfused patients. In the reperfused patients, the ratio of the mean myoglobin readings taken before streptokinase to 1 h after streptokinase was 3.1; this was higher than the ratio of 1.5 for the nonreperfused patients.

To determine coronary reperfusion, a doubling of myoglobin 1 h after streptokinase would achieve a sensitivity of 80%, a specificity of 80%, and a predictive accuracy of 80%. Thus, significantly more reperfused patients (12/15) at least doubled their myoglobin levels 1 h after initiation of streptokinase compared with those without reperfusion (2/10, $\chi^2 = 6.5$, $p < 0.05$). Figure 1 plots the release kinetics of myoglobin in the reperfused and nonreperfused patients.

TABLE I Patient characteristics

	Reperfused	Non-reperfused	p Value
Number of patients	15	10	
Age	62 ± 5	64 ± 10	NS
Sex (M/F)	10/5	7/3	NS
Inf/ant MI	11/4	5/5	NS
Previous MI	2	1	NS
Time pain to SK	2.8 ± 1.0	4.2 ± 0.9	< 0.01

Abbreviations: M/F = number of male/female patients, Inf/ant = number of patients with inferior/anterior myocardial infarction, MI = myocardial infarction, SK = streptokinase, NS = not significant.

TABLE II Myoglobin results (time measured in h)

	Reperfused	Non-reperfused	p Value
Pk Myo ($\mu\text{g/l}$)	1828 (1939)	2773 (2666)	NS
Time: SK to Pk Myo	2.4 (1.5)	5.1 (2.9)	< 0.01

Abbreviations: Pk = peak, Myo = myoglobin, SK = streptokinase. NS = not significant.

Discussion

In recent years, thrombolytic therapy has revolutionized the management of patients with AMI.¹⁻³ It is now established that early and complete coronary reperfusion leads to a better clinical outcome.^{4, 14} Unfortunately, despite early thrombolytic therapy, a significant number of patients are still left with an occluded or incompletely perfused coronary artery. In the angiographic arm of the GUSTO trial,⁴ a large number of patients did not achieve coronary reperfusion despite treatment with accelerated TPA and heparin.

Percutaneous transluminal coronary angioplasty (PTCA) may be superior to thrombolytic therapy in achieving coro-

FIG. 1 Mean levels of myoglobin in reperfused (—●—) and non-reperfused (---+---) patients.

nary patency and in improving clinical outcome.^{15–17} The Primary Angioplasty in Myocardial Infarction Study Group¹⁵ randomized 395 patients who presented within 12 h of onset of myocardial infarction to either immediate angioplasty or intravenous TPA therapy. The in-hospital mortality rates in the TPA and PTCA groups were 6.5% and 2.6%, respectively. Reinfarction or death occurred in the in-hospital period in 12.0% of the TPA patients and 5.1% of the PTCA patients ($p = 0.02$). By 6 months, the respective figures were 16.8 and 8.5% ($p = 0.02$). Percutaneous transluminal coronary angioplasty following thrombolysis may be a therapeutic option in a subgroup of patients who do not achieve coronary reperfusion.

Myoglobin rises early after AMI^{10–12} and occurs universally in patients with sizable infarct, whereas only about 60% of infarct patients demonstrate ST-segment elevation on the ECG.^{8,9} Compact and highly automated rapid myoglobin analyzers are now available which yield quantitative results within 10 min of blood collection;^{10,11} these analyzers are suitable for use by trained clinical staff.¹³ The release kinetics of patients with reperfusion are expected to be more accelerated than in those without reperfusion. Our results confirm this, with significantly more reperfused patients at least doubling their myoglobin levels 1 h after initiation of streptokinase. Our results are in accord with those of Laperche *et al.*¹⁸ who studied 20 patients with AMI treated with intravenous thrombolysis. They measured myoglobin and CK-MM₁ and CK-MM₃ isoforms serially and showed that the rates of increase in myoglobin and CK-MM₃ are higher in patients who achieve reperfusion. They could not compare the time from thrombolysis to enzyme peak because the non-reperfused patients were treated with rescue angioplasty. Their later study¹⁹ showed that a good diagnostic performance was achieved by a relative increase in myoglobin, especially in infarct patients who were thrombolized > 3 h after the onset of symptoms. The diagnostic performance of myoglobin was less susceptible to small changes in the diagnostic threshold value compared with troponin T and MM₃/MM₁ creatine kinase isoforms. The study by Hohnloser *et al.*²⁰ did not involve rescue angioplasty. It showed that patients with reperfusion had an earlier CK peak than those without reperfusion. Using a threshold of 12 h from thrombolysis to CK peak, the sensitivity, specificity, and the positive and negative predictive values were 84, 95, 98, and 64%, respectively. To be useful, however, reintervention must be considered much earlier. Our study supports Hohnloser *et al.*'s finding that the time to peak myoglobin is significantly lower in reperfused patients. In addition, our results show that reperfusion can be determined much earlier. Both of these studies assessed coronary patency by early angiography. Myoglobin, CK-MM, and even CK-MB are found in significant quantities in the skeletal muscle. Trauma at the time of angiography may cause release of these proteins from the skeletal muscle into the circulation. We, therefore, chose not to perform early angiography in these patients.

Instead, 50% ST-segment reduction at 3 h after initiation of thrombolytic therapy was used. Many studies have shown ST-segment reduction to be a useful predictor of reperfu-

sion,^{5–7} despite the fact that some studies were based on coronary angiography that was delayed from 3 to 12 days after AMI.^{21–23} Studies based on early coronary angiography (60 min to 8 h post infarction) demonstrated an even better predictive accuracy for reperfusion.^{6,7,24}

Conclusion

The results of this study suggest that serial rapid measurement of myoglobin is a useful noninvasive tool for assessing coronary artery reperfusion. This should be helpful in identifying patients who may need further intervention following thrombolytic therapy.

References

1. GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico): Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;i:397–402
2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;ii:349–360
3. GUSTO Investigators: An international randomized trial comparing thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673–682
4. Ross AM, for The GUSTO angiographic investigators: The effects of tissue plasminogen activator, streptokinase or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615–1622
5. Blanke H, Schereff F, Karsch KR, Levine RA, Smith H, Rentrop P: Electrocardiographic changes after streptokinase-induced recanalization in patients with acute left anterior descending artery obstruction. *Circulation* 1983;68:406–412
6. Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS: Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction: Use of the ST segment as a noninvasive marker. *Br Heart J* 1988;60:275–280
7. Saran RK, Been M, Furniss SS, Hawkins T, Reid DS: Reduction in ST-segment elevation after thrombolysis predicts either coronary reperfusion or preservation of left ventricular function. *Br Heart J* 1990;64:113–117
8. Yusuf S, Pearson M, Sterry H, Parish S, Eamsdale D, Rossi P, Sleight P: The entry ECG in the early diagnosis and prognostic stratification of patients with acute myocardial infarction. *Eur Heart J* 1984;5:690–696
9. Rude RE, Poole WK, Muller JE, Tuzi Z, Rutherford J, Parker C, Roberts R, Raabe DS Jr, Gold HK, Stone PH, Willerson JT, Braunwald E: Electrocardiographic and clinical criteria for recognition of acute myocardial infarction based on analysis of 3,697 patients. *Am J Cardiol* 1983;52:936–942
10. Lee HS, Cross SJ, Garthwaite P, Dickie A, Ross I, Walton S, Jennings K: The value of novel rapid myoglobin, creatine kinase and creatine kinase-MB analysis in the diagnosis of acute myocardial infarction: Comparison with the electrocardiogram. *Br Heart J* 1994;71:311–315
11. Lee HS, Cross SJ, Garthwaite P, Jennings K: Rapid exclusion of acute myocardial infarction in patients without ST elevation using serial cardiac enzyme analysis with novel analyzers (abstr). *Br Heart J* 1992;68:107
12. Ohman EM, Casey C, Bengtson JR, Pryor D, Tormey W, Horgan JH: Early detection of acute myocardial infarction: Additional di-

- agnostic information from serum concentrations of myoglobin in patients without ST elevation. *Br Heart J* 1990;63:335-338
13. Lee HS, Jamieson M, Cross SJ, Jennings K: Rapid nursing analysis of myoglobin, creatine kinase and creatine kinase-MB enzymes can aid the diagnosis of myocardial infarction—an extended role for the nurses? (abstr). *Eur Heart J* 1993;14(suppl):114
 14. Clemmensen P, Ohman EM, Sevilla DC, Wagner NB, Quigley PS, Grande P, Wagner GS: Importance of early and complete reperfusion to achieve myocardial salvage after thrombolysis in acute myocardial infarction. *Am J Cardiol* 1992;70:1391-1396
 15. Grines CL, Browne KF, Marco, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC, Ronald E, Vlietstra MD: A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1993;328:673-679
 16. Zijlstra F, Jan De Boer M, Hoorntje JCA, Reijfers S, Reiber JHC, Suryapranata H: A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;328:680-684
 17. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfensperger RN, Gersh BJ: Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. *N Engl J Med* 1993;328:685-691
 18. Laperche T, Steg PG, Benessiano J, Dehoux M, Juliaed JM, Himbert D, Gourgon R: Patterns of myoglobin and MM creatine-kinase isoforms release early after intravenous thrombolysis or direct percutaneous transluminal coronary angioplasty for acute myocardial infarction, and implications for the early noninvasive diagnosis of reperfusion. *Am J Cardiol* 1992;70:1129-1134
 19. Laperche T, Steg PG, Dehoux M, Benessiano J, Grollier G, Aliot E, Mossard JM, Aubry P, Coisne D, Hanssen M, Lliou MC for the PERM Group: A study of biochemical markers of reperfusion early after thrombolysis for acute myocardial infarction. *Circulation* 1995;92:2079-2086
 20. Hohnloser SH, Zabel M, Kasper W, Meinertz T, Just H: Assessment of coronary artery patency after thrombolytic therapy: Accurate prediction utilizing the combined analysis of three noninvasive markers. *J Am Coll Cardiol* 1991;18:44-49
 21. Bossaert L, Conraads H, Pintens H, and the Belgian EMS study group: ST-segment analysis: A useful marker for reperfusion after thrombolysis with APSAC? *Eur Heart J* 1991;12:357-362
 22. Hackworthy RA, Vogel MB, Harris PJ: Relationship between changes in ST-segment elevation and patency of the infarct-related coronary artery in acute myocardial infarction. *Am Heart J* 1986;112:279-284
 23. Barbash GI, Roth A, Hod H, Miller HI, Rath S, Har-Zahav Y, Modan M, Seligsohn U, Battler A, Kaplinsky E, Robinowitz B, Laniado S: Rapid resolution of ST elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase (recombinant tissue-type plasminogen activator): Results of the Israeli study of early intervention in myocardial infarction. *Br Heart J* 1990;64:241-247
 24. Clemmensen P, Ohman EM, Sevilla DC, Peck S, Wagner NB, Quigley PS, Grande P, Lee KL, Wagner GS: Changes in standard electrocardiographic ST-segment elevation predictive of successful reperfusion in acute myocardial infarction. *Am J Cardiol* 1990;66:1407-1411

Clin. Cardiol. 20, 762-766 (1997)

Direct Conversion of Atrial Flutter to Sinus Rhythm with Low-Output, Short-Duration Transesophageal Atrial Pacing

HIDEHIKO AJISAKA, M.D., TATSURO HIRAKI, M.D., HISAO IKEDA, M.D., ICHIRO KUBARA, M.D., TERUHISA YOSHIDA, M.D., MASANOBU OHGA, M.D., TSUTOMU IMAIZUMI, M.D.

The Third Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan

Summary

Background and hypothesis: Transesophageal atrial pacing (TAP) is useful for terminating paroxysmal non-selfterminating atrial flutter (PAF); however, high output pacing of long

stimulus duration causes severe symptoms such as chest pain. The objective of this study was to investigate the effect of low-output, short-duration TAP on the conversion of PAF.

Methods: We applied low-output (within 15 mA with a pulse duration of 10 ms), short-duration (within 4 s) TAP in 31 patients (50 ± 19 years) with PAF. Transesophageal pacing was delivered with 10 pulses of burst pacing at intervals that were 20 ms shorter than those of the flutter wave length. When the conversion was unsuccessful, we delivered 20 pulses of burst pacing.

Results: Sixteen patients (52%) were converted directly to sinus rhythm and 12 (38%) to atrial fibrillation. Transesophageal pacing was ineffective in 3 (10%) patients. The duration of atrial flutter, maximum flutter wave amplitude, effective pacing intervals, underlying heart diseases, and cardiac function were not different between patients who had direct conversion to sinus rhythm and those converted to atrial fibrilla-

Address for reprints:

Tatsuro Hiraki, M.D.
The Third Department of Internal Medicine
Kurume University School of Medicine
67 Asahi-machi
Kurume 830, Japan

Received: March 21, 1997

Accepted with revision: June 16, 1997