Myoglobin—A Marker of Reperfusion and a Prognostic Indicator in Patients with Acute Myocardial Infarction

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Summary

Background: Early noninvasive identification of patients with occluded infarct-related arteries after thrombolysis has important prognostic and therapeutic implications. Recent reports indicate that plasma kinetics of cardiac marker proteins could be very useful in diagnosis of myocardial reperfusion. Although angiographic assessment remains the ideal procedure for determining patency, it is expensive, invasive, not within the reach of most patients in developing countries, and the long-term follow-up data are still sparse.

Hypothesis: The present study was undertaken to investigate whether plasma kinetics of myoglobin in conjunction with clinical markers and another biochemical marker, creatine kinase, could be used to predict myocardial reperfusion more accurately and to investigate the correlation between myoglobin release after thrombolysis and mortality in patients with acute myocardial infarction (AMI) over a follow-up period of 18 months.

Methods: Eighty-three consecutive patients with AMI receiving streptokinase treatment were studied for plasma kinetics of myoglobin in conjunction with clinical markers and creatine kinase to predict reperfusion and were followed for a period of 18 months.

Results: Increased baseline mean $\pm$ standard deviation levels of myoglobin were observed among “nonresponders” to

streptokinase treatment compared with “responders” ($469 \pm 386 \mu\text{g/l}$ vs. $270 \pm 211 \mu\text{g/l}$). There was significantly more release of myoglobin following thrombolytic treatment among the responders than among the nonresponders (mean ratio of myoglobin levels at 90 min to 0 min 6.01 ± 9.2 vs. 1.03 ± 0.64). In a follow-up of 61 patients over a period of 18 months, 31% mortality was observed in the nonresponder group compared with 11.7% in the responder group. In responders, the mean ratio of myoglobin levels at 90 and 0 min was significantly less among those who died ($p = 0.019$) than among those who survived.

Conclusion: A myoglobin release profile in combination with other clinical markers offers inexpensive, noninvasive, and a reasonably reliable way of assessing coronary artery patency after thrombolytic treatment.

Key words: myoglobin, acute myocardial infarction, thrombolytic therapy, streptokinase, prognostic marker, reperfusion

Introduction

Early noninvasive identification of patients with occluded infarct-related arteries after thrombolysis has important prognostic and therapeutic implications.¹ Recent reports indicate that plasma kinetics of cardiac marker proteins, such as myoglobin, tropomyosin-binding component troponin T, and creatine kinase (CK), could be very useful in the diagnosis of myocardial reperfusion.^{2–11} Although angiographic assessment remains the ideal procedure for determining patency of infarct-related arteries, the procedure is expensive, invasive, and not within the reach of most patients in developing countries. Moreover, the long-term follow-up data on the outcome of such patients are still sparse.

The present study was undertaken to investigate whether plasma kinetics of myoglobin in conjunction with clinical markers and another biochemical marker, CK, could be used for predicting myocardial reperfusion more accurately. In addition, the study also aims at finding out whether there is any correlation between myoglobin release after thrombolysis and mortality in patients with acute myocardial infarction (AMI) over a follow-up period of 18 months.

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Patients and Methods

Eighty-three consecutive Pakistani patients with AMI receiving thrombolytic therapy with streptokinase (SK) were included in this study. All patients were admitted to the coronary care unit of The Aga Khan University Hospital between June 1998 and October 1999. The study had been approved by the Ethical Committee of The Aga Khan University. Demographic and clinical characteristics of the patients are shown in Table I.

Diagnosis of the patients was made on the basis of clinical history, electrocardiogram (ECG), and biochemical data. The patients had no recent history of streptococcal infection. Patients who had previous treatment with SK were excluded from the study. Patients with typical chest pain of ≥ 30 min duration, unresponsive to nitrates, and with ECG ST-segment elevation of ≥ 0.1 mV in at least two limb leads or ≥ 0.2 mV in at least two contiguous chest leads, were considered eligible for thrombolytic therapy.

Thrombolytic Therapy with Streptokinase

A dose of 1.5 million units of SK was administered intravenously over a period of 60 min, and the patients were assessed for clinical response to SK over a period of 90 min.

Clinical Assessment of Patients for Response to Streptokinase Treatment

Response to SK treatment was assessed using the criteria used by Kircher *et al.*¹² along with serum marker and CK activity as described by Zabel *et al.*² and Hohnloser *et al.*¹³ Briefly, the criteria used were as follows:

1. Resolution of chest pain < 90 min after the start of thrombolysis.
2. A $> 50\%$ reduction of ST-segment elevation in the two contiguous leads showing maximal elevations in a 12-lead ECG tracing.
3. Reperfusion arrhythmia, defined as arrhythmia noted during a 90 min period after SK treatment. The arrhythmias, which were considered suggestive of reperfusion, included accelerated idioventricular or junctional rhythm, paroxysmal sinus bradycardia (< 50 beats/min), second- or third-degree atrioventricular block, ventricular tachycardia, and ventricular fibrillation.
4. Creatine kinase activity: Blood samples collected before the initiation of thrombolysis and after 90 min of treatment were analyzed for CK activity. Slope of increase over a 90 min period after thrombolysis was calculated as: $\text{Slope} = T_{90} - T_0 / 1.5 \text{ h}$, where T_{90} is the value of CK in international units per liter at 90 min and T_0 is the value of CK before thrombolysis. The ratio T_{90}/T_0 was also calculated. A slope $> 60 \text{ U.l}^{-1} \cdot \text{h}^{-1}$ and a value of $T_{90}/T_0 > 1.9$ were considered a positive parameter for the response. All patients who fulfilled at least three components of the above-mentioned criteria were considered as "responders" to therapy, while those who were positive for two markers for reperfusion were classified as "probable responders." Patients who were negative for three or all four markers for reperfusion were considered to be "nonresponders."

As an example, individual values of the four components of the above-mentioned criteria in "responders" have been listed in Table II. It is evident that all 34 patients were positive for three or all four markers for reperfusion. Maximum variation was observed in the component of reperfusion arrhythmias.

Blood Collection

Ten ml blood was collected from each patient immediately before thrombolytic therapy. Five ml aliquot was transferred to a tube containing ethylene diamine tetraacetic acid (EDTA) as anticoagulant. Plasma was immediately removed from it by centrifugation at $1500 \times$ gravity for 15 min and stored frozen at -60°C until the time of analysis of myoglobin. The other 5 ml aliquot was allowed to clot, and serum was removed for CK activity. After 90 min, another 10 ml blood was collected from the patient. Plasma was removed for assay of myoglobin while serum was analyzed for CK activity.

Determination of Myoglobin Levels in Plasma

Myoglobin levels immediately before thrombolysis (0 min) and at 90 min after SK treatment were determined using an enzyme-linked immunosorbent assay (ELISA) developed in our laboratory. Monospecific antiserum to human myoglobin was obtained from Sigma Chemical Co. (St. Louis, Mo., USA). The procedure used was similar to the one described earlier.¹⁴

TABLE I Demographic and clinical characteristics of patients with acute myocardial infarction

Variable	Value	Frequency (%)
Age (years)	57.6 ± 11.7 (range 40–79)	
Sex		
Male	64	77
Female	19	23
Weight (kg)	68 ± 10	
Hematocrit	40.2 ± 5.5	
Prior history of MI	7	8.4
Interval between onset of symptoms and thrombolytic treatment (h)	3.14 ± 2.3	
MI location		
Anterior	37	45
Inferior and/or posterior	45	54
Others	1	1

Values are mean $\pm$ standard deviation.

Abbreviation: MI = myocardial infarction.

TABLE II Values of the four components of the criteria used for the assessment of response to streptokinase in responders

Patient No.	Resolution of chest pain within 90 min	Resolution of ECG changes	Reperfusion arrhythmias	CK-activity		Total score (out of 4)
				T90-T0/1.5 ($>60\text{U}\cdot\text{l}^{-1}\cdot\text{h}^{-1}=+$)	T90/T0 ($>1.9=+$)	
1	+	+	-	386	7.59	3
2	+	+	-	85	3.13	3
3	+	+	-	128	4.2	3
4	+	+	+	1,550	38.5	4
5	+	+	+	1,435	8.6	4
6	+	-	+	3.1	3.4	3
7	+	+	+	566	12.4	4
8	+	-	+	350	3.7	3
9	+	+	-	886	5.5	3
10	+	+	+	275	4.0	4
11	+	+	-	533	3.69	3
12	+	+	+	1,458	27.6	4
13	+	+	+	250	3.1	4
14	+	+	-	758	67.8	3
15	+	+	+	115	3.9	4
16	+	+	-	168	5.8	3
17	+	+	-	160	2.1	3
18	+	+	+	1,197	29.9	4
19	+	+	+	468	6.6	4
20	+	+	+	490	6.2	4
21	+	+	-	249	5.3	3
22	+	+	-	270	9.2	3
23	+	+	+	580	6.2	4
24	+	+	-	243	3	3
25	+	+	-	273	4.3	3
26	+	+	+	500	6.1	4
27	+	+	-	688	7.3	3
28	+	+	-	874	9.1	3
29	+	+	-	494	10.5	3
30	+	+	+	348	7.2	4
31	+	+	-	221	3.5	3
32	+	+	-	346	2.4	3
33	+	+	-	1,345	4.3	3
34	+	+	+	485	9.2	4

Number of patients with score of 3 = 20.

Number of patients with score of 4 = 14.

Abbreviations: CK = creatine kinase, ECG = electrocardiogram, + = yes, - = no.

The concentration of myoglobin was expressed in $\mu\text{g/l}$. The procedure has been validated using a commercially available kit based on immunoturbidimetric assay for myoglobin (Turbiquant® myoglobin, Behring Diagnostics GmbH, Marburg, Germany).

Statistical Analysis

Mean values are presented as means $\pm$ standard deviation (SD). Comparison of the two means was carried out by using paired *t*-test. One-way analysis of variance (ANOVA) followed by Tukey's "Honestly Significant Difference" (HSD) test was used for comparison of the mean values of more than

two groups. Comparison of the proportions was by chi-square analysis. A *p* value of <0.05 was considered significant.

Results

Table III shows plasma myoglobin levels at two time periods (just before and 90 min after SK treatment) and response to thrombolytic treatment. Among responders and probable responders, the baseline values were nearly the same. However, baseline values of myoglobin were significantly higher (*F*-statistic 1201, *p* = 0.0001) among nonresponders than among responders and probable responders. Since myoglobin

TABLE III Plasma myoglobin levels and response to streptokinase in patients with myocardial infarction

Group	No. of patients	Myoglobin ($\mu\text{g/l}$)		F-statistic	p Value ^a
		0 Min	90 Min		
Patients showing response to SK	34	270 $\pm$ 211	788 $\pm$ 744	4.285	0.0001
Patients showing partial response to SK	33	243 $\pm$ 220	629 $\pm$ 786	3.26	0.003
Patients showing no response to SK	16	469 $\pm$ 386	392 $\pm$ 208	0.117	0.908

Values are mean $\pm$ standard deviation.

^a Compares myoglobin levels at 0 min and 90 min within each group using paired *t*-test.

Abbreviation: SK = streptokinase.

begins to appear in peripheral blood 2–3 h after the onset of pain, this increased baseline level of myoglobin among nonresponders could be due to a longer time interval between onset of pain and thrombolytic treatment in this group. This is further supported by the fact that the mean $\pm$ SD time intervals between onset of symptoms and treatment with SK was found to be 4.45 $\pm$ 3.7 h, 3.03 $\pm$ 2.1 h, and 2.72 $\pm$ 1.4 h in nonresponders, probable responders, and responders, respectively. Moreover, this delayed time to thrombolytic treatment among nonresponders was significantly different ($p = 0.0006$) from the mean time interval among responders and probable responders when compared using one-way ANOVA followed by Tukey's HSD test. Table III also shows that when the mean values of myoglobin concentration in patients at two time periods were compared using the paired *t*-test, the values were found to be significantly different in responders ($p = 0.0001$) and probable responders ($p = 0.003$). However, no significant difference between the mean values was found in nonresponders ($p = 0.908$).

Table IV shows the ratio of plasma myoglobin levels at 90 and 0 min after thrombolytic therapy and response to SK treatment. The mean ratios among the responder, probable responder, and nonresponder groups were 6.01 $\pm$ 9.2, 3.02 $\pm$ 2.4, and 1.03 $\pm$ 0.64, respectively. When the mean values among the three groups were compared by one-way ANOVA followed

TABLE IV Ratio of plasma myoglobin levels at 90 and 0 min after thrombolytic therapy and response to streptokinase treatment in patients with acute myocardial infarction

Group	No. of patients	Myoglobin levels at 90 min	
		Myoglobin levels at 0 min	p Value ^a
Responders	34	6.01 $\pm$ 9.2	—
Probable responders	33	3.02 $\pm$ 2.4	0.117
Nonresponders	16	1.03 $\pm$ 0.64	0.023

Values are mean $\pm$ standard deviation.

^a Compares responders with probable responders and nonresponders using one-way ANOVA followed by Tukey's HSD test for multiple comparisons (one-way ANOVA p value = 0.019; F-statistic 4.148).

Abbreviation: ANOVA = analysis of variance.

by Tukey's HSD test for multiple comparisons, the ratio in the nonresponders was found to be statistically significant (one-way ANOVA $p = 0.019$; F-statistic = 4.148).

In a follow-up of patients in the three groups over a period of 18 months, the clinical outcomes in terms of cardiac death and reinfarction were studied. As expected, maximum mortality (31%) was observed in the nonresponder group compared with 16.7% in the probable responder group and 11.7% in the responder group (Table V); however, the values were not found to be statistically significant. A similar trend was also observed regarding reinfarction, which was 12.5% in nonresponders, 4.2% in probable responders, and 3.8% in responders.

Table VI shows the percent of patients who required revascularization among the three groups. Of the patients in the responder group, 58% required revascularization as against only 12.5% in the nonresponder group. A comparison of the proportions in the three groups by chi-square analysis re-

TABLE V Clinical outcomes (cardiac death and reinfarction) in responders, probable responders, and nonresponders to streptokinase treatment

Outcomes	Responders (n = 26)	Probable responders (n = 24)	Non-responders (n = 16)	p Value ^a
Death (%)	11.5	16.7	31	0.266
Reinfarction (%)	3.8	4.2	12.5	—

^a Comparison of proportions by chi-square analysis.

TABLE VI Revascularization in responders, probable responders, and nonresponders to streptokinase treatment

Group	Number (n)	Revascularizations (%)
Responders	26	57.7 ^a
Probable responders	24	37.5
Nonresponders	16	12.5

^a Comparison of proportions was carried out using the chi-square test. The responders group was significantly different from the nonresponder group. p Value = 0.0101; chi-square = 8.537.

vealed a statistically significant difference ($p = 0.0101$; chi-square 8.53).

To answer the question of whether there is any association between myoglobin release kinetics and mortality among the three groups of patients who underwent thrombolysis, the mortality and survival figures in each group were compared with the corresponding ratios of myoglobin levels at 90 and 0 min (Table VII).

In responders, the ratio of myoglobin levels at 90 and 0 min was significantly less among those who died ($p = 0.019$) than among those who survived, indicating that the myoglobin release profile during thrombolysis might be of value in predicting prognosis of the disease.

Discussion

Reperfusion of the infarct-related artery is the frontline approach in the management of patients with AMI. Globally, SK is still the most widely used thrombolytic agent, as other thrombolytic agents, namely, tissue plasminogen activator (t-PA), are very expensive and not easily available in many third-world countries such as Pakistan. Streptokinase has proved its efficacy in achieving coronary patency, preserving left ventricular function and improving survival rates;¹ however, nearly one-third of patients receiving SK fail to achieve successful reperfusion.¹⁵ The commonly used clinical criteria to predict the need for recanalization of the infarct coronary artery include reduction of chest pain, decrease in ECG ST-segment elevation, and occurrence of reperfusion arrhythmias.⁵ However, in several trials using these criteria, predictability of reperfusion often proved insufficient.¹⁶ As reported by Laperche *et al.*,³ predictability of patency of the infarct-related artery could be enhanced by combining clinical criteria with some biochemical markers.

In the present study, we investigated the role of release kinetics of myoglobin after thrombolysis to assess reperfusion in 83 patients with AMI. Forty percent of our patients responded to SK therapy, while 40% were probable responders and 19% appeared to have no response. These results conform well to

those reported by Shaila *et al.*,¹⁷ who have shown complete reperfusion in 48% of their patients, probable reperfusion in 28%, and no reperfusion in 28%. In another study, Hogg *et al.*¹⁸ have shown 53% reperfusion at 90 min from the start of therapy with SK.

On the basis of our observation that there were significantly higher baseline levels of myoglobin in patients who failed to respond to SK treatment (Table III), it is possible that there was a larger size infarct in these patients. Grenadier *et al.*¹⁹ and Groth *et al.*²⁰ have reported that myoglobin can serve as an invaluable aid in the diagnosis of infarct extension. Another possible reason for the higher baseline value of myoglobin in nonresponders could be an increased time interval between onset of symptoms and thrombolytic treatment in these patients compared with the patients in the responder and probable responder groups. This notion is further strengthened by our findings that there was a significant delay in getting thrombolytic treatment to the nonresponders compared with the patients in the responder and probable responder groups (4.45 ± 3.7 vs. 2.72 ± 1.4 and 3.03 ± 2.1 h, respectively). This time delay in the nonresponder group also appears to affect survival, as the mortality rate was greatest (31%) in this group (Table V). This points to an important and significant problem in effective treatment of patients with AMI in countries such as Pakistan. In our study population, the delay in treatment was due to late arrival of patients in the hospital as our "door to needle time" was approximately 120 min.²¹ Late recognition of symptoms and delays in transportation may have contributed to this delayed arrival. As early treatment of AMI is imperative for mortality and morbidity reduction, steps need to be taken at the community level to increase awareness and improve accessibility.

To determine the clinical outcomes of thrombolytic treatment in patients with AMI was an important component of this study. We successfully followed 66 patients over a period of 18 months; 17 patients were lost to follow-up.

Overall mortality in the SK-treated patients was 18.1%, which compares well with a previously published study from this hospital.²¹ These investigators reported 19.5% mortality in this group over a period of 1 month. However, our follow-up of patients with AMI was over a period of 18 months. The

TABLE VII Ratio of myoglobin levels at 90 and 0 min after thrombolytic treatment in different groups of patients with acute myocardial infarction who died or survived at 18 months follow-up after streptokinase treatment

Group		No. of patients	Myoglobin level at 90 min	p Value ^a	F-statistic
			Myoglobin level at 0 min		
Responders	Dead	3	1.44 ± 0.74	0.0197	6.11
	Alive	23	5.46 ± 7.59		
Probable responders	Dead	4	2.12 ± 2.42	0.196 (NS)	1.76
	Alive	20	3.31 ± 2.73		
Nonresponders	Dead	5	1.04 ± 0.84	0.982 (NS)	0.00
	Alive	11	1.04 ± 0.58		

Values are mean ± standard deviation.

^a Mean values within each group were compared using analysis of variance.

Abbreviation: NS = not significant.

mortality rate in the present study, however, appears higher compared with the Global Use of Strategies To open Occluded coronary arteries (GUSTO) trial, in which mortality at 30 days was 4.4% among patients with normal coronary flow at 90 min and 8.9% among patients with no flow,¹ and the Intravenous n-PA for Treating Infarction Myocardium Early (In Time-II) trial, in which the mortality rate at 30 days was 3.3% among patients with a negative baseline myoglobin assay versus 8.9% in patients with a positive assay.²² Again, the reason for the difference could be that our patients were followed for a longer period of time.

The responders who died during the follow-up period were found to have had low ratios of myoglobin levels at 90 min to levels at 0 min after thrombolysis (Table VII), demonstrating that the myoglobin release profile during thrombolysis might be of value in predicting prognosis of the disease. It also indicates that the criteria we used (in the absence of angiography) to predict reperfusion might not have been as perfect as one would have expected, and the patients with low myoglobin released during thrombolysis should have been classified as nonresponders. This lends further support to our above-mentioned results, indicating that myoglobin could serve as a reliable noninvasive marker for assessing reperfusion. Recently, Tanasijevic *et al.*²³ have also reported the probability of a patent infarct-related artery to be 90% in patients with a 60-min myoglobin ratio ≥ 4 . Miyata *et al.*²⁴ have also shown that the rate of increase in myoglobin was significantly higher in the reperfused than in the nonreperfused group. According to these authors, when reperfusion is evaluated on the basis of a cut-off level of the ratio of myoglobin levels at 15 min ≥ 2 , then the predictive accuracy of myoglobin is close to 95%.

Another study by Stewart *et al.*⁶ reported that a simple measurement of an increased serum concentration of myoglobin at 60 and 90 min can accurately predict failure to achieve Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow in the infarct-related artery at 90 min.

All of these reports, along with the data in our study, suggest that the myoglobin-release profile during thrombolysis is a reliable noninvasive marker of reperfusion and could be used to predict patency of an infarct-related artery fairly accurately when used along with other clinical markers. It is important to mention that myoglobin estimation alone may not correctly identify those who will benefit from thrombolytic therapy.²⁵

In the present study, 58% of patients in the responder group required revascularization during follow-up compared with 12.5% in the nonresponder group. It is not an unexpected finding, as successful thrombolytic treatment is likely to salvage myocardium that may remain ischemic due to underlying high-grade stenosis in the infarct-related artery, thus requiring a revascularization procedure.

Conclusion

To date, the most reliable determination of reperfusion status is only possible by coronary angiography; however, this technique is expensive and mostly unavailable in an emergen-

cy setting. In a third-world country such as Pakistan, the technique is beyond the reach of most people. Therefore, it is extremely important to have reliable noninvasive markers for detection of coronary reperfusion after thrombolysis in patients with AMI. Myoglobin release profile in combination with other clinical markers offers an inexpensive, noninvasive, and reasonably reliable way of assessing coronary artery patency after thrombolytic therapy. Myoglobin levels at admission also appear to have prognostic significance. On the basis of our data on follow-up of our patients over a period of 18 months, it appears that a rise in myoglobin levels after thrombolysis has a better correlation with long-term outcome than other noninvasive markers of reperfusion.

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Images in Cardiology: Left Main Coronary to Pulmonary Artery Fistula Causing Steal Phenomenon

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FIG. 1 Right oblique view of fistula during diastole. Steal phenomenon in the LAD (arrows) and concomitant fistula flow into the pulmonary artery are shown (arrowhead).

FIG. 2 Doppler color flow imaging shows the turbulent jet of the fistula into the pulmonary artery during diastole. Pulsed Doppler imaging of the fistula revealed diastolic flow.

A 40-year-old man presented with recurrent postmyocardial infarction angina, left anterior descending (LAD) stenosis, and left main coronary artery (LMCA) to pulmonary artery fistula. Angina persisted despite optimal medication. Physical examination revealed a diastolic murmur over the pulmonary region. Coronary angiography revealed severe LAD stenosis

and LMCA-pulmonary artery fistula (Fig. 1, arrowhead). Steal in the LAD was clearly observed (Fig. 1, white arrows) during diastolic flow of the fistula. Echocardiography showed retrograde turbulent color Doppler jet within the main pulmonary artery (Fig. 2). Recurrent angina was attributed to the LMCA-pulmonary artery fistula.