Serum myoglobin in acute myocardial infarction: A clinical study and review of the literature

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The diagnosis of acute myocardial infarction (AMI) is made conventionally on the basis of the clinical history, serial electrocardiograms, and serum enzyme changes. This approach suffices in the majority of instances. However, recent enthusiasm for early intervention to reduce infarct size and the attempt to optimize coronary care utilization on a cost-effective basis has raised the need for early, sensitive, and specific indicators of myocardial necrosis.

Recent reports have suggested that elevations of serum myoglobin (SMb) might provide such a parameter and permit estimation of prognosis and infarct size.[1-3] However, a recent editorial has questioned the value of SMb in assessing suspected myocardial injury.[4]

We report here a study of serum myoglobin in a consecutive series of patients with suspected acute myocardial infarction (AMI), and in several other noncardiac conditions. The sensitivity, specificity, and practical value of SMb are discussed in relation to a review of the literature.

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Table I. A rating system for suspicion of acute myocardial infarction (AMI)*

	Points		
Criteria	*0*	*1*	*2*
Chest pain	None	Atypical	Typical pain
ECG changes	No changes	Non-specific ST-T changes	New Q waves evolutionary ST-T changes
Enzyme changes	None	Transient slight elevation	Sequential rise and fall of levels

*Interpretation: 5 to 6 points = Definite AMI; < 5 points = No definite AMI.

Materials and methods

Sixty consecutive patients admitted to an intensive care unit with the initial diagnosis of possible AMI were studied. The diagnosis of AMI was established by a rating scale including chest pain, ECG changes, and enzyme elevations (Table I). Each case was evaluated for acute myocardial infarction by two independent observers without prior knowledge of the myoglobin data. Patients with 5 to 6 points on this rating scale were judged to have a definite AMI (Group 1) and the others were classified as having no definite MI (Group 2).

In all cases, the information which was recorded included age, sex, previous history of AMI, angina, heart failure, valvular disease, renal

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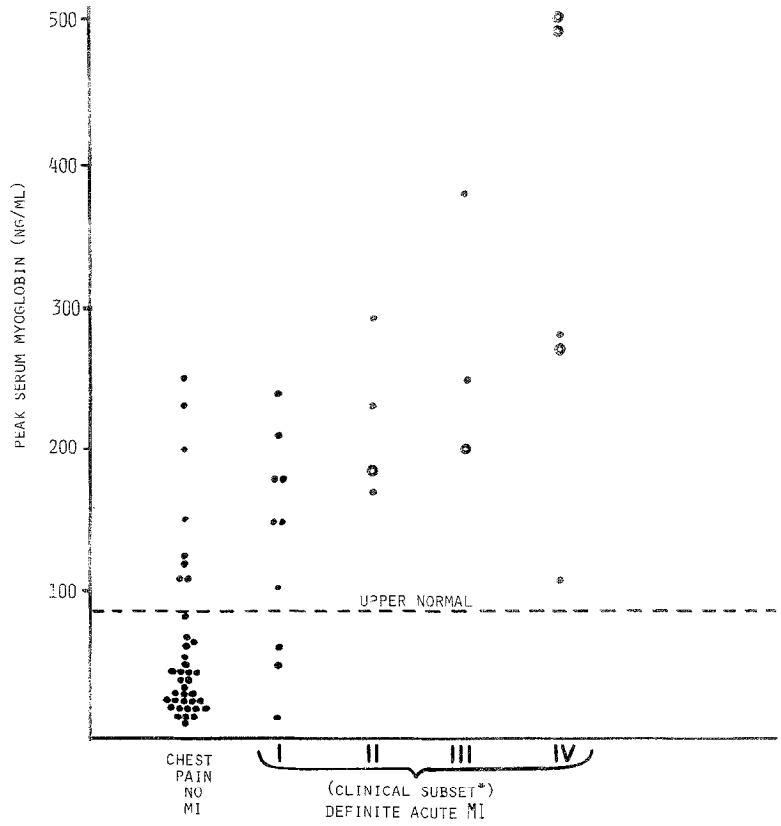

Fig. 1. Serum myoglobin in acute myocardial infarction. ● = alive at two weeks; ○ = dead at two weeks.* see *Table II.*

Table II. Definition of clinical subsets in acute myocardial infarction*

Subset	*Pulmonary† congestion*	*Peripheral‡ hypoperfusion*
I	−	−
II	+	−
III	−	+
IV	+	+

*After Forrester et. al.[5]
†‡See text for clinical criteria.

Table III. Profile of patients studied

Group	*Points**	*Number of cases*		*%*	*Sex*	*Age ± S.D.*
No definite AMI	1	10	38	63%	22 M 16 F	63.34 ± 14.27
	2	19				
	3	5				
	4	4				
Definite AMI	5	9	22	37%	14 M 8 F	63.41 ± 12.71
	6	13				

*See Table I.

disease, diabetes mellitus, liver disease, peripheral vascular insufficiency, alcohol abuse, or seizure disorder. There was also elicited information regarding recent history of unusual physical exertion, musculoskeletal trauma, seizures, intramuscular injections, alcohol, or drug intake. Careful inquiry was made as to the exact time of onset of the present episode of chest pain or discomfort. Complete physical examination was recorded with special attention to evidence of hypoperfusion (oliguria, altered mentation, skin changes, low BP or tachycardia), pulmonary congestion (rales, tachypnea, abnormal chest x-ray), presence of musculoskeletal trauma or peripheral vascular disease. Clinical and hemodynamic subsets were assigned according to the classification of Forrester[5] (Table II). All patients were evaluated and managed by a standard coronary care protocol, which included serial enzymes and electrocardiograms, and conventional blood chemistry. Intramuscular Demerol (meperidine)

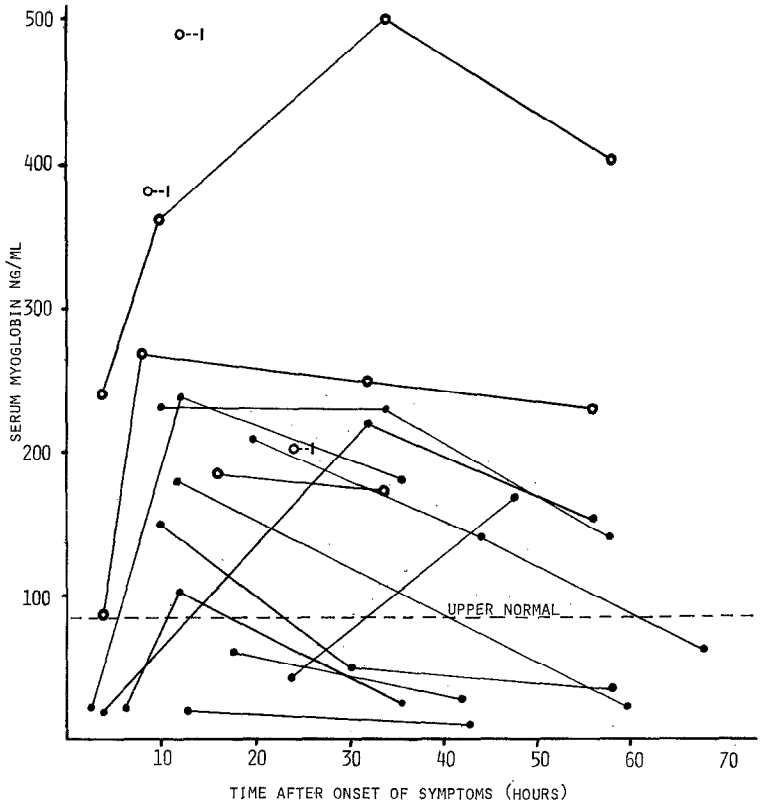

Fig. 2. Relationship of myoglobin levels to onset symptoms in acute myocardial infarction. ● = alive at two weeks; o = dead at two weeks; o–I = died shortly after sample collection.

was used for sedation and analgesia, and morphine for refractory pain. Patients in clinical subsets III and IV (i.e., with clinical evidence of hypoperfusion) had Swan-Ganz catheterization for measurement of pulmonary arterial wedge pressure. Management with diuretics, inotropic drugs, fluids, vasodilators and other agents followed accepted principles.[5] A record was kept of the number, route, type, and time sequence of administration of all medications. Details of cardiopulmonary resuscitations, defibrillation, and other procedures were recorded.

Patients with various other conditions were also studied including pre-and postoperative non-cardiac surgery (Group 3), critically ill patients in the intensive care unit without myocardial disease (Group 4), patients receiving multiple intramuscular injections (Group 5), and patients with heat stroke (Group 6).

In Groups 1 and 2 (acute or suspected myocardial infarction), samples were drawn by venipuncture upon admission (Day 1) and on Days 2 and 4 simultaneously with other conventional serial studies. In those cases where the time of onset of symptoms was reasonably certain (92 per cent of cases), the number of hours from onset was noted with each sample. Samples in the other groups were drawn at appropriate times. All samples were frozen at –20° C. for analysis in batches.

Serum myoglobin was determined by radioimmunoassay employing I^{125}-labelled myoglobin,* based on the method of Stone and colleagues[1] The assay was reproducible, sensitive, and specific. The normal value for serum myoglobin was 31 ± 25 ng./ml. A value of 85 ng./ml. is considered the extreme upper limit of normal.

All information was coded and analyzed.

Results

The profile of the population studied for possible AMI is indicated in Table III. Thirty-three per cent of patients (22 of 60) had definite AMI (Group 1), and 63 per cent (38 of 60) (Group 2) had equivocal or negative criteria. The two groups were comparable by age and sex distribution.

*From Nuclear Medicine Systems, Inc., Newport Beach, Cal. 92663.

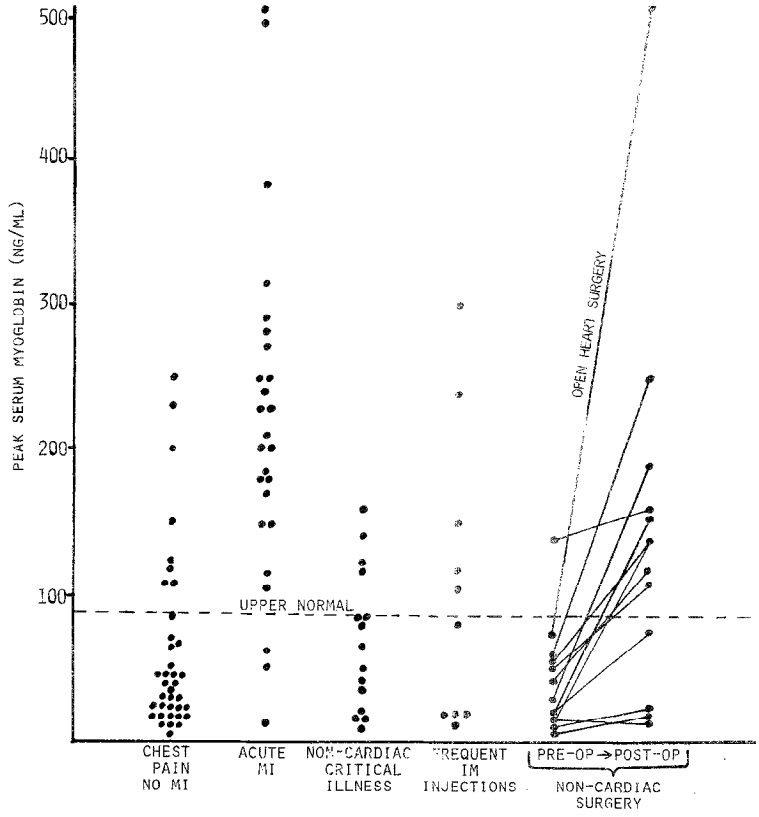

Fig. 3. Myoglobin levels in other conditions studied.

Fig. 1 shows actual myoglobin levels in the two groups. Values were significantly elevated in the group with acute myocardial infarction (172 ± 124.9 ng./ml.) ($p < 0.001$). There was a significant correlation of higher peak SMb values with higher clinical subsets. As expected, the immediate mortality rate (two weeks) was significantly lower in subsets I and II as compared with III and IV ($p < 0.01$) (Fig. 1).

Three patients with AMI failed to show significant elevations of SMb. All were in clinical subset I and had mild transient elevations of SGOT.

The exact time of onset of symptoms was known in 92 per cent of cases. Fig. 2 demonstrates SMb values as a function of total duration from the onset. Typically, elevations were noted at 6 to 8 hours. Early peaks were noted in two patients (less than 2 hours) and both died. Sustained elevation of SMb into the third day was associated with increased mortality ($p < 0.1$).

Twenty-one per cent of patients without definite evidence for AMI (1 to 4 points on the rating scale) showed peak myoglobin levels elevated above normal. There was no trend towards higher values in those patients with higher point ratings. Four of these patients had possibly alternative explanations for the rise in SMb (chronic renal failure, 3; trauma, 1). One patient had a final diagnosis of pericarditis secondary to a post-myocardial infarction syndrome.

Fig. 3 shows SMb values in the other groups of patients studied. Significant elevations were seen in postoperative (non-cardiac) states (58 per cent), heat stroke (100 per cent), critically ill patients in the intensive care unit without cardiac disease (27 per cent), and 50 per cent of those patients receiving frequent IM injections.

Discussion

Myoglobin is a low molecular weight heme protein synthesized and found exclusively in skeletal and cardiac muscle, and is immunochemically identical from the two sources.[5] Damage to either of these tissues would theorectically elevate serum myoglobin levels. Renal clearance is rapid, though variable, and hence, myoglobinemia following a single injury tends to be transient.[6]

Significant myoglobinuria following AMI has

Table IV. Reported studies of myoglobinemia in myocardial infarction

Reference	*Assay technique*	*Normal values of SMb. (ng./ml.)**	*Patient selection method*
Kagen et. al. 1975[2]	Complement fixation assay	Not detectable	Admissions to CCU†
Jutzy et. al. 1975[3] Abstract	Radio immunoassay (RIA)	20.9 ± 23.3	CCU admissions
Stone et. al. 1975[13]	RIA	6-85	CCU admissions (consecutive ?)
Stuart et. al. 1975[14] Abstract	RIA	Not detectable	Not specified
Klocke et. al. 1976[15] Abstract	RIA	25 ± 23 (5-75)	CCU admissions
Stone et. al. 1977[1]	RIA	31 ± 1.3 (SE) 6-85	CCU admissions
Kollman et. al. 1977[12] Abstract	RIA	NS < 75	Consecutive CCU admissions
Gilkeson et. al. 1978[19]	RIA	6-85	Patients with chest pain in Emergency room
Reichlin et. al. 1978[20]	RIA	25 ± 23	Admissions to CCU†
Present study	RIA	< 85	Consecutive CCU admissions

*Smb = Serum myoglobin values in ng./ml. ± 1 S.D.
†CCU = coronary care unit.
‡NS = not specified.
§AMI = acute myocardial infarction.

been reported in several studies.[7-11] However, urine myoglobin levels showed extreme variability with regard to the time course of excretion, and are poorly correlated with peak serum levels and severity of infarction.

Myoglobinemia following AMI was first reported by Kagen and colleagues,[2] utilizing a complement-fixation assay which would detect up to 30 ng./ml of SMb. Elevated levels over a wide range were demonstrated in 11 of 21 patients with conventional evidence of myocardial necrosis. Higher values tended to correlate with both increased severity of infarction and greater mortality. However, the assay technique tended to underestimate small quantities of myoglobin because of serum interference and normal persons had undetectable levels.

A sensitive, specific, and accurate radioimmunoassay for SMb was first reported by Stone and co-workers.[12] Currently accepted normal values for SMb are 31 + 50 (2SD) ng./ml., based on 135 normal subjects studied by this group. The highest value found in this population was 85 ng./ml. and this was considered the "upper limit of normal." Normal subjects studied by other groups showed similar results, with maximum values ranging from 75 to 85 ng./ml.[3, 13]

The available information on myoglobinemia following AMI in the English language literature is summarized in Table IV. Two factors make comparison of these studies difficult. First, with one exception,[14] none of the reports indicate whether the patient populations studied constituted random samples, consecutive series, or selected groups with suspected AMI. Secondly, while most studies analyzed the SMb values in

Sample collection		Serum myoglobin values				
		Acute myocardial infarctions			Chest pain, no AMI§	
Timing	Relationship to onset of symptoms	SMb.*	Elevated in	Peak values (hrs.)	SMb.*	Elevated in
On admission (5)-serial	NS‡	300 -3700	11/21 (52%)	?	Not Detectable	0/12 (0%)
Q1H × 6hrs Q3H × 12hrs Q2HH × 3days	Discussed in relation to onset of symptoms	216 -6800	30/30 (100%)	9-12hrs. from onset	2-88	0/20 (0%)
Variable serial in 9 patients	NS	380 ± 53 195 ± 47	18/20 (90%)	8-12hrs. from admission	41 ± 6	1/21 (4.8%)
Q1H × 12hrs 24hrs–from 48hrs onset	NS	46-200	5/5 (100%)	7-10hrs. from onset	Not detectable	0/2 (0%)
Not specified (frequent)	NS	1390 ± 1350	31/31 (100%)	Early	162 ± 52	8/18 (44%)
Variable (some serially)	NS Related to admission	528 ± 76	62/64 (96.8%)	4 hrs. from admission	44 ± 6.0	2/44 (4.5%)
Not specified	NS Related to admission	> 100	8/9 (88%)	?	> 75	0/13 (0%)
On admission	NS	–	5/13 (38%)	–	33.8 (Mean)	2/53 (3.8%)
6-8hrs.	NS	–	9/12 (75%)	–		
Not specified	NS	1368 ± 1357	32/32 (100%)	–	162 ± 52(8) 38 ± 16(11)	8/19 (42%)
On admission Day 2 & Day 3 (A.M.)	Discussed in relation to onset of symptoms	172 ± 124	19/22 (86%)	6-8hrs. from onset	63.6 ± 62.38	8/38 (21%)

relation to the time elapsed after admission to the hospital, a few (including the present one) attempted to relate the timing of sample collection to the onset of the symptoms of AMI. The duration of significant myoglobinemia was brief in most studies, and return to normal values often occurred in less than 24 hours. Hence, although the exact time of onset of symptoms is difficult to determine in some patients, correlation with the duration of symptoms is probably more valid than with duration of hospitalization. In the present study, it was possible to determine the time of onset of chest pain in 92 per cent of the cases.

In most studies, myoglobinemia was detected as early as four hours after admission and often preceded the appearance of elevated levels of CPK and the CPK-MB fraction.[1, 2, 14] The value of such early detection is questionable. First, confirming the diagnosis a few hours earlier is unlikely to alter the basic management of a case of AMI. On the other hand, the absence of significant elevation of SMb alone would not be sufficient to abandon intensive coronary care if there is any other evidence suggesting an AMI. Secondly, in most laboratories, RIA procedures are usually carried out in batches on stored samples for reasons of practicality and economy. To perform the assay on a single sample as an emergency procedure would not be cost-effective except under unusual circumstances. A practical approach would be to collect and store samples for SMb assay to be done only in those cases in which conventional parameters are equivocal.

Significant elevations in SMb were noted in the large majority of cases of AMI in various series (Table IV). With increased frequency of sampling, 100 per cent of cases showed myoglobinemia.[3, 13, 15] However, these studies used hourly

Table V. Conditions in which elevated serum myoglobin levels have been reported

1. Acute MI (See Table IV)
2. Angina without infarction (See Table IV)
3. Rhabdomyolysis[1, 18]
4. Multiple fractures,[2, 15] Muscle trauma[18]
5. Acute vascular occlusion[2, 15, 18]
6. Renal failure[2, 18, 19]
7. Myopathies, type not specified[18]
8. Vigorous exercise[6]
9. I.M. injections[16]*
10. Open heart surgery[1, 13]
11. Non-cardiac surgery*
12. Grand mal seizures[15]
13. ? Dig. toxicity[1]
14. Ventricular tachycardia[1]
15. Widespread cancer[2]
16. Pericarditis ?*
17. Circulatory shock[19]
19. Excessive alcohol ingestion?[19]

*Present study.

Table VI. Conditions in which elevated serum myoglobin levels were not found

1. Angina without infarction (See Table IV)
2. Congestive heart failure without AMI[1, 13]
3. Cardiac cath.[1]
4. Bicycle stress testing[1]
5. Moderate exercise[3]
6. I.M. injections (5 subjects—10 c.c. saline injections)[1, 14]
7. Liver disease[18]
8. Scleroderma[18]
9. Rheumatoid arthritis[18]
10. Thryotoxicosis[18]
11. Diabetic ketoacidosis[19]
12. Pancreatitis[19]

sampling for SMb, which is neither practical nor desirable in practice. In the present study, a *deliberate* attempt was made to evaluate the usefulness of a restricted number of samples obtained at the same time as other routine studies. Even with such infrequent, sampling, 86 per cent of cases of definite AMI showed significant elevations of SMb. It would appear that more frequent samples might be of value in individual cases where clinical suspicion of myocardial necrosis is high but other parameters are equivocal. It must be pointed out that Kagen and associates,[16] in an early study, suggested that there appeared to be a "staccato phenomenon" with considerable variation in the levels of SMb in the early hours following infarction.

In the present study, only three patients with definite evidence of AMI failed to show elevations of SMb. These three, all in clinical subset I, showed only mild transient elevations of cardiac enzymes. In one patient, sampling time (3 and 44 hours after onset of symptoms) may have missed a transient myoglobin peak. In the two others, modest evolutionary changes of SMb within the normal range were seen. However, there is no data available on day-to-day variations of SMb in normal individuals, and hence, no significance can be attributed to this.

Peak values for SMb in AMI were reported to occur in a varying period ranging from 4 to 12 hours after admission to 6 to 12 hours after onset of symptoms in various series (Table IV). Actual values also showed a considerable range, a few with levels as high as 3,000 to 6,000 ng./ml. Several studies attempted to correlate the peak myoglobin level with the severity and prognosis of the infarction. Significantly higher levels were noted in patients who also had congestive heart failure.[1, 2] In the present series, a significant correlation was noted between the height of the myoglobin peak and the severity of the infarction, as defined by the clinical subsets of Forrester and co-workers.[5] However, it must be noted that patients in subsets III and IV had renal hypoperfusion by definition, and hence might have had decreased clearance of myoglobin. It has also been suggested that severity of myoglobinemia might be used to estimate infarct size.[1] In studies on experimentally induced AMI in dogs, such correlation was possible.[17] However, the transient and unpredictable nature of the myoglobin peak and the possible "staccato phenomenon" alluded to above make it unlikely that SMb can be more reliable than currently available techniques for mapping infarct size.

The incidence of elevated SMb in patients with chest pain, but no definite AMI varies greatly, from 0 to 44 per cent in various series (Table IV). This may relate in part to variations in the diagnostic criteria for an AMI. Further, several other conditions are now known to produce elevations in SMb (see Table V). In the present study, 21 per cent of patients (8 of 38) with chest pain but no definite evidence of AMI showed elevated SMb levels. Of these, three patients had chronic renal failure and one had sustained musculoskeletal trauma before admission. One other patient was diagnosed as having a pericarditis probably secondary to a post-myocardial infarction syn-

drome. In the other three, no apparent explanation was found. It is possible that some of these patients may have had a "small" infarction which could not be detected by conventional methods. However, there was no trend towards increasing myoglobin levels with increasing suspicion (higher point count) of AMI.

Although SMb elevations are very sensitive for AMI, they are certainly not specific. Table V lists the conditions in which elevated myoglobin levels were found by various workers. In the present study, 58 per cent of postoperative (noncardiac) patients, 50 per cent of patients receiving frequent IM injections, and 27 per cent of patients admitted to an intensive care unit for critical noncardiac illnesses showed significant elevations of SMb (Fig. 3). Open heart surgery resulted in very high levels of SMb.[1, 12] Other conditions in which myoglobinemia has been reported include extensive trauma, rhabdomyolysis, acute vascular occlusion of an extremity, grand mal seizures, metastatic cancer and following ventricular tachycardia without definite evidence of myocardial infarction (Table V). Because myoglobin is normally cleared rapidly by the kidney, SMb values are difficult to interpret in the presence of acute or chronic renal failure. There is no data available at the present time which allows correlation of the severity of the renal failure with the degree of elevation of the SMb. While myoglobinuria by itself is well known to be associated with renal failure, the quantities released in AMI are not significant in this regard.

While rigorous exercise is well known to cause significant rhabdomyolysis, bicycle stress testing and moderate exercise did not appear to raise the SMb.[1, 3]

While Stuart and associates[15] found that five subjects given 10 c.c. saline injections did not show elevated SMb, other studies, including the present, indicate that patients receiving frequent deep IM injections can have significant myoglobinemia.[18] Stone and colleagues[1] found that cardiac catheterization did not alter myoglobin levels.

It is evident that many factors, some of them rather non-specific, can alter myoglobin levels. The SMb in myocardial infarction should, therefore, be interpreted only in light of other associated conditions.

The transient and dramatic nature of the myoglobin peak suggests that a distinct second peak might be of value in making the diagnosis of an early recurrent AMI or extension of infarction in the situation where other conventional parameters are still abnormal following the first infarction. Kollman and co-workers[14] have reported such a case. In this situation, SMb might be distinctly advantageous.

Conclusions

The results of this study and a review of the literature permit the following conclusions and suggestions regarding myoglobinemia in acute myocardial infarction:

1. Radioimmunoassay of serum myoglobin (SMb) is a sensitive indicator of myocardial damage in the early hours following an acute myocardial infarction (AMI). Even with infrequent sampling, more than 85 per cent of patients show significant elevations of SMb. Sensitivity is higher with frequent sampling.

2. It is suggested that serum for analysis should be collected on admission and daily for two days, i.e., at the same time as other conventional studies are obtained. The specimens may be frozen and the assay performed if, in retrospect, there is significant doubt regarding the diagnosis.

3. Careful note should be made of the relationship of the timing of sample collection to the time of onset of chest pain. Elevations of SMb may be expected to peak between 4 to 12 hours following the onset of pain.

4. Elevations of SMb are nonspecific for AMI. It is probably valueless in the presence of renal failure, rhabdomyolysis, extensive trauma, postoperative states (cardiac and noncardiac), acute vascular occlusions of extremities, and following seizures. It should be interpreted with care following intramuscular injections, vigorous exercise, ventricular tachycardia, and cardiopulmonary resuscitation. Inadequate data is available regarding pericarditis and cardiomyopathies. Twenty-five per cent of critically ill patients with multiple non-cardiac problems have a raised SMb which cannot be adequately explained in all instances.

5. At present, there is inadequate data to suggest that SMb is superior to any of the conventional methods for assessment of the extent of infarction. However, very high levels and sustained elevations tend to be associated with a poorer prognosis.

6. SMb may be of special value in the diagnosis

of early recurrent AMI or extension of infarction.

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