Myocardial Infarct Size Can Be Estimated From Serial Plasma Myoglobin Measurements Within 4 Hours of Reperfusion

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Background. **An early estimation of infarct size is useful for the appropriate early treatment of patients with acute myocardial infarction. We evaluated how early and how accurately infarct size could be estimated from serial plasma myoglobin (Mb) measurements in patients with successful reperfusion.**

Methods and Results. **We measured plasma Mb and creatine kinase (CK) in 35 patients in whom reperfusion therapy was successfully performed. Blood samples were collected at 15-minute intervals for 2 hours after reperfusion, at 30-minute intervals for the subsequent 2 hours, and at 3–6-hour intervals until 52 hours after reperfusion. Plasma Mb was measured by a newly developed turbidimetric latex agglutination assay. Total Mb and CK release (ΣMb, ΣCK) were calculated with a one-compartment model. The mean chord motion in the most hypokinetic 50% of the infarct-related artery territory was calculated from follow-up ventriculograms as an index of the severity of regional hypokinesis. There were significant correlations between ΣMb and ΣCK ($r=0.89$), between log ΣMb and the severity of regional hypokinesis ($r=-0.85$), and between log ΣCK and the severity of regional hypokinesis ($r=-0.74$). The time required for the cumulative Mb release curves to reach a plateau was 64±28 minutes. An additional 53±14 minutes was required to calculate the disappearance rate constant of Mb, and 15 minutes was necessary for the assay. Therefore, the total time required for ΣMb to be available was 132±40 minutes, significantly shorter than the time required for ΣCK, 24.3±9.1 hours ($p<0.001$). The infarct size could be estimated from the ΣMb in 34 of 35 patients within 4 hours of reperfusion.**

Conclusions. **Infarct size can be estimated accurately 4 hours after reperfusion by calculating the ΣMb in patients with successful reperfusion. (*Circulation* 1993;87:1840–1849)**

KEY WORDS • **creatine kinase** • **risk stratification** • **hypokinesis**

It is useful for risk stratification to estimate infarct size in patients with acute myocardial infarction as early as possible, because infarct size correlates closely with mortality[1] and prognostic indexes such as cardiac failure,[2] arrhythmias,[3] and ventricular function.[4] Infarct size can be estimated by electrocardiography, echocardiography, left ventriculography, radionuclide methods, or cardiac enzymes. The ECG is convenient for estimating infarct size clinically. However, because ST segment elevation and Q-wave amplitudes change spontaneously within 24 hours of the onset of acute myocardial infarction and change rapidly after reperfusion,[5–7] the estimation of infarct size from the ECG at the very early stage of myocardial infarction is unreliable. Stunned myocardium has been reported in patients with successful reperfusion of myocardial infarction. The motion of the postischemic myocardium without the development of necrosis may remain depressed for several days.[8] Therefore, the estimation of infarct size by echocardiography or left ventriculography at a very early stage is also of doubtful accuracy.

Estimation of infarct size by measurement of intramyocardial protein released from the injured myocardium may be the most precise method. Creatine kinase (CK), creatine kinase–MB isoenzyme (CK-MB),[9–11] and cardiac myosin light chains[12–14] have been used for estimating infarct size. These markers are not appropriate for the early estimation of infarct size because 1–6 days is required. Conversely, myoglobin (Mb) appears in the blood after infarction much earlier than CK[15] because of its lower molecular weight. In 1989, Ellis and Saran[16] reported that total Mb release into the blood, calculated with a one-compartment model, can be used as an index of infarct size in an animal model. Therefore, to evaluate how early and how accurately infarct size can be estimated from serial plasma Mb measurements in patients with successful reperfusion, we compared the infarct size estimated from total Mb release with that obtained from total CK release and left ventriculograms and the total time required for total Mb release to be available with that obtained for total CK release.

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Methods

Patients

The subjects were 42 consecutive patients with acute myocardial infarction admitted to hospitals within 6 hours of the onset of chest pain in whom complete occlusion of the infarct-related artery was confirmed by emergency coronary angiography and in whom thrombolysis and/or percutaneous transluminal coronary angioplasty (PTCA) was successfully performed. The diagnosis of acute myocardial infarction was based on chest pain lasting for more than 30 minutes and ST segment elevation ≥0.1 mV in at least two adjacent ECG leads. Exclusion criteria were persistent shock, the need for electric cardioversion, recent intramuscular injections, renal dysfunction, and a previous infarction in the same region.[17,18] Two patients were excluded because of reinfarction after reperfusion. Five patients with occlusion of the left circumflex coronary artery (LCx) were excluded because regional hypokinesis in patients with LCx occlusion can be underestimated from left ventriculograms.[19] The remaining 35 patients (29 men and six women 32–81 years old; mean, 62±11 years) were studied. All patients gave informed consent to participate in the study.

Coronary Angiography and Left Ventriculography

Emergency coronary angiography was performed by Judkins' technique. The infarct-related artery was confirmed in multiple projections with up to four contrast injections. The perfusion status of the infarct-related artery was determined according to standardized Thrombolysis in Myocardial Infarction (TIMI) criteria.[20] Reperfusion was defined as advancement of TIMI perfusion grade 0 flow to TIMI perfusion grade 2 or 3 flow. Collateral circulation to the infarct-related artery was also evaluated from the initial coronary angiograms according to the TIMI protocol.[21] Collaterals were graded on a three-point scale as absent (grade 1), minimal (grade 2), or well developed (grade 3). A patient was considered to have collaterals to the infarct-related artery if the collateral perfusion grade was 2 or 3. Reperfusion therapy was performed by thrombolysis and/or PTCA. When TIMI perfusion grade 2 flow or less was achieved after thrombolysis, PTCA was added. To confirm the perfusion status of the infarct-related artery, coronary angiography was performed every 5–8 minutes from the start of reperfusion until 2 hours after reperfusion.

Follow-up coronary angiography and ventriculography were performed an average of 32±9 days later in all patients. The patency of the infarct-related artery was evaluated, and left ventriculograms were recorded on cine films in the 30° right anterior oblique projection.

Blood Sampling

Blood samples for measurement of Mb and CK were collected at 15-minute intervals for 2 hours after reperfusion, at 30-minute intervals for the subsequent 2 hours, at 3-hour intervals for the next 24 hours, and at 6-hour intervals until 52 hours after reperfusion. All samples were immediately placed in test tubes containing EDTA disodium salt and promptly centrifuged at 3,000 rpm for 5 minutes. Plasma Mb concentrations were determined by a turbidimetric latex agglutination assay (reagent, Denka Seiken).[22,23] Plasma CK activity was determined by the enzymatic method (reagent, Boehringer Mannheim) with an autoanalyzer (Hitachi 7050). The assay time was about 10 minutes for each marker.

Estimation of Infarct Size

Total Mb and CK release from the injured myocardium into 1 mL of blood (ΣMb, ΣCK) were used as indexes of infarct size. ΣCK was calculated by the method of Sobel et al[9] as modified by Norris et al.[24] Since Mb kinetics correspond to a one-compartment model,[16] ΣMb was calculated similarly.[25] The equation for calculating total release is

$$\text{total Mb or CK release} = E(t) + Kd \cdot \Sigma E(t)dt$$

where E(t) is the plasma Mb concentration or CK activity at time t and Kd is the exponential disappearance rate constant of Mb or CK. The Kd of Mb and CK was determined from four semilogarithmic plots of plasma Mb concentrations or CK activity after baseline levels were subtracted. In addition, the time required for the cumulative release curves to reach a plateau after reperfusion was obtained.

Follow-up ventriculograms in the 30° right anterior oblique projection were analyzed to determine the severity of hypokinesis in the infarct region. The endocardial contours at end diastole and end systole were traced by two independent examiners and analyzed by the centerline method and the area–length method with a cardiac function analyzer (LVG analysis, CAMAC 300, Goodman). As an index of the severity of regional hypokinesis at the site of acute myocardial infarction, the mean chord motion in the most hypokinetic 50% of the infarct-related artery territory was calculated by the centerline method, as reported by Sheehan et al.[19,26] The severity of regional hypokinesis at the infarct site was expressed as standard deviations per chord. As an index of global wall motion, the ejection fraction (EF) was calculated by the area–length method. The results were expressed as the mean value of those obtained by the two examiners. The values obtained by the examiners correlated well (r=0.94 for severity of regional hypokinesis, r=0.92 for EF).

Statistical Analysis

All values were expressed as mean±SD. The difference in the time required for the cumulative release curves of Mb and CK to reach a plateau after reperfusion was evaluated by the paired t test. The relations among ΣMb, ΣCK, the severity of regional hypokinesis, and EF were analyzed by the least-squares method. The r values derived from these relations were compared by Fisher's Z transformation. The slopes were compared by calculating residual variance and using the t distribution test for significant differences. The unpaired t test was used to test for significant differences in age and in the time from onset of chest pain to reperfusion. χ^2 analysis was used to test for differences in the type of reperfusion therapy used in patients with left anterior descending coronary artery (LAD) occlusion and those with right coronary artery (RCA) occlusion or between the presence and absence of collateral circulation. Values of $p<0.05$ were considered to be significant.

TABLE 1. Characteristics of Patients Undergoing Reperfusion Therapy for Acute Myocardial Infarction

					Mb						
Patient	Age/ sex	Collateral grade	Reperfusion therapy	Time to reperfusion (hours)	Initial Mb (ng/mL)	Peak Mb (ng/mL)	ΣMb (ng/mL)	*K*d (min^{-1})	Time to plateau (minutes)	Time to *K*d (minutes)	Total time (minutes)
LAD occlusion											
1	81/F	1	t-PA	3.5	711	7,760	11,975	0.01213	45	45	105
2	70/F	1	t-PA	5.0	1,517	7,630	10,998	0.00606	90	60	165
3	60/M	1	t-PA	4.7	328	2,356	3,215	0.01061	60	45	120
4	58/M	2	t-PA	3.2	483	6,160	10,534	0.00673	60	45	120
5	61/M	1	t-PA+PTCA	3.5	96	6,910	11,260	0.00661	105	75	195
6	51/M	1	t-PA+PTCA	5.3	622	2,504	4,219	0.00961	120	90	225
7	51/M	1	t-PA+PTCA	3.3	1,044	14,240	29,471	0.01921	105	75	195
8	63/M	1	t-PA+PTCA	4.0	969	2,710	3,138	0.00340	30	45	90
9	63/M	1	t-PA+PTCA	6.8	1,268	6,350	10,852	0.00961	60	45	120
10	65/M	2	t-PA+PTCA	3.0	344	2,322	3,659	0.01708	45	45	105
11	39/M	2	t-PA+PTCA	2.5	135	2,770	4,075	0.00517	45	45	105
12	32/M	2	t-PA+PTCA	5.7	1,039	9,630	17,255	0.01351	60	45	120
13	53/M	2	pro-UK+PTCA	3.2	221	741	1,170	0.01017	90	75	180
14	66/F	1	PTCA	5.2	2,610	8,040	14,611	0.01337	45	60	120
15	72/F	1	PTCA	3.2	2,707	10,540	17,822	0.00583	150	90	255
16	62/M	1	PTCA	4.3	1,268	5,030	10,626	0.00898	75	45	135
17	81/M	1	PTCA	6.3	2,888	4,240	7,567	0.00543	60	45	120
18	67/M	1	PTCA	6.9	1,306	7,820	13,057	0.00671	90	60	165
19	78/M	2	PTCA	5.8	1,095	3,900	5,857	0.00459	75	45	135
20	62/M	2	PTCA	6.5	798	8,650	12,906	0.00776	60	45	120
21	72/M	3	PTCA	5.5	363	1,459	1,647	0.00289	45	45	105
Mean	62			4.6	1,039	5,798	9,805	0.00883	72	56	143
SD	12			1.4	823	3,457	6,752	0.00433	30	16	44
RCA occlusion											
22	65/M	1	t-PA	2.5	93	7,620	8,843	0.00852	45	45	105
23	55/M	2	t-PA	7.3	588	1,305	3,122	0.02041	30	45	90
24	78/M	2	t-PA	6.2	1,781	4,800	8,978	0.00789	75	75	165
25	68/M	3	t-PA	5.4	1,935	5,020	5,766	0.00196	30	45	90
26	65/F	1	t-PA+PTCA	3.2	43	1,164	1,212	0.00425	45	45	105
27	51/M	1	t-PA+PTCA	3.8	105	1,782	2,407	0.00865	60	45	120
28	50/M	3	t-PA+PTCA	7.5	643	4,770	6,867	0.00509	45	45	105
29	65/M	3	pro-UK+PTCA	4.8	235	3,660	4,398	0.00456	45	45	105
30	58/M	3	UK+PTCA	5.0	634	4,410	6,826	0.01648	45	45	105
31	56/M	1	PTCA	6.8	181	587	716	0.00872	45	45	105
32	76/F	1	PTCA	6.8	383	2,015	2,429	0.00307	75	45	135
33	73/M	1	PTCA	2.5	86	2,850	3,703	0.00439	90	60	165
34	60/M	2	PTCA	2.8	38	1,802	2,156	0.00890	30	45	90
35	45/M	3	PTCA	3.8	242	3,850	6,729	0.01590	60	45	120
Mean	62			4.9	499	3,260	4,582	0.00849	51	48	115
SD	10			1.8	615	1,961	2,749	0.00551	18	9	25
Mean	62			4.7	823	4,783	7,716	0.00869	64	53	132
SD	11			1.6	784	3,177	6,037	0.00476	28	14	40

Time to reperfusion, time from onset of chest pain to reperfusion; Mb, myoglobin; Initial Mb, plasma Mb concentrations at the time of reperfusion; ΣMb, total myoglobin release; *K*d, disappearance rate constant; Time to plateau, time required for cumulative release curves of Mb (CK) to reach a plateau after reperfusion; Time to *K*d, time required for a four-point blood sampling to calculate the *K*d after reaching a plateau of cumulative release curves; Total time (of Mb), time required for ΣMb to be available after reperfusion; CK, creatine kinase; Initial CK, plasma CK activity at the time of reperfusion; ΣCK, total creatine kinase release; Total time (of CK), time required for ΣCK to be available after reperfusion; LVG, left ventriculogram; Regional hypokinesis, the mean chord motion in the most hypokinetic 50% of the infarct-related artery territory calculated by the centerline method; EF, ejection fraction; LAD, left anterior descending coronary artery; RCA, right coronary artery; t-PA, tissue-type plasminogen activator; PTCA, percutaneous transluminal coronary angioplasty; pro-UK, prourokinase; UK, urokinase.

*$p<0.001$ compared with time to plateau of Mb; †$p<0.001$ compared with time to *K*d of Mb; ‡$p<0.001$ compared with total time of Mb.

TABLE 1. continued

CK							LVG	
Initial CK (mIU/mL)	Peak CK (mIU/mL)	ΣCK (mIU/mL)	*K*d (hr^{-1})	Time to plateau (hours)	Time to *K*d (hours)	Total time (hours)	Regional hypokinesis (SD/chord)	EF (%)
467	3,015	3,639	0.0416	10	9	19.3	−3.01	46
336	6,800	7,345	0.0544	3	7	10.3	−3.25	44
134	1,451	1,631	0.0428	28	18	46.3	−2.29	64
91	3,620	5,631	0.0514	13	9	22.3	−3.42	55
208	5,260	6,087	0.0546	7	9	16.3	−2.18	52
642	2,359	3,353	0.0479	16	9	25.3	−1.65	56
651	10,325	11,876	0.0535	25	15	40.3	−4.67	46
332	1,861	3,397	0.0574	19	9	28.3	−1.99	49
680	3,668	4,314	0.0415	7	9	16.3	−4.47	35
86	988	1,263	0.0453	10	9	19.3	−1.97	65
187	2,502	3,775	0.0366	19	9	28.3	−1.58	61
528	9,044	10,978	0.0462	7	9	16.3	−4.21	19
94	726	1,461	0.0775	22	12	34.3	−0.93	69
529	6,140	7,532	0.0416	19	9	28.3	−4.28	18
153	4,480	6,178	0.0319	19	9	28.3	−4.35	45
1,027	3,795	3,880	0.0393	13	9	22.3	−2.75	58
2,209	3,829	4,394	0.0428	4	9	13.3	−3.56	29
886	6,084	9,082	0.0436	16	9	25.3	−3.76	33
503	1,884	2,509	0.0401	13	9	22.3	−3.47	49
315	5,196	6,088	0.0443	4	9	13.3	−3.34	46
244	1,458	1,790	0.0440	7	9	16.3	0.24	67
491	4,023	5,057	0.0466	13.4	9.8	23.4	−2.90	48
475	2,583	3,006	0.0095	7.2	2.4	9.1	1.29	15
78	5,130	6,090	0.0595	7	9	16.3	−2.53	58
279	1,771	2,050	0.0345	4	9	13.3	−0.08	68
537	2,414	3,836	0.0463	22	12	34.3	−2.04	65
254	1,385	1,716	0.0480	10	9	19.3	−2.43	32
74	808	999	0.0376	19	9	28.3	−0.52	66
509	1,360	2,119	0.0391	19	9	28.3	−1.13	71
296	2,959	3,921	0.0371	13	9	22.3	−2.14	50
84	1,911	2,527	0.0499	16	9	25.3	−0.42	72
244	3,385	4,289	0.0581	7	9	16.3	−1.12	64
82	272	338	0.0308	16	9	25.3	0.91	78
561	2,112	3,081	0.0277	25	15	40.3	−1.03	64
35	2,375	2,650	0.0177	10	9	19.3	−1.43	53
103	1,395	1,794	0.0500	13	9	22.3	−1.69	66
81	3,557	6,233	0.0523	28	18	46.3	−0.96	55
230	2,202	2,974	0.0420	14.9	10.3	25.5	−1.19	62
187	1,254	1,741	0.0120	7.2	2.8	9.4	0.96	11
386	3,295	4,224	0.0448	14.0*	10.0†	24.3‡	−2.21	53
404	2,312	2,747	0.0107	7.1	2.6	9.1	1.43	15

Results

Patient Characteristics

Clinical characteristics are summarized in Table 1. Emergency coronary angiogram demonstrated complete occlusion of the LAD in 21 patients and of the RCA in 14. No significant difference between the two groups was seen in age, time from the onset of chest pain to reperfusion, and the type of reperfusion therapy used. Collateral circulation to the infarct-related artery was TIMI collateral grade 1 in 19 patients, grade 2 in 10, and grade 3 in six. No significant difference was seen in age, time from the onset of chest pain to reperfusion, and type of reperfusion therapy in patients with (TIMI collateral grade 2 or 3) or without (TIMI collateral

grade 1) collateral circulation. Thrombolysis alone was performed in eight patients, thrombolysis followed by PTCA in 14, and direct PTCA in 13. PTCA was performed by means of a guide wire (USCI) and balloon catheter (diameter, 2.5–3.5 mm) (USCI or Advanced Cardiovascular System). TIMI perfusion grade 3 flow was obtained in all patients after reperfusion therapy. Follow-up coronary angiography performed 32±9 days after onset of chest pain showed patency of the infarct-related artery in all patients.

Calculation of ΣMb and ΣCK

The mean plasma Mb concentration in all patients was 823±784 ng/mL at the time of reperfusion, increased markedly after reperfusion to a peak of 4,783±3,177 ng/mL, and decreased rapidly thereafter. The mean plasma CK activity was 386±404 mIU/mL at the time of reperfusion, increased to a peak of 3,295±2,312 mIU/mL, and decreased gradually thereafter. The time to the peak Mb concentration was 52±26 minutes after reperfusion, whereas the time to peak CK activity was 8.7±5.3 hours. In spite of frequent blood sampling, we did not observe the "staccato phenomenon" of Mb release reported by Kagen et al.[27] The mean *K*d of Mb was 0.00869±0.00476/min, and that of CK was 0.0448±0.0107/hr.

The time required for the cumulative Mb release curves to reach a plateau after reperfusion was 30–150 minutes (mean, 64±28 minutes). The sampling time required for a four-point plot to calculate the *K*d of Mb was 45–90 minutes (mean, 53±14 minutes) after the plateau of the cumulative Mb release curves was reached. In addition, the assay time, including the centrifugation time, was 15 minutes for Mb. Thus, a total of 90–255 minutes (mean, 132±40 minutes) was required for ΣMb to be available as an index of infarct size. The total time required for ΣMb to be available was within 3 hours of reperfusion in 31 of the 35 patients and within 4 hours of reperfusion in 34. The time required for the cumulative CK release curves to reach a plateau was 3–28 hours (mean, 14.0±7.1 hours). The time required to obtain a four-point plot to calculate the *K*d of CK was 7–18 hours (mean, 10.0±2.6 hours) after the plateau was reached. The assay time, including the centrifugation time, was also 15 minutes. Thus, a total of 10.3–46.3 hours (mean, 24.3±9.1 hours) was required until ΣCK was available. Therefore, ΣMb was calculated significantly earlier than ΣCK ($p<0.001$).

Comparison of ΣMb, ΣCK, Severity of Regional Hypokinesis, and EF

There were good correlations between ΣMb and ΣCK ($r=0.89$, $p<0.001$) (Figure 1) and between the severity of regional hypokinesis and EF ($r=0.92$, $p<0.001$). Log ΣMb was negatively correlated with the severity of regional hypokinesis ($r=-0.85$, $p<0.001$). Log ΣCK was also negatively correlated with the severity of regional hypokinesis ($r=-0.74$, $p<0.001$) (Figure 2). Although the *r* values for log ΣMb tended to be higher than those for log ΣCK, there was no significant difference between these two values. Log ΣMb was negatively correlated with EF ($r=-0.71$, $p<0.001$). Log ΣCK was also negatively correlated with EF ($r=-0.66$, $p<0.001$) (Figure 3).

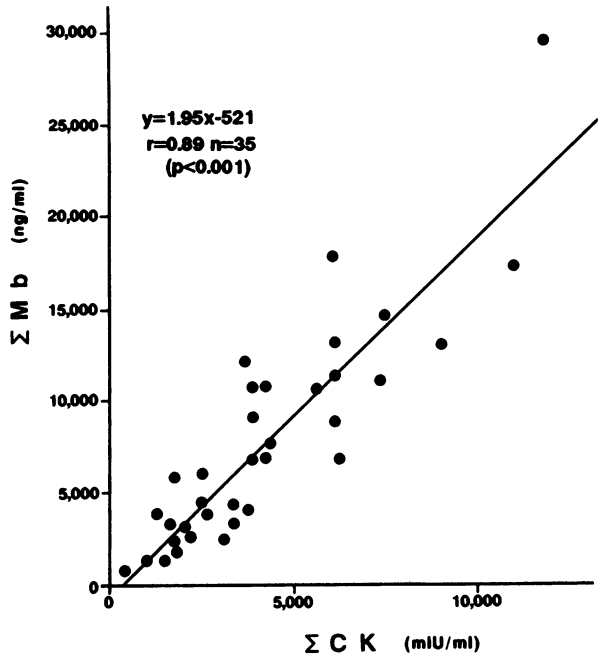

FIGURE 1. *Plot showing the correlation between total myoglobin release (ΣMb) and total creatine kinase release (ΣCK) in 35 patients with acute myocardial infarction. Mb concentration was determined by a turbidimetric latex agglutination assay. CK activity was determined by the enzymatic method. ΣMb and ΣCK were calculated by use of a one-compartment model.*

Log ΣMb was well correlated with the severity of regional hypokinesis in patients with LAD occlusion ($y=-0.25x+3.16$; $r=-0.88$; $p<0.001$) and in those with RCA occlusion ($y=-0.25x+3.26$; $r=-0.73$; $p<0.01$) (Figures 4A and 4B). The slopes and *y* intercepts of these two regression lines and the two *r* values were not significantly different between patients with LAD occlusion and those with RCA occlusion. The relation between log ΣMb and the severity of regional hypokinesis was represented by $y=-0.26x+3.13$ ($r=-0.93$, $p<0.001$) in the absence of collateral circulation and by $y=-0.18x+3.37$ ($r=-0.73$, $p<0.01$) in its presence (Figures 4C and 4D). There was no significant difference between these two *r* values. The slopes and *y* intercepts were also not statistically different. The correlation between log ΣMb and the severity of regional hypokinesis was represented by $y=-0.23x+3.22$ ($r=-0.87$, $p<0.001$) in patients who underwent PTCA and by $y=-0.17x+3.44$ ($r=-0.76$, $p<0.001$) in patients who underwent thrombolysis alone. There were no significant differences between these two *r* values, the slopes, and the *y* intercepts.

Discussion

In the present study, log ΣMb measured by a turbidimetric latex agglutination assay correlated well with the severity of regional hypokinesis, which is an index of infarct size ($r=-0.85$).[26] Since this *r* value is not significantly different from that between log ΣCK and the severity of regional hypokinesis ($r=-0.74$), infarct size can be estimated from ΣMb with an accuracy similar to that of ΣCK. In addition, the total time required for

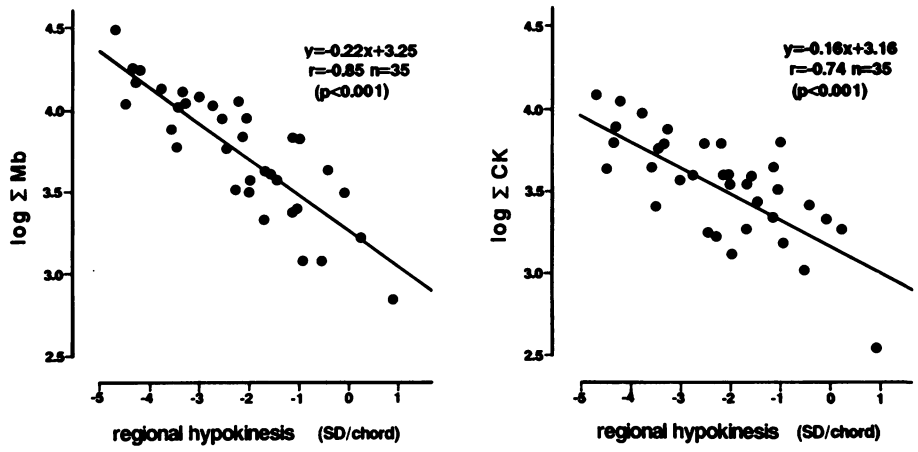

FIGURE 2. *Plots showing the correlation between the logarithmic values of total myoglobin release (log ΣMb) and the severity of regional hypokinesis (left panel) and between the logarithmic values of total creatine kinase release (log ΣCK) and the severity of regional hypokinesis (right panel). As an index of the severity of regional hypokinesis, the mean chord motion in the most hypokinetic 50% of the infarct-related artery territory[26] was calculated from follow-up ventriculograms.*

ΣMb to be available after reperfusion was 132±40 minutes, significantly shorter than that required for ΣCK (24.3±9.1 hours) ($p<0.001$).

Comparisons With Previous Studies

Stone et al[28] were the first to estimate infarct size from serial plasma Mb changes, using an animal model with persistent coronary artery occlusion. They observed a significant correlation between the peak Mb levels and the histological infarct size. Ellis and Saran[16] have demonstrated that Mb kinetics can be usefully described with a one-compartment model. ΣMb calculated with a one-compartment model correlated well with Mb depletion from cardiac tissue ($r=0.97$) in 12 dogs with reperfusion after a 2-hour coronary artery occlusion. Thus, infarct size could be estimated from serial plasma Mb measurements with and without coronary reperfusion in animal models.

Several clinical studies in which infarct size was estimated from serial plasma Mb measurements have been reported. Maddison et al[25] collected blood samples at 4-hour intervals in 29 patients and showed a significant correlation between ΣMb and ΣCK-MB ($r=0.71$). Tommaso et al[29] observed a good correlation between the area under the Mb concentration–time plot and ΣCK ($r=0.98$) by blood sampling at 3-hour intervals in eight patients. Groth et al[30] collected blood samples in 33 patients with acute myocardial infarction at 1–2-hour intervals after admission and reported a significant correlation between ΣMb calculated with a two-compartment model and ΣCK-MB ($r=0.72$). However, these clinical studies have several problems. First, the perfusion status of the infarct-related artery was not demonstrated by coronary angiography in these studies. Therefore, they might have included patients with spontaneous reperfusion of the infarct-related artery before or during treatment. Several reports have suggested that reperfusion increases the release of CK from the infarct area into the blood; therefore, the infarct size determined by ΣCK may be overestimated compared with the histological infarct size.[31–33] A similar phenomenon may occur with Mb, making estimation of the infarct size difficult. The second problem is the long intervals used in previous studies for blood sampling. As shown in this study, plasma Mb reached a peak 52±26 minutes after reperfusion and rapidly decreased thereafter. Therefore, blood sampling at 1–4-hour intervals is insufficient to determine the peak level or *K*d of Mb in patients with successful reperfusion. The third problem is that the infarct size estimated from Mb measurements in these

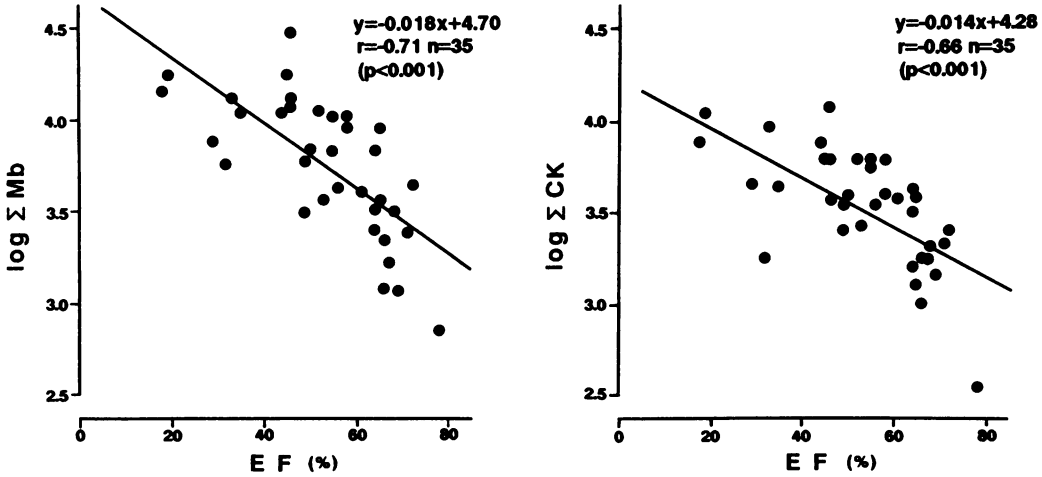

FIGURE 3. *Plots showing the correlation between logarithmic value of total myoglobin release (log ΣMb) and ejection fraction (EF) (left panel) and between logarithmic value of total creatine kinase release (log ΣCK) and EF (right panel). EF was calculated from follow-up ventriculograms.*

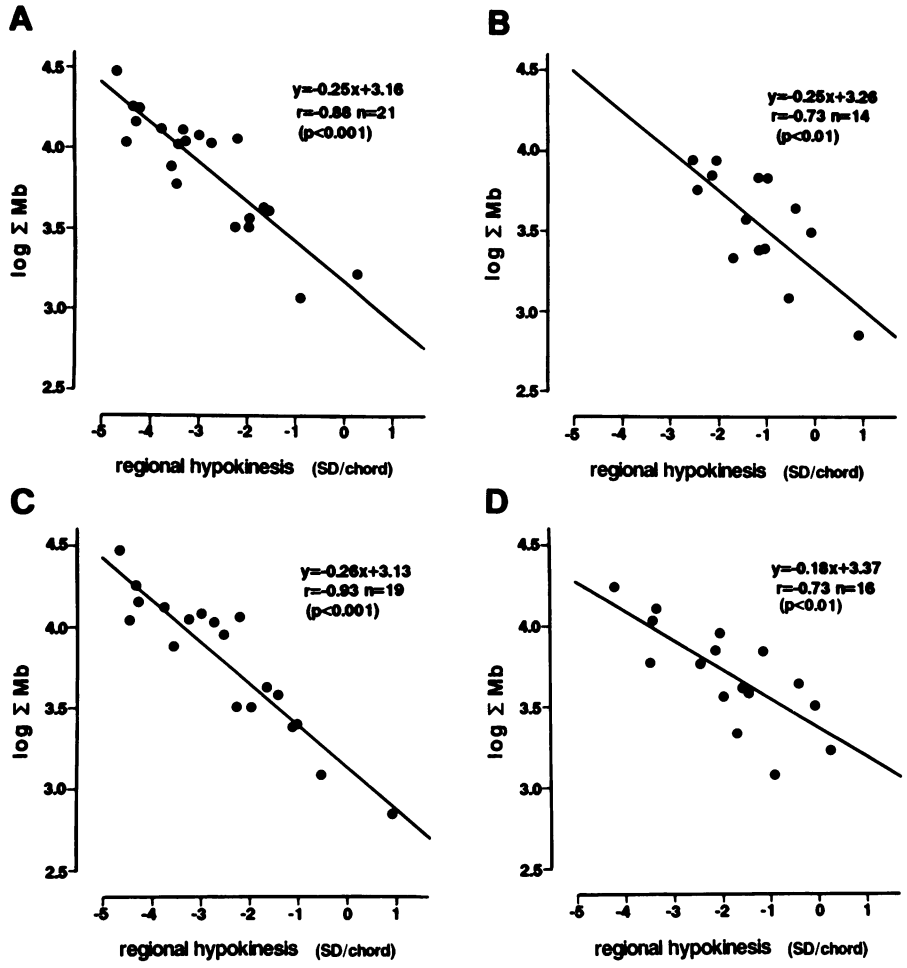

FIGURE 4. *Plots showing the correlation between logarithmic values of total myoglobin release (log ΣMb) and the severity of regional hypokinesis in 21 patients with left anterior descending coronary artery occlusion (panel A), in 14 patients with right coronary artery occlusion (panel B), in 19 patients without collateral circulation to the infarct-related artery (panel C), and in 16 patients with collateral circulation (panel D). As an index of the severity of regional hypokinesis, the mean chord motion in the most hypokinetic 50% of the infarct-related artery territory was calculated from follow-up ventriculograms.*

studies was compared with only that estimated from ΣCK or ΣCK-MB. As stated above, reperfusion increases the release of CK or CK-MB and may cause overestimation of the infarct size.[31-33] In contrast, in extensive myocardial infarction involving more than 20% of the left ventricle, the release of CK from the infarct area is decreased, and the infarct size from ΣCK is underestimated compared with the histological infarct size.[34] Therefore, to clarify whether or not ΣMb is a reliable index for estimating infarct size, ΣMb must be compared not only with biochemical parameters but also with other indexes, such as left ventriculograms. The final problem seen in previous studies was that plasma Mb concentrations were measured by radioimmunoassay, and thus, there was a delay of more than 2 hours before results were available. Consequently, the analysis of serial plasma Mb changes could not have been useful in clinical practice.

We attempted to overcome these problems in the present study. We confirmed the perfusion status of the infarct-related artery by serial coronary angiography and accurately evaluated the peak levels and *K*d of Mb from blood samples drawn at 15-minute intervals. In addition, we evaluated the severity of regional hypokinesis from follow-up ventriculograms and compared ΣMb not only with ΣCK but also with the severity of regional hypokinesis. Moreover, we used the turbidimetric latex agglutination assay, which required about 10 minutes for the determination of plasma Mb concentrations.

Relation Between ΣMb in LAD Occlusion and in RCA Occlusion and Between ΣMb in Presence and Absence of Collateral Circulation

The slopes and *y* intercepts of the regression line and the *r* values for log ΣMb and the severity of regional hypokinesis were quite similar between the patients with LAD occlusion and those with RCA occlusion. These findings suggest that the infarct size from serial plasma Mb measurements can be accurately estimated in patients with occlusion of either vessel.

The time to peak CK from the onset of chest pain in patients with persistent occlusion of the infarct-related artery was reported to be shorter in patients with collateral circulation than in those without collateral circulation.[35] This suggests that the presence of collateral circulation may affect the release of Mb from injured myocardium into the blood and the calculation of ΣMb. In the present study, however, the slopes, *y* intercept, and *r* values did not differ significantly between the presence and absence of collateral circulation. Thus, infarct size estimated from serial plasma Mb measurements was useful in patients with and without collateral circulation.

Temporal Advantage of ΣMb

Mb has been reported as a very early parameter for the diagnosis of acute myocardial infarction and the

detection of coronary reperfusion.[15,36-39] Although several investigators have reported that infarct size can be estimated precisely from the analysis of serial plasma Mb changes, there have been no previous studies on whether Mb can estimate infarct size earlier than CK. We first compared the temporal advantage of Mb measurements to that of CK measurements in the estimation of infarct size in patients with successful reperfusion. In the present study, the time required for the cumulative release curves to reach a plateau after reperfusion was 64±28 minutes for Mb, which was significantly shorter than that obtained for CK (14.0±7.1 hours). In addition, the sampling time required for a four-point plot to calculate the *K*d was 45–90 minutes for Mb after the plateau of the cumulative release curves was reached, whereas that obtained for CK was 7–18 hours. However, since plasma Mb concentrations have been measured by radioimmunoassay, which requires special equipment and an assay time of >2 hours, plasma Mb measurements have not been used clinically at the very early stage of myocardial infarction. Recently, the turbidimetric latex agglutination assay, a rapid, quantitative, and convenient assay for measuring Mb, has been developed.[22,23] We used this assay, and assay time, including centrifugation time, was 15 minutes to estimate infarct size from ΣMb. As shown in Table 1, the total time required for ΣMb to be available after reperfusion was 90–255 minutes (mean, 132±40 minutes), significantly shorter than that required for ΣCK (10.3–46.3 hours; mean, 24.3±9.1 hours). Infarct size could be estimated from ΣMb in 31 of 35 patients with acute myocardial infarction within 3 hours of reperfusion and in 34 of them within 4 hours of reperfusion. Sixty minutes or more was necessary for a four-point blood sampling to calculate the *K*d of Mb in 10 patients, because our protocol for blood sampling was 15-minute intervals for 2 hours and 30-minute intervals for the next 2 hours after reperfusion. If blood samples were collected at 15-minute intervals for 3 hours after reperfusion, the total time required for ΣMb to be available after reperfusion might be shortened because of reduction of the time required for the four-point blood sampling. Therefore, Mb measurement based on our method is markedly superior to CK measurement for the early estimation of infarct size.

Clinical Implications and Limitations

Coronary care units have contributed to reducing mortality and preventing life-threatening complications in patients with acute myocardial infarction.[40] However, because of their large cost and lack of a sufficient number of beds to accommodate all prospective admissions, the development of a cost-effective alternative to the coronary care unit has been sought. The intermediate care unit is more cost-effective than a coronary care unit for low-risk patients with acute myocardial infarction.[41] For cost-effective use of the coronary care unit, a good predictor is required for early and accurate identification of low-risk patients who are not likely to have major complications. According to several studies concerning infarct size, life-threatening events occur only occasionally in patients whose infarct size is estimated to be small,[1,3,4,42,43] whereas in patients with large infarct size, left ventricular dysfunction is severe, and life-threatening events frequently occur.[1,3,4,42,43] Silverman et al[44] performed ^{201}Tl scintigraphy within 15 hours of the onset of chest pain and showed that the extent of perfusion defect was a better predictor of in-hospital mortality than clinical variables such as the location of myocardial infarction, history of previous myocardial infarction, and pulmonary edema on the chest x-ray. Their high thallium defect score identified a subgroup whose in-hospital mortality rate was 46%, compared with a subgroup with a low defect score whose in-hospital mortality rate was only 3%. Therefore, the risk of life-threatening complications is expected to be small in cases of a small infarct estimated at an early stage. If risk stratification can be estimated early and accurately, it is possible to admit low-risk patients directly to an intermediate care unit.[45,46] Since ΣMb is calculated accurately within 4 hours after reperfusion in our study, the low-risk patients can be selected shortly after reperfusion and admitted to an intermediate care unit directly. On the other hand, intra-aortic balloon counterpulsation has been reported to result in a favorable clinical and hemodynamic response in patients with cardiogenic shock, although inotropic and vasopressor agents were ineffective.[47,48] Thus, in high-risk patients who seem to have severe left ventricular dysfunction or cardiogenic shock, risk stratification based on our method may be useful to decide on the requirement of aggressive intervention such as intra-aortic balloon counterpulsation, hemopump insertion, percutaneous cardiopulmonary support, and a ventricular assist device to prepare for hemodynamic deterioration.[49]

The CK level has been reported to be elevated after PTCA.[50] We evaluated whether the correlation between log ΣMb and the severity of regional hypokinesis differs between patients who underwent PTCA and those who underwent thrombolysis alone. However, there were no significant differences between the *r* values, slopes, and *y* intercepts of the two regression lines. Thus, our method may be applicable to the early estimation of infarct size in patients who underwent both PTCA and thrombolysis.

We examined patients with first acute myocardial infarction who achieved successful coronary reperfusion. The infarct size from ΣMb cannot be used to predict the risk stratification in patients with reinfarction. In these patients, risk stratification must be evaluated not only from the recent infarct size but also prior infarct size.

Since reperfusion increases the release of CK from the infarct area, the infarct size from ΣCK is overestimated in patients with reperfusion compared with those without reperfusion.[31-33] Mb is a cytosolic protein, as is CK, and the Mb kinetics may differ between patients with reperfusion and those without reperfusion. Moreover, we examined the serial Mb measurements on patients with successful reperfusion and did not obtain data on patients without reperfusion. Therefore, it is not clear whether our method is applicable to the estimation of infarct size in patients without reperfusion. Further studies are necessary to clarify the usefulness of the estimation of infarct size from serial plasma Mb measurements in patients without reperfusion.

Since we excluded patients with LCx occlusion, it is not clear whether Mb is applicable to the early estimation of infarct size in such patients.

Infarct size from ΣMb may be overestimated in patients with severe renal dysfunction, because Mb is rapidly excreted in the urine.[51]

Since Mb is not specific to the myocardium,[52] the infarct size determined from ΣMb may be overestimated in patients with shock, trauma, alcoholism, muscle disorders, or those who received intramuscular injections. Skeletal muscle damage was reported in patients who received β-adrenergic blockers, calcium channel blockers, antihyperlipidemic drugs, diuretics, antiarrhythmic drugs, and corticosteroids.[53–56] Accordingly, infarct size from ΣMb may be influenced in patients receiving these drugs. Since ΣMb may be inaccurate for the estimation of infarct size in patients with skeletal muscle damage as described above, the measurement of CK-MB or cardiac myosin light chains, which have myocardial specificity, may be more suitable for estimation of infarct size. However, 1–6 days is required for estimation of infarct size using these markers.[12–14,25]

It is suggested that infarct size can be estimated accurately within approximately 4 hours of reperfusion by calculating ΣMb from blood samples collected at 15-minute intervals in patients with acute myocardial infarction.

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