Eur. J. Clin. Chem. Clin. Biochem.
Vol. 30, 1992, pp. 823–830



# Acute Myocardial Infarction Size and Myoglobin Release into Serum

By *J. R. Delanghe*[1], *M. L. De Buyzere*[2], *L. P. Cluyse*[1], *H. M. Thierens*[3] and *D. L. Clement*[2]

[1] *Department of Clinical Chemistry, University Hospital, Gent, Belgium*
[2] *Department of Cardiology, University Hospital, Gent, Belgium*
[3] *Department of Medical Physics, State University of Gent, Gent, Belgium*

(Received November 4, 1991/August 3, 1992)

**Summary:** The kinetics of myoglobin release after acute myocardial infarction were studied. Various algorithms for calculation of infarct size, based on immunonephelometric determination of myoglobin and cumulative myoglobin release into the circulation were compared. The cumulative myoglobin release and maximal serum myoglobin concentration were compared with various measures of infarct size: cumulative release of creatine kinase, electrocardiographic changes, and left ventricular ejection fraction. After acute myocardial infarction, time to peak for myoglobin in serum was correlated with time to peak for creatine kinase ($r = 0.645$). On average, the myoglobin concentration peaked 8.8 h earlier than creatine kinase activity. The rate of elimination of myoglobin showed a large variation ($0.041 - 0.628\ h^{-1}$) and was not correlated with the elimination rate of creatine kinase. The elimination rate of myoglobin after acute myocardial infarction was shown to depend on the patient's age and infarct size. The elimination constant of myoglobin is preferably estimated on an individual basis in large and complicated infarctions. Cumulative myoglobin release correlated with algorithms based on the cumulative release of creatine kinase ($r = 0.622$) and its isoenzyme MB ($r = 0.660$), and to a lesser extent with the residual left ventricular ejection fraction ($r = 0.513$) and the sum of ST-segment deviations on electrocardiography ($r = 0.469$). Maximal myoglobin values in serum correlated moderately with the calculated infarct size ($r = 0.488$; based on creatine kinase-MB) and electrocardiographic changes ($r = 0.554$). In combination with fast immunological methods for myoglobin determination, myoglobin peak height offers the advantage of providing reliable results within 12 h after onset of symptoms. The method based on cumulative myoglobin release is an equivalent alternative; it also requires a limited number of consecutive determinations of myoglobin in serum, but yields results only after 36 h. As is the case for methods based on cumulative enzyme release, the proposed algorithms cannot be used if concomitant skeletal muscle damage has also occurred.

## Introduction

The prognosis of acute myocardial infarction is largely determined by infarct size (1). Infarct size can further be used as a measure for studying effects of thrombolytic therapy in acute myocardial infarction (2). In clinical practice, calculation of infarct size in patients however remains cumbersome. In the past, a number of sophisticated non-invasive techniques have been proposed, such as electrocardiographic mapping techniques (3), nuclear scintigraphy (4), and nuclear magnetic resonance (5). Infarct size can also be determined from the appearance of cardiac enzymes[1]) (creatine kinase, α-hydroxybutyrate dehydrogenase[1])) in serum following infarction (2, 6). However, because of the relatively slow elimination rate of cardiac enzymes from plasma, the minimal duration of the integration period necessary for calculating infarct size by these methods ranges from two to seven days, depending on the enzyme chosen. Myoglobin, a mus-

[1] Enzymes:
Creatine kinase (ATP : Creatine N-Phosphotransferase; EC 2.7.3.2)
α-Hydroxy butyrate dehydrogenase ([S]-3-Hydroxybutanoate : $NAD^+$-oxidoreductase; EC 1.1.1.27)

cle protein of $M_r$ 17 700 is rapidly released into serum after acute myocardial infarction and can be used for its diagnosis (7, 8). In contrast to cardiac enzymes, myoglobin disappears relatively rapidly from the plasma compartment and is partly excreted in the urine (9). Potential interference from the release of acute myocardial infarction marker molecules from damaged skeletal muscle during a further stay in hospital can be minimized by choosing marker molecules characterized by a relatively short appearance in the plasma. The recent availability of reliable, fast immunological assays for measuring serum myoglobin in the emergency laboratory has created new possibilities for the estimation of infarct size within 36 h after onset of symptoms (10, 11). In the present work, we studied the kinetics of myoglobin release after myocardial infarction. Maximal myoglobin concentration in serum and the cumulative release of myoglobin were compared with the cumulative release of creatine kinase and its MB isoenzyme after acute myocardial infarction. Furthermore, we evaluated the possibilities of using peak myoglobin values and serial myoglobin measurements in serum for infarct sizing within 36 h after onset of symptoms. Infarct sizes calculated by cumulative myoglobin release were compared with electrocardiographic findings. As the prognosis of acute myocardial infarction can be predicted by both infarct size and the left ventricular ejection fraction (12), we also compared this cumulative myoglobin release with the residual left ventricular ejection fraction.

## Materials and Methods

### Patients

Thirty two acute myocardial infarction patients (21 males: mean age ± 65.4 ± 12.3 years; body weight: 71.8 ± 10.7 kg; 11 females: mean age: 60.7 ± 15.3 years, body weight: 67.0 ± 5.8 kg) were diagnosed acute myocardial infarction according to the WHO criteria (13). The mean time interval between onset of symptoms and hospital admission was 185 ± 170 min. Twenty seven patients (84%) with acute myocardial infarction received thrombolytic therapy, 30 U anistreplase, administered intravenously. Five other patients did not receive thrombolytic therapy because of medical contraindications (14). Blood was sampled immediately on admission, then every 4 h during the first 48 h of hospitalization. Upon admission, serum creatinine concentrations for males and females were 75 ± 17 µmol/l and 61 ± 14 µmol/l. None of the acute myocardial infarction patients showed clinical signs of preexisting renal insufficiency.

### Analytical methods

Serum creatine kinase activity was assayed at 37 °C according to IFCC (15), using commercially available reagents (Boehringer Mannheim, Germany) on a Hitachi 717 analyser (Hitachi, Tokyo, Japan). Serum creatine kinase-MB activity was assayed at 37 °C on an aca analyzer (DuPont, Wilminton, DE 19898). Serum myoglobin and myoglobin in tissue extracts was assayed using an immunonephelometric assay (inter-assay CV: 6%) on a BNA nephelometer (Behringwerke, Marburg, Germany) (10). Serum creatinine was measured enzymatically (16) on a Hitachi 717 anlayser.

Infarct size, based on a standard 12 lead electrocardiogram was calculated using the sum of all ST-segment deviations obtained at the moment of maximal repolarisation disturbances (17). In 14 acute myocardial infarction patients (43%), infarct size could not be estimated using electrocardiographic data because of uninterpretable patterns. Infarct size based on the use of cumulative creatine kinase and creatine kinase-MB activity in serum was calculated according to *Roberts* (6). Individualized elimination constants ($k_d$) were determined by fitting serum creatine kinase and creatine kinase-MB activities in the decline part of the time-activity curves into a first-order equation: $A = A_0\, e^{-k_d \cdot t}$, in which A represents serum enzyme activity at time $t$, and $A_0$ the enzyme activity at time $t = 0$.

Heart tissue was obtained at autopsy from acute myocardial infarction patients without other pre-existing myocardial disease. Samples were taken in a homogeneous section of normal (n = 5) and infarcted (n = 5) myocardium. Tissue extracts were prepared according to *Tsung* (18). The left ventricular ejection fraction was determined during the second week of hospitalization using echocardiography (19).

### Compartment model describing quantitative release of myoglobin after acute myocardial infarction

In order to describe myoglobin kinetics after acute myocardial infarction, a compartment model was developed. In this model, the infarcted zone and the plasma pool are considered as different compartments. Animal models showed little differences in myoglobin kinetics between one- and two-compartment models (20). The biexponential character of iodine-labelled myoglobin washout curves, however, may reflect recirculating radioactive fragments of the parent molecule rather than true two-compartment kinetics of the parent molecule (20). Since a one-compartment model requires fewer measuring points for calculating cumulative myoglobin results, we used a one compartment model for routine clinical purposes. The myoglobin concentration in the human myocardium is about 110 nmol/g wet weight (9). After acute myocardial infarction, leakage of molecules occurs due to the faulty regulation of transmembraneous concentration gradients (21). Our experiments demonstrated relative losses of more than 65% of the initial myoglobin content of the infarcted zone, corresponding to an average myoglobin loss of 73 ± 15 nmol/g wet weight. After being released into the plasma, myoglobin is catabolized in the kidney (22). Otherwise, as long as plasma myoglobin concentrations exceed renal threshold values, myoglobin is partly excreted in the urine. In patients, renal threshold values for myoglobin have been reported to be 280 to 850 nmol/l (9). As maximal myoglobinaemia in acute myocardial infarction is between 6 and 250 nmol/l, the loss of myoglobin in the urine can be quantitatively neglected.

### Cumulative myoglobin release and infarct size

When using cumulative release as a model for estimating infarct size, inter-individual variations of post-acute myocardial infarction myoglobin kinetics must be taken into account. Mathematically, cumulative myoglobin release during a time interval 0-T can be estimated according to the following equation (6):

Cumulative myoglobin release

$$Mb_r = k_d \cdot \int_0^T Mb(t)dt \qquad \text{(Eq. 1)}$$

in which Mb($t$) represents the myoglobin concentration in serum at sampling time $t$, and $k_d$ the elimination constant for myoglobin in serum. The elimination constant was calculated from serially determined myoglobin concentrations after the myoglobin concentration had passed its peak, and during the time interval between 80% of the maximal myoglobin concentration and the moment that myoglobin concentrations were twice the upper reference range. In the presence of renal dysfunction or heart failure, and in cases of extended tissue injury, the haemodynamics are not always stable, and may show an unpredictable prolongation of the elimination rate (20). As the $k_d$ for myoglobin shows variations, the effects of $k_d$ variation on the determination of infarct size were studied by comparing algorithms using a fixed $k_d$ value with algorithms using an individualized $k_d$ value. In order to calculate infarct size, a proportionality constant K is introduced (6):

$$K = D \cdot [P_{Mb} \cdot (Mb_N - Mb_I)]^{-1},$$

in which $Mb_N$ represents the myoglobin concentration in normal myocardium, $Mb_I$ the myoglobin concentration in myocardium undergoing homogeneous infarction, D the volume into which myoglobin released from the heart is distributed, and $P_{Mb}$ the proportion of myoglobin released into the blood compared with myoglobin depleted from the heart. One gram myoglobin equivalent is defined as the amount of ischemic myocardium releasing myoglobin into the circulation equivalent to the amount released by 1 gram of myocardium undergoing homogeneous infarction. In the present study, we prefer a $P_{Mb}$-value of 0.15 as a compromise between direct efflux of the marker molecule and its post-acute myocardial infarction degradation. In experimental dog models, total recovery of myoglobin from infarcted zones is only observed in larger infarctions (total myoglobin release > 70 mg) (20). Furthermore, in vitro stability of myoglobin at physiological temperature over a 24 h period is about 20% (23). Finally, infarct size (g myoglobin equivalent) is obtained by taking into account the patient's body weight (kg). In view of the important variation in body weight in acute myocardial infarction patients (CV values of 15% (males) and 8% (females)), this quantity needs to be individualized: infarct size = $K \cdot Mb_r \cdot BW$.

*Practical calculation of infarct size*

In clinical practice, only a finite number of data on myoglobin concentration can be obtained. Infarct size was calculated from N consecutive myoglobin determinations as follows:

Cumulative myoglobin release

$$Mb_r = Mb(t_N) + k_d \sum_{i=1}^{N-1} Mb_i \, \Delta t_i \qquad \text{(Eq. 2)}$$

in which $Mb(t_N)$ represents the last myoglobin concentration of the observation period, $Mb_i$ the mean myoglobin concentration between two consecutive measurements after subtraction of the baseline concentration for serum myoglobin, and $\Delta t_i$ the time interval between two measurements.

With a median time interval of 8 h between onset of symptoms and the myoglobin peak, and a $k_d$ ranging from 0.041 $h^{-1}$ to 0.628 $h^{-1}$, the time needed to restore myoglobin concentrations to twice the baseline level in uncomplicated acute myocardial infarction was 30.2 ± 0.9 h after onset of symptoms. The summation interval for myoglobin release was chosen as 36 h (n = 19) or the time taken for serum myoglobin values to decrease to 3.4 nmol/l (n = 13). Prolonged integration may lead to overestimation, because myoglobin may be released for other reasons. In the rare acute myocardial infarction case (1/32) where myoglobin release occurred in two waves (due to discontinuity of infarction or the occurrence of reinfarction), both waves were sized independently. The intermediate minimal serum myoglobin concentration was used as the cut-off point between the two integration periods. Table 1 summarizes the values for the variables used in the algorithm for calculation of infarct size.

Tab. 1. Typical values for the different variables in the calculation of infarct size from cumulative myoglobin release

| Variable[1]) | Typical value |
|---|---|
| $Mb_N - Mb_I$, nmol/g wet weight | 73 |
| $k_d$, $h^{-1}$ | 0.127 |
| D, ml/kg body weight | 44 |
| $P_{Mb}$ | 0.15 |
| K, g myoglobin equivalent·ml/nmol·kg | 4 |
| T, h | 36 |
| Baseline serum myoglobin concentration, nmol/l | 2 |

[1]) $Mb_N$, tissular myoglobin concentration; $Mb_I$, myoglobin concentration in the infarcted myocardium; $k_d$, elimination constant; D, distribution volume; K, proportionality constant; $P_{Mb}$, proportion of immunoreactive myoglobin released into blood compared with myoglobin depleted from the heart; T, integration time interval.

Statistics

Results were expressed as mean and standard deviation. Statistical analysis was performed using non-parametric methods. Differences between groups were evaluated using two-tailed *Mann-Whitney* U test. Correlation analysis was performed by means of the *Pearson* correlation test.

## Results

### Appearance of myoglobin into the circulation after acute myocardial infarction

In acute myocardial infarction patients, repetitive serum samples were taken in order to study the kinetics of creatine kinase and myoglobin release after acute myocardial infarction. In 31 patients, one single myoglobin peak was observed. In one patient, a secondary myoglobin peak was observed 37 h after onset of symptoms. The median time interval between onset of symptoms and maximal myoglobin concentration in serum was 8 h (range 3 – 20 h). Thrombolytic treatment had no significant effect on the time to peak: 7.5 ± 2.9 h (non-thrombolysis group) vs. 8.0 ± 4.0 h, which is in agreement with the results obtained for creatine kinase-MB (19.2 ± 7.0 h vs 16.7 ± 5.9 h, respectively). Time to peak for myoglobin correlated moderately with time to peak for creatine kinase: y (time to peak for myoglobin, h) = 0.395 x (time to peak for creatine kinase, h) + 1.379, r = 0.645, $S_{yx}$ = 2.852. On average, peaks for myoglobin in serum preceded those for creatine kinase by 8.8 ± 4.6 h (fig. 1).

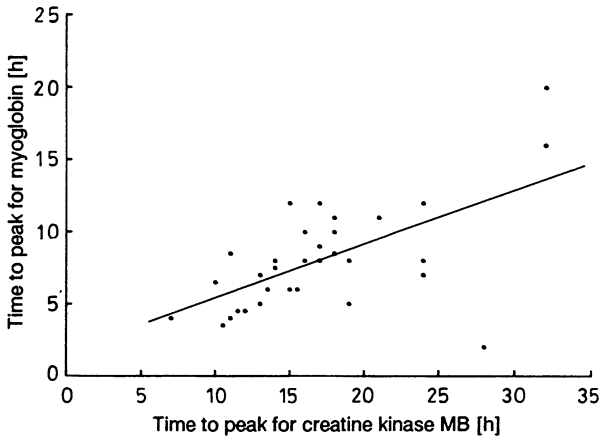


Fig. 1. Comparison between time to peak for creatine kinase (x-axis, h) and myoglobin (y-axis, h) after acute myocardial infarction. The equation for the correlation: $y = 0.395x + 1.379$ ($r = 0.645$, $n = 32$, $S_{yx} = 2.852$).

## Elimination of myoglobin from the circulation after acute myocardial infarction

Calculated $k_d$ values for myoglobin showed a large variation (median: $0.127\ h^{-1}$; range: $0.041-0.628\ h^{-1}$). In males, the median $k_d$ for myoglobin was found to be $0.128\ h^{-1}$ (range $0.041\ h^{-1}-0.270\ h^{-1}$), with comparable values in females (median $0.107\ h^{-1}$; range $0.041\ h^{-1}-0.628\ h^{-1}$). The highest $k_d$ values ($0.410\ h^{-1}-0.628\ h^{-1}$) were obtained in two cases who needed cardiopulmonary resuscitation during the acute phase. The elimination rate of myoglobin was not correlated with infarct size, as calculated by cumulative creatine kinase-MB release: y ($k_d$, $h^{-1}$) $= -3.44\ 10^{-2}x$ (log infarct size, g creatine kinase-MB equivalent) $+ 0.186$ ($r = -0.177$, $n = 29$, $S_{yx} = 0.069$). Elimination constants of myoglobin in anterior infarctions ($0.110 \pm 0.061\ h^{-1}$; $n = 12$) were comparable to those of inferior infarctions ($0.144 \pm 0.071\ h^{-1}$; $n = 16$). In the group of patients where thrombolytic therapy was contraindicated ($n = 5$), the median $k_d$ value was $0.134\ h^{-1}$ (range: $0.055-0.249\ h^{-1}$), which was not significantly different from the thrombolysis group.

Maximal serum myoglobin concentrations (median: 33.3 nmol/l; range: 7–320 nmol/l) were reached 3–20 h (median 8 h) after onset of symptoms. The myoglobin elimination constant was negatively correlated ($p < 0.05$) with patient age: y (elimination constant, $h^{-1}$) $= -2.69\ 10^{-3}x$ (patient's age, years) $+ 0.314$ ($r = -0.505$, $n = 30$, $S_{yx} = 0.06$). Table 3 summarizes the distribution of the elimination constant of myoglobin according to age. The effect of the initial serum creatinine concentration on $k_d$ values for myoglobin, was, however negligible.

## Correlations between maximal serum myoglobin concentration, cumulative myoglobin and enzyme release, and other indices of infarct size

Table 2 shows the individual data on creatine kinase-MB and myoglobin kinetics, together with the infarct size based on serial creatine kinase-MB and myoglobin release. Maximum myoglobin serum concentrations correlated well with cumulative myoglobin release: log(y) (maximal myoglobin concentration, nmol/l) $= 0.793$ log(x) (infarct size, g myoglobin equivalent) $+ 0.569$ ($r = 0.837$, $n = 29$, $S_{yx} = 0.254$).

Cumulative myoglobin release correlated well with cumulative release of creatine kinase: log(y) (infarct size, g myoglobin equivalent) $= 0.993$ log(x) (infarct size, g creatine kinase equivlanet) $-0.254$, $r = 0.622$, $n = 29$, $S_{yx} = 0.383$. Correlation with the heart-specific creatine kinase-MB isoenzyme was comparable: log(y) (infarct size, g myoglobin equivalent) $= 0.862$ log(x) (infarct size, g creatine kinase-MB equivalent) $+ 0.146$, $r = 0.660$, $n = 29$, $S_{yx} = 0.374$. The latter correlation coefficient was not statistically different from the one obtained between myoglobin-peak and cumulative creatine kinase-MB release (tab. 3). Figure 2 illustrates the correlation between infarct size calculated by cumulative myoglobin release and by cumulative creatine kinase-MB activity. Elimination constants for myoglobin and creatine kinase after acute myocardial infarction, however, did not corre-

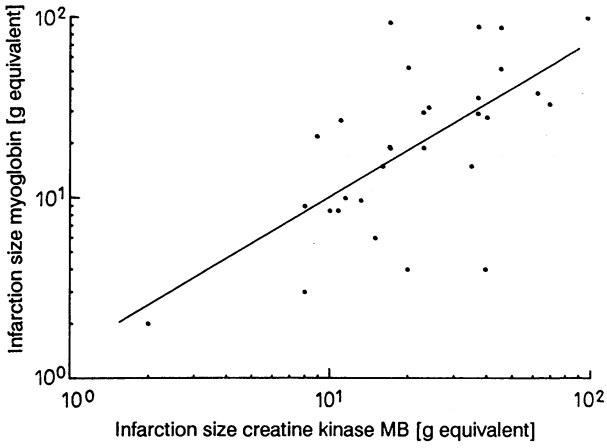


Fig. 2. Comparison between calculated infarct size based on cumulative release of creatine kinase-MB (x-axis, g creatine kinase-MB equivalent) and myoglobin (y-axis, g myoglobin equivalent) using individualized values for $k_d$. The unit of infarction size as calculated by our proposed method is an *artificial unit* obtained after calculations and after comparison with healthy myocardial tissue, therefore termed g equivalent. The same procedure has been done earlier by the group of *Roberts* et al. (6). The equation for the correlation: log(y) $= 0.862$ log(x) $+ 0.146$ ($r = 0.660$, $n = 29$, $S_{yx} = 0.374$).

Tab. 2. Individual data of acute myocardial infarction patients

| Patient no. | Thrombo-lysis (Yes/No) | Time to peak | | Peak value | | Infarct size[1]) | |
|---|---|---|---|---|---|---|---|
| | | creatine kinase-MB (h) | myoglobin (h) | creatine kinase-MB (U/l) | myoglobin (nmol/l) | creatine kinase-MB (g creatine kinase-MB eq) | myoglobin (g myoglobin eq) |
| 1 | No | 18 | 10 | 87 | 40.0 | 22.9 | 29 |
| 2 | Yes | 13 | 7 | 73 | 17.7 | 17.1 | 18.9 |
| 3 | No | 28 | 3 | 368 | 173 | 40.0 | 28.0 |
| 4 | Yes | 11 | 4 | 145 | 84.2 | 24 | 31.8 |
| 5 | Yes | 12.5 | 4.5 | 138 | 320 | 18 | 70 |
| 6 | Yes | 21 | 11 | 229 | 196 | 37 | 82 |
| 7 | Yes | 19 | 8 | 95 | 39.1 | 17 | 19.2 |
| 8 | Yes | 14 | 7 | 59 | 9.2 | 14 | 5 |
| 9 | Yes | 18 | 8 | 71 | 45.8 | 21 | 10 |
| 10 | Yes | 7 | 4 | 76 | 13.9 | 11.5 | 10 |
| 11 | Yes | 14 | 7.5 | 27 | 20.5 | 8 | 9 |
| 12 | Yes | 12 | 4.5 | 111 | 89 | 22 | 51 |
| 13 | Yes | 13 | 5 | 87 | 33.3 | 16 | 16 |
| 14 | Yes | 17 | 8 | 71 | 12 | 9 | 3 |
| 15 | Yes | 19 | 4 | 51 | 31.8 | 10 | 8 |
| 16 | No | 10 | 6.5 | 210 | 24 | 14 | 3 |
| 17 | No | 24 | 8 | 176 | 270 | 45 | 70 |
| 18 | Yes | 13.5 | 6 | 204 | 110 | 60 | 39 |
| 19 | Yes | 16 | 8 | 90 | 32 | 12 | 24 |
| 20 | Yes | 15 | 12 | 31 | 7 | 2 | 2 |
| 21 | Yes | 32 | 16 | 175 | 42.3 | 23 | 19 |
| 22 | No | 16 | 10 | 165 | 17 | 60 | 32 |
| 23 | Yes | 15.5 | 6 | 150 | 8 | 19 | 4 |
| 24 | Yes | 14 | 8 | 320 | 94.3 | 37 | 36 |
| 25 | Yes | 24 | 7 | 296 | 51.6 | 15 | 33 |
| 26 | Yes | 15 | 6 | 735 | 88.8 | 91 | 94 |
| 27 | Yes | 24 | 12 | 79 | 64 | 37 | 29 |
| 28 | Yes | 18 | 11 | 115 | 18.1 | 11 | 9 |
| 29 | Yes | 10.5 | 3.5 | 100 | 28 | 13 | 10 |
| 30 | Yes | 15 | 12 | 221 | 10 | 38 | 4 |
| 31 | Yes | 32 | 20 | 175 | 17.8 | 15 | 6 |

[1]) Data based on individualized $k_d$ values

Tab. 3. Distribution of elimination constant of myoglobin in acute myocardial infarction patients according to age

| Age group, years | n[1]) | Median (range), $h^{-1}$ |
|---|---|---|
| Under 50 | 5 | 0.224 (0.127–0.270)* |
| 51–70 | 12 | 0.110 (0.041–0.210) |
| Over 70 | 13 | 0.107 (0.055–0.249) |

[1]) The two female patients who needed intensive resuscitation procedures, which caused considerable skeletal muscle damage, were excluded.

* $p < 0.05$ *Mann-Whitney* U-test for difference with the acute myocardial infarction patients aged over 70.

late: y(myoglobin-$k_d$, $h^{-1}$) = 0.342x (creatine kinase-$k_d$, $h^{-1}$) + 0.125, r = 0.077, n = 29, $S_{yx}$ = 0.070. Correlations between measures of myoglobin release and other indices of infarct size are summarized in table 4. A moderate correlation was obtained with infarct size calculated using a standard 12-lead electrocardiography: log(y) (infarct size, g myoglobin equivalent) = 0.389x (sum of ST-deviations, mV) + 0.857, r = 0.470, n = 18, $S_{yx}$ = 0.424. The correlation coefficient between electrocardiogram and myoglobin release is comparable to the one obtained between electrocardiogram and creatine kinase-MB release: log(y) (infarct size, g creatine kinase-MB equivalent) = 0.323x (sum of ST-deviations, mV) + 1.07, r = 0.628, n = 18, $S_{yx}$ = 0.23.

Effects of body weight and $k_d$ variation on infarct size results were studied: for males and females, CVs of body weight distribution were 15% and 8%, respectively. Variation of $k_d$ was more important, with CVs of 46% (males) and 63% (females). Infarct size calculated by cumulative myoglobin release was inversely proportional to the residual ventricular function, as expressed by the left ventricular ejection fraction: y (log(infarct size), g myoglobin equivalent) = 15.13 (1/x) (left ventricular ejection fraction, %) + 0.885, r = 0.513, n = 15, $S_{yx}$ = 0.490.

Tab. 4. Correlation between quantities of myoglobin release and other indicators of infarct size

| y | Infarct size based on cumulative creatine kinase-MB release, g creatine kinase-MB equivalent (n = 29) | Infarct size based on electrocardiographic findings, mV (n = 18) |
|---|---|---|
| Maximum myoglobin concentration, nmol/l | log(y) = 0.626log(x) + 0.738<br>r = 0.488, $S_{yx}$ = 0.407 | log(y) = 0.747x − 0.394<br>r = 0.554, $S_{yx}$ = 0.503 |
| Cumulative myoglobin release, g myoglobin equivalent | | |
| fixed[1]) $k_d$ | log(y) = 0.763log(x) − 0.260<br>r = 0.435, $S_{yx}$ = 0.561 | log(y) = 0.579x + 0.702<br>r = 0.530, $S_{yx}$ = 0.530 |
| individualized $k_d$ | log(y) = 0.862log(x) + 0.146<br>r = 0.660, $S_{yx}$ = 0.374 | log(y) = 0.389x + 0.857<br>r = 0.470, $S_{yx}$ = 0.424 |

[1]) $k_d$: 0.127 $h^{-1}$

## Discussion

After acute myocardial infarction, the kinetics of myoglobin show large interindividual variations. The rate of appearance of myoglobin in the plasma correlates with the rate of appearance of creatine kinase. The effect of the pre-infarction glomerular filtration rate on the apparent myoglobin elimination rate during acute myocardial infarction is negligible. Patient's age correlates negatively with the apparent elimination rate of myoglobin from plasma, which can be explained by a decreased capacity of the kidney tissue to eliminate myoglobin from the plasma compartment upon ageing. These findings are in agreement with the increase of serum myoglobin reference values with age (11). Previously, *Roe* et al. (24) demonstrated in dogs that individualisation of $k_d$ data did not improve the estimation of infarct size. However, data from post-acute myocardial infarction creatine kinase kinetics in the dog model cannot be directly translated into human post-acute myocardial infarction myoglobin kinetics, due to the difference in physiological background in the release of myoglobin vs creatine kinase molecules from damaged myocardium (21). Moreover, different mechanisms operate in the elimination of myoglobin and creatine kinase molecules from the circulation. As the plasma half-life of myoglobin shows a considerable variation after infarction, an individualized estimation of the elimination constant is preferable for calculating the cumulative myoglobin release from serum myoglobin determinations, particularly in patients with large and complicated infarctions.

Maximal myoglobin values in serum correlate well with cumulative myoglobin release and infarct sizes calculated by cumulative creatine kinase-MB release and electrocardiography. These results are in agreement with earlier work involving non-thrombolysed infarctions (25).

In combination with fast quantitative myoglobin measurements (10, 11), the algorithm based on cumulative myoglobin release allows a relatively simple estimation of infarct size within 36 h after onset of symptoms, which is significantly shorter than the integration periods used in the methods based on cumulative release of cardiac enzymes (2, 6). This is advantageous in cases of muscle trauma, or reinfarction occurring from the second day of hospitalization onwards. From a theoretical point of view, the largest source of calculation errors potentially arises from uncertainty in estimating the myoglobin elimation rate, which is significantly faster than that for the majority of cardiac enzymes (26). Therefore, to obtain reliable sizing results, multiple myoglobin determinations in serum during the elimination phase are preferable.

In humans, cumulative myoglobin release is largely determined by the down-hill part of the curve (8 − 36 h after onset of symptoms). Thus, considerable post-acute myocardial infarction losses of immunoreactive myoglobin occur between its myocardial release and the prelevation of serum samples. A good correlation was obtained between sizing results obtained by cumulative myoglobin release and the results obtained by the method of *Roberts* (6). The method described allows much simpler calculations in comparison with the sizing algorithms proposed by *Groth* (27 − 29). Furthermore, changes in myoglobin elimination rate induced by age are taken into account and secondary myoglobin peaks (staccato phenomenon, (30)) can be quantified. Although results obtained with non-individualized $k_d$ do not differ significantly from the results using individualized $k_d$ values, differences may be considerable in certain cases. Values obtained by calculation of cumulative myoglobin release are generally lower than those obtained by cumulative release of creatine kinase or creatine kinase-MB. This can be

explained by the faster kinetics of myoglobin, which induce a larger relative difference between the area under the curve, as calculated for the ideal situation (Eq. (1)) and the clinical approximation (Eq. (2)). The use of a one compartment model can lead to a small underestimation of infarct size (20). Moreover, cumulative activity measurements of cardiac enzymes may overestimate the actual infarct size, because of post-synthetic changes occurring after enzyme release from the myocardium, which lead to rapid loss of specific activity (31). Methods based on cumulative enzyme activity measurements overestimate infarct size after reperfusion (32).

In contrast to methods based on 12-lead electrocardiography or nuclear scintigraphy, the results obtained by cumulative myoglobin release are not influenced by infarct localization. Particularly, infarctions involving the posterior wall are difficult to diagnose, as none of the standard leads directly interrogates this region (33). In non-Q wave infarctions, nuclear scintigraphy is an insensitive test for detecting acute myocardial infarction (34). Infarct sizes calculated by the proposed algorithm correlated moderately with the residual left ventricular ejection fraction, which is known to be a prognostic factor, related to infarction size (35).

If the acute myocardial infarction is accompanied by significant skeletal muscle damage during the early phases (e. g. intramuscular injections, cardio-pulmonary resuscitation), the proposed sizing method described cannot be used, because of concomitant release of myoglobin from skeletal muscle (typical tissue myoglobin content: 200 to 250 nmol/g wet weight), resulting in a significant overestimation of infarct size. However, this problem is also encountered when using cardiac enzymes as marker molecules, because skeletal muscle contains large quantities of "cardiac" enzymes. When infarct size is calculated from the results of other immuno-assays for myoglobin (RIA, ELISA), the values for $Mb_N$ and $Mb_I$ may differ, because the results for heart tissue myoglobin are assay-dependent (10).

We compared algorithms for calculating infarct size based on post-acute myocardial infarction myoglobin release. In contrast to former RIA methods, the fast immunonephelometric and immunoturbidimetric assays produce quick results, available on a 24 h basis. Infarct size obtained by myoglobin peak height allows a first approximation of infarct size within 12 h. Results based upon cumulative myoglobin release give data comparable to those based on cumulative creatine kinase or creatine kinase-MB release, but are only available after 30 to 36 h. Whether the estimation of infarct size one or two days earlier is clinically relevant remains to be proven in further studies. However, the shorter integration interval needed for myoglobin protects against errors due to non-cardiac enzyme release from the 36th hour onwards. Individualisation of the elimination constant is preferable for calculating cumulative myoglobin release, particularly in patients with large and complicated infarctions.

**Acknowledgement**

We thank Dr. *T. Fiers* for his helpful discussions.

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Joris R. Delanghe, MD, PhD
Dept. of Clinical Chemistry (1B2)
University Hospital
De Pintelaan 185
B-9000 Gent
Belgium