

Quantification of Myocardial Infarction: Template Model for Serial Creatine Kinase Analysis

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SUMMARY A self-modeling procedure was used to develop a template $g(z)$ from the serial creatine kinase (CK) release in 32 patients with acute myocardial infarction. An additional 16 patients were used as an extrinsic test of the template model. For a given patient the fitted CK curve $\gamma(t)$ is related to the template $g(z)$ by the expression $\gamma(t) = \beta_1 g\left(\frac{t - \beta_2}{\beta_3}\right) + \beta_4$, where β_1 is equal to the peak height of the CK transient above background,

β_4 , β_2 is the time at which CK begins to rise, β_3 is the time taken for CK to rise to its maximum value. Calculations of infarct size using the template and a numerical estimate yielded values of 34.6 g-Eq and 33.5 g-Eq, respectively, with good agreement ($r = 1.00$). Comparisons of all point numerical estimations of infarct size with early point predictions revealed that the template and lognormal models performed equally well with 7 and 6 points; however, the template model was superior with 5 and 4 points. The template model also provides insight into the CK time activity curve. In particular, total CK activity and hence infarct size, are shown to be proportional to the peak of the excess CK curve, and the time course of CK appearance is revealed by the appearance and cumulative appearance functions.

We found a high correlation between all point estimates of completed infarct size and a linear estimate obtained by fitting a straight line to the ascending portion of the CK curve.

THE RELEASE of creatine kinase (CK) from damaged myocardial cells is a useful marker of myocardial infarction. In animal experiments of acute myocardial necrosis, analysis of the serial changes in this enzyme has been performed using a one-compartment mathematical model with a numerical calculation to quantitate the extent of myocardial damage.¹ This analysis has shown good agreement between indirect enzymatic estimates of infarct size and those directly estimated histologically 24 hours later. Although the validity of quantitating myocardial infarction by this method has been questioned,² a recent study by Bleifeld and co-workers suggests a good correlation between estimates of infarct size in man from serial CK determinations and those made histologically.³

A refinement of this approach involving the fitting of a lognormal function to serial CK data by a least-squares method has permitted estimation of the extent of myocardial damage during the early hours of evolution of the infarction.⁴ Using this technique experimentally, infarct size estimated on the basis of CK curves projected from early data points agreed favorably with infarct size measured from all data points and with direct histologic measurements of infarct size. However, important difficulties remain in using the lognormal model to predict infarct size.⁵ We

present a new empirical model for the analysis of serial CK data using the method of self-modeling nonlinear regression.⁶ This procedure extracts an average shape or template from a group of patients, and then fits this template to each patient's serum CK curves.

The template approach provides insight into the CK time-activity curve and its relation to infarct size, quantification of the error involved in infarct size estimation, efficient use of data, more accurate early projections of ultimate infarct size, a new method of predicting infarct size from analysis of the ascending slope of the CK curve, and estimates of sample sizes required for studies of therapeutic intervention.

Methods

Twenty-eight males and four females (mean age 57 years, range 37–82 years) with acute myocardial infarction formed the initial study group. Patients were excluded if they had sustained hypotension (less than 85 mm Hg systolic), an intramuscular injection, or if their initial CK was above the normal range. All patients had myocardial infarction documented by typical evolutionary electrocardiographic changes and serial rises in serum glutamic oxaloacetic transaminase and CK. Sixteen patients had transmural inferior, seven transmural anterior, and nine nontransmural myocardial infarctions. Sixteen other patients with myocardial infarction who were not included in the development of the template formed a second study group and were used as an extrinsic test of the template model. In this group, there were 11 males and five females (mean age 60, range 39–76 years). Twelve had transmural inferior, two had transmural anterior and two had nontransmural myocardial infarctions.

None of the patients took cardiotonic agents during the study, and four received diuretic therapy. There was no clinical, electrocardiographic or enzymatic

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evidence of extension of myocardial infarction during the study period.

After admission to the coronary care unit, a heparin lock was inserted into a peripheral vein. Blood was sampled hourly for the first 8 hours, every 2 hours for the next 16 hours and every 4 hours for the next 24 hours. The analysis of total CK activity was carried out using the automated ABA-100 System* and the A-Gent Test Pack.* The assay was carried out at 37°C and is based on Oliver's modification of the Rosalki method,^{7, 8} except that NAD is substituted for NADP. Results are expressed in milli-units per milliliter of serum (mIU/ml). The normal range is 33–188 mIU/ml at 37°C and corrected to 30°C is 22–113 mIU/ml.

Terms

ISO = observed infarct size calculated by a numerical approximation and using an individualized K_d .

ISP = predicted infarct size from early data points and decay data.

IS = estimate of infarct size using template parameters.

ISN = numerical infarct size using template parameter estimates for baseline subtraction and K_d calculation.

ISL = linear estimate of infarct size from early points only without decay data.

AvISN = average of the numerical estimates of infarct size (i.e., of ISO and ISN).

Analysis of Data

The One-Compartment Model

The assumptions involved in determining infarct size from serial measurements of CK activity are 1) that the instantaneous change in excess CK activity $E(t)$ is due to the difference between an appearance function $f(t)$ and the disappearance function, 2) that the rate of disappearance of CK is a constant fraction K_d , of excess CK activity, 3) that infarct size is directly proportional to CK_r , the total amount of CK released into the blood, and 4) that CK_r is a constant fraction (P_{CK}) of the total CK depleted from damaged myocardium.

Using (1) and (2), the appearance function is

$$f(t) = \frac{dE(t)}{dt} + K_d E(t)$$

and the cumulative activity of CK per unit volume of blood at time T is

$$CK_r = \int_0^T f(t) dt.$$

Using assumption 3, a gram equivalent (g-Eq) estimate of infarct size is

$$BW \cdot K \cdot \int_0^T f(t) dt \quad (1)$$

where $K = \frac{DV}{P_{CK}(CK_N - CK_I)}$ is the proportionality constant, BW = body weight (kg), DV expresses plasma volume as a proportion of body weight, P_{CK} is the proportion of CK depleted from the heart which is released into the blood, CK_N is the activity of CK in a homogeneous section of normal myocardium, and CK_I is the activity of CK in a homogeneous section of infarcted myocardium.

We have used the following values; $K = 0.32$, $DV = 44$ ml/kg, $P_{CK} = 0.15$, $CK_N = 680$ U/g, $CK_I = 180$ U/g (by analogy from percent of myocardial CK depleted measured directly in conscious dogs 24 hours after occlusion), $(CK_N - CK_I) = 910$ U/g; corrected from 500 U/g for A-Gent (Abbott) determination.

Conventional Estimation of Infarct Size

Determination of infarct size by serial analysis of CK was initially done according to the method of Shell et al., incorporating recent modifications.⁹ Thus, the integral expressed in equation 1 was calculated by numerical approximation. This estimate has been called an observed estimate of infarct size (ISO). Baseline subtraction was performed according to the method previously described.⁴ Individualized values for K_d were obtained from the slope of the best-fitting straight line to the logarithm of a portion of the descending part of the CK curve. This modification was incorporated because the ISO is directly proportional to the K_d value used and K_d varies widely in humans.¹⁰

Early Point Predictions Using the Lognormal Model

Patients with uncomplicated myocardial infarction have a common shape to their serum CK curve that resembles a lognormal function. Projections of infarct size have been obtained using the serum CK values in the first 7 hours exceeding the normal range by selecting the best-fitting lognormal function and integrating the projected excess CK values.⁴ The lognormal function used to describe the excess CK activity is

$$E(t) = \frac{b}{t} \exp - \frac{1}{2} \left(\frac{\ln t - c}{d} \right)^2 \quad (2)$$

where \exp = the exponential function, t = time, b , c , d are parameters estimated by a least squares fit to each patient's data, and \ln is the natural logarithm.

The parameters b , c , and d were estimated using nonlinear least squares, an iterative procedure that requires accurate starting values. These were obtained from published bounds on the parameters.^{4, 11} As with ISO, baseline levels of CK activity must be subtracted before analysis.

Projections of infarct size (ISPs) using the lognormal model have been performed in this study using an individualized K_d , which is different from the previous approach.

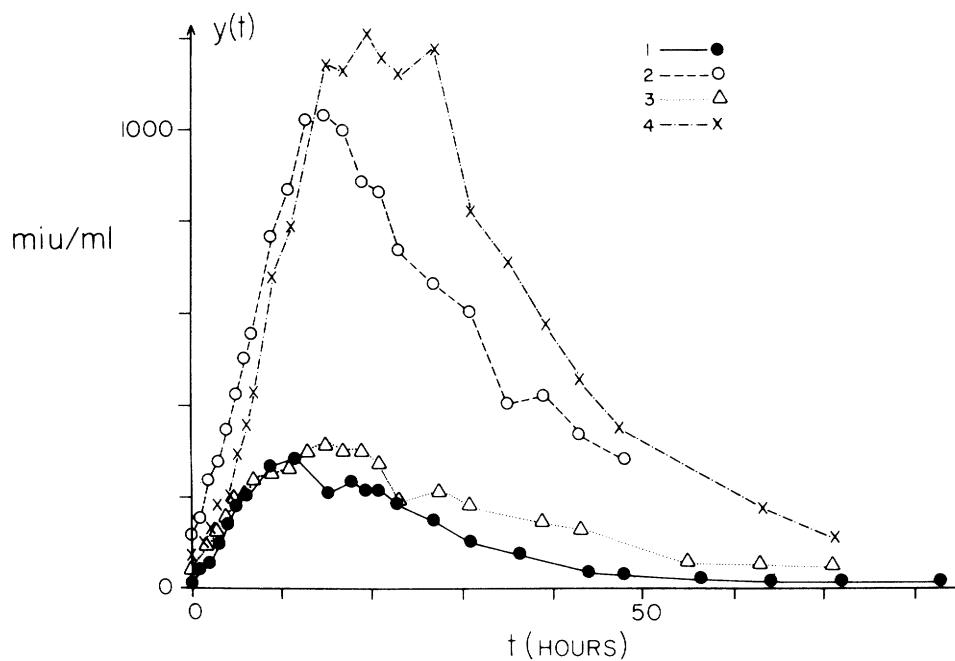


FIGURE 1. Individual serum creatine kinase data for patients 1-4 (see table 1).

Development of the Template Model

Instead of imposing a lognormal function upon serial CK data, we used the self-modeling approach of Lawton and Sylvestre on the 32 patients in the initial study group to determine a template or common intrinsic functional relationship of serum CK concentration over time.⁶ Figure 1 shows CK data $y(t)$ plotted against time (t) for four patients. Although there is general similarity in the shape of the curves, they start from different levels at different times and rise to different peaks at different times. The similarity in shape suggests that transformation of the data by shifting and scaling in both vertical and horizontal directions would result in a common intrinsic function.

In figure 2, the data are transformed and plotted so that each set of CK data starts from a height near zero around time zero and rises to its peak value arbitrarily defined as 1, at a time likewise defined as 1. The data thus transformed show a fairly consistent CK transient response or template.

Figure 3 shows patient 2's data and fitted CK curve $\gamma(t)$. Mathematically, an individual patient's curve $\gamma(t)$ is related to the template $g(z)$ by the expression

$$\gamma(t) = \beta_1 g\left(\frac{t - \beta_2}{\beta_3}\right) + \beta_4 \quad (3)$$

where β_1 is the peak height of the CK transient above background (mIU/ml), β_2 is the time in minutes at which CK begins to rise above baseline, β_3 is the time in minutes for CK to rise above the background β_4 to its maximal value of $\beta_1 + \beta_4$, and β_4 denotes background CK level in MIU/ml.

The template function $g(z)$ is obtained through the use of cubic splines, a set of cubic functions defined over adjacent regions. At the end points of each region

the contiguous cubics are constrained to match in height, slope and curvature. Once these constraints are satisfied and the heights are determined, the spline function is specified. The procedure for determining $g(z)$ is an iterative one in which the template and parameter estimates are alternately revised and improved. An important refinement introduced into the self-modeling approach was the use of weighted rather than simple least squares to account for the intrinsic variability of the CK method.

Templates were obtained using four groups of eight patients who were randomly allocated. These templates were very consistent on the rise portion and reasonably stable on the decay side. The plot of $g(z)$ in figure 4 shows the final template which was obtained from all 32 patients and is the template used in all subsequent calculations.

CK Activity

In figure 4 $g(z)$ rises almost in a straight line until it reaches 85% of its peak value; on the decline side, from 85% of the peak value, the template falls exponentially, suggesting the appropriateness of the first-order equation describing CK disappearance. This was clearly demonstrated by a log-linear plot of the decay portion of the template which gave no evidence of more complicated dynamics than first order.

The assumption of a common intrinsic functional form for CK activity implies a common shape for the appearance function and the cumulative CK activity curves. This cumulative activity represented by $CK_r(z)$ in figure 4 shows, for example, that 50% of the CK is released by approximately 0.5 units of z , which corresponds to about 7 hours from onset time in our patients. Also shown in figure 4 is the CK appearance

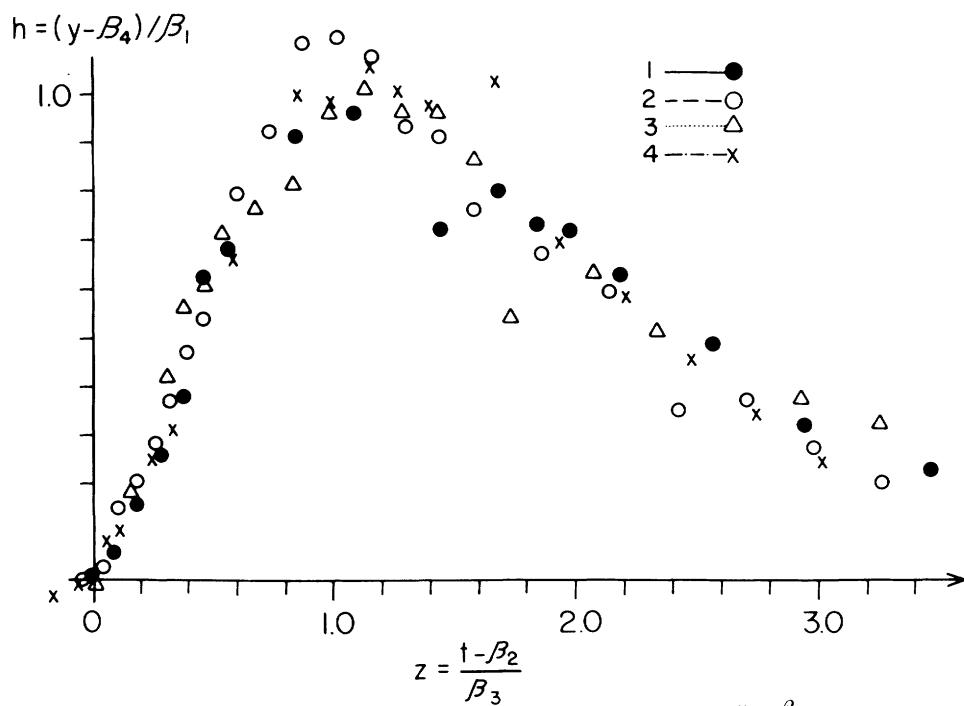


FIGURE 2. Figure 1 reported with standardized data; h (standardized CK) = $\frac{y - \beta_4}{\beta_1}$ where y = a particular CK observation, β_4 = background in mIU/ml and z (standardized time) = $\frac{t - \beta_2}{\beta_3}$ where t = a particular time, β_2 is time (hours) at which CK begins to rise above baseline, β_3 = time (hours) for CK to rise from β_4 to its maximal value $\beta_1 + \beta_4$.

function $f(z)$ which peaks at its maximum at about 0.5 units of z .

For a patient with peak excess CK, onset time, rise time and baseline parameters given by β_1 , β_2 , β_3 and β_4 , respectively, for the template model, CK_r (and hence infarct size) is directly proportional to β_1 and is independent of β_2 , β_3 and β_4 (see Appendix). The decay parameter K_d is inversely proportional to β_3 and is

therefore not involved in the calculation of infarct size. Numerical estimates and lognormal ISP implicitly involve an individualized K_d value in the calculation of the area under $E(t)$. Thus an individual K_d value must be used in these instances to effect the proper calculation. The slope of the ascending part of the CK curve is proportional to β_1/β_3 ; this is useful when decay data are not available for analysis.

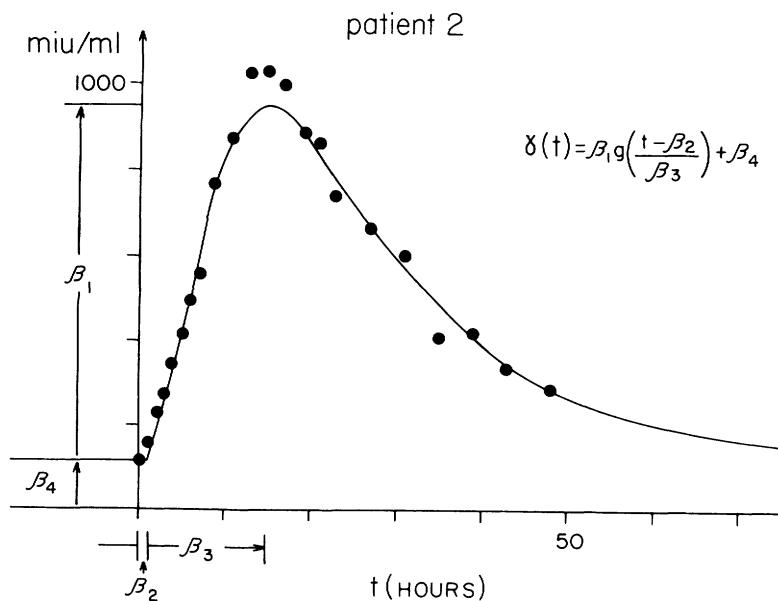


FIGURE 3. Individual data of patient with fitted curve to the data.

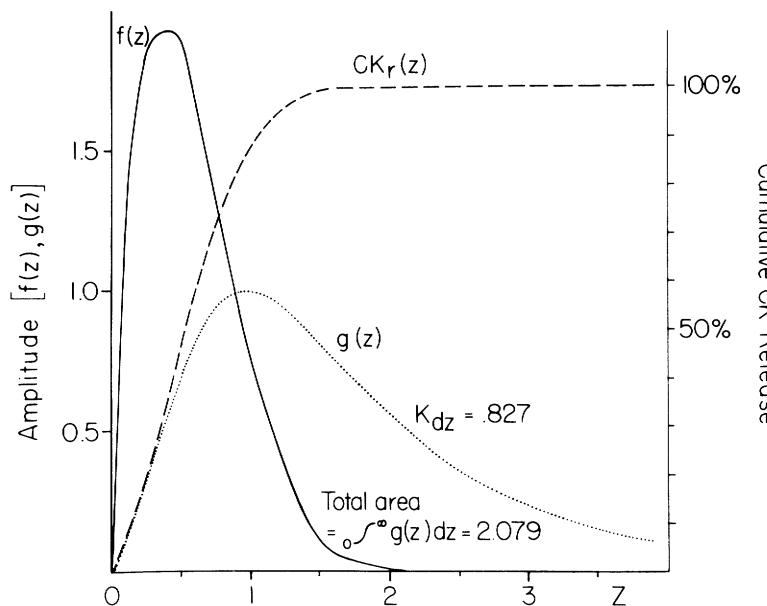


FIGURE 4. Plots of the template $g(z)$, $CK_r(z)$ and the appearance function $f(z)$ are shown. The left vertical axis represents amplitude for $f(z)$ and $g(z)$. The right vertical axis represents percent cumulative CK release. Since the data provide little information about the early part of the template and the subsequently derived $f(z)$, the early behavior of $f(z)$ has been schematized.

Estimation and Projection of Infarct Size Using the Template Model

Given an observed serum CK curve for a patient, an estimate of infarct size (IS) was obtained by first estimating the four parameters using weighted nonlinear least squares and the formula

$$IS = 5.542 \cdot 10^{-4} \cdot BW \cdot \beta_1 \quad (4)$$

which is derived in the Appendix. The standard error of this estimate was obtained from the standard error of β_1 . Starting values for the iterative estimation procedure were obtained from visual inspection of the data curve.

To project infarct size, we fit the first part of the template to the early data and the exponential decay portion of the template to the decay data. Early data were defined as CK readings up to 7 hours from onset and decay data as CK readings whose values were less than 80% of the peak. The composite model is

$$\gamma(t) = \begin{cases} \beta_{1g} \left(\frac{t - \beta_2}{\beta_3} \right) + \beta_4, & t \leq t_p, \\ \beta_5 \exp - K_{dz} \left(\frac{t - t_d}{\beta_3} \right) + \beta_4, & t \geq t_d, \end{cases} \quad (5)$$

where t_p is the time of the last early value, t_d is the time of the first decay value, β_5 is an extra parameter representing the height of the CK curve at the beginning of the decay phase, and K_{dz} is the decay constant of the template. This procedure incorporates early and decay data, and hence efficiently estimates β_1 , and so infarct size using equation 4. If the shape of the serum CK curve does not conform to the shape of the template, e.g., after a therapeutic modification, a numerical calculation (ISN) must be made. This calculation is identical to that of ISO except that a correct baseline value for subtraction is provided by

the β_4 estimate and an individual estimate of K_d is derived from the estimate of β_3 .

Estimation of Infarct Size Using a Linear Model

During our analysis we could obtain a good estimate of infarct size from early data only because there was a strong relationship between the template estimate of infarct size and the initial rate of rise, K_r . Therefore, we developed a procedure to estimate the initial rate of rise, K_r , by fitting a linear model to the first seven points on the rise using weighted least squares. We then regressed \ln infarct size against $\ln(K_r \cdot BW)$ and obtained the following relationship for linear infarct size (ISL) using the template group of 32 patients:

$$\ln ISL = -4.161 + 0.9016 \ln K_r \cdot BW \quad [r = 0.84, SE = 0.345] \quad (6)$$

This relationship was then tested using the extrinsic group of 16 patients.

Results

Infarct size estimates were calculated numerically as well as using the lognormal and template models. For ISO and lognormal infarct size, K_d was estimated using the Norris method; for ISN and template infarct size, β_1 , K_d (derived from β_3), and the β_4 estimates were used in the calculations (see equation 4 and the Appendix). Lognormal infarct size averaged 35.6 ± 3.3 g-Eq (SEM) and template infarct size averaged 34.6 ± 3.8 g-Eq. Percent standard errors for each template model estimate of infarct size were calculated and averaged 4.6%. There was good agreement between ISO and lognormal infarct size ($r = 0.99$) and between ISN and template infarct size ($r = 1.00$). There was also a high correlation between ISO and

TABLE 1. Comparison of ISP with AvISN

	n	Lognormal ISP				Template ISP			
		7	6	5	4	7	6	5	4
Correlation (r)	32	0.76	0.75†	0.39†	0.44††	0.84	0.79	0.71	0.68
(ISP with AvISN)	16	0.78	0.66	0.18†	0.43†	0.92	0.91	0.88	0.88
	48	0.77	0.71†	0.29**	0.43‡‡	0.87	0.82	0.75	0.72
Mean differences	32	-0.036	-0.144	-0.066	-0.414	-0.100	-0.094	-0.094	-0.155
(log ISP - log AvISN)	16	-0.144	-0.240	-0.473	-0.274	-0.259†	-0.329‡	-0.409‡	-0.521§
	48	-0.072	-0.176	-0.209	-0.368	-0.153†	-0.172*	-0.199*	-0.277‡
Root mean square	32	0.452	0.606	0.923*	1.418§	0.404	0.490	0.543	0.687
	16	0.531	0.746	1.327‡	1.102	0.425	0.489	0.569	0.673
	48	0.480	0.656*	1.074§	1.321§	0.407	0.490	0.579	0.682

A *t* test was used to assess whether mean differences were significantly different from 0; an *F* test was used to assess whether mean square values for the lognormal and template models were significantly different.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.005$.

§ $p < 0.001$.

†ISP < 1 and was replaced by 1 so log ISP = 0 for 1 patient.

**ISP < 1 and was replaced by 1 so log ISP = 0 for 2 patients.

††ISP < 1 and was replaced by 1 so log ISP = 0 for 5 patients.

‡‡ISP < 1 and was replaced by 1 so log ISP = 0 for 6 patients.

Abbreviations: ISN = numerical calculation of infarct size; ISP = projection of infarct size; ISO = observed estimate of infarct size; AvISN = average of ISO and ISN; n (horizontal) = number of points used for prediction; n (vertical) = number of patients in study group.

ISN ($r = 0.95$) and lognormal and template infarct size ($r = 0.92$).

The characteristics peculiar to each model make direct comparison of infarct size estimates impossible without the selection of a common standard; we have chosen the average of ISO and ISN (AvISN) because they are relatively model-free. (Differences in these values are due to different baseline estimates and K_d estimates.) Comparison of the differences between any estimate of infarct size with the standard revealed a variability proportional to the estimate. Hence, to account for heterogeneity of variance, we decided to use a logarithmic transformation of all infarct size estimates. All subsequent comparisons use natural log (\ln) estimates.

Table 1 shows summary statistics comparing AvISN with early data point ISPs (made with 7, 6, 5 and 4 data points) using the ISP program.¹¹ Because lognormal predictions of infarct size were less than 1 in some instances, they were replaced with the value 1 so that the log would be 0. This procedure allows comparison of all patients and favors the lognormal model, because it accommodates those instances where very small predictions were made. For this and subsequent tables, in addition to correlations tabulated in the upper panel, we compared the mean log differences in the midpanel and the root mean square (RMS) values in the lower panel. Mean log differences were used to test bias of infarct size estimates against a chosen standard. The RMS was used as an index of total variability of the estimate about the standard. The RMS values are a composite of the mean differences and the variability of these

differences. The template projections have a consistently higher correlation with AvISN than do the lognormal projections, and this difference becomes particularly apparent with the 5- and 4-point projections. This is achieved with consistently lower total variability, which accounts for some mean differences of the template showing statistical significance.

Table 2 shows summary statistics comparing template and lognormal projections of infarct size with the corresponding numerical estimates of infarct size for 7, 6, 5 and 4 early data points. The template model predictions were compared against differing ISNs, depending on the number of early points available, since this influences the β_4 and K_d estimates. Previously reported lognormal predictions are compared against a single standard, i.e., ISO. There is little difference in the correlation between 7- and 6-point projections and numerical estimates using either model, but there is a much higher correlation for the template model with 5 and 4 points. In the additional 16 and in the combined group of 48 patients, correlations are consistently better for the template model regardless of the number of points used for prediction. Again, the RMS values are generally larger for the lognormal model than the template. The mean differences for the template are generally smaller, i.e., the template projections are less biased.

Using the linear regression relationship developed for the template group, we estimated ISL for the extrinsic group and compared it with infarct size. This revealed a good correlation ($r = 0.84$) with a mean difference of -0.337 ($p < 0.05$) and an RMS of 0.538. This technique requires a good method for deter-

TABLE 2. Comparison of ISP with Numerical Estimates of Infarct Size

	n	Lognormal				Template			
		7	6	5	4	7	6	5	4
Correlation of ISP with ISO for lognormal and ISN for template	32	0.77	0.76†	0.40†	0.43††	0.77	0.70	0.61	0.56
	16	0.80	0.69	0.20†	0.42†	0.87	0.85	0.82	0.83
	48	0.78	0.73†	0.29**	0.43††	0.81	0.75	0.68	0.64
Mean differences	32	-0.091	-0.197	-0.118	-0.467	-0.099	-0.087	-0.086	-0.145
	16	-0.217	-0.313	-0.566	-0.347	-0.182	-0.256*	-0.388*	-0.431‡
	48	-0.131	-0.235*	-0.268	-0.427*	-0.127	-0.143	-0.170	-0.241*
Root mean square	32	0.451	0.604	0.926*	1.439§	0.491	0.567	0.662	0.771
	16	0.534	0.744	1.339‡	1.128*	0.470	0.520	0.583	0.649
	48	0.480	0.654	1.081§	1.344§	0.484	0.552	0.637	0.732

A *t* test was used to assess whether mean differences were significantly different from 0; an *F* test was used to assess whether mean square values for the lognormal and template models were significantly different.

**p* < 0.05.

†*p* < 0.01.

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†ISP < 1 and was replaced by 1 so log ISP = 0 for 1 patient.

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Abbreviations: ISP = projection of infarct size; ISO = observed estimate of infarct size; ISN = numerical calculation of infarct size; n (horizontal) = number of points used for prediction; n (vertical) = number of patients in study group.

mining the onset of CK elevation since the inclusion of points before onset would lead to underestimation of K_r and hence of infarct size. Using the CK data between the onset time, β_2 , as determined by using all the data, and the seventh point on the rise, we improved the correlation to 0.90 and reduced the standard error to 0.306 in the template group; in the extrinsic group, the *r* value rose to 0.91 and the mean difference and RMS value changed to -0.242 (*p* < 0.05) and 0.440 respectively. Furthermore with this refinement, reasonable linear projections using fewer than 7 points were achievable; for example, in the extrinsic group using 5 points we obtained a correlation of *r* = 0.86, a mean difference of -0.323 and an RMS of 0.512.

Discussion

The template model has been shown to provide valuable information about the behavior of the CK time-activity curve. First, total CK activity, and hence infarct size, are directly proportional to the peak of the excess CK curve. Although this has been suspected, a close correlation has previously not been obtained. Second, CK_r , and hence infarct size using the template, do not depend on K_d as do the numerical and lognormal estimates of CK_r . Third, the temporal relationship between the excess CK curve, the appearance function and the cumulative CK activity curve demonstrated in figure 4 highlight the necessity of early interventions if jeopardized myocardium is to be salvaged. Finally, the rate of rise of the CK curve has been shown to contain data pertinent to the estimation of infarct size.

These observations do not depend on the empirical function we have used for the template. The critical assumption is that each patient's curve when shifted and scaled in both horizontal and vertical directions conforms approximately to the same standard shape. Should future research provide a more physiologically based model for $f(t)$ or $E(t)$ that fits the data as well, it could be substituted. A change in one or more of the assumptions concerning the relationship between CK appearance and actual infarct size could easily be incorporated into this procedure. For example, if a smaller proportion of CK is released into the blood during larger infarcts, this relationship could be estimated and used in place of the simple proportionality constant in equation 1.

To estimate infarct size using a complete CK curve, we recommend fitting of the template to the data to obtain β_1 and then calculating infarct size using equation 4. This estimate should be more accurate than the numerically calculated ISO, since 1) the onset time and baseline value are determined in a reasonable fashion, 2) the fitted template smooths the irregularities in the observed data, allowing a good estimate of true peak excess CK, and 3) the selection of a value for K_d is unnecessary. The standard error of the estimate quantifies the uncertainty involved in calculated infarct size and can be used, for example, to compute confidence intervals.

To project infarct size, we have departed from previous work by using data on the decay part of the curve. Such data will generally be available, and projections obtained using a common value for K_d will not provide as true an estimate of actual infarct size. The rising portion of the curve before intervention

contains information about β_2 , β_4 and the ratio β_1/β_3 . Decay data provide further additional information about β_4 and β_3 ; including decay data allows for the extraction of an estimate of β_1 and, hence, infarct size. Thus both template and lognormal models in this study include decay data. Even if K_d were to change as a result of an intervention, the template model may be modified to provide reasonable predictions if the form of this change is known.

The average standard error of infarct size estimates made from the template model increased from 5% for all points to 17, 20, 22 and 28% for 7, 6, 5 and 4 early points, respectively. The standard error of predictions made without decay data would be much larger. Standard error limits about projected lognormal curves have been used to demonstrate deviations of actual projected CK values after extension or interventions.¹² However, such limits are not true prediction limits since they do not account for the error involved in choosing the best fit curve; hence, true prediction limits would be much wider.¹³

In comparing the capacity to project completed infarct size from early data points in table 1, the template proves superior, and as the number of data points available for early point projections is reduced, the lognormal model rapidly breaks down, as reflected by the much lower correlations and higher RMS values at 4- and 5-point projections. The data in table 2 relate ISP to numerical estimates (ISO or ISN) and are relevant to intervention studies. The lognormal and template models perform equally well with 7- and 6-point projections. The performance of both models diminishes when 5- and 4-point projections are made; in the case of the template, the estimates, while less reliable, are still reasonable; in the case of the lognormal model, they are unreliable.

Studies that use the template model to assess the effects of an intervention on infarct size estimation can use the measures of variability obtained in our study. Table 3 shows the approximate sample size required to estimate the change in \ln (infarct size) with specified precision. For example, using the template model and the first six points on the rising portion of the CK curve, a sample of 18 patients in a particular intervention study would yield a 95% confidence region of ± 0.25 about the observed average difference. If the

observed average difference was -0.28 , for example, then one can state with 95% confidence that the intervention produced a reduction of between -0.03 and -0.53 ; if the observed difference was only -0.14 , the 95% confidence interval would be -0.39 to $+0.11$; since this includes 0 there is insufficient evidence that the intervention caused any real reduction. These sample sizes were obtained by assuming that in subsequent studies the standard deviation of \ln ISN - \ln ISP will be the same as the observed values recorded in the last column of table 3, which are based on all 48 patients. (For ease of interpretation, small differences and small confidence interval end points for the logs may be regarded as approximately equal to the same proportional change in infarct size. For the second example, the values -0.39 , -0.14 and $+0.11$ correspond to actual proportional changes of $e^{-0.31} = 0.68$, $e^{-0.14} = 0.87$, and $e^{+0.11} = 1.12$, giving changes of -0.32 , -0.13 and $.12$).

There are many difficulties involved in using the lognormal function for prediction. First, it is restricted in form so that it cannot adequately represent CK data, as can be demonstrated by considering a plot of $\ln E(t)$ vs $\ln t$ as in figure 5; in this metric, it is clear that $\ln E(t)$ is a parabola and hence, for the lognormal model to be appropriate, plots of $\ln CK$ vs $\ln t$ should be symmetric. In figure 5, which represents the data for the four patients used in figure 1, this is not the case, and a consistently steeper fall from the peak is noted compared with the rise to the peak. The template, on the other hand, was generated from observed CK values in 32 patients and fits closely the curves of the 48 patients in both the development group and extrinsic test group.

Second, in fitting the lognormal model, the baseline is assumed to be the first value judged to be on the rising portion of the curve and the time origin is assumed to be the t value at that observation. Arbitrarily setting the baseline and time origin to the value and time of the first rising observation respectively, constrains the model-fitting and adversely affects the parameter estimates and subsequent derived quantities. This can influence the lognormal calculations of infarct size; in particular, infarct size predictions for patients who are well into infarction at their first CK data point would be underestimated. In our procedure, no such assumptions about the baseline, β_4 , or the onset time, β_2 , are made, so a truer integration of excess CK is possible.

Third, the parameters of the lognormal model do not allow simple meaningful interpretations, nor do they bear a simple relationship to infarct size. By contrast, the parameters in the template model have simple direct interpretations. In particular, β_1 is the peak excess CK, and is directly proportional to β_1 . Hence, the standard error on infarct size is directly proportional to the standard error on β_1 . Using the lognormal model, however, it is not possible to determine confidence limits on infarct size or ISP for a patient because of their complicated dependence on b and d . In addition, because the ISP program imposes arbitrary constraints, even approximate confidence regions would be difficult to determine.¹¹ For example,

TABLE 3. Sample Size Required to Estimate Average Change in \ln (Infarct Size) with Specified 95% Confidence Interval

No. of early data points used for prediction	Confidence interval about the observed difference (\ln ISN - \ln ISP)			sd (\ln ISN - \ln ISP)
	± 0.15	± 0.20	± 0.25	
7	38	22	14	0.472
6	50	28	18	0.538
5	66	37	24	0.620
4	84	47	30	0.699

Abbreviations: ISN = numerical calculation of infarct size; ISP = projection of infarct size.

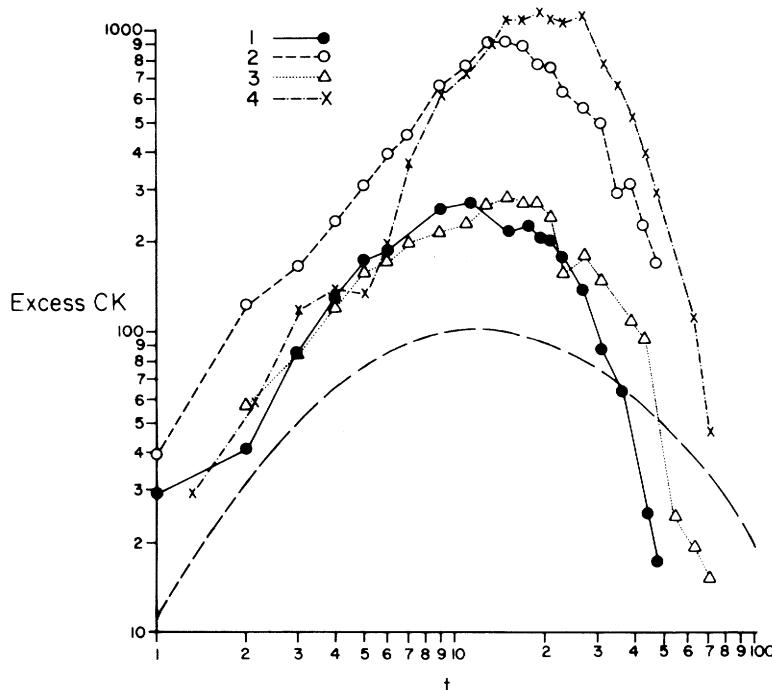


FIGURE 5. Logarithmic plot of excess CK in mIU/ml vs (t) in hours for patients 1-4. The lognormal model is shown by the dashed line.

limits are placed on the parameter c restricting it to lie within certain ranges that change abruptly according to whether the patient's CK value at 300 minutes is greater or less than 300 mIU/ml. Moreover, the nonlinear subroutine used in the ISP program can force the other parameters b and d to become pegged at specific values. Thus, in 24 of the 32 patients in the template group, the value of c was fixed at one of the boundary levels even when calculating infarct size based on all points. In contrast, for the template none of the parameters had to be constrained in any of the calculations of infarct size.

Finally, in the lognormal fitting process, it is assumed that the error variances are constant, since simple nonlinear least squares is used. For our data, this is doubtful, as demonstrated by a calculation of the standard deviations for CK values near the peak for each patient. These increase with the average so that in our procedure we use weighted nonlinear least squares, where the weights are proportional to the fitted values.

Linear estimation of infarct size provides an additional approach which allows true prediction of infarct size when decay data are unavailable. Moreover, it provides an additional prognostic aid in the early hours of acute myocardial infarction, thereby potentially influencing the decision of whether protective intervention is especially desirable. Its correlation and agreement with the template estimates of completed infarct size compared favorably with early point projections incorporating decay data; this emphasizes the relatively small importance of decay data in the calculation of infarct size. In addition to providing an early prognostic estimate of infarct size, the simplicity of this approach makes it potentially more generally available. Efforts are being made to further simplify this approach by using ordinary linear least squares rather than weighted nonlinear least squares for the

determination of K_r and to develop improved estimates of onset time.

If a serial enzymatic sampling technique is to be used to evaluate therapeutic interventions in acute myocardial infarction, it must provide both an accurate estimation of infarct size as well as the opportunity to apply interventions as early as possible. The template model provides a significant advantage in that respect. Further studies of early predictions using more samples within a shorter time frame are indicated.

In conclusion, we have used a self-modeling approach to develop an empiric model generated from actual patient data for purposes of analysis of serial CK release in man. This model permits good projections of infarct size from early data points and provides a method for estimating infarct size without decay data. The role of this approach in quantifying myocardial infarction awaits further study.

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Appendix

The salient characteristics of a particular patient's CK curve are related to his parameters and the template $g(z)$ as follows:

$$\gamma(t) = \beta_4 + \beta_1 g\left(\frac{t - \beta_2}{\beta_3}\right).$$

Rate of rise at onset, K_r

$$K_r = \left. \frac{d\gamma(t)}{dt} \right|_{t=\beta_2} = \left. \frac{\beta_1 \frac{dg}{dz}}{\beta_3} \right|_{z=0} = \frac{\beta_1}{\beta_3} \cdot K_{rz}$$

For the template of figure 4, $K_{rz} = 1.244$. Thus the initial slope of a patient's CK curve is proportional to β_1/β_3 , and the constant of proportionality is the initial slope of the template.

Decay constant, K_d

$$K_d = -\left. \frac{d}{dt} \ln(\gamma(t) - \beta_4) \right|_{t=\infty} = \left. \frac{1}{\beta_3 g(z)} \cdot \frac{dg(z)}{dz} \right|_{z=\infty} = \frac{K_{dz}}{\beta_3}.$$

For the template of figure 4, $K_{dz} = 0.827$. Thus a patient's K_d is inversely proportional to the β_3 parameter, and the constant of proportionality is the decay parameter of the template.

Infarct Size

For a patient with body weight BW and decay constant K_d , the estimated infarct size is

$$IS = K \cdot BW \cdot K_d \cdot \int_{\beta_2}^{\infty} \beta_1 g\left(\frac{t - \beta_2}{\beta_3}\right) dt = K \cdot BW \cdot K_{dz} \cdot \beta_1 \cdot \int_0^{\infty} g(z) dz$$

where $\int_0^{\infty} g(z) dz = 2.079$ and is the area under the template. Therefore

$$IS = (.32) \cdot (.827) \cdot (2.079) \cdot 10^{-3} \cdot BW \cdot \beta_1 \\ = (5.542) \cdot 10^{-4} \cdot BW \cdot \beta_1.$$

The Template

The template is a cubic function completely determined by the knot positions, the heights at the knots and the second derivatives at the knots, as follows:

knot positions	0	.01071	.2750	.5921	1.649	2.707	4.714
heights	0	.01332	.3581	.7998	.7303	.3047	.05788
second derivatives	0	0	1.404	-3.477	.3375	.2155	0

For

$z > 4.714$,

$$g(z) = .05788 \exp(-.827(z - 4.714)),$$

For $z < 0$,

$$g(z) = 0.$$