Quantitative influence of serum creatine kinase isoenzyme MB estimated infarct size and other prognostic variables on one year mortality after acute myocardial infarction

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SUMMARY The aim of the present study was to determine the strength of the relation between serum creatine kinase isoenzyme MB estimated infarct size, other prognostic variables, and mortality after acute myocardial infarction. Serum creatine kinase MB estimated infarct size and 11 other prognostic variables were obtained in 317 patients. By Cox regression analysis the prognostic variables significantly related to mortality were identified: congestive heart failure, estimated infarct size, New York Heart Association class, number of previous infarcts, and age. Congestive heart failure and estimated infarct size were most strongly related to mortality. The relation between the prognostic variables and mortality was non-linear, and the variables influenced each others' relation to mortality. A prognostic index based on all five prognostic variables provided the best means of estimating the probability of survival after acute myocardial infarct. Neither serum creatine kinase MB estimated infarct size nor any of the other prognostic variables had a significant independent influence on mortality, and the probability of survival was high in the absence of any of the prognostic variables in combination.

During recent years methods for the *in vivo* estimation of infarct size have been developed since the extent of an acute myocardial infarct influences prognosis.^{1,2} Methods of estimating infarct size based on serial serum creatine kinase and creatine kinase isoenzyme MB activities correlate closely with the extent of necrosis measured at necropsy.^{3,4} Creatine kinase isoenzyme MB estimated infarct size has also correlated well with several indirect measures of infarct size, such as angiographic estimates of left ventricular asynergy and ejection fraction,⁵ precordial mapping of Q wave and ST segment changes,⁶ and myocardial positron emission tomography with carbon-11-labelled palmitate.⁷

A few studies have compared enzymatically esti-

mated infarct size with mortality and morbidity due to acute myocardial infarction. Patients with such complications as heart failure, cardiac arrhythmias, or early or late death had generally larger infarcts than those without.^{2,8,9} Furthermore, when groups of patients were stratified by estimated infarct size a significant positive relation was found between both creatine kinase isoenzyme MB and creatine kinase estimated infarct size and these complications.^{8,10-12}

Several studies have identified various prognostic variables for mortality after acute infarction. Nevertheless, no data are available on (a) the strength of the relation between mortality and different infarct size, (b) the relation between estimated infarct size and other prognostic variables, and (c) the influence of other prognostic variables on the relation between estimated infarct size and mortality. The aim of the present study was to evaluate these relations and to formulate a prognostic index based on the most important prognostic variables.

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Patients and methods

During a one year period, 393 patients were consecutively admitted to the coronary care unit at Glostrup Hospital with acute myocardial infarction. Seventy six patients were excluded from the study: 48 in whom the symptoms of infarction had lasted for more than 15 hours before admission, 24 in whom a sufficient number of blood samples had not been obtained because the patient had died or been transferred to another department, and four who were admitted unconscious after cardiac arrest. Thus 317 patients were eligible for the study, of whom 43 died before the clinical evaluation and are not included in this report.

BLOOD SAMPLING AND ELECTROCARDIOGRAMS

Blood samples were drawn immediately after admission, and at 0800, 1400, and 2100 on the first three days, and at 0800 on the following four days. If pronounced pain recurred the frequent sampling procedure was repeated. Serum creatine kinase activity was measured according to the Scandinavian recommended method and serum creatine kinase isoenzyme activity by electrophoresis on agarose gel followed by fluorescence scanning.¹³ The interassay variation of the creatine kinase isoenzyme MB activity is between 5% and 10% depending on the absolute value. An electrocardiogram in nine leads was recorded daily; changes indicating either transmural or subendocardial infarction were both considered to be positive. Infarct localisation was determined as anterior or inferior.

Every patient underwent electrocardiography during the entire hospital admission initially by Holter monitoring cable and later by telemetry. All were monitored with a sound track for time marking and for spoken comments, and all tapes were analysed daily by playback at increased speed with all abnormalities of the types mentioned below described and recorded on paper.

DEFINITION OF DIAGNOSIS

An acute myocardial infarction was defined as the occurrence of at least two of the following: (a) typical clinical symptoms, (b) typical electrocardiographic changes and (c) a temporary rise in serum creatine kinase isoenzyme MB activities above 30 U/l.¹⁴ Congestive heart failure was diagnosed by the appearance on x ray film of cardiac enlargement or pulmonary congestion or both or by the presence of unequivocal clinical signs and symptoms. Cardiogenic shock was diagnosed when systolic blood pressure was persistently below 80 mm Hg, and the patient presented clinical signs of shock in the absence of any extracardiac cause. All the following cardiac arrhythmias were

considered: ventricular extrasystoles, tachycardia and fibrillation, sinus arrest, supraventricular extrasystoles and tachycardia, second and third degree atrioventricular block, and asystole. Cardiac arrest was defined as ventricular fibrillation or asystole. The New York Heart Association functional class of symptoms of heart failure was estimated on day 7.

CALCULATION OF INFARCT SIZE

The estimation of infarct size by serum creatine kinase isoenzyme activity is based on the equation:

$$\text{Infarct size} = \int_0^T f(t)dt = k_d \cdot$$

$$\int_0^T E(t)dt + E(T) \approx k_d \cdot \int_0^T E(t)dt$$

$E(t)$ is the specific creatine kinase isoenzyme MB activity (U/l) in serum at time t (hours). The function $f(t)$ is the appearance function—that is, the hypothetical value for dE/dt without elimination. The factor k_d is the elimination constant (assuming first order kinetics). T is the time until creatine kinase isoenzyme MB activity can no longer be detected. We used the compartment as a model, which is described in detail elsewhere.⁴

FOLLOW UP

The patients were followed after discharge at intervals depending on late complications. Nevertheless, all survivors were given a full clinical examination one year after discharge. The time of death was ascertained as far as possible, either on readmission to hospital or by communication with the official registrar of persons and, when necessary, with relatives. The follow up was 100%.

STATISTICAL MODEL

The survival data were analysed by a regression model originally proposed by Cox.¹⁵ The simplest formulation of Cox's model is as a model for the death rate $\lambda(t)$, which uniquely determines the distribution of survival time. $\lambda(t)$ can be thought of as the probability of dying on the t -th day, assuming that the patient survived the first $t-1$ days. $\lambda(t)$ is assumed to depend on certain prognostic factors (covariates) and to be as follows for a patient with covariates $z_1, \dots, z_p$:

$$\lambda(t; z_1, \dots, z_p) = \lambda_0(t) e^{\beta_1 z_1 + \dots + \beta_p z_p}, \quad t > 0.$$

Here $\lambda_0(t)$, the underlying death rate, is an unknown and unspecified function of time. A consequence of the model is that death rates for any two patients are proportional—that is, the ratio between the death rates is not dependent on the time t .

If a covariate z_i is defined to take the value 1 if some characteristic is present in the patient and 0 if it is not

present (a qualitative covariate), but all other prognostic factors are equal, then the model assumes that the death rate at any time t after entrance for a patient with the characteristic is e^{β_i} times the death rate at t for a patient without it. If $\beta_i = 0$ then the factor z_i has no influence on the death rate. Similar interpretation can be made for quantitative covariates such as age or estimated infarct size.

Estimates $\beta_1, \dots, \beta_p$ of the regression coefficients were found by maximising the likelihood function of Cox.¹⁵ Estimates of the survival function and the corresponding standard deviations were calculated for different values of the covariates according to Breslow¹⁶ and Tsiatis.¹⁷ In this analysis it can be determined by the graphical and numerical techniques by Andersen¹⁸ whether the effects of various covariates can be described adequately by proportionality factors as mentioned above, and whether they enter the linear way, which the model assumes.

Not all the prognostic factors (Table 1) were available on the day of admission; for example, the estimate of infarct size was first available on the second or third day. The incidence of rhythm disturbances and cardiogenic shock was highest during the first days of admission. We chose to use the information available during the seven days after admission for practical reasons. By day 7 most of the serious complications had appeared, the clinical course has been determined, and the long term treatment plan had to be developed.

The evaluation of the variables was begun by using the 12 covariates shown in Table 1. The model was then reduced to a minimal set of covariates with a significant influence on the prognosis—that is the covariates from the set originally considered which did not contribute significantly to the prognosis were eliminated. Furthermore, we checked by a graphical technique¹⁸ whether the effect of the covariates could be described by proportionality factors and whether they entered in a linear fashion. In cases where this was not so, the covariates were transformed accordingly. A prognostic index was defined as: prognostic index (PI): $\beta_1 z_1 + \dots + \beta_5 z_5$, where $z_1, \dots, z_5$ are the covariates in the minimal set.

Results

Forty of the 274 (15%) patients who were alive on the seventh day died within the first year. Table 2 shows the prognostic variables which were significantly related to the one year survival: number of previous infarcts, age, estimated infarct size, heart failure, and NYHA class. Inclusion of other variables did not contribute significantly to the estimated prognosis. Graphical analysis showed that age and estimated infarct size had to be transformed to fit the model, and

that NYHA class should enter as a bivariate (NYHA 1 or >1). Table 3 shows the estimates of the regression coefficients $\hat{\beta}_i$, estimates of the standard deviations for these, the statistic $\hat{\beta}_i/\text{SD}(\hat{\beta}_i)$ and the corresponding p values. $\hat{\beta}_i/\text{SD}(\hat{\beta}_i)$ is an approximate standard normal deviate when $\beta_i = 0$, so that it yields a test for the hypothesis that one of the covariates in the model is without effect, assuming that the other covariates are still taken into account. Heart failure and creatine kinase isoenzyme estimated infarct size were the prognostic variables most strongly related to mortality.

To illustrate the prognostic value of the estimated infarct size, the estimated survival function for two values of estimated infarct size are shown in Fig. 1. The estimated infarct sizes were 200 U/l (≈ 10 g) and 2000 U/l (≈ 120 g), and the other four significantly important prognostic variables were equal. The one year probability of survival was 0.87 and 0.69 respectively.

Figures 2 and 3 show the probability of survival as a function of time; (a) and (b) compare the effects of the qualitative variable on the probability of survival. The effects of the quantitative variable (age and estimated infarct size) are compared by considering Fig. 2a against 2b and Fig. 3a against 3b respectively. For the different ages and estimated infarct sizes illustrated, the presence of heart failure was the most important single prognostic variable followed by NYHA class

Table 1 Prognostic variables

Variable	Time evaluated
Hypertension	Before admission
No of previous infarcts	Before admission
Age	On admission
Sex	On admission
Infarct localisation (ECG)	Days 1–3
Estimated infarct size (creatin kinase isoenzyme activity)	Days 2–3
Heart failure	Days 1–7
Pulmonary oedema	Days 1–7
Cardiogenic shock	Days 1–7
Cardiac arrhythmias	Days 1–7
Cardiac arrest	Days 1–7
NYHA class	Days 1–7

Table 2 Prognostic variables of significant importance for the one year survival according to the formula:

$$\lambda(t; z_1, \dots, z_5) = \lambda_0(t) e^{\beta_1 z_1 + \beta_2 z_2 + \beta_3 z_3 + \beta_4 z_4 + \beta_5 z_5}$$

$$\begin{aligned} z_1 &= \log_e (\text{age } 20 \text{ years}) \\ z_2 &= \begin{cases} 0 & \text{if NYHA class is } 1 \\ 1 & \text{if NYHA class is } >1 \end{cases} \\ z_3 &= \text{No of previous infarcts} \\ z_4 &= \begin{cases} 0 & \text{if heart failure is absent} \\ 1 & \text{if heart failure is present} \end{cases} \\ z_5 &= \log_e (\text{estimated infarct size}) \end{aligned}$$

Table 3 Estimates of regressions coefficients ($\hat{\beta}_i$), standard deviations (SD), and p values for the five prognostic variables of significant importance for the one year survival

Prognostic variable	$\hat{\beta}_i$	SD ($\hat{\beta}_i$)	$\frac{\hat{\beta}_i}{SD(\hat{\beta}_i)}$	p
Age ($z_1 = \log_e(\text{age} - 20)$)	1.67	0.73	2.29*	0.022
NYHA class (z_2)	1.04	0.42	2.50*	0.013
No of previous infarcts (z_3)	0.51	0.21	2.42*	0.015
Heart failure (z_4)	1.48	0.45	3.26*	0.001
Estimated infarct size ($z_5 = \log_e$ estimated infarct size)	0.41	0.16	2.60*	0.009

* $\frac{\hat{\beta}_i}{SD(\hat{\beta}_i)}$ is an approximate standard normal deviate when $\beta_i = 0$.

Fig. 1 Probability of survival at least t days after the seventh day after admission, assuming that the patient was alive on day 7, for two patients aged 55 years old, in NYHA class >1 , with no previous infarcts, and no heart failure. The patient indicated by the upper line had an estimated infarct size of 200 U/l, the other (lower line) one of 2000 U/l. Bars represent 1 SD.

>1 and the presence of previous infarcts. The clinical importance of large infarct size or older age changes rapidly with the presence of other prognostic variables.

Figure 4 shows the relation between creatine kinase isoenzyme MB estimated infarct size and the probability of one year survival. The upper function represents a low risk combination of the other prognostic variables, the lower function a high risk combination. In patients without other poor prognostic variables the overall prognosis is good, and the clinical importance of the estimated infarct size is small. In the presence of other poor prognostic variables the probability of survival deteriorates rapidly as a function of infarct size. The difference in probability of one year survival between patients at low and high risk ranges between 8% and 35% depending on the estimated infarct size.

Figure 5 summarises the results of the analyses and shows the relation between the prognostic index (PI) and the probability of one year survival. The presence of few risk factors—that is, $PI < 10$ —indicates a

very high probability of one year survival. A prognostic index above this level indicates a rapidly deteriorating one year prognosis.

Discussion

Recently estimated infarct size has been shown to be a prognostic variable which significantly influences the short as well as long term prognosis after acute myocardial infarction.^{10,12} The aims of the present study were to quantify the relation between creatine kinase isoenzyme MB estimated infarct size and mortality and to determine its clinical importance in relation to other prognostic variables.

Two types of studies have been performed to evaluate the relation between serum enzyme estimated infarct size and mortality. Most studies have found an increased mean peak enzyme value or high estimated infarct size in those who died compared with survivors.^{9,19,20}

These studies, however, provide no information on the prediction of the probability of mortality. Two studies have shown that in patients stratified according to creatine kinase or creatine kinase isoenzyme MB estimated infarct size, there is a significant prospective relation between estimated infarct size and mortality.^{10,12} Nevertheless, neither the strength of the relation as a function of infarct size nor the influence on the relation of other prognostic variables have been determined.

The present study confirms that the creatine kinase isoenzyme MB estimated infarct size is a significant prognostic variable for mortality (Table 3). As shown previously, the mortality is highest during the first months after infarction (Fig. 1).^{10,12} The influence of infarct size on the probability of one year survival is, however, dependent on the other prognostic variables (Fig. 2). In the absence of the other variables negatively influencing prognosis, the estimated infarct size has little influence on the probability of one year survival (Fig. 3). In the presence of these other prognostic variables the probability of one year survival is more influenced by infarct size (Fig. 4).

The 12 covariates estimated in the present study

have previously been shown to be related to mortality after infarction.²¹ Use of the Cox model of multivariate analysis provides the means of determining which of the covariates do not contain further information in the presence of the others. Of the covariates shown to be significantly related to mortality—infarct size, heart failure, NYHA class, number of previous infarcts, and age—only the creatine kinase isoenzyme

MB estimated infarct size is not universally available in patients with myocardial infarction. Nevertheless, the estimate is easily calculated from serum samples drawn three times daily.^{22*}

A few previous studies have compared creatine kinase estimated infarct size with other prognostic variables after infarction. Geltman *et al* showed that

*A full description of the estimation of infarct size is available on request.

Fig. 2 Probability of survival as a function of time for patients with different combinations of the prognostic variables. For the quantitative variables relevant constants were chosen: estimated infarct size 692 U/l (median value in the study population); age 45 and 70 years. The qualitative prognostic variables were: 1, presence of previous infarct; 2, NYHA class >1; 3, presence of heart failure.

Fig. 3 Probability of survival as a function of time for patients with different combinations of the prognostic variables. For the quantitative variables relevant constants were chosen: age 62 years (mean of the study population); estimated infarct size 200 U/l and 2000 U/l. The qualitative prognostic variables were: 1, presence of previous infarct; 2, NYHA class >1; 3, presence of heart failure.

Fig. 4 Probability of one year survival as a function of estimated infarct size. The functions represent the following combination of prognostic variables; the patient indicated by the upper line was aged 55 years, had no previous infarct, was in NYHA class 1, had no heart failure; the patient indicated by the lower line was aged 55 years, had no previous infarct, was in NYHA class >1, had heart failure. Bars represent 1 SD. CK-MB, creatine kinase isoenzyme.

Fig. 5 Relation between prognostic index ($\hat{\beta}_1 x_1 + \dots + \hat{\beta}_5 x_5$) and probability of one year survival (see text).

creatinine kinase estimated infarct size and heart failure were the two variables most significantly associated with mortality after infarction.¹⁰ Henning *et al* found creatine kinase estimated infarct size to be significantly related to mortality, and the estimate was included in a multivariate index together with several other variables to predict the mortality.²³ Nevertheless, total serum creatine kinase activity may be influenced by many clinical conditions and proce-

dures, and the correlation between serum creatine kinase estimated infarct size and infarct size measured at necropsy is relatively low ($r=0.63$, $SEE=42\%$).⁴ In the present study, however, infarct size was estimated by a method based on measurements of the heart specific enzyme creatine kinase isoenzyme MB. This method has proved to be reliable for estimating infarct size in man, which is closely related to the extent of necrosis measured at necropsy ($r=0.85$, $SEE=25\%$).⁴

The use of creatine kinase isoenzyme MB estimation provides an inexpensive, readily available non-invasive method for estimating infarct size. This method might be of primary importance for two main clinical reasons. Firstly, it may be useful as an endpoint in clinical trials aimed at limiting the extent of myocardial damage during myocardial infarction. Secondly, the clinician might use the estimated infarct size to determine the prognosis after infarction. The main purpose, however, of assessing the prognosis is to be able to improve treatment of the diseased patient. Thus, although a reliably estimated infarct size seems to be valuable for determining the prognosis, further clinical trials are needed to show if treatment based on the estimated infarct size improves the prognosis after an infarction.

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