

## **Methods for Diagnosis, Estimation and Prediction of Myocardial Damage from Serum Observations of Marker Substances**

Torgny L. Groth

*Unit for Bio-Medical Systems Analysis, Uppsala University,  
Box 2103, S-75002 Uppsala, Sweden*

Laboratory tests are today commonly used, in addition to acute symptoms, patient history and objective signs of functional disturbances, in order to detect and assess cardiac injury for diagnostic and prognostic purposes. These tests are all based on serum observations of intracellular constituents which are lost from the myocardium to extracellular space and which ultimately appear in the circulating blood. The following enzymes are established markers of acute myocardial infarction (AMI): total creatine kinase (CK), creatine kinase isoenzyme (CK-MB), aspartate aminotransferase (ASAT), lactate dehydrogenase (LD) and  $\alpha$ -hydroxybutyrate dehydrogenase (HBD). For an extensive review see reference (6). Myoglobin is another marker of special interest for early diagnosis of AMI (see e.g. (9)).

The methods applied for interpretation of observations of these substances in serum are largely empirical, even though there are also theoretical approaches:

The conventional method of comparing single observations with the upper reference limit of a reference sample group of healthy individuals, may be improved by determining more optimal decision limits on the basis of prevalence of disease and the relative costs of misclassification (cf. (2,12)). Such decision limits should also be expressed as functions of time for specimen collection (measured from onset of symptoms) in order to take into account the typical time course of serum activities during the infarction.

The use of the peak serum value as an empirical measure of infarct size is another possibility to increase the discriminatory power. This means, however, that several observations have to be performed to find the peak value. The "area under the concentration curve", "extrapolated concentration at time for onset of symptoms", and "initial slope of the concentration curve" are other examples of empirical measures which have been tried.

The theoretical approaches to the interpretation of serum observations of AMI-markers are based on simple compartment models of the appearance, distribution and elimination of marker substance. The purpose of this technique is to estimate or predict "infarct size". It is then tacitly assumed that the release of the marker from the infarct area into circulation is directly related to cell death, and furthermore that the depletion of marker from the myocardium is proportional to infarct size. The requirements on data collection and dataprocessing are generally higher than in previous methods.

Accurate assessment of myocardial infarct size from serial observations of serum enzymes and myoglobin critically depends on a reliable description of the kinetics of these substances. Time-activity curves of CK and CK-MB have commonly been analysed with use of the simple one-compartment model introduced by Shell et al.(11). In its simplest form infarct size is estimated as the product of plasma clearance rate and the total cumulative release of enzyme. Since basic data on CK and CK-MB kinetics in man are still largely missing, the calculations have been based on corresponding values measured on dogs.

Modifications of the method include individual estimation of the elimination rate constant from the final slope of the serum curve. Recent work (6) has shown that some of the basic assumptions of the model are not valid. For instance, it is obvious that CK and CK-MB do not follow one-compartment kinetics, and as a consequence the final slope underestimates the true elimination rate constant with a factor of about 2. Furthermore, inter-

individual variability of critical parameters like elimination rate and serum entry ratio has to be considered more carefully (cf. (8)).

Attempts have been made to apply two-compartment models in assessing myocardial release of enzymes like CK, ASAT etc. (see e.g. (7)). However, the results of such calculations are severely hampered by the circumstance that the basic kinetic constants of these enzymes are not known for man.

In a recent study this problem complex has been investigated for myoglobin (4). The basic kinetics was studied by single injection of  $^{125}\text{I}$ -labelled myoglobin in eight patients suffering from AMI, and in six healthy individuals (5). The effect of using patient-mean values instead of individual estimates of fractional rate constants and distribution volumes was then evaluated when estimating infarct size from serum myoglobin observations with use of a two-compartment model. The results showed

- that it is crucial to have good individual estimates of the elimination rate constant and the distribution volume in order to get an accurate estimate of infarct size;
- that a mean difference of about 35 percent could be expected between infarct size estimated with individual and patient mean values for the kinetic constants;
- that the final slope of the myoglobin curve does not constitute a good estimate of the elimination rate constant, but underestimates the correct value by a factor of 10 on the average;
- that different types of infarct processes could be distinguished, as reflected in the shape of the estimated "blood appearance function";

- that the peak serum values of both myoglobin and CK-MB were highly correlated with infarct size as estimated from the total serum curve.

The clinical usefulness of an infarct size estimate is highly dependent on the availability of such an estimate in the early stage of the infarction process. For instance, therapy has to be started within 4-6 hours after onset of symptoms in order to be successful. Shell et al. have reported (10) that they were able to predict infarct size 2 hours after initial CK rise, with a sampling frequency of 3-4 samples per hour. The predictions were based on the fitting of a log-normal density function to the serum CK observations with strong constraints on the parameters (cf. (6)). Infarct size was calculated with the simplifying assumption that CK follows mono-compartment kinetics. However, their results have not been possible to repeat by other groups (cf. (1)). The possibilities of predicting infarct size from early serum myoglobin observations were investigated in another recent study (3).

It was found

- that the large interindividual variability of the infarction process as reflected in the "blood-appearance function" limits the possibilities of accurate prediction;
- that infarct size (as estimated from the total curve) could be predicted rather well with use of a two-compartment model of myoglobin kinetics, provided data are available up to and including the peak serum value ( $r=0.70-0.85$  with an average observation time up to 10 hours after onset of symptoms);
- that the correlation between infarct size and the initial slope of the serum curve was unexpectedly high ( $r=0.80$  for an average observation time up to 4 hours after onset of symptoms).

In summary it may be concluded that model-based approaches for infarct size estimation are very demanding concerning access to patient specific data and long observation periods, and therefore these methods are today not practical in clinical

routine, but seem to be more suitable for clinical research problems. Empirical measures like the "peak serum value" and the "initial slope" are preferable in clinical routine, in addition to classification of single serum observations with use of optimized decision limits.

## REFERENCES

1. Danner, S.A., Smit, E.M., Hart, G.A.M., Oosting H. and Dunning, A.J.: Prediction of infarct size from serial CK-determinations. Evaluation by clinical studies and computer simulation. *Clin. Chim. Acta*, 97, 45, 1979.
2. Groth, T., Hakman, M., Hällgren, R., Roxin, L.E. and Venge, P.: Diagnosis, size estimation and prediction of acute myocardial infarction from serum myoglobin observations. A systems analysis to assess the influence of various sources of variability. In *Assessing Quality Requirements in Clinical Chemistry* (ed. M. Hörder), *Scand J. Clin. Lab Invest. suppl.* 155, 40, 111, 1980.
3. Groth, T., Hakman, M. and Sylvén, C.: Prediction of myocardial infarct size from early serum myoglobin observations. Submitted for publication.
4. Groth, T., Hakman, M. and Sylvén, C.: Size estimation of acute myocardial infarction from serial serum myoglobin observations with due consideration of individual differences in basic kinetics. *Scand J. Clin. Lab. Invest.* 44, 1984.
5. Groth, T. and Sylvén, C.: Myoglobin kinetics in patients suffering from acute myocardial infarction in its early phase - as studied by the single injection method. *Scand. J. Clin. Lab. Invest.* 41, 79, 1981.
6. Hearse, D.J. and Leiris, J (eds). *Enzymes in cardiology*, J. Wiley & Sons, Chichester- New-York-Brisbane-Toronto, 1979.
7. Hyltoft Petersen, P., Hörder, M., Thygesen, K., Lyager Nielsen, B. and Hansen, L.: Plasma enzymes in myocardial infarction. Application of a two-compartment model in assessing myocardial release of enzyme. *Scand J. Clin. Lab. Invest.* 41, 735, 1981.
8. Roe, C.R. and Starmer, C.F.: A sensitivity analysis of enzymatic estimation of infarct size. *Circulation* 52, 1, 1975.
9. Roxin, L.E., Cullhed, I., Groth, T., Hällgren, R. and Venge P.: The value of serum-myoglobin determinations in the early diagnosis of acute myocardial infarction. Accepted for publication in *Acta Med. Scand.*

10. Shell, W.E., Groaseth-Robertson, M.F. and Vas, R.: Infarct size prediction 2 hours after initial CPK rise. *Circ.suppl.* II, 53 and 54, II-28, 1976.
11. Shell, W.E., Kjekshus, J.K. and Sobel, B.E. Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity. *J. Clin. Invest.* 50, 2641, 1971.
12. Werner, M., Brooks, S.H., Mohrbacker, R.J. and Wasserman, A.G. Diagnostic performance of enzymes in the discrimination of myocardial infarction. *Clin.Chem.* 28/6, 1297, 1982.