Individualized Values for the Disappearance Rate Parameter (K_d) in the Enzymatic Estimation of Infarct Size

A Critique

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SUMMARY A mathematical model to measure infarct size from serial estimates of CPK has been developed by Shell et al. Norris et al. have recently introduced a modification of this method by calculating an individualized disappearance rate parameter (K_d) from the uniformly monoexponential portion of the CPK vs time curve. This modification is based on the assumption that when CPK is decaying monoexponentially, the amount of CPK appearing in the circulation is zero. This paper presents a mathematical analysis which shows that the method of Norris et al. is theoretically unsound, as the CPK appearance function may be significantly different from zero and yet CPK vs time may still be monoexponential. Their method may lead to erroneous results in the calculation of infarct size.

PUMP FAILURE following an acute myocardial infarction remains a major source of morbidity and mortality. As the degree of pump failure is related to the amount of myocardium infarcted and as a number of factors have been shown to alter infarct size,1,2 an estimate of the extent of infarction is important for evaluating the benefits of various pharmacological interventions. One of the most commonly used methods of estimating infarct size is the mathematical model proposed by Shell et al.3 which utilizes serial serum levels of CPK to calculate the total CPK released from the heart. This value can then be directly related to the mass of cardiac tissue infarcted. There are, however, a number of problems with this method and a recent editorial has analyzed the sensitivity of the results, to reported variations in each of the parameters of the model.4 This sensitivity analysis has shown that the value of the disappearance rate parameter (K_d) is critical for the accurate assessment of damage. As the range of K_d may be quite wide in dogs, varying from −0.0068 to −0.0028 (± 2σ) in the 11 dogs that Shell et al. originally reported,5 Norris et al.6 have introduced the concept of the individualized K_d in which the terminal slope of the CPK vs time curve of each subject is used to calculate K_d. However, there has been no evidence that this method improves the correlation between the predicted infarct size and myocardial CPK depletion estimates of damage.6 The purpose of the present report is to show that the method of Norris et al. lacks mathematical rigor and as such may theoretically lead to grossly erroneous results.

Mathematical Model with Norris' Modification

Shell’s model describes the change in serum enzyme activity of CPK as the sum of the amount of CPK released from the heart into the periphery minus the amount eliminated from the distribution space, assuming first order kinetics. Mathematically, this can be expressed by the following equation:

\[ \frac{dE(t)}{dt} = f(t) + K_d \cdot E(t) \]

where E (t) is the serum level of CPK and f (t) is the CPK appearance function, which is the concentration of CPK released into the distribution space at time, t. The final equation to describe infarct size using this model is:

\[ \text{Infarct size} = \frac{W \cdot K_w}{K_R \cdot CPK_D} \left[ E(T) - K_a \int E(t) \cdot dt \right] \]

where:

- W = Body weight,
- K_w = Proportionality parameter for distribution space of CPK, as a function of body weight,
- K_R = Fraction of released CPK appearing in the distribution space,
- CPK_D = Total CPK per gram of tissue,
- K_a = First order decay constant of CPK in the distribution space (which by convention is negative),
- E(t) = Serum CPK value at time t.

Shell et al. originally used the mean value of K_d = −0.0045 in their calculation of infarct size in all their dogs. Norris et al.’s modification (Norris’ method) involves calculating individualized K_a’s using the patient’s postinfarct CPK values. These values are plotted against time on semilogarithmic graph paper and then inspected to determine the value at which log (CPK) activity started to decline rapidly and uniformly to near normal levels. During this period of enzyme decay, the assumption was made that enzyme release was zero, thus enabling the CPK disappearance function to be studied independently of CPK release. If the slope of the regression line describing this fall in CPK had 95% confidence limits of less than ±15%, they used the slope as an estimate of the individual’s K_d.

Norris et al. state that there are at least three factors which might obscure a monoexponential decline in CPK activity after myocardial infarction but feel that none of these are a major source of error in their model. First, myocardial CPK consists of two isoenzymes and there is some evidence to show that the MB isoenzyme has a faster clearance constant than the MM form. This would result in a decline in CPK activity with an early rapid phase and a later slow phase of decline. This pattern appeared infrequently and thus did not seem to be an important factor. This problem has been overcome by Roberts et al.7 who have used cardiac
specific CPK MB. Secondly, decline of CPK activity could possibly be modelled more accurately by a two-compartment distribution space for CPK. This should also be manifest by a rapid decline in CPK followed by a slow decline, which did not occur in most of their experiments.

Thirdly, release of CPK from the myocardial infarct into the circulation might continue during the early phase of CPK decline. Norris et al. feel their method appears to avoid the underestimation of $K_d$ due to nonrecognition of continued slow CPK release as their use of the 95% confidence limits for $K_d$ allows for rejection of values which do not attain an arbitrary selected confidence limit.

However, the 95% confidence limits on $K_d$ are not the confidence limits on the "true" disappearance rate parameter but rather are confidence limits on the degree to which log (CPK) declines monoexponentially. There may be CPK continually being released but the kinetics of the system may be such that a monoexponential decay results. If this were to be true, the absolute value of the estimate of $K_d$ using Norris' method may underestimate the "true" $K_d$.

Analysis

The following analysis will show that although the log of CPK activity may decline uniformly to near normal levels, the amount of enzyme appearing in the circulation from the heart during this time period does not necessarily have to be zero.

Let, $t = 0$ be the time at which uniform decay of CPK starts.

$$E(t) = \text{Serum CPK value at time } t.$$  
$$E_o = \text{The value of CPK activity at which this decay starts to take place}.$$  
$$K_d = \text{The "true" fractional disappearance rate}.$$  
$$f(t) = \text{Concentration of enzyme appearing in the circulation at time } t \text{ Norris et al. assume this function to be zero during monoexponential decay of } E(t).$$  
$$K = \text{The value of the observed slope of log } E(t) \text{ vs } t \text{ during the time that } E(t) \text{ is declining uniformly to near normal levels (this is the value of the fractional disappearance rate which would be calculated using Norris' method).}$$

Since $E(t)$ is declining exponentially from an initial value of $E_o$, with a rate constant $K$, it can be written in the form:

$$E(t) = E_o \cdot e^{Kt} \quad \text{[1]}$$

Differentiating this expression we obtain:

$$dE(t)/dt = K \cdot E_o \cdot e^{Kt} \quad \text{[2]}$$

Shell's equation states that:

$$dE(t)/dt = f(t) + K_d \cdot E(t) \quad \text{[3]}$$


$$K \cdot E_o \cdot e^{Kt} = f(t) + K_d \cdot E_o \cdot e^{Kt} \quad \text{[4]}$$

Therefore:

$$f(t) = E_o \cdot e^{Kt} (K-K_d) \quad \text{[5]}$$

Thus, if the "true" decay constant were $K_d$, any appearance function given by $f(t) = E_o \cdot e^{Kt} (K-K_d)$ would give a monoexponential decay constant $K$ not $K_d$. Since $f(t)$ given by equation [5] must be greater than or equal to zero, the true decay constant, $K_d$, could be any number such that $K-K_d \geq 0$, i.e., $K \geq K_d$. Norris' method would therefore provide a value of the decay constant ($K$) which would be equal to or greater than the "true" $K_d$. Since both $K$ and $K_d$ are negative numbers the absolute value of the "true" decay constant, $K_d$, would be greater than or equal to the absolute value of Norris' decay constant, $K$.

Results

To illustrate the possible discrepancies in estimating $K_d$ we have used data from Norris' paper. The data are presented in table 1 and in figure 1. The left side of figure 1 is a plot of the CPK activity of a 51-year-old male with a transmural infarct. The right side of figure 1 is a plot of various functions of $f(t)$ which could theoretically give the plot shown on the arbitrary left side of the figure. The circles represent the values of CPK activity which would have been calculated using Norris' method, which gave a $K_{d0}$ of $-0.00096$. Using these values, the integrated appearance function ($f(t)$) would be 3.69 IU/ml. Equally compatible with the E(t) is the f(t) shown in figure 1 by the triangles (a) with a $K_{d0}$ of $-0.0020$, but the integrated appearance function would now be 7.68 IU/ml. Similarly, the f(t) represented by the squares (**) in figure 1 corresponds to a $K_{d0}$ of $-0.0040$ which would give an integrated appearance function of 15.36. As the integrated appearance function is directly proportional to infarct size, gross errors may arise by Norris' method of calculating $K_d$.

These are only two examples of possible "true" values of $K_d$; theoretically, an infinite number of $K_{d0}$, $f(t)$s and infarct sizes are possible.

### Table 1. Serial CPK Measurements and Calculated Appearance Functions ($f(t)$) Using Various $K_d$s

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>$E(t)$</th>
<th>$K_d$ = $-0.00006$</th>
<th>$K_d$ = $-0.0020$</th>
<th>$K_d$ = $-0.0040$</th>
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<td>12</td>
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<td>0.82</td>
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<td>28</td>
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<tr>
<td>112</td>
<td>31</td>
<td>-0.09</td>
<td>0.06</td>
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</tr>
</tbody>
</table>

*Serial CPK measurements, $E(t)$, of a 51-year-old male with an inferior transmural infarct (data obtained from Norris et al.).

†Appearance function ($f(t)$) calculated using Norris' method.

‡Appearance function ($f(t)$) for two hypothetical cases using Norris' method.

-0.0020 and -0.0040. Both sets of data would produce exactly the same $E(t)$ given on the left.
INDIVIDUALIZED VALUES FOR $K_d/\text{Slutsky}$

Discussion

Norris et al. have introduced a new method of determining individualized disappearance rate parameters ($K_a$) of Shell's model for calculating infarct size. Their method uses the assumption that when the CPK appearance function ($f(t)$) is zero, $E(t)$ will decay monoexponentially. This assumption is true; however, the converse that if $E(t)$ is decaying monoexponentially, the $f(t)$ must be equal to zero is not necessarily true. In estimating $K_a$, it is this converse which is important as we have a monoexponential decay of $E(t)$ but we do not know $f(t)$. This paper has shown that for any monoexponential decay of $E(t)$ there exists an infinite number of possible combinations of $K_a$ and $f(t)$ which would produce the observed $E(t)$. Thus the calculation of the integrated appearance function ($\int f(t)$) and infarct size may be significantly different from the values calculated using the method proposed by Norris et al.

The likelihood of $f(t)$ assuming exactly the unique shape for this problem to occur is remote. However, the likelihood of $f(t)$ assuming a shape which may provide inaccuracies in the calculation of $K_a$ using Norris' method is not so remote. In an article by Roe et al., comparing enzymatic and histologic estimates of infarct size, the absolute value of the $K_a$ as calculated using Norris' method was consistently less than the absolute value of Shell's average $K_a$. This finding could be explained by continual release of CPK during the time of the monoexponential decay of CPK, thus giving a falsely low value for $K_a$. Also, using Norris' modification, Roe et al. have recently recalculated the serial CPK data reported by Shell et al. and have shown that this modification did not improve the correlation between these estimates and myocardial CPK depletion. Yasmineh et al. have provided experimental evidence that problems exist with Norris' method. They showed that myocardial enzyme depletion in baboons correlated poorly with CPK MB release when $K_a$ was individualized for each animal.

This paper has shown that very large errors in estimating infarct size using Norris' technique are theoretically possible but further experimental work will be required to determine what practical limitations exist. A method for further investigating this problem has recently been described. The method, which has not been tested, involves injecting labelled CPK into each subject during the infarction period. The decay of the labelled CPK provides an independent measure of the value of the disappearance rate parameter which can now be regarded as a function of time, $K_a(t)$. This method has the advantage of providing a dynamic estimate of the disappearance constant and would thus also reflect changes in the disappearance rate parameter or the distribution space, caused as a result of pharmacologic, hemodynamic or other phenomena which are thought to influence CPK dynamics. However, it has the disadvantage of assuming that the behavior of injected CPK is equivalent to CPK released from ischemic myocardium — an issue that remains unresolved.

References

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A S Slutsky

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