A Method for the Estimation of Peak Serum LDH Activity Based on a Single Post-Peak Level after Acute Myocardial Infarction

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SUMMARY

A new method was developed to estimate the peak serum lactic dehydrogenase (LDH) value in patients with acute myocardial infarction from a single determination of serum LDH activity in the post-peak period (3rd to 5th day after the onset of infarction) using nomogram method based on the monoexponential decay of serum LDH with a decay constant of 0.012 hours^{-1}.

To develop this nomogram, the serial changes in serum LDH activities were studied in 30 patients with acute myocardial infarction admitted to the coronary care unit within the pre-peak period. The mean errors in estimation from data of the 3rd, 4th, or 5th day after the onset were acceptably small, 10.5±1.9%, 14.5±2.8%, and 15.9±3.3%, respectively.

Furthermore, a correction formula was obtained to improve the accuracy of estimation, since the peak values were underestimated in patients with actual peak values less than 300 units and overestimated in the case of more than 500 units.

Estimation in 9 patients of an external sample group confirmed that this nomogram is useful clinically with mean errors of less than 25%.

Additional Indexing Words:
Acute myocardial infarction Enzyme-nomogram Peak serum LDH activity Infarct size

As the recent effective coronary care has diminished mortality resulting from arrhythmia in patients with myocardial infarction, pump failure has aroused a considerable clinical interest as a major cause of this disease.1,2)

This symptom is believed to depend to a great extent on the size of the...
infarction and therefore it is very important clinically to estimate the infarct size which would be of great prognostic value. Although some investigators assessed the infarct size quantitatively by a mathematical analysis of serial serum creatine phosphokinase (CPK) activities, this method is not applicable in patients whose serum enzyme activities in an early stage are unknown. In practice, however, not a few patients are admitted to a hospital only after several days following the onset of infarction and the peak values of serum enzyme activities, which would be roughly correlated to infarct size, are not available, because the serum enzyme activities usually increase to a peak value within 1 or 2 days after the onset of infarction.

It is possible, however, to estimate the peak value of serum enzyme which remains abnormal for a long period from the values in the post-peak period because serum enzyme levels usually decay monoexponentially to their normal levels following the peak. In this study, a new enzyme-nomogram was developed to estimate the peak lactic dehydrogenase (LDH) value from one serum LDH activity of the 3rd to the 7th day after the onset of infarction.

**Materials and Methods**

Serial changes of serum LDH, CPK, GOT (glutamic oxaloacetic transaminase), and HBD (α-hydroxybutyric dehydrogenase) activities were determined for 7 days in 30 patients with acute myocardial infarction admitted to the Coronary Care Unit of Sakurabashi Watanabe Hospital within 12 hours after the onset of symptoms. The selection of the patients was based on the presence of (1) typical pain with a well defined onset, (2) serial electrocardiographic changes unmistakably compatible with acute myocardial infarction, and (3) a characteristic pattern of serial changes in serum enzyme activities without reelevation within the week.

The patients were divided into 2 groups: Group I consisted of 20 patients without any major complications such as cardiogenic shock or heart failure. Group II consisted of 10 patients complicated with heart failure in the early phase of infarction. Table I summarizes the pertinent data of the patients.

Additional 9 (out of 12 consecutive patients) were also studied to confirm the accuracy of the enzyme-nomogram in the estimation of the peak serum LDH value as an external sample group (1 of the 12 patients died from cardiogenic shock on the 2nd hospital day and 2 were admitted on the 3rd day after infarction, whose serial serum LDH activities had already passed the peak). Although 1 of these 9 patients exhibited a slight reelevation of serum enzymes (CPK, GOT, HBD, and LDH) on the 3rd day without any electrocardiographic evidence of extension of infarction, we felt that this reelevation could not have been detected retrospectively in a clinical situation.

*Determination of serum enzyme activities*

Sampling of blood was usually done every 4 hours for the first 24 hours, every 6 hours during the next 2 days and thereafter once or twice a day until the 7th
Fig. 1. Serial changes of serum enzyme levels after subtracting the basal value (98 units for LDH) in a representative case of acute myocardial infarction.

day at least. Serum LDH was determined by the method of Nacklas11) and the normal range in our laboratory was 30 to 140 units.

*Estimation of peak serum LDH activities*

In acute myocardial infarction without infarct extension, serial changes of serum LDH activities subtracting the basal value show a characteristic pattern, declining monoexponentially to near normal from the peak.

A representative pattern of changes of the serial serum enzyme activities (after subtracting the basal value) plotted on semi-logarithmic paper is shown in Fig. 1. The basal value of serum LDH, as determined in a previous study in our laboratory was 98 units.13) The peak value of serum LDH activity (LDH_{max}) is theoretically presented as follows:

\[ \log (LDH_{max} - LDH_b) = k(t_p - t) + \log (LDH_t - LDH_b) \]

where LDH_b is a basal value of serum LDH activity, k is a disappearance rate (hours^{-1}), t_p is the time (in hours) from the onset to the peak in serum LDH activity and LDH_t represents serum LDH activity at t hours after the onset.

Fig. 2 shows an enzyme-nomogram for estimation of the peak serum LDH activity from a single determination in the post-peak period. The oblique straight lines in the nomogram represent disappearance curves of serum LDH activities and the slope of these lines is 0.012 hours^{-1}, which is the mean value of disappearance rates as previously reported.13) A vertical line at time t_p shows a "peak line". A mean value of individual peak time (a period from the onset to the peak) was substituted for t_p (39.5 hours) because individual variations were not so large, although the mean peak time of Group I (35.1 hours) was less than that of Group II (42.3 hours, see Table I).

The coordinates of point A in Fig. 2, shows the time from the onset and the serum LDH activity at time t subtracting the basal value. A line parallel to the
Fig. 2. Enzyme-nomogram for estimation of peak value of serum LDH activity. This figure also shows the method of estimation of peak value from a single determination of serum LDH activity in the post-peak period.

Table I. Mean Peak Value and Mean Peak Time from the Onset of Infarction of Serum LDH in the Patients of Groups I and II

<table>
<thead>
<tr>
<th></th>
<th>Age (y.o.)</th>
<th>Observed peak serum LDH activity (units)</th>
<th>Peak time of serum LDH activity (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (20)</td>
<td>54.0 ± 2.1</td>
<td>471 ± 78</td>
<td>35.1 ± 2.3</td>
</tr>
<tr>
<td>Group II (10)</td>
<td>64.0 ± 2.3</td>
<td>627 ± 148</td>
<td>42.3 ± 4.0</td>
</tr>
<tr>
<td>Total (30)</td>
<td>57.9 ± 1.8</td>
<td>523 ± 73</td>
<td>37.5 ± 2.1</td>
</tr>
</tbody>
</table>

The number of cases is shown in the parenthesis.

disappearance lines passing through point A represents the disappearance slope of serum LDH activity for this patient. The point of intersection of this line with the peak line (0) gives the estimated peak value of serum LDH activity minus the basal value (LDH_{max} − LDH_{b}). Thus, the actual estimated peak value (LDH_{max}) is obtained by adding the basal value (98 units).

In this study the errors in estimation of peak value according to this enzyme-nomogram were investigated. The serum LDH activities on the 3rd to 7th day in 30 patients with acute myocardial infarction described above were used as internal test samples to obtain the correction formula (see Results). Nine patients in the external sample group were used to evaluate this new method.

Another method to estimate the peak value according to the regression line of 3 daily determinations was also evaluated. In this method, a point of intersection (0' in Fig. 3) of a regression line obtained from the 3 points (A, B and C), with the peak line also gives an estimated peak value. This method was applied to 3 sets of data obtained from the 3 consecutive daily determinations—data of 3rd~5th day, 4th~6th day, and 5th~7th day in each patient. The errors in estimation by this method were compared with those of the former method (enzyme-nomogram method).
RESULTS

Table II summarizes the mean percent difference between observed peak values and estimated peak values of serum LDH activity according to the enzyme-nomogram (see Method) from a single determination on the 3rd, 4th, 5th, 6th, or 7th day after the onset of infarction. Although estimation from the LDH activities of the 6th and 7th day after the onset gave non-negligible errors, 20.7±3.3% at 6th day and 29.8±6.7% at 7th day, mean percent errors in estimation from the data of the 3rd, 4th, and 5th day were satisfactorily small—10.5±1.9%, 14.5±2.8%, and 15.9±3.3%, respectively. Thus, a close correlation was obtained between the actually observed peak values and the estimated peak values based on a single measurement on the 3rd, 4th, or 5th day, correlation coefficients being 0.990 (n=29) at 3rd day, 0.985 (n=30) at 4th day, and 0.982 (n=28) at 5th day (Figs. 4, 5, and 6).

Table II. Mean Percent Errors in Estimation of Peak Serum LDH Based on a Single Determination on the Day Indicated According to the Enzyme-Nomogram without Correction

<table>
<thead>
<tr>
<th>Day after the onset of infarction</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>8.0±1.7</td>
<td>10.5±1.7</td>
<td>11.4±2.4</td>
<td>18.9±4.0</td>
<td>21.6±5.1</td>
</tr>
<tr>
<td>Group II</td>
<td>15.4±4.0</td>
<td>22.6±6.8</td>
<td>25.4±8.0</td>
<td>23.7±5.6</td>
<td>40.7±13.2</td>
</tr>
<tr>
<td>Total</td>
<td>10.5±1.9</td>
<td>14.5±2.8</td>
<td>15.9±3.3</td>
<td>20.7±3.3</td>
<td>29.8±6.7</td>
</tr>
</tbody>
</table>
Fig. 4. Relationship between observed peak value and estimated peak value from the serum LDH activity on the 3rd day after the onset of infarction. Abbreviations: LDHo = observed peak value of serum LDH activity subtracting the basal value, LDHe = estimated peak value of serum LDH activity subtracting the basal value.

Fig. 5. Relationship between observed peak value and estimated peak value from the serum LDH activity on the 4th day after the onset of infarction. Abbreviations: LDHo = observed peak value of serum LDH activity subtracting the basal value, LDHe = estimated peak value of serum LDH activity subtracting the basal value.

It should be noted, however, that significantly large errors were seen in Group II with heart failure than in Group I without symptoms of pump failure (see also Table II).

On the other hand, there was no improvement in accuracy by the regres-
Fig. 6. Relationship between observed peak value and estimated peak value from the serum LDH activity on the 5th day after the onset of infarction. Abbreviations: \(LDH_o\) = observed peak value of serum LDH activity subtracting the basal value, \(LDH_e\) = estimated peak value of serum LDH activity subtracting the basal value.

Table III. Mean Percent Errors in Estimation of Peak Serum LDH Values by Regression Method from 3 Daily Determinations

<table>
<thead>
<tr>
<th>Day after the onset of infarction</th>
<th>Mean±SE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3, 4, 5</td>
</tr>
<tr>
<td>Group I</td>
<td>11.5±1.8</td>
</tr>
<tr>
<td>Group II</td>
<td>12.9±3.8</td>
</tr>
<tr>
<td>Total</td>
<td>12.0±1.8</td>
</tr>
</tbody>
</table>

Fig. 7 shows the relationship between the actually observed peak values of serum LDH activity and the percent errors in estimation by nomogram from the serum LDH activity of the 3rd day after the infarction. It is obvious that the peak values were underestimated in patients with actual peak values of less than 300 units and conversely overestimated when the peak values were more than 500 units. This was also seen in the estimation method based on 3 consecutive daily measurements. Mean percent errors in estimation from the values of 3rd to 5th, 4th to 6th, and 5th to 7th day after the onset were 12.0±1.8%, 22.9±5.1%, and 26.9±5.4%, respectively (Table III). Thus, the nomogram method seems better than the regression method because it requires only a single determination and the procedure of estimation is simpler.
Fig. 7. Relationship between the observed peak values of serum LDH activities and the percent errors in estimation from serum LDH activity on the 3rd day after the infarction.

from the data of other days. Thus, to improve the accuracy of estimation, the corrected peak values were obtained by regression analysis of the relationship between observed peak values and estimated peak values according to the nomogram. Regression analysis revealed the following relationship between these 2 values.

\[
\text{LDH}_0 = 0.751 \times \text{LDH}_e + 79.4 \quad \text{for estimation on the 3rd day}
\]
\[
\text{LDH}_0 = 0.778 \times \text{LDH}_e + 53.5 \quad \text{for estimation on the 4th day}
\]
\[
\text{LDH}_0 = 0.790 \times \text{LDH}_e + 49.8 \quad \text{for estimation on the 5th day}
\]

where LDH₀ and LDHₑ represent the observed peak LDH value and the estimated peak LDH value, respectively.

For great simplicity, a single correction formula using the mean values of the 2 coefficients in the above regression equations, \( \text{LDH}_0 = 0.774 \times \text{LDH}_e + 61.9 \) was applied to more precisely estimate the peak values from data of the 3rd, 4th, and 5th day after the onset of infarction. With this correction, estimation was improved over that without correction (see, Table IV and Fig. 8). Mean percent errors from the data of the 3rd, 4th, and 5th day were 7.7±1.2%, 10.1±1.9%, and 11.7±2.1%, respectively and estimation at 6th and 7th day were also improved. This suggests that, if the enzyme-nomogram and the correction formula are applied, estimation of peak serum LDH value from a single determination of serum LDH on the 3rd, 4th, or 5th day after the onset of infarction can be done with errors less than 15%.

In 9 patients in an external sample group, the individual peak LDH values were also estimated from a single value of serum LDH of the 3rd to 5th
Table IV. Mean Percent Errors in Estimation of Peak LDH Values According to the Enzyme-Nomogram with Correction

<table>
<thead>
<tr>
<th>Day after the onset of infarction</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>7.1±1.4</td>
<td>8.5±1.2</td>
<td>10.4±1.7</td>
<td>15.6±3.3</td>
<td>15.5±3.9</td>
</tr>
<tr>
<td>Group II</td>
<td>8.7±2.5</td>
<td>13.4±4.8</td>
<td>14.4±5.3</td>
<td>15.2±3.3</td>
<td>21.9±9.6</td>
</tr>
<tr>
<td>Total</td>
<td>7.7±1.2</td>
<td>10.1±1.9</td>
<td>11.7±2.1</td>
<td>15.5±2.5</td>
<td>18.1±4.5</td>
</tr>
</tbody>
</table>

Fig. 8. Relationship between the observed peak values of serum LDH activities and the peak values estimated from a single value on the indicated day.

day after the onset, with the nomogram and the correction formula. Although mean percent errors in estimation were significantly larger than that in the internal samples, 18.2±2.7% at 3rd day, 22.7±3.3% at 4th day, and 23.2±3.2% at 5th day, they were within 25% of the observed value, suggesting that this method can be applied for clinical use.

DISCUSSION

It is thought that the peak value of serum enzyme activity in acute myocardial infarction is roughly correlated to infarct size\(^7,8\) and is therefore useful to estimate the prognosis in the early stage.\(^4\) No studies, however, have reported the estimation of peak values from serum levels in the post-peak period. In this study, a new method using an enzyme-nomogram with a correction formula was developed to estimate the peak value of serum LDH
from a single determination on the 3rd to 7th day after the onset of symptoms. The reasons for the selection of serum LDH are: (1) This enzyme remains abnormal for a long period, usually for 7 to 11 days after the infarction,14) (2) errors in determination are relatively small,15) (3) this enzyme assay is as commonly done as serum glutamic oxaloacetic transaminase (GOT) which unfortunately returns to normal much more rapidly than LDH.14) In our series, the peak values of serum LDH were well correlated to those of serum GOT and HBD (Figs. 9 and 10).

The disappearance course of serum LDH has been investigated in patients with acute myocardial infarction, following the monoexponential decay after the peak in patients without extension of infarction.13) The disappearance course represented by the parallel oblique straight lines in the nomogram
(see Fig. 2) was determined from the disappearance rate (averagely 0.012 hours⁻¹) obtained in our previous study. Individual disappearance rates were also obtained by regression from the 3 daily determinations to estimate peak values (regression method) but the results were not better than the nomogram method which assumes a constant disappearance rate. This is probably because the errors in determination of serum LDH values on the 6th or 7th day, which have already returned to almost normal, would greatly influence the slope of the regression line, leading to significantly large errors in the estimation of peak value.

Without correction, the enzyme-nomogram gave an overestimated peak value for a patient with an actual peak value of more than 500 units and an underestimated peak value in case of less than 300 units (see Fig. 7). This is apparently due to the fact that peak time of serum enzyme in a patient with extensive infarction is later than in a patient with a small infarct. Indeed, mean peak time in the patients whose peak values were underestimated was 31.6 hours, while that in the patients whose peak values were overestimated was 46.9 hours.

The peak values were overestimated in many of the patients in Group II (with heart failure) whose mean time (42.3 hours) was later than the average (37.5 hours), since the peak time for the nomogram was set up as the mean time of all patients investigated in this study. Another cause for the overestimation of peak values in Group II may be the absence of a sharp peak in these more severe cases.

The correction formula, however, which improved the accuracy of estimation (averagely 29.6% improved), we believe, makes this method applicable to clinical use. It should be noted, however, this method is not applicable in patients whose symptoms or electrocardiograms indicate an extension of infarction.

**Acknowledgement**

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