Does Lactate Dehydrogenase Isoenzyme-5 Contribute to the Predictive Power of Total Lactate Dehydrogenase in Myocardial Infarction?

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In 385 patients with acute myocardial infarction, lactate dehydrogenase (LD; EC 1.1.1.27) isoenzymes were determined electrophoretically 24, 48, and 72 h after admission. At those times, LD-1/LD-2 ratios exceeding 1 were recorded in 78.9, 88.8, and 92.2% of the cases, respectively. LD-1 ranged from 181 to 2674 U/L, or 21.9 to 66.1% of the total activity. On the first day of hospitalization, 27.3% of the patients demonstrated abnormal LD-5 (>6% of total LD); this finding dropped to 20.5% and 17.4% in the two following days. Early increases in LD-5 were most frequently observed in patients associating inferior infarcts with posterior or lateral extension and having a previous history of myocardial infarction. On day 1, LD-5 was significantly increased in early deceased patients as compared to long-term survivors (9.7% vs 4.9% of total LD, p < 0.01). LD-5 definitely contributes to the prognostic efficiency of total LD in acute myocardial infarction, but does not replace it as a risk predictor. This study confirms the superiority of total LD over the isoenzyme measurements to achieve short-term prognostication.

Additional Keyphrases: risk prediction • prognostic aid • enzyme activity • heart disease • myocardial infarction

In patients with myocardial infarction (MI), the cardiосpecific lactate dehydrogenase (LD) fractions, LD-1 and LD-2, have been widely studied, and either an increased LD-1 (for example, greater than 40% of total LD) or a LD-1/LD-2 ratio greater than 1 (the classical "flipped" LD-1 pattern) has been regarded as a diagnostic criterion (1–5). Important changes in proportions of LD-5 after MI have been described, but little is known about the time and frequency of appearance of this isoenzyme in the serum.

When comparing the efficiency of various enzyme measurements performed at the acute phase of MI for predicting short-term mortality, we demonstrated the superiority of total LD over LD-1 and LD-2 (6). The present study was intended to investigate the changes in the other LD isoenzymes during the first three days of hospitalization and to evaluate their contribution to the already known power of total LD for predicting cardiac deaths during the first 15 days after the acute event.

Materials and Methods

The study involved 385 patients admitted to the University Hospital between March 1979 and December 1980. Acute MI was diagnosed on the basis of electrocardiographic evidence, typical clinical history, and increases and decreases in certain enzyme activities in serum. Blood was sampled at 4-h intervals during the first day of hospitalization and every eighth hour for the next two days.

Procedures

Creatine kinase (CK; EC 2.7.3.2) and LD were measured in all samples by optimized spectrophotometric methods (CK and LDH UV tests, no. 3388 and 3399; Merck, Darmstadt, F.R.G.) at 37 °C, with an ABA-100 analyzer (Abbott Labs., North Chicago, IL 60064). In the samples having the greatest total CK activity, we also measured creatine kinase MB (CK-MB) activity by immunoinhibition (CK-MB UV test, no. 14300; Merck).

LD isoenzymes were determined 24, 48, and 72 h after admission, with use of a commercially available assay kit (Universal Electrophoresis Film agarose, no. 470100; Corning, Medfield, MA 02052). The isoenzymes were stained with Nitroblue Tetrazolium (7) and were quantified with a densitometer (Model R115; Beckman Instruments Inc., Fullerton, CA 92634).

Mean values ± SD for total LD and total CK, determined in 153 healthy subjects (ages 36.6 ± 11.3 years), were 295 ± 54 and 59 ± 27 U/L, respectively. The distributions for both enzymes were significantly skewed to the right (skewness: 0.75 and 0.90, respectively). In this control group, the 0.95 reference intervals for the LD isoenzymes, expressed in percent of total LD, were 10.0–31.0% (LD-1), 35.0–53.0% (LD-2), 24.0–38.0% (LD-3), 0.0–6.0% (LD-4), and 0.0–6.0% (LD-5).

Patient Population

Patients entering the study were selected as follows: their CK activity had to rise continuously after admission and peak at the earliest 8 h after admission; this was to ensure that the MI was of recent onset. In the overall patient population, mean CK activities were 390 (SD 456) U/L on admission and 1205 (SD 914) U/L at the end of the first day. Among the 385 patients investigated (64 of whom were women), 337 were still alive six months afterwards. Twenty-seven patients died during hospitalization: four on the second day, six on the third day, eight between days 4 and 6, and nine between days 7 and 15; 21 died after hospital discharge, i.e., between 15 days and six months after the infarction.

Primarily because of hemolysis of some samples (8), LD isoenzymes could not be electrophoretically separated for all patients: 11 values were missing on day 1, 20 on day 2, and 20 on day 3.

The mean age of these patients was 58.2 years (SD 10.8). Among the 374 patients for whom LD isoenzyme measure-
ments were available on day 1, 73 (19.5%) had evidence of previous MI (history of a hospital admission for documented MI or Q-wave abnormality on the electrocardiogram, indicating an old infarction). The criteria used to differentiate transmural from subendocardial infarction were those of Cook et al. (9); 92% of the patients demonstrated transmural infarction (50.8% with inferior location and 41.2% with anterior location), the other 8% having non-transmural infarctions.

Statistical Analysis

Multiple group mean values were compared by one-way analysis of variance (F-test). The chi-square test was used to compare proportions of patients with a given finding in different groups. Total LD and LD isoenzyme response curves obtained by linear interpolation between serial measurements were compared in various patient categories by applying the method described by Zerbe (10). This method provides a global assessment of group differences, and the hypothesis of equal mean response curves between groups can be tested by an F-criterion.

Results

All patients showed an increase and decrease in total LD activity in serum, the maximum LD values ranging from 406 to 7326 U/L (n=385, mean ± SD = 1618 ± 794 U/L) and occurring, on the average, 36 ± 12 h after admission. Mean LD activity decreased during the subsequent hours to 1332 (SD 691) U/L on day 3.

The classical increase in LD-1 activities after MI was observed at each measurement time, the highest percentages occurring at the end of the investigation period. On day 3, LD-1 ranged from 181 to 2674 U/L, or 21.9 to 66.1% of the total activity (mean 47.8%). At the peak for total LD the mean LD-2, LD-3, and LD-4 percentages were 36.0, 11.5, and 1.6% of total LD, respectively. LD-5 declined from 5.4% on day 1 (range: 0.0 to 43.6%) to 4.1 and 4.0% on days 2 and 3. An abnormal LD-5 fraction (>6% of total LD) was recorded in 27.3, 20.5, and 17.4% of the patients on days 1, 2, and 3, respectively.

At the same measurement times, inverted (“flipped”) LD-1/LD-2 ratios were observed in 78.9, 88.8, and 92.2% of the cases, respectively. As shown in Table 1, noninverted LD-1/ LD-2 ratios were associated with a lower enzyme release, while the highest ratios (>1.20) were related to markedly increased activities of CK, CK-MB, and LD. Noninverted LD-1/LD-2 ratios were more frequently associated with an increased LD-5 fraction.

Predictive Power of LD Measurements

The average response curves of total LD (obtained by linear interpolation between LD measurements performed on admission, and 24, 48, and 72 h later) were calculated for longer-than-six-month survivors, early deaths (four to 15 days), and patients who died later (16 days to six months). Comparing the response curves over three days (10), we found significant differences (F = 24.8, p < 0.001) among the three groups. The use of the same test to compare LD isoenzyme curves (in enzyme units) indicated significant differences for LD-1 (F = 17.2, p < 0.001), LD-2 (F = 21.0, p < 0.001), and, among the extracardiac isoenzymes, for LD-5 (F = 7.8, p < 0.005) only. LD-5 proved to be even more discriminating (F = 14.8, p < 0.001) when only survivors and early deaths were compared.

We compared the average percentages obtained for the five LD isoenzymes during the first three days of hospitalization in survivors and cases of early death (Figure 1). Greater proportions of LD-5 in nonsurvivors than in survivors were apparent. The most pronounced differences were recorded on day 1 (LD-5 was 9.5% of total LD in early deaths vs 5.2% in the low-risk group, p < 0.01) and on day 2 (9.0% vs 4.0%, p < 0.02). On day 3, the two groups did not significantly differ (6.1% vs 4.0%). Early deaths also demonstrated lower percentages of LD-1 and LD-2, but the differences observed were only significant for LD-2 on day 2 (38.5% in survivors vs 35.1% in nonsurvivors, p < 0.05). The relatively more important decrease in LD-2 than in LD-1 in nonsurvivors probably accounts, in part, for a slightly higher mean LD-1/LD-2 ratio in this group (Table 2).

Significance of Increased LD-5 Fraction

The overall population of patients was divided into three classes according to the percentage of LD-5 determined on day 1: class I, LD-5 fraction within the normal range, i.e., <6% (n = 272); class II, LD-5 slightly increased, 6–10% (n = 48); class III, LD-5 >10% (n = 54). The increases in LD-5 fractions were unrelated to age and sex; however, the proportion of previous episodes of MI for patients of class I (19.0%) was lower than in the two other groups (25.0% in class II; 23.2% in class III), though not significantly. Peak values for enzyme activities were lower in the patients with normal LD-5. Mean CK peaks averaged 1475 (SD 481) U/L, 1699 (SD 1467) U/L, and 1710 (SD 1738) U/L in classes I through III, respectively, but the differences were not significant.

Table 1. Relationship between LD-1/LD-2 Ratio, Total Enzyme Release, and LD-5 Proportion

<table>
<thead>
<tr>
<th>LD-1/LD-2 ratio*</th>
<th>(n)</th>
<th>CK peak value, U/L</th>
<th>LD peak value, U/L</th>
<th>LD-5 &gt; 6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.00 (n = 79)</td>
<td>1.00–1.20 (n = 84)</td>
<td>1.20–1.40 (n = 89)</td>
<td>&gt; 1.40 (n = 122)</td>
<td></td>
</tr>
<tr>
<td>CK peak value, U/L</td>
<td>1060 ± 856</td>
<td>1603 ± 1114</td>
<td>1777 ± 1405</td>
<td>1637 ± 900</td>
</tr>
<tr>
<td>CK-MB at CK peak, U/L</td>
<td>90 ± 73</td>
<td>125 ± 71</td>
<td>154 ± 98</td>
<td>156 ± 90</td>
</tr>
<tr>
<td>LD peak value, U/L</td>
<td>1195 ± 601</td>
<td>1630 ± 673</td>
<td>1803 ± 923</td>
<td>1743 ± 868</td>
</tr>
<tr>
<td>LD-5 &gt; 6%</td>
<td>31 (39.2%)</td>
<td>26 (30.9%)</td>
<td>18 (20.2%)</td>
<td>27 (22.1%)</td>
</tr>
</tbody>
</table>

*At 24 h after admission. b No. (and %). c χ²; df = 3.
LD-5 and MI Location

Although the distribution of purely inferior or posterior infarcts was not statistically different in the three classes, the proportion of transmural infarctions of the inferior area with posterior or lateral extension (infero-posterior, infero-lateral, or infero-postero-lateral infarcts) was definitely greater in patients with increased LD-5 on day 1: 16.7% (17/102) vs 5.1% (14/272) for patients with normal LD-5 ($\chi^2 = 12.9$, $p < 0.001$). In addition, the group of patients with LD-5 $>10\%$ (class III) demonstrated a significantly higher proportion of infarctions of the infero-posterior wall complicated by lateral or antero-lateral transmural lesion: 24.1% (13/54) vs only 4.0% (11/272) in patients with normal LD-5 ($\chi^2 = 26.5$, $p < 0.001$).

The 344 patients with transmural MI were subdivided into eight groups according to the CK peak activity, infarct location, and history of MI; the mean LD-5 value was calculated in each group (Table 3). In patients presenting with their first MI, there was little correlation between LD-5 percentages and CK activity, irrespective of infarct location. Patients with a previous MI and an inferior infarct, on the other hand, demonstrated significant differences ($p < 0.02$) in LD-5 percentages according to serum CK activity: the most pronounced increases in LD-5 (13.6%) were found in the group with CK activity $>1500$ U/L. In cases of reinfarction with an anterior location of the infarct, LD-5 also increased according to CK activity, but not significantly.

Discussion

In our series, the number of MI patients demonstrating increased LD-5 is remarkably high. At the end of the first day after admission, we found LD-5 increases (>6% of total LD) in more than 25% of the subjects investigated; this proportion dropped to 17% by day 3.

LD-5 is never found in significant amounts in the heart, and no regional heterogeneity in the distribution of LD isoenzymes in the myocardium has been reported (11, 12). Admittedly, modifications of the LD patterns as a metabolic adaptation of ischemia have been reported (13, 14) and the possibility of small amounts of LD-5 originating from the ischemic myocardium cannot be ruled out. However, the earliness and magnitude of the changes in LD-5 (up to 43% of total LD) may suggest a possible hepatic origin of this isoenzyme. Increased LD-5 activity is frequent after liver hypoxia, and LD-5 activities more than 17-fold normal have been described in patients with congestive heart failure (15), exceeding 87% of total LD in severe cases (16).

Although the previous history of MI, inferior location of the infarct, and extent of the jeopardized myocardium, when considered individually, were not significantly related to increased LD-5, the greatest serum LD-5 activities were found in the patients combining the three factors, i.e., 13% in inferior infarcts demonstrating CK peak $>1500$ U/L associated with previous lesions. Undoubtedly, the extent and size of the infarct plays a role in the occurrence of LD-5 after MI (Table 3). That LD-5 increases were most frequently seen in poor MI conditions was confirmed by greater proportions of this isoenzyme in nonsurvivors than in survivors.

In a recent report on the importance of total LD for assessing the patient's risk in the early phase of MI (6), we demonstrated that the discriminant power of total LD activities recorded at the time of CK peak (20–24 h after admission) was greater than that of maximum LD activity, which occurs about 15 h later. Moreover, total LD measured on day 1 proved to be a better predictor for short-term mortality than the cardio-specific isoenzyme LD-1. In the present work, we have confirmed the superiority of total LD assay over measurements of the individual isoenzymes. However, the comparison of the response curves of total LD and LD isoenzyme activities during the first three days of hospitalization in groups of patients with increasing risk (six-month survivors, deaths after hospital discharge, and early deaths) also demonstrated that, in addition to the cardiospecific isoenzymes, LD-5 significantly differentiated the different risk groups, particularly during the first two days of hospitalization. This probably accounts for the fact that measurement of total LD, which integrates both cardiac and extra-cardiac fractions, is a better predictor of risk than LD-1 and LD-2.

In conclusion, this study indicates that, during the early phase of MI, the LD-5 electrophoretic fraction (a) appears frequently in the serum, (b) is associated with combinations of factors likely to cause heart failure, and (c) has a clearly relevant predictive value for short-term mortality. Therefore, in addition to LD-1 and LD-2, LD-5 contributes to the high predictive power of total LD. We believe these results partly explain why LD is superior to other enzymes, and particularly to CK (6), in the assessment of risk after MI.

References


