Lactate Dehydrogenase Isoenzyme-1: Changes during the First Day after Acute Myocardial Infarction

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We studied the time course of change of lactate dehydrogenase isoenzyme-1 (LD-1) in serum of patients suspected of having had an acute myocardial infarction. LD-1 was measured at intervals of 4-8 h during the first and second hospital days, by an immunochemical method. Of the 65 patients in this study, 26 had acute myocardial infarctions by traditional criteria. The ratio of LD-1 to total LD had greater diagnostic value than did LD-1 alone. In 90% of patients with myocardial infarction this ratio was increased within 12 h of admission, and all had increased ratios within 24 h. The false-positive rate was <1%, and an increased LD-1/total LD ratio had a predictive value of 96% for myocardial infarction. These results suggest that LD-1 is useful in the diagnosis of myocardial infarction on the first day of hospitalization.

Additional Keyphrases: heart disease • diagnostic aid • LD-1/total LD ratio • cutoff value

Serum lactate dehydrogenase (LD) increases after a myocardial infarction (1). However, this is not a highly specific test for myocardial infarction, because such increases are seen in a wide variety of other disorders. Improved specificity for infarction is seen with LD-1, the "heart" isoenzyme of LD. Serum LD-1 routinely is estimated electrophoretically and compared to LD-2. A "flipped" LD 1:2 ratio—i.e., LD-1 > LD-2—has excellent specificity for myocardial infarction but may occur only as a late event, one or more days after the infarction, and is not observed at all in 15-20% of patients (2). These clinical considerations limit the utility of the test.

A method has been described recently for rapid isolation of LD-1 by an immunochemical technique (3). This allows LD-1 to be assayed by optimized methods, providing maximal precision of the measurement. Unlike the LD 1:2 ratio, results with the new assay are independent of the amount of LD-2.

The aim of our study was to evaluate the potential of this new technique to provide clinically useful information. Thus it was important to ascertain the time course of the increase in LD-1 and to determine the diagnostic value of LD-1 during the first 24 h of hospitalization after myocardial infarction.

Materials and Methods

We prospectively studied 65 patients admitted to the Coronary Care Unit (CCU) of the University of Virginia Hospital on whom serial creatine kinase isoenzyme tests were ordered (4). Blood was sampled on admission and at 4-h intervals during the first 24 h of hospitalization. Samples were drawn at 8- to 12-h intervals during the second hospital day and once every 24 h thereafter. Samples were no longer drawn after three consecutive negative results for creatine kinase (CK)-MB isoenzyme had been reported. For non-infarct patients this usually occurred within the first 16 h after admission. An average of 3.52 blood samples were obtained per patient within the first 16 h after admission. During this time the numbers of samples obtained from patients with and without myocardial infarction did not differ significantly. For this reason, we used only values obtained during the first 16 h in Figure 2, in which patients with and without myocardial infarctions are compared, because at later times the numbers of samples per patient were different for those with and without myocardial infarction.

The estimated time of onset of chest pain was noted for each patient. For data analysis we restricted our patient pool to those patients from whom we obtained the initial serum sample within 24 h of the onset of chest pain. Two patients were excluded from the patient pool because they were referred from outlying area hospitals several days after they had sustained myocardial infarcts; both had above-normal values for LD-1 on admission.

The diagnosis of myocardial infarction made by the attending cardiologist was based on standard criteria, which included clinical history, evolutionary electrocardiographic findings, and serial enzyme changes including CK-MB (2). The LD isoenzyme results were not available to the cardiologists for use in making the diagnoses.

Serum LD-1 was separated by an immunochemical procedure (3), with use of antiserum against the M subunit of LD, which is present in all LD isoenzymes except LD-1. The antigen–antibody complexes were precipitated by using an insoluble secondary antibody. The antiserum was purchased from Roche Diagnostics, Nutley, NJ 07110. The LD activity not precipitated by this procedure (i.e., LD-1) was measured at 30 °C in a centrifugal analyzer, with a pyruvate-to-lactate assay (BMC UV System LDH-P; Bio-Dynamics/BMC, Indianapolis, IN 46250). We have reported the performance of this assay (5). The day-to-day reproducibility (CV) of the LD-1 assay was 2.5%. Total serum LD was measured by the same centrifugal analyzer method, also with similar excellent precision.

After electrophoretic separation (ACI system; Corning Medical, Medfield, MA 02052), CK-MB was measured fluorometrically.

Results

Of the 65 patients in our study, 26 were diagnosed as having had myocardial infarcts. The other 39 patients comprised the non-myocardial infarct group. LD-1 was found to increase during the first 12 h after admission for myocardial infarction. Figure 1 shows the results of serial enzyme tests on a single infarct patient. In this patient LD-1 exceeded the upper limit of the reference interval at about the same time as CK. This figure also demonstrates that LD-1 and the ratio of LD-1 to total LD (LD-1/total LD) became abnormal before total LD activity was first noted to be abnormal. This was a common observation: 37 samples from infarct patients had total LD activities within the reference range (100–350 U/L) and 43% of these were found to have a
positive LD-1/total LD result. From non-infarct patients we found one false-positive LD-1 result among 124 samples each of which had a total LD of <350 U/L.

Measuring the LD-1/total LD ratio provided excellent discrimination of patients with and without myocardial infarction, and Figure 2 illustrates that this discrimination was evident within the first 16 h after admission. Usategui-Gomez et al. (3) used as their cutoff an absolute value of LD-1. In our study we found that the ratio of LD-1 to total LD (“LD-1 ratio”) was a better discriminator for myocardial infarction than was the absolute value of LD-1 (Figure 2). Clinical discrimination was obtained when 40% was used as the cutoff value for this ratio (>40% being a positive result). Using this cutoff, we saw only one false-positive result during the first 16 h of admission among the 124 samples tested from non-infarct patients. The value for this one false-positive result was 40.6%.

Results for the LD-1 ratio and for CK-MB were compared for the myocardial infarct group (Figure 3). By 12 h after admission, 90% of LD-1 results were positive (ratio >40%); all were positive by 24 h after admission. The ratio remained increased for several days after infarction, whereas almost 40% of the CK-MB results had reverted to normal by 48 h after admission.

We also determined the time when the LD-1 ratio first became positive relative to the time when CK-MB first became positive for each patient. In over half of the myocardial infarct patients (62%, or 16 of 26 patients) a positive LD-1 ratio was noted simultaneously with the first positive CK-MB. In some of these cases both tests were positive on admission. For five of the remaining 10 patients the LD-1 ratio became positive within 4 h after CK-MB was first noted to be positive. The LD-1 ratio followed the CK-MB in becoming positive by 8–16 h in four of the five remaining patients. One patient had a positive CK-MB on admission and the LD-1/total LD ratio did not become positive until 24 h later.

LD-1 studies were also conducted on the two patients who were excluded from the patient pool because of delayed admission to our hospital. In these patients the LD-1 ratios were still above normal upon admission at six and 12 days after infarction.

**Discussion**

The immunochemical approach we used to assay LD-1 activity, that first described by Usategui-Gomez et al. (3), has the advantages of simplicity, speed, and quantitative precision (5). In our study, the predictive value of a positive result during the first 16 h after admission was 96% (25/26 patients) and the predictive value of a negative result was 97% (38/39 patients).

Numerous studies have been conducted to determine the interval during which CK-MB is increased after a myocardial infarction, but the optimal time for sampling LD isoenzymes has been less clearly defined. This may be due in part to the methods that have been used to demonstrate changes in the LD isoenzyme pattern. The electrophoretic methods are tedious and only semi-quantitative. As mentioned previously, up to 15–20% of patients with myocardial infarction may not demonstrate the “flipped” LD 1:2 pattern as measured electrophoretically, and in other patients the “flip” may only be detected two to three days after the infarction. Another problem in establishing the time course for LD isoenzymes has been that some laboratories obtain and test samples only on a daily basis. Additionally, in most laboratories LD isoenzymes are measured only when total LD activity is increased; however, isoenzyme patterns may be abnormal while values for total LD are normal (6).

This is the first study of the LD-1 assay to utilize frequent blood sampling during the first 24 h after admission to a CCU. The sensitivity of the new quantitative LD-1 assay combined with the high initial sampling frequency allowed us to demonstrate effectively the early time course of changes in LD-1. The LD-1/total LD ratio became positive for all infarct patients during the first 24 h after admission, simultaneously with or within hours of CK-MB being positive. Moreover, we
found a number of true-positive LD-1 results in samples with normal total LD activity. We would have failed to detect these positive results if we had waited to assay LD-1 until the total LD became abnormal.

In conclusion, the LD-1 immunoassay appears to be a reliable addition to the laboratory evaluation of patients with suspected myocardial infarction. The test appears to be useful for early confirmation of CK-MB results and for laboratory confirmation of myocardial infarction in patients presenting to the hospital after the CK-MB has reverted to normal.

References