Lactate Dehydrogenase Isoenzymes in Serum during Unstable Angina

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Values for total lactate dehydrogenase (LD, EC 1.1.1.27) activity in serum, LD isoenzymes 1 and 2, and the LD 1:2 ratio in 25 patients with unstable angina were compared with the same variables in 25 patients whose angina was stable 24, 48, and 72 h after admission. Mean total LD activity and mean LD-2 activity were found to be within the normal range, both in the unstable angina and stable angina groups of patients. In the unstable angina group the mean LD-1 was significantly higher (p<0.01) than in the stable angina group at each time studied. The mean LD 1:2 ratio was also significantly different (p<0.001) between the two groups of patients. In the unstable angina group of patients the ratio was increased (0.85, SD 0.09), as in patients with acute myocardial infarction, whereas in the stable angina group of patients the ratio was normal (0.60, SD 0.06). We conclude that a high LD 1:2 ratio, even in the presence of normal total LD activity, may indicate myocardial damage in some patients with unstable angina and could therefore help in the clinical and functional evaluation of patients with unstable angina.

In unstable angina, the activities of cardiac enzymes are seldom increased, there being only a few reports (1, 2) of an increased creatine kinase (CK; EC 2.7.3.2) MB fraction (CK-MB) in some patients with unstable angina up to 24 h after onset of chest pain. If the pathological basis for this finding is myocardial damage such as myocardiolysis and coagulation necrosis, as has been found in patients with unstable angina (3–7), one might expect that other cardiac-specific enzymes would also be increased in unstable angina.

The aim of our study was to determine total lactate dehydrogenase (LD, EC 1.1.1.27) activity, LD-1 and LD-2 proportions, and the LD 1:2 ratio in patients with unstable angina 24, 48, and 72 h after admission.

Patients and Methods

The study population consisted of 50 consecutive patients hospitalized in our medical department and coronary-care unit: 35 men, mean age 62 (range 40–85), and 15 women, mean age 55 (range 40–70) years.

The 50 patients were divided into two groups:

(a) 25 patients with unstable angina, defined as new onset of angina or an aggravation of a pre-existing angina not responding to rest and nitrates and accompanied by electrocardiographic ST-T changes (ST elevation, ST depression, or T-wave inversion), without the development of Q waves or increase in cardiac enzymes, and

(b) 25 patients with stable angina, defined as typical chest pain with exertion and a positive response to rest and (or) sublingual nitrates.

Patients with congestive heart failure were excluded from the study. None of the 50 patients had clinical or laboratory findings suggesting hemolysis or renal injury. Total serum LD activity and LD isoenzymes were determined in each patient 24, 48, and 72 h after admission for chest pain. Total LD was measured by the method of Wacker et al. (8) at 37 °C, in a Gemaac centrifugal analyzer (Electro-Nucleonics, Fairfield, NJ). The normal reference interval in our laboratory is 100–225 U/L, and the coefficients of variation for normal and abnormal serum LD values are 3.2–4.2%. The proportions of the LD isoenzymes were determined by electrophoresis on cellulose acetate plates, with the Helena kit (cat. no. 5451) and instrumentation (Helena Laboratories, Beaumont, TX). The normal reference interval for LD-1 in our laboratory is 30–90 U/L and for LD-2 it is 55–100 U/L. The reference interval for the LD 1:2 ratio, based on data from 200 healthy subjects (9) and findings in our laboratory, is 0.45–0.74. CK-MB was measured concomitantly in the two groups of patients.

We compared total LD activity, LD-1 and LD-2 isoenzymes, and the LD 1:2 ratio for the two groups of patients. Differences between means were assessed by Student's t-test, and were considered significant at the p<0.05 level.

Results

Table 1 lists the mean serum total LD activity, LD-1, LD-2, and LD1:2 ratios in samples obtained from the two groups of patients 24–72 h after admission. Values for serum total LD activity and LD isoenzymes 1 and 2 peaked 48 h after admission, although these values did not differ significantly from those obtained 24 and 72 h after admission. Total LD activity in serum was within the normal range for both groups of patients throughout the 72 h after admission and were not significantly different between the groups. The same was true of mean serum LD-2 activity. However, the mean (±SD) LD-1 values for serum, although within the

| Table 1. Mean Total LD, LD-1, LD-2, and LD 1:2 Ratio (Mean ± SD) in Patients with Unstable Angina (U.A.) or Stable Angina (S.A.) |
|-----------------|-----------------|-----------------|-----------------|
| Hours after admission | Total LD U/L | LD-1 U/L | LD-2 U/L | LD 1:2 |
| 24 U.A. | 186 ± 22 | 63 ± 14<sup>a</sup> | 73 ± 13 | 0.86 ± 0.09<sup>b</sup> |
| S.A. | 184 ± 20 | 45 ± 12 | 74 ± 12 | 0.59 ± 0.07 |
| 48 U.A. | 192 ± 25 | 64 ± 14<sup>a</sup> | 73 ± 13 | 0.85 ± 0.09<sup>b</sup> |
| S.A. | 184 ± 29 | 46 ± 7 | 76 ± 12 | 0.60 ± 0.06 |
| 72 U.A. | 185 ± 25 | 61 ± 13<sup>a</sup> | 72 ± 13 | 0.85 ± 0.09<sup>b</sup> |
| S.A. | 182 ± 23 | 43 ± 12 | 74 ± 11 | 0.60 ± 0.07 |

<sup>a</sup>Significantly different from mean in stable angina (a, p<0.01; b, p<0.001).

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normal range in both groups of patients, were significantly higher ($p < 0.01$) in the unstable angina group of patients than in the stable angina group; $63 \pm 14$ vs $45 \pm 12, 64 \pm 14$ vs $46 \pm 7$, and $61 \pm 13$ vs $43 \pm 12$ U/L at 24, 48, and 72 h after admission, respectively. The LD 1:2 ratio was also markedly higher in the unstable angina group than in the stable angina group ($p < 0.001$): $0.86 \pm 0.09$ vs $0.59 \pm 0.07, 0.88 \pm 0.09$ vs $0.60 \pm 0.06$, and $0.85 \pm 0.09$ vs $0.60 \pm 0.07$ at 24, 48, and 72 h after admission, respectively.

CK-MB was not increased in any of the 50 patients at any of the intervals after admission.

Discussion

In normal healthy individuals LD-1 occurs in lesser quantities than LD-2 (10), the normal ratio of LD 1:2 being 0.45–0.75 (9). Because the myocardium has a preponderance of LD-1, with lesser amounts of LD-2, necrosis of the myocardium releases relatively more LD-1 than LD-2 into the serum, reversing the normal ratio. A similar "flipped" LD ratio may be found in hemolysis and renal injury (10,11). Cohen et al. (12) demonstrated an increase in the LD 1:2 ratio to >1.0 in all of their myocardial infarction patients. Vasudevan et al. (13), studying 100 patients hospitalized for chest pain, found that a peak LD 1:2 exceeding 0.76 appeared to be the cutoff point for the diagnosis of myocardial infarction. The peak LD 1:2 ratio did not exceed 0.76 in 44 patients with no myocardial infarction. Leung and Henderson (9) also found an LD 1:2 ratio >0.76 in 101 patients with acute myocardial infarction; the ratio was between 0.45 and 0.74 for 250 healthy subjects.

In our 25 patients with unstable angina, mean values for total LD activity and LD-1 and LD-2 isoenzymes in serum were within the normal reference interval 24, 48, and 72 h after admission, but the LD 1:2 ratio, $0.65 \pm 0.09$, was similar to that usually found in patients with acute myocardial infarction (9,12). In the stable angina group, however, the LD 1:2 ratio was within the normal range in all patients.

Subendocardial myocytolysis and coagulation necrosis may be present in patients with unstable angina who die after either a relatively brief (3–5) or a protracted (6) clinical course. Early myocytolysis is characterized by sarcoplasmic vacuoles that later enlarge and replace or displace the myofibrils. The most severely affected cells have a sarcolemma without organelles in the cytoplasm, and with peripheral clumping of nuclear chromatin (6,7). Just external to the subendocardial layer of myocytolysis are foci of coagulation necrosis. This necrosis differs from that typically seen in myocardial infarction patients (6), in whom the pathognomonic histological finding is contraction-band necrosis, suggesting severely damaged myocardial cells.

The pathological findings described above in patients with unstable angina may explain our findings that even if total LD activity is within normal limits in patients with unstable angina, the LD 1:2 pattern in the serum of these patients may be relatively high 24, 48, and 72 h after onset of pain. These findings may suggest that there is release of relatively more LD-1 than LD-2, from foci of damaged myocardial cells undergoing myocytolysis or even coagulation necrosis without development of the contraction-band necrosis and total tissue necrosis seen in patients with myocardial infarction.

Marmor et al. (1,2) found that 11 of 26 patients with unstable angina had high proportions of CK-MB fraction in the presence of normal total CK up to 24 h after admission for chest pain. Our findings, showing a steady increase of LD 1:2 up to 72 h after admission in most patients with unstable angina, suggest that determination of the LD 1:2 ratio may be more useful than CK-MB detection, especially in patients in whom the acute coronary event occurred more than 24 h before admission. In these patients the proportion of CK-MB may have returned to normal by the time of admission. Moreover, the prolonged increase of LD 1:2 ratio through the first three days after admission for chest pains may indicate a continuous myocardial damage in these patients.

We conclude that determining the LD 1:2 ratio, even in the presence of normal total LD activity, may be of significant assistance in the clinical and functional evaluation of patients with unstable angina.

References