SERUM ENZYMES IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

IKUHIRO YAMASAWA, M. D*, MICHINARI MORIMOTO, M. D*,* SEN-ICHIRO KONNO, M. D*,
YOSHIKAZU NAGAI, M. D*, EIKO SAKOTA, M. D*, NOBUTAKA YAOITA, M. D*,
YOSHINOBU KANEKO, M. D*, HAJIME TAKAHASHI, M. D*, SADAMICHI KIYOMI, M. D*,
KENJI TSUBOUCHI, M.D*, HIROSHI MINAMI, M.D*,
HIDEO AMARI, M.D* AND YOSHITSUGU NOHARA, M.D*

This paper describes the various serum enzyme patterns, the H-type of SLDH (serum lactate dehydrogenase) isoenzymes with special reference to their differences in acute myocardial infarction, cerebrovascular disease, renal failure, and megaloblastic anemia. Characteristic differences in the patterns of change in the various serum enzymes were noted in these diseases.

In the acute myocardial infarction group, the H-type pattern of SLDH isoenzymes appeared in 94.4%, and SLDH, SGOT, and SCPK activities were elevated in all cases.

In the cerebrovascular disease group, the H-type pattern of SLDH isoenzymes appeared in 66.7% of the patients, and there were elevations of SLDH in 37.8%, SCPK in 69.7%, and SGOT in 43.1%.

In this group, the peak values of both SCPK (serum creatine phosphokinase) and the H-type of SLDH isoenzymes were reached about 3-5 days after the onset of symptoms, and the SCPK level returned to normal more slowly. The rate of increase of total SLDH activity and the LD5/LD4 ratio of SLDH isoenzymes were generally lower than in the acute myocardial infarction group. The amount of total SLDH activity was also less and in some cases did not increase in this group.

In the renal failure group, H-type pattern of SLDH isoenzymes appeared in 33.0% of the patients, and in many cases (75% of the patients) there was an elevation of SCPK activity; the reason for this phenomenon must be investigated. The SGOT and SGPT activities remained almost within the normal range in most of the patients in this group.

Both patients with megaloblastic anemia showed a clear H-type pattern of SLDH isoenzymes, but there was no elevation of SCPK, or SGOT and SGPT activities. SLDH activity, however, was normal in one case, and markedly increased in the other.

Key Words:

Acute ischemic heart disease
Cerebrovascular disease
Renal failure
Megaloblastic anemia
LDH isoenzymes
Various serum enzymes

RECENTLY, SLDH isoenzymes have been studied in a wide variety of pathological conditions, such as cardiac, hepatic, hematological, muscular, renal, and other diseases. The most common clinical application of the analysis of the pattern of SLDH isoenzymes has been in

(Received on December 25, 1976; Accepted on April 8, 1978)

* The 2nd Dept. of Intern. Med., Tokyo Medical College, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan.

** The Dept. of Intern. Med. Shinko Hospt., Kobe, Japan.

The outline of this study was presented at the 36th annual meeting of the Japanese Circulation Society.

Reprint requests to the 2nd Dept. of Intern. Med., Tokyo Medical College, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan. (Dr. I Yamasawa)

TABLE I MEAN VALUES OF ACTIVITIES OF VARIOUS SERUM ENZYMES IN 50 HEALTHY PERSONS.

Serum Enzyme	Mean	S. D.	Range
GOT	16.2(R-F unit)	± 5.8 (n)	4.6 to 27.9 (n)
GPT	12.7(R-F unit)	± 7.4 (n)	0 to 27.5 (n)
CPK	23.9(mU/ml)	± 9.0 (n)	5.9 to 42.0 (n)
LDH	234.0(W unit)	± 37.7 (n)	158.6 to 309.4 (n)
LD5	23.1(%)	± 5.9 (n)	11.4 to 34.7 (n)
LD4	48.1(%)	± 6.7 (n)	34.6 to 61.6 (n)
LD3	20.9(%)	± 4.9 (n)	11.6 to 30.6 (n)
LD2	4.9(%)	± 2.5 (n)	0 to 9.8 (n)
LD1	3.1(%)	± 2.1 (n)	0 to 7.3 (n)
LD5/LD4	0.50	± 0.16	0.18 to 0.81

Fig.1. Serial changes of SLDH activity & ratio LD5/LD4 in 17 cases of acute myocardial infarction.

the diagnosis and prognosis of various disease.^{2,3,6,14}

Previously, we reported that the H-type of SLDH isoenzymes is very helpful in the diagnosis of acute ischemic heart disease with chest pain and myocardial damage^{5,10-13,18,19}

Other investigators have described the H-type pattern of SLDH isoenzymes in many other physical disorders.

This paper describes the various serum enzyme patterns in diseases showing the H-type pattern of SLDH isoenzymes. Their application to differential diagnosis is discussed.

MATERIALS AND METHODS

This research was performed on serum from 18 patients with acute myocardial infarction, 48 patients with various from of cerebrovascular disease, such as cerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage, 14 patients with renal failure, and 2 patients with megaloblastic anemia.

Control serum was obtained from 50 healthy persons.

Blood was obtained by venipuncture, usually from the cubital vein, and allowed to clot at room temperature for about one hour. The clotted blood was centrifuged at 3,000 r.p.m. for about ten minutes.

SGOT and SGPT activities were determined by the method of Reitman & Frankel, and SCKP activity by the method of Nielsen-Ludvigsen using "CPK STAT-PACK" made by CALBIO-

Fig.2. Electrophoretic pattern of SLDH isoenzymes about 4 hours after acute myocardial infarction (cardiogenic shock).

CHEM. SLDH activity was determined by the method of Cabaud-Wroblewski⁹

The electrophoretic pattern of SLDH isoenzymes was analyzed by means of agar-agarose gel electrophoresis, and the fractions were designated LD₅, LD₄, LD₃, LD₂, and LD₁, seriatim from the anode side to the cathode side, as described by Wroblewski⁹

RESULTS

1) Controls

The normal values of various enzymes in the serum of 50 healthy persons are summarized and tabulated in Table I. The pattern of SLDH isoenzymes with an LD₅/LD₄ ratio of more than 0.81 was referred to as the H-type, and that with more than 7.2% LD₁, as the M-type. Patterns of SLDH isoenzymes within the normal range were termed N-type.

2) Acute myocardial infarction

There were one woman (aged 61 years) and 17 men (aged 40–77 years) in this series.

After acute myocardial infarction, the SLDH activity and the LD₅/LD₄ ratio began to increase four hours following the attack and reached their peak in about two days on the average. Thereafter, the SLDH activity gradually decreased and returned to normal in about two weeks, while the LD₅/LD₄ ratio of SLDH isoenzymes became normal in three weeks on the average as seen in Fig. 1. SGOT and SCPK activities began to increase about four hours after the attack, reached their peak in about 12 hours and returned to normal in about seven days. However,

in only one case, in which cardiogenic shock was present, the electrophoretic pattern of SLDH isoenzymes was definitely of the M-type in Fig. 2.

3) Cerebrovascular disease

The major of cerebrovascular disease are cerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage, but the clinical differentiation is not always clear.

This paper reports the serial changes of various serum enzymes in these cerebrovascular diseases.

There were 19 women (aged 45–79 years) and 29 men (aged 36–76 years) in this series.

SCPK was markedly increased in 69.7% of the patients, and the H-type of SLDH isoenzymes appeared in 66.7%.

A rise in total SLDH was observed in 37.8% of the patients, but the amount of increase was less than in patients with acute myocardial infarction. The “dissociation type” (SLDH activity within the normal range, but the serial changes in the LD₅/LD₄ ratio of SLDH isoenzymes resembling those seen in acute myocardial infarction) was observed in 33.3% of the patients in this group. The peak values of both SCPK and the H-type of SLDH isoenzymes were reached 3–5 days after the onset of symptoms (Fig. 3 and 4).

The rate of increase was generally slower than in acute myocardial infarction, and the SCPK level returned to normal more slowly.

A rise in SGOT activity was observed in 43.1% of the patients. As seen in Fig. 5, the ratio of increase of SGOT activity was similar to that in acute myocardial infarction, but it returned to normal more slowly.

The serial changes of various serum enzymes in two typical cases of cerebrovascular disease were as follows:

Case H. S., a 51-year-old male had a cerebral hemorrhage on March 26th, 1969, and was hospitalized. Five days later, he had a second cerebral hemorrhage and died. An autopsy was performed. As seen in Fig. 6, the SCPK and SGOT levels and the LD₅/LD₄ ratio of SLDH isoenzymes increased markedly, while the SLDH activity displayed a transient slight increase. SGOT activity remained within the normal range.

Case K. Y., a 50-year-old male had a subarachnoid hemorrhage on Nov. 24th, 1970, and was hospitalized. His cerebral angiogram showed an aneurysm of the anterior communicating artery, which was treated surgically.

Fig.3. Serial changes of SLDH and LD5/LD4 ratio of SLDH isoenzymes in 48 patients with cerebrovascular disease.

Fig. 7 shows the serial changes of various serum enzymes before his operation. SCPK and the LD5/LD4 ratio of SLDH isoenzymes were markedly increased, while SLDH & SGOT activities showed a slight increase. SGPT activity remained within the normal range. The peak values of both SCPK and the H-type of SLDH isoenzymes were reached six days after his first symptoms.

In these two cases of cerebrovascular disease, the rate of increase of SLDH activity was slower than in cases of acute myocardial infarction, and the total SLDH activity was lower.

4) Renal failure

There were nine women and six men in this series. In the group of patients with renal failure, as seen in Fig. 8, the amount of SLDH increased in 53.8% of the patients, and the H-type of SLDH isoenzymes was observed in 33.3%. SGOT and SGPT activities increased in a few cases. A rise in SCPK was observed in 75.0% of the

Fig.4. Serial changes of SCPK activity in 48 patients with cerebrovascular disease.

Fig.5. Serial changes of SGOT activity in 48 patients with cerebrovascular disease.

patients.

5) Megaloblastic anemia

In the two patients with megaloblastic anemia, a clear H-type of SLDH isoenzymes was noted.

Fig. 6. Serial changes of various serum enzymes in a patient with cerebral hemorrhage.

SLDH activity, however, was normal in one case, as seen in Fig. 9, and markedly increased in the other (SLDH 3,000 w.u.↑). SCPK, SGOT, and SGPT activities remained within normal limits.

DISCUSSION

Among patients with acute myocardial infarction, the H-type pattern of SLDH isoenzymes appeared in 94.4%, and SLDH, SGOT, and SCPK activities were elevated in all cases (Table II). In only one case, in which cardiogenic shock was present, the electrophoretic pattern of SLDH isoenzymes was definitely of the M-type (LDI=28.1%, LD5/LD4=0.62). In patients with severe ischemic heart disease, especially with cardiogenic shock, the M-type pattern of SLDH isoenzymes tended to appear earlier than the H-type pattern.¹³ Two of the 18 patients who had cardiogenic shock and showed a marked M-type, pattern of SLDH isoenzymes (one case: M-type, another case H + M type) died. This phenomenon may be interpreted as follows; the amount

Fig. 7. Serial changes of various serum enzymes in a patient with subarachnoid hemorrhage.

Fig. 8. Various serum enzymes in 14 patients with renal failure.

of hepatic tissue injured in cardiogenic shock is very large in comparison with the grade of the myocardial damage; also, the release of enzymes from skeletal muscle may occur as a result of acute circulatory failure.¹³

In the cerebrovascular disease group, many cases showed the H-type pattern of SLDH isoenzymes (Table II). However, brain tissue extracts have been reported to show the N-type pattern but not the H-type pattern of SLDH isoenzymes.^{15,16}

In 1969, Wroblewski et al. examined the e-

lectrophoretic pattern of LDH isoenzymes in the serum and in various organs of patients and found similar electrophoretic patterns in the serum and damaged organs.⁹ As mentioned above, in the cerebrovascular disease group, there is a discrepancy between the serum LDH isoenzymes and the LDH isoenzyme pattern in tissue extracts. In cerebrovascular disease, therefore, the H-type pattern of SLDH isoenzymes may have its origin not in the brain, but in some other tissue.

The reason of this discrepancy may be related to hemorrhage in the brain or subarachnoid space, but more detailed investigation is necessary.

In the patients with renal failure, the electrophoretic pattern of SLDH isoenzymes was of the H-type (33.0% of the patients) (Table II). The probable explanation of this phenomenon is that the kidney contains a marked H component.¹⁷ In many cases (75.0% of the patients), SCPK activity was elevated (Table II). The enzymatic characteristics in renal failure remain obscure in many respects.

Both patients with megaloblastic anemia showed a clear H-type pattern of SLDH isoenzymes (Table II). This H-type pattern of SLDH isoenzymes may have its origin in the erythrocytes.¹⁷ These patients differed from those in the other groups with the H-type pattern of LDH isoenzymes in that they showed no elevation of SCPK, SGOT, or SGPT activities.

CASE S.I. 68 ↑

Fig.9. Serial changes of various serum enzymes in a patient with megaloblastic anemia.

Acknowledgement

The authors wish to express their deep gratitude to Sadamu Hiraide, M. D., of the Dept. of Internal Medi-

TABLE II SUMMARY OF VARIOUS SERUM ENZYMES IN ACUTE MYOCARDIAL INFARCTION, CEREBROVASCULAR DISEASE, RENAL FAILURE, AND MEGALOBlastic ANEMIA.

	No. of Cases	Elevation (%)			
		SLDH	LD5/LD4	SCPK	SGOT
Fresh Myocardial Infarction	18	100	94.4	100	100
Cerebro-Vascular Disease	48	37.8	66.7	69.7	43.1
Renal Failure	14	53.8	33.3	75.0	14.3
Megaloblastic Anemia	2	50	100	0	0

cine, Shinko Hospital and Mrs. Masako Tomita, the secretary of the 9th Laboratory, Tokyo Medical College.

REFERENCES

1. COHEN, L. et al.: Serum lactic dehydrogenase isozyme patterns in cardiovascular and other diseases, with particular reference to acute myocardial infarction. *J. Lab. Clin. Med.* 64: 355, 1964.
2. EISOLO, A., PERASALO, J., and HALONEN, P. I.: Electrocardiographic abnormalities and some laboratory findings in patients with subarachnoid hemorrhage. *British Heart J.* 34: 217, 1972.
3. GLICK, J. H.: Serum lactate dehydrogenase isoenzymes and total lactate dehydrogenase values in health and disease, and clinical evaluation of these tests by means of discriminant analysis. *Am. J. Clin. Path.* 52: 320, 1969.
4. HUNT, D. et al.: Electrocardiographic and serum enzyme changes in subarachnoid hemorrhage. *Am. Heart J.* 77: 479, 1969.
5. NOHARA, Y., YAMASAWA, I., HARA M., et al.: Variant form of angina pectoris with special reference to serum lactate dehydrogenase isoenzymes with some histological findings. The 7th World Congress of Cardiology in Argentina. Sept., 1974.
6. NOZAWA, T.: Studies on serum enzymes in cardiovascular disease with special reference to serum lactic dehydrogenase isoenzymes. *Jap. Circ. J.* 34: 257, 1970.
7. WIELAND, T. H., PFLEIDERER, G.: Chemical differences between multiple forms of lactic dehydrogenases. "Multiple molecular forms of enzymes" *Ann. New York Acad. Sci.* 94: 691, 1961.
8. WIEME, R. J. & HEPPOL, J. E.: Origin of the lactate dehydrogenase isoenzyme pattern found in the serum of patients having primary muscular dystrophy. *Nature* 194: 287, 1962.
9. WROBLEWSKI, F. & GREGORY, K. F.: Lactic dehydrogenase isozymes and their distribution in normal tissues and plasma and in disease states. *Ann. New York Acad. Sci.* 94: 912, 1961.
10. YAMASAWA, I.: Serum enzyme patterns in acute ischemic heart disease with special reference to LDH isoenzymes in intermediate types of ischemic heart disease, fresh myocardial infarction and cardiogenic shock. *Jap. Circul. J.* 37: 509, 1973.
11. YAMASAWA, I., NOHARA, Y., et al.: Continuous electrocardiographic recordings and serial changes of various serum enzymes in a patient with variant form of angina pectoris. *Jap. Circul. J.* 37: 1375, 1973.
12. YAMASAWA, I., & MORIMOTO, M., et al.: Cardiac arrhythmias and serial changes of various serum enzymes in a patient with pheochromocytomas of both adrenals. *Jap. Circul. J.* 38: 1005, 1974.
13. YAMASAWA, I., NOHARA, Y., and TAKAYASU, M.: Serial changes of various serum enzymes with special reference to LDH isoenzyme complex in acute ischemic heart disease. The 5th Asia-Pacific Congress of Cardiology in Singapore. Sept., 1972.
14. ZONDAG, H. A., et al.: Clinical application of lactate dehydrogenase isozyme: Alterations in malignancy. *Ann. New York Acad. Sci.* 151: 578, 1968.
15. WIEME, R. J. and VAN MAERCKE, Y.: The fifth (electrophoretically slowest) serum lactic dehydrogenase as an index of liver injury. *Ann. New York Acad. Sci.* 94: 898, 1961.
16. LOWENTHAL, A., VAN SANDE, M. and KARCHER, D.: Heterogeneity of lactic dehydrogenase in serum, cerebrospinal fluid, and brain extracts in man and sheep. *Ann. New York Acad. Sci.* 94: 988, 1961.
17. VESELL, E. S. and BEARN, A. G.: Isozymes of lactic dehydrogenase in human tissues. *J. Clin. Invest.* 40: 586, 1961.
18. NOHARA, Y., YAMASAWA, I., KONNO, S., et al.: Clinical and experimental investigation on unstable angina. The 10th International Congress of Angiology. Proceedings: 361, 1976.
19. NOHARA, Y., YAMASAWA, I., KONNO, S., et al.: Experimental study on enzyme distribution and its relation to myocardial ischemic changes following coronary circulatory disturbances. *Recent Advances in Studies on Cardiac Structure and Metabolism.* 12: 391, 1978.