Lactate Dehydrogenase Isozymes in Human Cardiac Transplantation

Abstract. *Lactate dehydrogenase (LDH) isozyme activities have been followed in 17 human cardiac allografts. A pattern of abnormality associated with cardiac rejection during the first month after operation has been determined: (i) LDH-1 activity is greater than LDH-2 activity; (ii) LDH-1 activity is greater than 35 percent of total LDH activity; and (iii) LDH-1 activity is greater than 100 international units. The LDH-1 abnormality helps to meet the need for an index of cardiac rejection during the early weeks after operation when the electrocardiogram is least reliable.*

The distribution of lactate dehydrogenase (LDH) isozymes in mammalian tissues has been extensively studied and reported (*1*). The fast electrophoretic fraction LDH-1 predominates in myocardium, and its presence in human serum in excessive quantities has been considered to reflect myocardial damage (*2*).

We have followed LDH isozyme activities in 17 human cardiac transplantations in patients ranging in age from 2 months to 62 years. The purpose of the investigation was to determine the usefulness of LDH isozyme activities as a clinical guide to rejection of the transplanted human heart.

Serums were obtained daily from each patient with a cardiac allograft during the first 2 weeks after transplantation and then gradually lessened to twice weekly after 2 months. Total LDH activity was determined by quantitative assay (*3*) and converted to international units (I.U.). Isozymes of LDH were separated by microzone electrophoresis on cellulose acetate from which densitometric tracings were made (*4*). The presence of rejection was judged by clinical and laboratory parameters which predictably should be altered in human cardiac allograft rejection. These parameters were initially derived from canine and murine allograft rejection studies and were promptly amplified by observations of human cardiac rejection (*5*).

The clinical parameters considered to reflect cardiac rejection in a consistent manner were: (i) congestive heart failure; (ii) pericardial friction rub (early acute rejection); (iii) fever; and (iv) malaise. The laboratory guides to rejection were: (i) electrocardiogram; (ii) hematologic findings, including complete blood count and Rebuck window; (iii) hemodynamic findings, including cardiac output, cardiac catheterization, and response to exercise; and (iv) phytohemagglutinin leukocyte stimulation.

Twenty-one episodes of cardiac rejection, as judged by the above clinical and laboratory methods, occurred in the patients in this series. In 11 patients the clinical judgment of rejection was confirmed by gross and histological examination of the heart following necropsy.

All patients in the period immediately after the operation and throughout their individual courses had total LDH activities above our accepted upper limits of normal (150 I.U.). All patients, with the exception of two, had LDH-1 activities initially and persistently above normal (50 I.U.). The means of total LDH and LDH-1 activities for all patients are displayed in Fig. 1 together with the mean activities of total LDH and LDH-1 in patients with and without clinical and laboratory evidence of rejection of cardiac allograft.

During the first month after surgery, the mean activity of LDH-1 in patients with cardiac rejection is significantly higher ($.02 > P > .01$) than that in patients not having evidence of rejection. After 1 month the difference is no longer significant, although LDH-1 activity is persistently higher in patients with cardiac rejection than in those without apparent rejection.

The percentage of LDH-1 activity during rejection episodes occurring in the first month after operation always exceeded 35 percent of the total LDH activity. After 1 month obvious clinical rejection was not accompanied by LDH-1 activities in excess of 35 percent.

The activity of LDH-1 was greater than that of LDH-2 in eight of nine patients with cardiac rejection during the first month after operation ($P < .01$), but after 6 weeks clinical rejection occurred without this finding in eight of ten patients (Table 1).

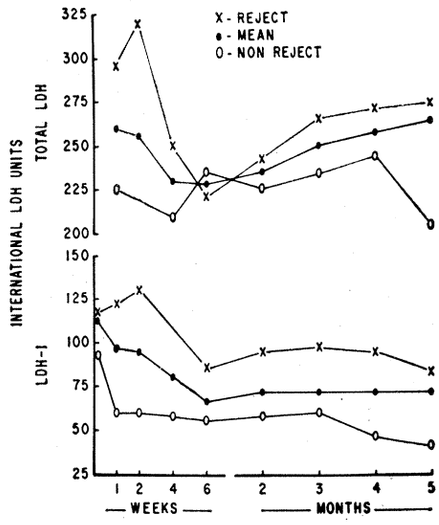

Fig. 1. Mean activities of LDH-1 and total LDH in 16 cardiac transplant patients with and without diagnostic evidence of cardiac rejection. The LDH-1 activity is significantly higher ($.02 > P > .01$) in patients undergoing rejection than in those not rejecting during the first 4 weeks.

Our present criteria for LDH isozyme abnormality, suggestive, if not diagnostic, of human cardiac rejection during the first month after transplant, are: (i) LDH-1 activity is greater than LDH-2 activity; (ii) LDH-1 activity is greater than 35 percent of total LDH activity; and (iii) LDH-1 activity is greater than 100 I.U.

The need for reliable indicators of acute cardiac allograft rejection early enough to undertake aggressive preventive therapy is urgent. From previous animal studies the electrocardiographic abnormality was the one parameter considered valid enough to

Table 1. Correlation between the activities of LDH-1 and LDH-2 and the rejection episodes. An immediately detectable qualitative guide to rejection during the first 4 weeks after operation is that the LDH-1 activity is greater than the LDH-2 activity. After 6 weeks following the operation, this diagnostic feature disappears. Rej, rejection; Non, nonrejection.

Isozyme activity	Time (weeks)								Total rejection episodes
	0–2		2–4		4–6		>6		
	Rej	Non	Rej	Non	Rej	Non	Rej	Non	
LDH-1 > LDH-2	8	0	1	1	1	0	1	0	11
LDH-1 = LDH-2	1	0	0	0	0	2	1	0	2
LDH-1 < LDH-2	0	5	0	8	0	7	8	9	8
Total rejection episodes	9		1		1		10		21

carry into the monitoring of human cardiac rejection (*6*). The electrocardiogram is least discriminating during the early period after operation, especially during the first 2 weeks when nonspecific changes related to heart surgery may obscure signs of rejection. After this early period the electrocardiogram is a highly reliable indicator of rejection (*7*). The employment of LDH isozyme activities appears to meet the need for an early indicator of human cardiac allograft rejection in the first month after operation.

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Postsynaptic Membrane Response Predicted from Presynaptic Input Pattern in Lobster Cardiac Ganglion

Abstract. *Given the pattern of impulses impinging on a neuron, it should be possible to predict its output firing pattern if enough is known about pre- and postsynaptic properties. A quantitative reproduction of the first part of this input-output conversion is reported, namely the translation of input pattern into a sequence of postsynaptic membrane potential variations.*

A step toward the quantitative analysis of input to output conversion by the nervous system is the ability to predict the exact pattern of output impulses of a single neuron given the input pattern of presynaptic impulses converging on it. The conversion proceeds through the intermediate stage of a pattern of synaptic potentials, which is produced by the patterned presynaptic input and which in turn produces the patterned output firing. Using computer modeling techniques, we have attempted to reproduce quantitatively the first step: the conversion of a known pattern of presynaptic impulses into a pattern of postsynaptic membrane potential changes.

We used the isolated cardiac ganglion of the lobster *Homarus americanus*. This consists of nine neurons, four driver cells and five motor neurons. The drivers provide synaptic input to the motor neurons, which in turn innervate the muscle of the lobster's heart. Periodic synchronized bursts of impulses in the driver cells excite the motor cells, and the resulting bursts of motor impulses cause the heart to contract rhythmically (*1–3*). The motor neurons can be penetrated with a glass microelectrode, and the membrane potential changes associated with the burst activity can be recorded by conventional means. The impulses of individual presynaptic driver cells can be identified in simultaneous records from several pairs of extracellular electrodes (*4*). Figure 1 shows a typical intracellular record with simultaneous extracellular records on which the presynaptic impulses have been identified. Our goal was to use the times of occurrence of the identified presynaptic impulses to reproduce the observed time course of the intracellular record from the motor neuron.

The complex synaptic response of a given postsynaptic cell can be thought of as the sum of individual synaptic potentials, one for each firing of a driver cell. Each synaptic potential is characterized by (i) a delay by which its beginning follows the extracellularly observed driver cell impulse (assumed to be constant for a given driver cell); (ii) a particular shape (assumed, when scaled to fixed amplitude, to be the same for all synaptic potentials); and (iii) an amplitude, which not only is dependent on the efficacy of the synapse, but also is found to vary from impulse to impulse. The variation of amplitude is such that the closer in time the previous impulse in a given driver cell, the smaller the observed synaptic potential for the next impulse. As the interval between impulses increases, the amplitude of the synaptic potential recovers toward an asymptotic value along an approximately exponential time course with a time constant around 100 msec. This phenomenon, termed "defacilitation" or more properly "antifacilitation," also occurs in *Panulirus* cardiac ganglion (*1*).

The above-mentioned factors constitute a sufficient description of the system for the computer to generate a predicted postsynaptic response given the firing times of the presynaptic units. The critical basic parameters—delay, shape, and synaptic efficacy—were measured from intracellular records from the particular motor neuron being simulated. The uncritical antifacilitation parameters were taken to be the same for all postsynaptic units (*5*).

The firing times of the driver cells in a particular burst were then specified, and the computer calculated the individual synaptic potentials and added them together to produce the predicted membrane response for that burst (*6*). Results of this process are illustrated in Fig. 2A, which shows the predicted membrane potentials for the latter parts of three successive bursts. The corresponding actual bursts are shown in Fig. 2B. The predicted potential matches in detail the observed potential (impulses spread decrementally from axon to soma seen in bursts 2 and 3 were not simulated—see caption). The waviness of burst 1 and the smoothness of burst 2 in Fig. 2B are reproduced in the corresponding predicted bursts; in fact, almost every notch and minor peak present in the actual records is reflected in the predicted ones.

Figure 3A shows a property of certain bursts that can be explained in terms of the pattern of presynaptic impulses. The initial and final portions of the record have a wavy appearance, while the middle portion is smooth. Figure 3B shows that the phenomenon is reproduced by the computer model, while Fig. 3C shows diagrammatically the underlying pattern of presynaptic impulses responsible for it. The wavy regions correspond to the firing of all