Serum Activity Patterns of Glutamic Oxaloacetic Transaminase, Glutamic Pyruvic Transaminase and Lactic Dehydrogenase Following Graded Myocardial Infarction in Dogs

By Paul Rueggesser, M.D., Irwin Nydick, M.D., Alvin Freiman, M.D., and John S. Ladue, M.D.

Following experimental myocardial infarction in the dog elevations of serum levels of glutamic-oxaloacetic transaminase (SGO-T), glutamic-pyruvic transaminase (SGP-T) and lactic dehydrogenase (LD) were consistently noted in decreasing order. Evidence is presented that leakage into the serum from the damaged myocardium plays an important role in these elevations. This concept is supported by analyses of original tissue to blood enzyme concentration gradients, activities of homogenates of infarcts of varying ages, simultaneous measurements of coronary sinus and peripheral venous blood following infarction and contrasting results in man and the dog following infarction.

Clinical or experimentally induced myocardial necrosis is consistently associated with rises in the serum activity of the enzyme, glutamic-oxaloacetic transaminase. It appears that these alterations result in part from leakage of the enzyme from the necrotic heart muscle into the serum. The alterations in activity of glutamic-oxaloacetic transaminase in the serum (SGO-T) are roughly proportional to the extent of myocardial necrosis. Reversible myocardial damage without necrosis, such as that seen in coronary insufficiency and pericarditis, does not appreciably influence the serum activity of the enzyme.

Studies of the activity of lactic dehydrogenase and glutamic pyruvic transaminase (LD, SGP-T) as well as of SGO-T in the serum after heart muscle damage also suggested that these enzymes were released from the necrotic muscle resulting in serum activity variations proportional to the original gradients in concentration between the intact myocardium and the serum. These gradients are 10,000:1 for glutamic-oxaloacetic transaminase (GO-T), 1,250:1 for glutamic pyruvic transaminase (GP-T) and 1,000:1 for lactic dehydrogenase (LD). In the present study an attempt was made to simultaneously analyze the patterns of serum activity of the 3 enzymes following experimental myocardial infarction and to study the mechanisms of these variations. In order to exclude serum enzyme alterations due to injury to skeletal muscle, hepatic or other enzyme-rich sources, a two-stage experimental procedure was utilized.

Methods

Measurement of Enzymes. Serum activity of SGO-T, SGP-T and SL were determined by the methods previously described. In normal dogs, the range of SGO-T activity is 5 to 40 units, of SGP-T 5 to 40 units and of SL 100 to 600 units (table 1).

Production of Myocardial Infarction. Mongrel dogs were anesthetized with intravenous sodium pentobarbital 25 mg./Kg. body weight, and respiration was sustained by intermittent positive pressure oxygen through an indwelling tracheal tube. No dog was anesthetized for more than 3 hours. A left lateral chest incision was made and the thorax entered through the fourth intercostal space without rib resection, and nooses of braided silk were loosely placed around selected branches of the coronary arteries. The ends of the ties...
were brought out through stab wounds in the chest, buried subcutaneously, and the chest was closed. With this technic myocardial infarction was produced at any chosen interval subsequent to the operation by traction upon the ties at a time when the enzyme rises due to the trauma of interruption of the chest musculature had subsided.

Immediately prior to infarction most animals received 30 mg. of morphine sulfate subcutaneously. One mg. atropine sulfate and 250 mg. of aminophylline were administered intravenously in an attempt to promote vasodilatation of collateral coronary circulation.

Eight dogs received dioxylline phosphate (Pavercil) instead of the aminophylline and atropine mixture. Serial venous blood samples and electrocardiograms were obtained in the control period and for 1 to 9 days after infarction. All animals received penicillin and streptomycin daily following operation. All animals were autopsied and appropriate microscopic sections obtained.

In 2 dogs the same operative procedure was utilized, but 1 hour before infarction the right external jugular vein was exposed, and under fluoroscopic control a cardiac catheter was introduced through it and guided through the coronary sinus into the great cardiac vein. Indwelling polyethylene catheters were threaded through the left femoral vein and artery into the vena cava and aorta respectively. Blood specimens were obtained from these 3 sources simultaneously every 2 to 3 hours for 18 to 24 hours following infarction.

Homogenates. Homogenates of infarcted and normal areas of dog heart were prepared in an ice-water bath as soon after death of the animal as possible. When tissues were not homogenized at once, they were frozen and stored in dry ice. Homogenization of saline suspensions of minced muscle was complete, except for very small amounts of residual collagen. A dilution of the homogenates of 1:1,000 to 1:1,500 was utilized in the analyses. Calculations of the enzyme content were based on the wet weight of the fresh heart muscle. The spectrophotometric analyses were performed in the standard fashion allowing at least 10 min. for the blank reaction when necessary.

**RESULTS**

Seventeen dogs were operated upon, one dying immediately postoperatively. Of the 16 remaining dogs, 3 died within 1 hour following coronary artery ligation and a fourth dog expired within 24 hours, representing a mortality of 25 per cent. Of the 13 dogs surviving more than 12 hours, myocardial infarcts of varying sizes were produced in 11. In all dogs the usual postoperative increases in serum activity of the 3 enzymes were noted but returned to normal within 3 days.

In 2 dogs serving as controls, aminophylline, atropine, dioxylline and morphine were administered as in the infarction group, for a test of the effect of these drugs upon the serum activity of the 3 enzymes. No effect was noted.

Figure 1 shows the alterations of enzyme activity during the evolution of a 30 Gm. myocardial infarction. In this and all subsequent figures the scales are adjusted, so that proportional increases of activity of all 3 enzymes from their control levels fall at the same point on the graph. The postoperative

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**Table 1.** Serum and Tissue Levels of Activity of GO-T (Glutamic Oxaloacetic Transaminase), GP-T (Glutamic Pyruvic Transaminase) and LD (Lactic Dehydrogenase)

<table>
<thead>
<tr>
<th>Enzyme—Serum (units/ml.)</th>
<th>GO-T</th>
<th>GP-T</th>
<th>LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>5-</td>
<td>5-</td>
<td>5-</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>100-</td>
<td>100-</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Enzyme—Heart muscle (units/Gm.)</td>
<td>155,000</td>
<td>150,000-</td>
<td>7,130</td>
</tr>
<tr>
<td>20,000-</td>
<td>20,000-</td>
<td>300,000-</td>
<td>80,000</td>
</tr>
<tr>
<td>40,000-</td>
<td>40,000-</td>
<td>700,000-</td>
<td>700,000-</td>
</tr>
</tbody>
</table>
enzyme elevations returned to normal within 4 days. On the fourteenth day the ligature that had been placed about the left coronary artery was pulled tight, occluding the artery permanently. Within 6 to 10 hours the serum activity of all 3 enzymes began to rise. The peak SGO-T was 290 units at 16 hours falling to normal within 3 days, the SGP-T 155 units in 30 hours and the SLD remaining elevated for 3 days. Thus, there is an increase in activity of SGO-T, SGP-T and SLD following infarction in decreasing order, with the peak elevation of SGP-T occurring later than the other 2 enzymes. This pattern is typical of that seen following similar infarcts in the remainder of the animals observed during this study.

Figure 2 shows the alterations in serum levels of the 3 enzymes following a 1 Gm. infarct. Transient increases in activity to 87 units for SGO-T, 66 units for SGP-T and 740 units for SLD are seen. The degree of rise is greatest for SGO-T, and least for SLD. All 3 enzymes returned to the normal range within 24 hours. In only 1 dog in this and our previous series did the enzyme activities increase before 4 to 6 hours after coronary ligation. This dog showed minor elevations of the 3 enzymes within 20 min. following ligation, and at autopsy had a tiny infarct of a papillary muscle. The reason for the early rise in this animal is not clear.

Table 2 shows the relationship of the size of myocardial infarction to the peak rises of activity of SGO-T, SGP-T and SLD. In general, the larger the infarct the higher the peak elevations of the enzymes.

Transient electrocardiographic changes of injury and ischemia (ST and T-wave abnormalities) were produced in 2 dogs without any gross or microscopic evidence of myocardial necrosis at autopsy. Permanent coronary artery occlusion was not possible in these animals because the silk ties were inadvertently severed during the traction upon them. Figure 3, although again portraying the postoperative rise of the 3 enzymes, shows no significant alteration in enzyme activity following traction upon the string in one of these animals. The slight elevation shown for SLD was caused by hemolysis of this specimen of blood. The second day also showed no increase in enzyme activity. Marked ST-segment and T-wave changes of injury and ischemia with reversal to normal within 6 min. after severance of the string were pro-

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Infarct size (Gm.)</th>
<th>Peak levels of enzyme activity in serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>B112</td>
<td>60</td>
<td>328 346 2380</td>
</tr>
<tr>
<td>A279</td>
<td>50</td>
<td>274 201 1056</td>
</tr>
<tr>
<td>B140</td>
<td>50</td>
<td>512 163 2652</td>
</tr>
<tr>
<td>B280</td>
<td>30</td>
<td>248 113 1812</td>
</tr>
<tr>
<td>B264</td>
<td>30</td>
<td>228 152 1680</td>
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<tr>
<td>X72</td>
<td>10</td>
<td>386 292 1410</td>
</tr>
<tr>
<td>B72</td>
<td>5</td>
<td>186 100 680</td>
</tr>
<tr>
<td>B74</td>
<td>1</td>
<td>88 52 800</td>
</tr>
<tr>
<td>B174</td>
<td>0</td>
<td>43 22 576</td>
</tr>
<tr>
<td>B51</td>
<td>0</td>
<td>40 31 952</td>
</tr>
</tbody>
</table>
duced in this animal. No Q-wave changes of necrosis developed. At autopsy no gross or microscopic evidence of myocardial infarction was found.

**Enzyme Concentrations in Normal and Infarcted Heart Muscle.** Figure 4 demonstrates the differences in enzyme concentration between infarcted and normal heart muscle in animals autopsied at different stages during the evolution of myocardial infarction. It can be seen that there is much less activity in the necrotic heart muscle than in the normal myocardium. The most rapid loss of enzyme activity occurred during the first 48 hours after infarction, corresponding to the most rapid rise in the serum activity. The total loss of enzyme is also a function of duration of infarction. Ratios of enzyme concentration of normal to infarcted myocardium may be as high as 45:1 in the older infaracts. Infarctions less than one hour old showed almost normal residual concentrations. The high residual concentrations in some small infarcts after 7 days is presumably due to the unavoidable admixture of normal myocardium with spotty areas of necrosis in the homogenates of these hearts. These small infarcts are represented in figure 4 by the points in the graph of apparent discrepancy on the seventh and eighth days.*

**Coronary Sinus Versus Peripheral Venous Enzyme Alterations.** Figure 5 demonstrates the enzyme variations in coronary sinus and peripheral venous blood during the 18 hours following myocardial infarction. The usual pattern of increase in serum activity of the 3 enzymes is seen. The enzyme activity of the coronary sinus blood is seen to be 10 to 15 per cent higher than simultaneously taken samples of peripheral venous blood for each of the 3 enzymes throughout the course of the experiment, although they were equal in the control period. There was no significant difference between simultaneous samples of femoral arterial and venous blood.

*In our previous study of this phenomenon, in which only the SGO-T was measured, larger infarcts were homogenized later in the course of infarction, and a progressive decrease in enzyme activity was also noted.

**Human Myocardial Infarction.** Figure 6 depicts the typical pattern of altered serum enzyme activity following an extensive acute myocardial infarction in man. Simultaneous changes of this type have been noted in a large series of clinical cases. Peak concentrations of SGO-T of 305 units, SLD 2,200 units and SGP-T of 52 units are noted. A delay in the return of SLD activity to normal limits is seen. The minor elevation of SGP-T activity correlates with the small gradient in concentration between the GP-T in the myocardium and serum in the human being (table 1), unlike that in the dog. Serum concentrations of GP-T often remain within normal

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*Fig. 4. Loss of enzyme activity from the myocardium into the serum. Note the rapid loss during the first 48 hours postinfarction, the continued loss of enzyme activity from the heart during the further course of infarction, and the altered ratios of activity between the normal and infarcted myocardium. The points of apparent discrepancy on the 7th and 8th days represent small infarcts in which it seems certain that normal areas of myocardium were admixed during homogenization of the area.*
limits following smaller myocardial infarcts in man, as might be expected.

**Discussion**

The activity of serum glutamic oxaloacetic transaminase (SGO-T), serum glutamic pyruvic transaminase (SGP-T), and serum lactic dehydrogenase (SLD) was invariably elevated following experimental myocardial infarction in dogs. No alterations in activity of these 3 enzymes were noted following reversible electrocardiographic changes of myocardial ischemia and injury. This indicates that severe myocardial injury must occur to permit escape of the enzyme from the heart muscle into the serum. The sensitivity of these measurements is demonstrated by the fact that infarcts as small as 1 Gm. in size result in significant, although transient, increases in serum activity. The serum activity of the 3 enzymes increases in proportion to the original gradient in concentration of the enzymes between the heart muscle and the serum before infarction, as well as the size of the infarct. Since these gradients are 10,000:1 for GO-T, 1,250:1 for GP-T and 1,000:1 for LD, rises of SGO-T, SGP-T and SLD are seen in decreasing order, respectively. On this basis, we may predict that no significant change in serum enzyme concentration would result if the original concentrations before infarction were approximately equal in the heart and serum. Since the SGP-T does not rise to high levels following myocardial infarction in man, and the concentration of glutamic pyruvic transaminase is quite low in human myocardium, species differences are to be expected, depending upon the original enzyme concentration gradients between heart and serum.

The peak elevations and durations of abnormality in serum activity of SGO-T, SGP-T and SLD are roughly proportional to the size of the myocardial infarct. The exact metabolic rate of these enzymes is not well known, although excretion in the bile and urine does not appear to play a critical role.

Indirect and direct evidence have been obtained that suggest that the mechanism of the rise of serum activity of the 3 enzymes is primarily one of leakage of enzymes from the necrotic areas of the myocardium into the blood stream. The reasons are as follows:

1. The most rapid rise in serum enzyme concentration corresponds to the period during which there is the most precipitous decrease
in concentration in the infarcted myocardium. 2. The enzyme concentration in the infarcted muscle diminishes progressively with the duration of infarction. 3. Following myocardial infarction, coronary sinus blood is consistently 10 to 15 per cent richer in each enzyme than is peripheral blood obtained simultaneously. 4. The relative rises of serum enzyme activity are proportional to the original concentration gradients between myocardium and the serum for each enzyme, as well as the size of the infarct.

The phenomenon of enzyme leakage appears to follow the loss of electrolytes and other crystallloids, such as organic acids, and indicates the severity of structural dissolution of the myocardial tissue. As dissolution of the integrity of the myocardial fiber occurs during infarction, there is loss of large quantities of intracellular materials in addition to the 3 enzymes studied. Elevations of serum levels of copper, ceruloplasmin, aldolase, phosphohexose isomerase, and malic dehydrogenase have been reported following myocardial infarction, although there is some doubt about the quantitative validity of the method utilized in the assay of malic dehydrogenase activity. The extensive loss of these vital enzymes undoubtedly perpetuates many of the derangements of myocardial function following infarction. The relationship of histologic change in the myocardium to altered enzyme content has not been fully studied.

The extension of the concept of leakage of various enzymes from damaged tissues has encouraged study of many disease in new perspective. With the application of the principle of the lowering of enzyme concentration gradients following tissue injury, new means have been obtained for the study of such diverse disease states as cerebrovascular accidents, the muscular dystrophies, hepatitis, and traumatic injuries.

Thoractomy, per se, resulted in elevations of each of the enzymes measured in the present report, presumably by release from damaged chest musculature, and this fact must be taken into consideration in the evaluation of the test following major surgery.

Simple methods are available for measuring small variations in serum enzyme activity, and are valuable adjuncts in the diagnosis of myocardial necrosis in experimental and clinical situations. Other enzymes may be found to rise higher and to be more specific of injury to myocardium and other specific tissues.

**Summary**

Elevations of serum activity of glutamic oxaloacetic transaminase (SGO-T), glutamic pyruvic transaminase (SGP-T) and lactic dehydrogenase (LD), in decreasing order, have been consistently noted following experimental myocardial infarction. The elevations of activity are proportional to the original concentration gradients of the enzyme between the myocardium and serum. Evidence is presented that the increases in serum enzyme activity follow leakage from the myocardium into the serum.

In man, increases in SGO-T and SLD activity follow myocardial infarction in decreasing order. Minor alterations are noted in SGP-T activity, except after extensive infarction. The implications of these serum enzyme alterations and their application to the study of other diseases are discussed.

**Summario in interlingua**

Elevationes del nivellos de activitate seral de transaminase glutamic-oxaloacetica (T-GOS), de transaminase glutamic-pyruvica (T-GPS), e de dehydrogenase lactic (DLS)—in
ordine descendente—essava constatate uniformemente post le induction experimental de infarcimento myocardial. Le augmentos de activitate del enzymes es proportional al gradientes de lor concentration original inter le myoeardio e le sero. Es presentate datos que supporta le conclusion que le augmentos del activitate serai del varie enzymes resulta del escappamento de illos ab le myoeardio a in le sero.

In homines, augmentos del activitate de T-GOS e de DLS occurre post infarcimento myocardial in ordine descescente. Alterations minor occure in le activitate de T-GPS, exepcte in casos de infarcimento extense. Es discutite le signification de iste alterationes in le activitate de enzymes serai e le application de lor studio al investigation de altere morbos.

REFERENCES
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