High Serum Transaminase Activity in Heart Disease
Circulatory Failure and Hepatic Necrosis

By Thomas Killip III, M.D., and Mary Ann Payne, M.D.

In the past few years, determination of the serum or plasma activity of predominantly intracellular enzyme systems has become a valuable adjunct in the study of disease. Since the original report of Ladue et al.1 many groups have investigated the levels of serum glutamic oxalacetic transaminase activity in a wide variety of conditions. Both myocardium and liver contain high concentrations of this enzyme, and clinical experience has demonstrated the value of repeated determinations of blood transaminase activity in the diagnosis and evaluation of myocardial infarction and liver disease.2

In animals an uncomplicated acute myocardial infarction is associated with increases in serum glutamic oxalacetic transaminase activity that correlate roughly with the amount of infarcted muscle.3-6 In the majority of patients suffering from an acute myocardial infarction, the changes in blood enzyme activity resemble those produced in the experimental animal; after the first day, the level increases, usually to less than 400 units, and then gradually falls to normal within a 3- or 4-day period.7 Infrequently, however, the blood enzyme activity soars to very high levels following an acute myocardial infarction. In animal experiments, such high levels of enzyme activity have been recorded only in instances of very large infarcts.3-6 Occasional patients have been cited with very high serum levels of glutamic oxalacetic transaminase activity prior to death from a myocardial infarction, and autopsy disclosed central necrosis of the liver.7 8 It has been postulated that the liver may contribute to these unusual levels of blood enzyme activity.8 9 There has not, however, been an extensive clinical survey of this problem.

Recently we observed a young man with advanced rheumatic heart disease and tight aortic stenosis who developed progressive hepatic dysfunction (fig. 1) during his final illness and showed a rise in serum glutamic oxalacetic transaminase activity to 1,912 units (W.D., table 1). At postmortem examination there was severe acute central necrosis of the liver (fig. 2). Coincidentally there was a report of a similar patient with a very high transaminase activity in whom a clinical diagnosis of hepatitis had been considered although hepatic central necrosis was demonstrated at autopsy.10 These observations stimulated an extensive review of our experience at The New York Hospital with patients having cardiac disease and high levels of serum glutamic oxalacetic transaminase activity, and this review forms the basis of the present report.

Materials and Methods

The records were reviewed of every patient who had a serum glutamic oxalacetic transaminase activity (SGOT) greater than 500 units per milliliter per minute as determined in the Liver Laboratory of The New York Hospital from January 1956 through July 1958. The records of those patients who had primary cardiovascular disease and high levels of enzyme activity were selected for special study. No patients with clinically evident viral hepatitis, toxic hepatitis, cirrhosis, or biliary tract disease were included.

The recorded clinical information was scrutinized for evidence of heart failure and hypotension. Right heart failure was diagnosed when the venous pressure was elevated and the liver was enlarged and tender. The level of venous pressure was measured by direct saline manometry and referred to the estimated level of the right atrium, or was estimated by inspection of the neck veins. Hypotension was diagnosed when the systolic blood pressure was 90 mm. Hg below the previously recorded levels on 2 or more consecutive bedside determinations. A diagnosis of clinical shock was made when specific comments indicated...
the presence of severe hypotension, cold wet skin, and peripheral cyanosis, usually accompanied by changes in mentation.

In those cases in which an autopsy had been performed, the sections of the liver and other tissues were carefully reviewed. The microscopic appearance of the hepatic sections was categorized as follows: normal, central congestion, central hepatic cord atrophy, central fibrosis, acute central necrosis. A careful attempt was made to distinguish between chronic or long-standing and acute changes in the hepatic architecture. Central fibrosis or atrophy was interpreted as evidence of chronic change. Central atrophy was diagnosed when the plates or cords of hepatic cells radiating toward the hepatic vein were thin, often not reaching the central vein, without evidence of acute necrosis, and the sinususes were dilated. In evaluation of acute central necrosis the criteria described by Osserman and Ellenberg were utilized: eosinophilic staining of the central area sharply contrasting with the basophilic stain of the normal liver cells; nuclear changes including pyknosis, fragmentation, occasional large pale nuclei, and occasional free nuclei; invasion by polymorphonuclear leukocytes; more or less architectural disruption depending on the age of the lesion. Central congestion, though often present, was not considered essential for a diagnosis of acute central necrosis.

Further to evaluate the clinical and autopsy correlations that became apparent among those patients with high transaminase activity, a second series was accumulated from the autopsy files of The New York Hospital. This group will be termed a "Control Series," since it was selected without regard for the level of SGOT activity. The records of all patients who died primarily from cardiac disease and were autopsied during the 30-month period from January 1956 to July 1958, and who had SGOT activity determined within 30 hours before death, were reviewed. Eighteen patients met these criteria, none of whom had clinical or autopsy evidence of primary hepatic disease, and constitute the "Control Series."

Serum transaminase activity was determined by a modification of the method of Karmen and was reported as units per milliliter of serum per minute (hereafter abbreviated to units). Blood samples showing hemolysis were routinely discarded.

Results

During the 30-month period covered by this study, 12,566 glutamic oxalacetic transaminase determinations were performed upon 4,761 patients in the Liver Laboratory of The New York Hospital. In 157 patients, at least

Figure 1

Clinical course of case 3. Hepatic and renal insufficiency accompanied progressive circulatory failure from multivalvular rheumatic heart disease.

1 determination was above 500 units; most of these had liver disease. In 17, however, the high SGOT levels occurred in patients suffering from cardiac disease without evidence of primary liver or biliary tract involvement (table 1). Eleven of these 17 patients were originally admitted because of an acute transmural myocardial infarction proved by the development of a Q-wave and RT-segment elevation in certain leads of the electrocardiogram. The 6 other patients were admitted for treatment of severe heart failure due to various causes. Ten patients died after the SGOT elevation was recorded; 5 of these had myocardial infarction and 5 had severe failure without recent myocardial infarction. Postmortem examinations were performed in 8 of these patients; 4 had myocardial infarction, 4 did not (table 2).

The maximum transaminase levels recorded in each patient ranged from 524 to 6,570 units. Five patients had peak levels of more
than 1,200 units, and only 1 of these survived. Although the number of patients involved is small, table 1 indicates that the higher the SGOT in patients with cardiac disease, the worse is the prognosis. Five of 7 with SGOT between 500 and 700 units survived, whereas 8 of 10 with levels greater than 700 units died.

Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical diagnosis</th>
<th>Right heart failure</th>
<th>Severity</th>
<th>Duration hours</th>
<th>Peak SGOT activity, units</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.T.</td>
<td>HCVD, acute MI, CHF, aortic dissection</td>
<td>+ + +</td>
<td>+ +</td>
<td>8</td>
<td>6570</td>
<td>Died, autopsy</td>
</tr>
<tr>
<td>D.O.</td>
<td>Acute MI</td>
<td>++ ++</td>
<td>+ ++</td>
<td>24</td>
<td>3850</td>
<td>Died, autopsy</td>
</tr>
<tr>
<td>W.D.</td>
<td>RHD, CHF</td>
<td>++ ++</td>
<td>+ ++</td>
<td>32</td>
<td>1912</td>
<td>Died, autopsy</td>
</tr>
<tr>
<td>H.S.</td>
<td>HCVD, arrhythmias, CHF</td>
<td>++ ++</td>
<td>+</td>
<td>8</td>
<td>1588</td>
<td>Died, autopsy</td>
</tr>
<tr>
<td>C.L.</td>
<td>Acute MI</td>
<td>0 +</td>
<td>+</td>
<td>12</td>
<td>1256</td>
<td>Survived</td>
</tr>
<tr>
<td>L.R.</td>
<td>ASHD, previous MI, CHF</td>
<td>+ +</td>
<td>+</td>
<td>24</td>
<td>870</td>
<td>Died suddenly</td>
</tr>
<tr>
<td>R.L.</td>
<td>Acute MI</td>
<td>+ +</td>
<td>+</td>
<td>24</td>
<td>554</td>
<td>Survived</td>
</tr>
<tr>
<td>N.S.</td>
<td>HCVD, acute MI</td>
<td>+ +</td>
<td>+</td>
<td>14</td>
<td>760</td>
<td>Survived</td>
</tr>
<tr>
<td>A.T.</td>
<td>Acute MI</td>
<td>++ ++</td>
<td>+</td>
<td>8</td>
<td>736</td>
<td>Died, autopsy</td>
</tr>
<tr>
<td>A.G.</td>
<td>ASHD, CHF</td>
<td>+ + + +</td>
<td>&gt;8</td>
<td>734</td>
<td>Died, autopsy</td>
<td></td>
</tr>
<tr>
<td>J.C.</td>
<td>RHD, CHF</td>
<td>++ + + +</td>
<td>&gt;6</td>
<td>653</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>L.G.</td>
<td>Acute MI</td>
<td>+ +</td>
<td>&gt;6</td>
<td>568</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>H.P.</td>
<td>RHD, CHF</td>
<td>++ + + +</td>
<td>&gt;6</td>
<td>554</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>E.K.</td>
<td>HCVD, acute MI</td>
<td>+ + + +</td>
<td>&gt;8</td>
<td>550</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>D.D.</td>
<td>Acute MI</td>
<td>+ +</td>
<td>&gt;6</td>
<td>546</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>W.S.</td>
<td>Acute MI</td>
<td>+ +</td>
<td>?</td>
<td>526</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>W.L.</td>
<td>Acute MI</td>
<td>+ +</td>
<td>8</td>
<td>524</td>
<td>Survived</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SGOT, serum glutamic oxalacetic transaminase; HCVD, hypertensive cardiovascular disease; MI, myocardial infarction; CHF, congestive heart failure; RHD, rheumatic heart disease; ASHD, arteriosclerotic heart disease; +, present, moderate; ++ +, present, severe.

The clinical association between the peak serum transaminase activity and the level of blood pressure was striking. In all 17 patients, the elevation of SGOT to more than 500 units was preceded by a fall in blood pressure producing significant hypotension or overt clinical shock (table 1). The duration of the hypotension could not always be determined precisely from the available record, but in those patients from whom adequate data were available hypotension had been present for at least 6 hours prior to the SGOT elevation. Sixteen of the 17 patients also had right heart failure of varying severity. The hypotension, heart failure, and very high transaminase level occurred in different settings: as a direct complication of acute myocardial infarction, in association with severe myocardial failure, and secondary to a rapid arrhythmia in a patient with a diseased heart.

Liver-function tests were frequently abnormal when SGOT activity rose to high levels. Serum bilirubins were elevated in 7 of 8 patients in whom the determination was available. Four patients had excessive increases in prothrombin time (over 60 seconds by the
Quick 1-stage method) following the administration of usual doses of coumadin-derivative anticoagulants and required treatment with vitamin K. In 3 other patients anticoagulants were administered without difficulty. Five patients without anticoagulant therapy had prothrombin time determinations more than 2 seconds above the control. Serum alkaline phosphatase activity and flocculation tests were normal. Bromsulfaleinphthalein tests were not performed.

**Pathology**

Review of the protocols and histologic material from the 8 autopsied patients revealed 1 common pathologic finding—acute central necrosis of the liver. Four of the patients also had recent myocardial infarction, and 1 of these had a recent dissection of the aorta. Necrosis in other organs was not observed. Thus in 4 of the autopsied patients necrosis within the liver was the only source identified that could have been responsible for the elevation of the SGOT activity.

When the liver sections were graded according to the degree of central architectural collapse, loss of hepatic-cell outlines, and amount of liver-cell regeneration, the apparent age of the lesion correlated with the time from peak transaminase activity until death. In patients H.S., A.T., and D.O., in all of whom peak transaminase activity was recorded within 24 hours before death, the central liver cells were acutely necrotic but the cords extended to the central vein and the architecture was intact (fig. 4). In W.D. and W.T., in whom peak SGOT activity occurred 8 to 10 days prior to death, the central hepatic cells had disintegrated and the central stroma was compressed (fig. 2). The central spaces were filled with polymorphonuclear leukocytes, proteinaceous debris, red blood cells, and occasional free nuclei. There was also fibroblastic proliferation.

Patient R.L. was unusual in that the evidence for central necrosis was the regeneration of the cells around the central veins as indicated by large, pale, double nuclei with pale-staining cytoplasm. This observation, however, correlated with the clinical data (fig. 3) of a transient SGOT rise to high activity after an episode of hypotension followed by clinical recovery for 2 weeks until a sudden and unexpected death.

In patients W.D., I.R., and L.G. there were central atrophy and some central fibrosis in addition to recent central necrosis in the liver. These findings correlated with the clinical data, since all 3 had long-standing cardiac disease with multiple episodes of right heart failure prior to their final admission.

*Figure 2*

Top. Section of liver from case 3 showing extensive necrosis of cells around central veins (CV). Note bridges of necrotic tissue connecting central areas. Bottom. Higher power of same section of liver. Area surrounding central vein contains islands of hepatic cells, round cells, polymorphonuclear leukocytes, proteinaceous debris. Note preservation of hepatic cells around portal triad (PT). Hematoxylin and eosin stain.
A few selected cases are presented to illustrate the clinical and pathologic correlations encountered in this group of patients with heart disease and high SGOT activity.

Case Reports

Case 1

D.O., a 62-year-old woman, known to have mild diabetes and hypotension, was admitted to The New York Hospital 6 hours after the onset of severe crushing precordial pain. Physical examination revealed hypotension, shock, a pulse of 20 per minute, pulmonary congestion, distended neck veins, edema, and an enlarged liver. The hematocrit value was 27 per cent, a white blood count 30,400 per mm.$^3$ with 93 per cent polymorphonuclear leukocytes. A blood urea nitrogen was 108 mg. per cent. An electrocardiogram showed complete heart block and an acute posterior transmural myocardial infarction.

Twenty-four hours after admission SGOT activity was 3,850 units and a total bilirubin was 1.2 mg. per cent, with 1.0 mg. in the direct fraction. During the second day her blood pressure rose to 160/70 and the rhythm became normal at 80 per minute. Despite gradual improvement, she died on the third hospital day. Three hours before death, SGOT activity was 1,400 units.

Postmortem examination revealed a large, acute posterior infarction of the left ventricle extending into the intraventricular septum, right ventricle, and right atrium. There was an extensive acute central necrosis of the liver involving approximately 60 per cent of each lobule. Other findings were intercapillary glomerular sclerosis and patchy fat necrosis in the pancreas.

Comment

High SGOT activity in this patient was associated with a large myocardial infarction complicated by severe heart failure, complete heart block, and prolonged shock. Autopsy revealed in addition to the myocardial infarction an extensive central necrosis of the liver of recent origin. If the sections viewed under the microscope are representative a large proportion of the liver was necrotic. Although there was extensive destruction of heart muscle, leak of enzymes from the necrotic liver cells must have contributed in large part to the very high levels of serum transaminase activity recorded prior to death.

Case 2

A 47-year-old man, R.L., was admitted to The New York Hospital 6 hours after the onset of severe precordial pain. During the 18 months prior to admission he had occasional attacks of angina pectoris, and his physician had recorded blood pressures of 150 to 170/80 to 110.

On admission he had a blood pressure of 120/90 mm. Hg and a regular pulse of 100 per minute. There were basal rales, distended neck veins, and

---

Table 2

Autopsy Data in Eight Patients with Heart Disease Who Died after Serum Glutamic Oxalacetic Transaminase Activity Exceeded 500 Units

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time from peak SGOT to death</th>
<th>Autopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.T.</td>
<td>10 days</td>
<td>ASHD, HCVD, recent MI, LVH, recent aortic dissection</td>
</tr>
<tr>
<td>D.O.</td>
<td>24 hours</td>
<td>ASHD, HCVD, acute MI, LVH, intercapillary glomerulonecrosis, minimal microscopic pancreatic necrosis</td>
</tr>
<tr>
<td>W.D.</td>
<td>8 days</td>
<td>RHD, LVH, RVH, aortic and mitral stenosis, mitral and tricuspid insufficiency</td>
</tr>
<tr>
<td>H.S.</td>
<td>24 hours</td>
<td>HCVD and ASHD with myocardial fibrosis, LVH, chronic cholecystitis, cholelithiasis</td>
</tr>
<tr>
<td>I.R.</td>
<td>3 hours</td>
<td>ASHD, old MI, LVH, RVH</td>
</tr>
<tr>
<td>R.L.</td>
<td>15 days</td>
<td>Recent MI, ASHD, small renal infarcts</td>
</tr>
<tr>
<td>A.T.</td>
<td>24 hours</td>
<td>ASHD, acute MI</td>
</tr>
<tr>
<td>A.G.</td>
<td>24 hours</td>
<td>ASHD, LVH, RVH</td>
</tr>
</tbody>
</table>

Abbreviations: ASHD, arteriosclerotic heart disease; HCVD, hypertensive cardiovascular disease; RHD, rheumatic heart disease; MI, myocardial infarction; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy.
an enlarged, tender liver. The venous pressure was 145 mm. of saline. An electrocardiogram showed a recent transmural anterior myocardial infarction.

SGOT activity 8 hours after the onset of chest pain was 77 units. Twelve hours after admission his blood pressure fell to 100/70 mm. Hg, without signs of clinical shock, remained low for 24 hours, and then gradually rose to 120/80. SGOT activity 8 hours after the onset of the hypotension had increased to 870 units (fig. 3). The patient improved until the sixteenth day after admission, when he suddenly had a recurrence of his chest pain and died.

Postmortem examination revealed a recent occlusion of the circumflex branch of the left coronary artery with an infarction of the anterior wall of the left ventricle estimated to be 2 weeks old. A mural thrombus was adherent to the infarcted area, and there were several small infarcts of the kidneys. Microscopic sections of the liver showed active regeneration of the hepatic cells around the central vein with large, pale, reduplicated nuclei.

Comment

High SGOT activity in this patient occurred after an acute myocardial infarction was complicated by heart failure and hypotension. The serum transaminase activity several hours after the fall in blood pressure was considerably higher than that usually encountered in patients with an uncomplicated myocardial infarction. The regeneration of liver cells around the central vein demonstrated at postmortem examination 2 weeks after the infarction is interpreted as evidence of an acute but limited hepatic central necrosis that was undergoing repair. The hepatic injury was probably secondary to the fall in blood pressure that occurred shortly after admission and was undoubtedly an important factor in the high level of SGOT activity that occurred at that time. The renal infarctions were quite small and most likely did not contribute significantly to the SGOT elevation.

Case 3

W.D., a 43-year-old man was admitted to The New York Hospital complaining of orthopnea and jaundice. Physical examination revealed deep jaundice and cyanosis with severe respiratory distress. Although he had profuse diaphoresis, cold skin, and an almost imperceptible pulse, his blood pressure was 120/95 mm. Hg. The cardiac rhythm was atrial fibrillation at a rate of 90 per minute. He had physical findings of aortic stenosis and insufficiency, mitral stenosis and insufficiency, and tricuspid insufficiency. There were bilateral pleural effusions, rales over both lung fields, an enlarged tender liver, and ankle edema.

Shortly after admission SGOT activity was 1,206 units, a blood urea nitrogen was 45 mg. per cent, and a serum bilirubin was 4.9 mg. per cent (fig. 1). Two days later the blood pressure fell and became unobtainable for 32 hours, despite intermittent norepinephrine therapy. The rhythm then reverted spontaneously to normal at a slow rate and the blood pressure was maintained at 110/80 mm. Hg. On the fourth day the serum transaminase activity was 1,912 units, the serum bilirubin was 15.0 mg. per cent, with 9.2 mg. in the direct fraction, and the blood urea nitrogen was 105 mg. per cent. Five days after admission a venous blood ammonia was 190 gamma per cent (normal <100). He died on the thirteenth hospital day.

At autopsy the heart weighed 700 Gm. There was tight aortic stenosis, moderate mitral stenosis and insufficiency, and a widely dilated tricuspid valve. Both ventricles were hypertrophied. There was no evidence of necrosis in the myocardium or in any other organ but the liver. Sections of the liver demonstrated acute central necrosis involving about 40 per cent of the hepatic lobule engrafted on chronic central fibrosis and atrophy (cardiae cirrhosis) of moderate degree (fig. 2). The kidneys were hyperemic but otherwise unremarkable.

Comment

In this patient very high transaminase levels were associated with heart failure, shock,
the effect of progressive circulatory failure on liver function and structure. Several experienced clinical observers were of the opinion that the patient had developed a viral hepatitis. A case presenting similar clinical manifestations and diagnostic difficulties has been recently reported.\textsuperscript{10} It has not been generally recognized that prolonged circulatory failure, manifested by hypotension, may lead to massive hepatic parenchymal destruction and liver failure.

**Case 4**

A 58-year-old man, H.S., was admitted to The New York Hospital, June 22, 1957, because of progressive dyspnea. His blood pressure was 160/94 mm. Hg, and the pulse was 130 per minute. There were basal rales, an enlarged tender liver, and peripheral edema. The day after admission a blood urea nitrogen was 15 mg. per cent and SGOT activity was 15 units. He developed sinus tachycardia with a rate between 135 and 150 per minute with frequent atrial premature contractions, then atrial fibrillation with a ventricular rate of 195 per minute and later atrial flutter (fig. 5). His blood pressure was unobtainable for 12 hours. Following quinidine therapy, normal sinus rhythm returned and his blood pressure rose to 130/70, but he died 2 days later. Twelve hours after the onset of hypotension his blood urea nitrogen had risen to 66 mg. per cent and SGOT activity was 1,588 units.

At autopsy the heart weighed 790 Gm. Both ventricles were dilated and hypertrophied. There were scattered small areas of myocardial fibrosis, but no coronary occlusion or myocardial infarction. Sections of the liver revealed extensive, acute central necrosis involving about 40 per cent of each hepatic lobule (fig. 4). The necrotic cells were sharply demarcated from the normal liver cells, but the over-all architectural pattern was well preserved without fibrosis, indicating recent injury. The kidneys were normal. There was also chronic cholecystitis and cholelithiasis without evidence of recent acute inflammation.

**Comment**

In this patient progressive myocardial failure and a very rapid ventricular rate were associated with low blood pressure and high SGOT activity. The hypotension was almost certainly a manifestation of a very low cardiac output with a concomitant reduction in hepatic perfusion. The central necrosis of the liver was the only source identified at post-
Clinical course of case 4. High SGOT activity and hepatic necrosis occurred in setting of heart failure, arrhythmias, and hypotension.

Control Series. The clinical and autopsy data from the control series confirm and amplify the correlations noted in the group of patients with high transaminase activity. SGOT activity ranged from 17 to 408 units in the 18 patients of the control series.

Seven patients had normal SGOT activity prior to death (table 3). In none was central necrosis of the liver demonstrated at autopsy, and none had hypotension or shock prior to death. Four of these patients died during a bout of right heart failure, and in 3 the failure was severe. Noteworthy is case 3, who died from cor pulmonale associated with kyphoscoliosis, severe right heart failure (venous pressure greater than 300 mm. saline) and deep cyanosis. Despite these abnormalities the blood pressure was maintained and SGOT activity was normal 16 hours before death. At postmortem examination the liver showed central congestion without necrosis (fig. 6). In case 4, SGOT activity was normal 4 hours prior to death from advanced rheumatic heart disease with severe right and left heart failure without hypotension. Autopsy revealed a severely congested liver without evidence of acute necrosis (fig. 7). From this small group of patients it may be concluded that venous hypertension alone is probably not associated with either acute central necrosis of the liver or elevation of the SGOT activity.

The data from the 11 patients with elevated SGOT activity (table 3) provide further confirmation of the relationships noted previously in the group of patients with very high serum enzyme activity. All 5 of the patients with hepatic central necrosis had hypotension for more than 6 hours prior to death. In all but 2 of the patients with elevated SGOT ac-
activity, the increased enzyme activity could be related to either myocardial necrosis or acute hepatic necrosis or both. Of the 2 without evident tissue necrosis at postmortem examination, 1, case 13, died of a saddle embolus. The other, case 11, died of rheumatic heart disease and failure. One patient, case 17, died after prolonged hypotension, but did not have central necrosis. Precise correlation of the level of SGOT activity with the hepatic architecture and the degree and duration of the hypotension was not possible because of the variation in the time blood samples were obtained for enzyme activity determinations.

Discussion

This study has demonstrated that a group of patients suffering from heart disease with very high levels of SGOT activity had several factors in common: right heart failure, hypotension or shock preceding the SGOT elevation, and, in those autopsied, central necrosis of the liver. All 8 patients who came to autopsy had acute central necrosis of the liver, which appeared to be related in time to the elevated serum transaminase activity. Clinical and laboratory data from the 9 patients who were not autopsied were essentially similar to those from the autopsied group, and it is reasonable to assume that they also had an acute central necrosis of the liver at the time of the high SGOT activity. In no patient was there clinical, laboratory, or pathologic evidence of either hepatitis or active biliary tract disease. In none could other causes of elevated transaminase such as pulmonary infarction, skeletal muscle injury, brain injury, acute pancreatitis or drugs be incriminated.

In 11 patients the acute central necrosis of the liver was related to circulatory changes associated with an episode of acute myocardial infarction. Necrosis of both the heart and the liver undoubtedly contributed to the elevated SGOT activity in this group, but the level of activity was considerably higher than that usually associated with an uncomplicated myocardial infarction. In 6 patients, 4 of whom were autopsied, there was no evidence of infarction of the heart and the very high levels of transaminase activity were probably related to liver necrosis alone.

Although both Popper and Sherlock have emphasized the difficulties in interpreting postmortem sections from the liver, the acute hepatic necrosis encountered in this study is clearly a reflection of antemortem events. Acute central necrosis is not an invariable finding at autopsy, even in patients with severe heart disease, and was not encountered in the 7 patients from the control series who had normal SGOT activity prior to death.

It may be concluded, then, that irrespective of whether or not recent myocardial infarction be present, very high levels of SGOT activity (>500 units) in patients with cardiovascular disease and circulatory failure who do not have primary liver disease are a reflection of an acute necrosis of hepatic cells surrounding the central veins. Presumably loss of hepatic cellular integrity results in leak of the intracellular enzymes into the peripheral circulation and very high serum activity. Since current technics for enzyme assay measure the activity of the enzyme system, not the concentration, it cannot be stated with
certainly that an increase in blood enzyme activity means an increase in blood enzyme concentration. The possibility that the changes in blood enzyme activity are secondary to changes in inhibitors or activators cannot be ruled out completely.

The data from the control series, selected without regard for the level of serum enzyme activity, reinforce the observation that, in patients with heart disease, central necrosis of the liver is associated with elevated SGOT activity and hypotension. Venous hypertension alone was not associated with either increased SGOT activity or acute central necrosis of the liver in the absence of a fall in blood pressure. That prolonged hypotension does not invariably lead to hepatic necrosis or elevated SGOT is indicated by case 17 of the control series. We have too few observations in patients with prolonged hypotension and no right heart failure to draw firm conclusions. Melby et al. have reported moderate increases in SGOT activity in hypotension due to endotoxin, a condition not usually accompanied by heart failure. Plasma GOT activity increases to very high levels in dogs subjected to hemorrhagic shock, and the liver is a major source of this increase. Any form of peripheral circulatory failure, if severe enough, can probably produce deficient hepatic perfusion and hepatic central necrosis with increased SGOT activity.

Isolated instances of acute central necrosis of the liver in patients with high SGOT activity have been previously reported. Published protocols indicate that most patients with acute myocardial infarction and very high serum transaminase levels have been hypotensive. Chinsky et al. presented a patient with high SGOT activity and central necrosis of the liver following a prolonged arrhythmia, and postulated that the hypotension associated with the arrhythmia produced the liver damage.

The pathogenesis of acute central necrosis of the liver has been the subject of speculation since F. B. Mallory first described the histologic details more than 50 years ago. He was careful to differentiate this lesion from chronic passive congestion of the liver and interpreted the acute necrosis as due to an acute ‘‘toxic state’’ in the antemortem period. Many workers have held that acute necrosis is caused by acute congestion of the liver. Balton and Zimmerman and Hillsman produced central necrosis by complete or partial occlusion of the thoracic inferior vena cava. Although the histologic lesions in the liver were interpreted as secondary to acute congestion (greatly increased hepatic venous pressure), their experimental procedures must also have severely compromised hepatic blood flow and oxygen supply.

Experiences during World War II indicated that acute central necrosis of the liver could develop in previously healthy patients following prolonged shock. In a detailed study of central necrosis Lambert and Allison had probably recognized this same factor when they stated that the ‘‘only constant etiological factor in cases of hemorrhagic necrosis is a severe circulatory disturbance.’’ In a recent study of centrilobular necrosis following myocardial infarction, Clarke found 8 of 9 patients with central necrosis had developed shock after the myocardial in
Section of liver from patient with severe right heart failure, normal blood pressure, normal SGOT 4 hours before death. Note intense central congestion and atrophy without acute necrosis. Control series, case 4. Hematoxylin and eosin stain.

He concluded that the shock and not the frequently accompanying heart failure was the cause of the hepatic lesion. Ellenberg and Osseman amplified and extended this opinion in a review of 200 unselected autopsies. Prolonged shock had been present in 32 of 34 patients with acute central necrosis. Noteworthy was the observation that severe congestive failure was not associated with acute central necrosis in the absence of shock.

Although every patient in the present series had a fall in blood pressure prior to the increased serum transaminase activity, only 6 developed overt clinical shock. That more did not have classic clinical shock is probably related to at least 2 factors. First, a diagnosis of shock was predicated on rigid criteria. Second, the absolute level of blood pressure is not an accurate measure of the absolute level of systemic or regional blood flow, and the latter are important in the production of acute central necrosis of the liver.

In patients with advanced heart disease and severe heart failure, a decline in blood pressure is generally an indication that cardiac output has fallen to such a low level that changes in peripheral vascular resistance are insufficient to maintain the previous levels of arterial pressure. Although it has been argued, particularly in reference to the hypotension of acute myocardial infarction, that the low blood pressure is largely the result of an inadequate adjustment of peripheral vascular resistance, the weight of the evidence at the present time favors the view that an inadequate cardiac output is a primary fault. In patients with advanced aortic or mitral stenosis and reduced arterial pressures, data obtained at cardiac catheterization have shown a low cardiac output and high peripheral resistance. Rapid arrhythmias are frequently accompanied by a fall in cardiac output and arterial pressure. Several studies have demonstrated that the hypotension of acute myocardial infarction is accompanied by a fall in cardiac output; resistance changes are variable. It seems reasonable, then, to assume that the hypotension encountered in the 17 patients with very high transaminase activity reflected a significant drop in cardiac output.

It has been shown that hepatic blood flow parallels the level of cardiac output in patients with chronic heart failure and that the proportion of systemic flow diverted through the splanchnic bed remains essentially constant. Similarly, in burn shock and hemorrhagic shock hepatic blood flow declines in proportion to the changes in cardiac output. Cardiogenic shock must also be accompanied by severe restriction of hepatic blood flow and very low oxygen content in the hepatic veins. Hepatic and mesenteric oxygenation are maintained during shock by an increase in oxygen extraction per unit of flow producing a widened arteriovenous oxygen difference. Under such circumstances, those liver cells farthest from the arterial and portal supply and closest to the central veins are bathed in blood almost depleted of oxygen and other nutrients. At some critical point the vitality of the central cells is compromised and necrosis and loss of intracellular enzymes follow. If the circulatory reduction is prolonged, cells more and more distal to the central vein begin to deteriorate, producing a picture of massive necro-
sis such as was encountered in W.T., D.O., W.D., and H.S.

In several cases with extensive central necrosis, there was a bridging of necrotic cells from one central area to another (fig. 4). If a patient should survive under such conditions, it is not difficult to visualize an extensive network of fibrous tissue eventually linking one hepatic lobule with another and resulting in a cardiac cirrhosis. The bridging between the central necrotic areas is completely in accord with Rappaport’s experimental evidence that the terminal branches of the hepatic inflow circulation arborize not only around the central vein but also in the border area between the lobules equidistant from the hepatic triads.40 These bridges of necrotic tissue, therefore, are further evidence of the role of circulatory changes in the pathogenesis of acute central necrosis.

Although all but 1 of the 17 patients with high SGOT activity had right heart failure, it is unlikely that venous hypertension alone produces either acute central necrosis or high levels of transaminase activity.8,41 We have studied 8 patients with proved chronic constrictive pericarditis and severe elevation of venous pressure; SGOT activity was normal in all. Four patients in the control series died from heart failure with severe venous hypertension, and although all had varying degrees of atrophy and fibrosis around the central vein, none had either acute central necrosis or elevated SGOT activity prior to death. The chronic reduction in oxygen tension in the terminal branches of the hepatic veins associated with right heart failure may set the stage, however, for the rapid deterioration of the central cells after the development of cardiogenic shock and thus be synergistic with the acute reduction in hepatic blood flow.

The patients with high SGOT activity and myocardial infarction had extensive myocardial necrosis by electrocardiographic criteria and at autopsy. In the experimental animal the level of SGOT activity correlates well with the size of the infarct.3-6 At least one of the experimental technics utilized to produce myocardial necrosis, however, is associated with prolonged cardiogenic shock. It is possible that in some experiments the high SGOT activity reflected both myocardial and hepatic necrosis. A correlation between the size of the myocardial infarction and the level of SGOT activity has not been established in man.

The association of high levels of transaminase activity and a poor prognosis in patients with cardiac disease has been noted by others particularly with myocardial infarction.7,8 Since this study has demonstrated that a high level of SGOT activity in such patients implies hepatic necrosis, the correlation between serum enzyme activity and prognosis is probably not related strictly to the amount of myocardial tissue damage, but rather to the functional consequence of a given infarction. It is well known that myocardial infarction associated with shock carries a grave prognosis.44 In terms of the function of the cardiovascular system, high levels of SGOT activity have the same clinical significance as shock and therefore signify a poor prognosis. Such high values, however, are more sensitive indicators of the level of hepatic perfusion than the blood pressure. This information may be useful at the bedside. Very high levels of SGOT in patients with cardiovascular disease should be an indication for vigorous attempts to treat the circulatory inadequacy whether or not overt clinical shock be present.

There is one final implication of this study that merits mention. Changes in blood enzyme activity are widely utilized to corroborate a diagnosis of myocardial infarction. Not infrequently if neither the clinical history nor the electrocardiogram is diagnostic, the interpretation of the changes in blood activity of SGOT or some other non-organ-specific enzyme such as lacte dehydrogenase may determine whether or not a patient is treated for acute myocardial infarction. If, as we have demonstrated, severe acute central necrosis of the liver produces striking elevation of serum enzyme activity, it is not unlikely that a minor degree of hepatic necrosis following

Circulation, Volume XXI, May 1960
acute circulatory changes may result in lesser elevations and indeed produce an activity curve mimicking that seen in myocardial infarction. We have recently observed 2 elderly patients with complete heart block who had transaminase activity curves typical of myocardial infarction when their ventricular rate slowed and blood pressure fell for several hours. In one the bradycardia was secondary to high potassium and in the other to overdigitalization. In neither was there clinical or other laboratory evidence of acute myocardial infarction. The implication is clear: SGOT activity changes similar to those of myocardial infarction may occur secondary to central necrosis of the liver unrelated to a myocardial infarct. Caution should be used in interpreting serum transaminase changes in patients with cardiac disease without diagnostic electrocardiographic or clinical abnormalities. Determination of glutamic pyruvic transaminase levels may be helpful in such situations, since elevation of the serum activity of this enzyme appears largely to reflect liver necrosis and is unusual in uncomplicated myocardial infarction.

Summary

A survey of all patients with very high serum glutamic oxalacetic transaminase activity encountered during a 30-month period at The New York Hospital revealed 17 patients with cardiac disease who had 1 or more serum glutamic oxalacetic transaminase (SGOT) determinations exceeding 500 units. None had clinical evidence of primary liver or gallbladder disease. Eleven were admitted with acute myocardial infarction, 6 with severe heart failure. All 17 developed hypotension or shock and all but 1 right heart failure prior to high SGOT activity.

Several patients had abnormalities of liver function when SGOT activity was very high. In 4 there was an excessive increase in prothrombin time following administration of anticoagulants.

In the 8 patients who came to autopsy there was histologic evidence of acute hepatic central necrosis. In 4 there was necrosis of both heart and liver, in 4 necrosis of liver alone.

Clinical and autopsy data from a control series of patients with heart disease selected without regard for the level of SGOT activity corroborate the association between hypotension, central necrosis of the liver, and increased SGOT activity. Increase in venous pressure in the absence of hypotension was not associated with acute central necrosis or elevated SGOT activity.

It is concluded that very high SGOT activity (>500 units) in patients with heart disease is at least in part caused by acute hepatic central necrosis secondary to a drop in cardiac output and reduced hepatic blood flow. Caution is urged in the interpretation of increased blood activity of intracellular enzyme systems as evidence for myocardial necrosis. Acute circulatory changes may result in hepatic necrosis and increased blood enzyme activity without myocardial infarction.

Acknowledgment

We wish to express our gratitude to Dr. Henry R. Erle for invaluable assistance during the collection of the transaminase data and to Dr. John T. Ellis, who reviewed the pathologic material.

Addendum

Since this manuscript was submitted for publication a similar study has been published, which also demonstrates a correlation between very high levels of SGOT and central hepatic necrosis in patients with heart disease. The authors concluded, however, that acute right heart failure was the precipitating cause of the liver necrosis. (Bang, N. U., Iversen, K., Jagt, T., and Tobiassen, G.: Serum glutamic-oxalacetic transaminase activity as an index of centriflobular liver cell necrosis in cardiac and circulatory failure, Acta med. Scandinav. 164: 385, 1959.)

Summario in Interlingua

Un revista de omne le patientes con elevatissime activitates de transaminase glutamico-oxalacetic del sero, incontrate al Hospital New York in le curso de un periodo de 30 menses, resultava in un lista de 17 casos con morbo cardine in que un o plures determinations de transaminase glutamico-oxalacetic del sero (TGOS) monstrava valores de plus que 500 unitates. Nulle patiente in iste serie exhibiva signos de un morbo primari del hepat o vesica biliari. Deceun un habeva essite hospitalisate a causa de acute infarcimento myocardial, 6 a causa de sever discompensation cardiace. Omne le 17 disveloppava hypotension o choc e omnes, con un exception, habeva discompensation.
dextero-cardiac ante le accession del elevate activi-
tate de TGOS.
Plure patientes habeva anormalitates del function hepatic quando le activitate de TGOS esseva muito elevate. In 4, un excessive augmento del tempore de prothrombina esseva notate post le administration de anticoagulantes.
In le 8 patientes presentate al necropsia, provas histologie de acute necrosis central del hepate esseva constatate. In 4 il habeva necrosis del hepate e del corde, in 4 solmente del hepate.
Datos clinie e necroptic ab un serie de controlo de patientes con morbo cardiac sed seligite sin reguardo al nivello del activitate de TGOS supporta le association inter hypotension, necrosis central del hepate, e augmento del activitate de TGOS. Augmento del tension venose in le absentia de hypotension non esseva associate con acute necrosis central o elevation del activitate de TGOS.

References
7. LaDue, J. S., and Wroblewski, F.: The significan-
ces of the serum glutamic oxalacetic trans-
9. —, Wolff, R. J., and Sherry, S.: Serum trans-
17. Chinsky, M., and Sherry, S.: Serum trans-
24. Darmandy, E. M.: Renal anoxia and the trauma-
29. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the circulatory dynamics in mitral...

Neuroses of the Heart
Angina Pectoris

Stenocardia, or the breast-pang described by Heberden, is not an independent affection, but a symptom associated with a number of morbid conditions of the heart and vessels, more particularly with sclerosis of the root of the aorta and changes in the coronary arteries. True angina, which is a rare disease, is characterized by paroxysms of agonizing pain in the region of the heart, extending into the arms and neck. In violent attacks there is a sensation of impending death.—WILLIAM OSLER, M.D. The Principles and Practice of Medicine. New York, D. Appleton & Company, 1893, p. 655.
High Serum Transaminase Activity in Heart Disease: Circulatory Failure and Hepatic Necrosis

THOMAS KILLIP III and MARY ANN PAYNE

_Circulation_. 1960;21:646-660
doi: 10.1161/01.CIR.21.5.646

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1960 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/21/5/646