THE LIVER IN CONGESTIVE HEART FAILURE

Medical Grand Rounds

Parkland Memorial Hospital

December 11, 1969

THE LIVER IN CONGESTIVE HEART FAILURE

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A. DEFINITION OF PROBLEM (1, 2, 3)

Congestive Heart Failure (low output):

Definition: Abnormality in myocardial function results in failure of heart to pump blood at rate commensurate with body requirements. This results in redistribution and retention of fluid in organs served by the heart.

Pathogenesis (sequential):

1) Heart muscle (ventricle) damaged.

2) Inadequate emptying of blood by chamber.

3) a) Proximal congestion. Left ventricle $\longrightarrow$ lung = left heart failure. Right ventricle $\longrightarrow$ great veins = right heart failure. Usually some degree of both.

b) $\uparrow$ Diastolic ventricular volume $\longrightarrow$ $\uparrow$ in diastolic fiber length $\longrightarrow$ increased contraction (Starling). Eventually if this increase in ventricular filling pressure (and $\uparrow$ in rate) inadequate to meet demand = heart failure.

Mechanism of failure of contraction of dilated heart:

a) not energy production but b) poor utilization of energy for contraction. At least one facet of the problem is mechanical, i.e., inadequate interaction of actin and myosin in muscle fibril where these are stretched too much (1).

4) Retention of salt and water. Mechanisms? Tubular, aldosterone effect, etc. (2).

This discussion pertains to the effects of combined left and right heart failure on the liver. Low output failure is primarily considered.

B. Pathology of Congested Liver

1. Reliability of Autopsy vs Biopsy Data:

Grossly - liver is usually enlarged but post mortem weight often bears no close relationship to clinical size - probably due to post mortem loss of tissue blood. Organ purplish with rounded edges. On cut surface - veins distended and nutmeg appearance: red (hemorrhagic) central vein areas and yellow (? fat) portal areas. In the presence of cardiac cirrhosis - may be small but not as coarse and nodular as in other types of cirrhosis.

Microscopically - major alterations post mortem, hepatic autolysis is very rapid in patients dying in heart failure.

In the agonal period and 12 hours after death, liver cells shrink, disappear and the remaining ones become dissociated from each other. As result, parasinusoidal spaces enlarge and cell cords shrink. Glycogen is lost from liver cells and increased fat noted.

Net result: Post mortem liver less congested than in life but hepatic parenchyma more damaged.

These conclusions based on: 1) biopsy vs portmortem exam of liver within hours on same patients (4) and 2) comparison of histology in many biopsied and autopsied patients (5).

2. Biopsy Data

Theoretically biopsy more risky since liver under high venous pressure may bleed more. However in two series of 75 (6) and 41 patients (4) no difficulties. It is, however, our current recommendation to biopsy the liver (when indicated) after resolution or improvement of congestion.

Histology of Congested Liver (biopsy):

Mild: Central veins dilated, sinusoids which enter into them engorged. Liver cells surrounding central veins atrophic and compressed.

Moderate: Hemorrhage around central veins. Liver cells surrounding central veins in varying states of degeneration and necrosis. Surviving cells in area are normal. May see brown, granular pigment in central area - negative iron stain - probably breakdown product of bilirubin. May see slight increase in fat in central area (? malnutrition) but this is not important aspect of lesion.

Portal tract cells are normal. Normal periportal areas vary inversely in diameter with centrizonal necrosis. May see bile thrombi in canaliculi but this is not an important feature.

With collapse of centrizonal liver cells, reticulin stroma condenses around central vein.

Severe: With prolonged and recurrent failure (apparently more important than severity), the connective tissue extends outward from central veins. Eventually fibrous tissue of adjacent central veins joins and rings relatively normal portal areas. This is called reverse lobulation and is characteristic of cardiac cirrhosis. (In some very severe cases, may also see fibrosis around portal veins = mixed cirrhosis, but most striking lesion is around central veins.)

If the failure continues, necrosis spreads toward periphery (portal area) of hepatic lobule. If failure responds, centralobular necrosis may heal and even if there is cirrhosis, fibrous bands become narrower and acellular and cirrhosis becomes functionally not important.

Conclusion: Key to congestive liver failure are Centrizonal changes.

Other diseases which give biopsy picture similar to congested liver due to heart disease are: Budd-Chiari Syndrome, veno-oclusive disease and radiation damage to liver.

C. CLINICAL ASPECTS

a) Type of Heart Disease:

All studies agree that the highest incidence of severe hepatic congestion occurs in rheumatic heart disease - 53 - 75% (4, 5, 7, 8). Most common valves effected: mitral stenosis with tricuspid incompetence. Second most common is probably hypertensive heart disease (37%), followed by ASHD and constricting pericarditis. The latter almost invariably causes severe congested liver but is, of course, relatively rare in overall spectrum of heart disease. Congested liver may occur in all types of failure. Incidence depends on selection and patient population.

b) Symptoms and Signs:

uncommon 10-20%

Abdominal Pain: RUQ - Most common in acute stage or acute exacerbation. Pain due to stretch of liver capsule and mediated via phrenic nerve.

Hepatomegaly: 95 - 99% (6, 9). Firm, smooth, and tender diffusely. In absence of hepatic vein obstruction, hepatojugular reflex present.

Right auricular pressure increase is transmitted to inferior vena cava and hepatic veins. In tricuspid insufficiency (T.I.), the hepatic vein tracing resembles that obtained from right auricle and the liver may exhibit systolic pulsation related to this transmitted auricular pressure. In cardiac cirrhosis, this pulsation may be lost (10). Hepatic pulsations from T.I. and those transmitted from abdominal-aorta can be distinguished sometimes in the presence of cardiac PVC's since for T.I. one detects two transmitted hepatic pulsations over liver (coupled hepatic pulsations) for every one pulsation in peripheral pulse (11).

Splenomegaly: 12 - 25% in absence of overt cardiac cirrhosis (6, 8, 9). May reach higher incidence in cardiac cirrhosis - 79% (8) although this is debated (4).

Ascites: 7-64% (6, 8, 9). Most series run about 25%. The protein concentration of the ascitic fluid is variable but there is a fairly high number of high values (50% over 3 g/100 ml), (12). Causes discussed below under Pathogenesis.

Jaundice: 21% or less (6, 8, 17). Edematous tissue areas (usually dependent) may escape jaundice, presumably because the accumulated fluid has a low protein content and does not bind and retain the bile pigment well (15).

Signs of Portal Hypertension: Rare even with full blown cardiac cirrhosis (4). Varices and distended collateral superficial veins seldom seen.

Hepatic Encephalopathy - Rare. (Have to keep in mind possibility of hypoglycemic coma (13) and inadvertent precipitation of hepatic coma by use of ammonium chloride for diuresis (14). Also, confusion, lethargy, and coma are occasional accompaniments of heart failure (unrelated to liver failure) and appear to be due to cerebral hypoxia (16).

c) Correlation of Symptoms and Signs with Duration of Congestive Failure.

Table I (6)

Incidence of Abnormal Physical Findings in Patients With Acute and Chronic Congestive Heart Failure

	Acute Failure* (106 pts.)	Chronic Failure (69 pts.)
Hepatomegaly	99 %	95 %
Splenomegaly	20 %	22 %
Ascites	7 %	20 %
Peripheral edema	77 %	71 %
Pleural Effusion	25 %	17 %

* Duration 2 weeks or less

Conclusion:

Both groups quite similar as to abnormal clinical findings.

Laboratory Data

a) BSP

↑ in 80%; 78%; 97%; 96%; 100% (6, 9, 18, 19, 20, 13) - most sensitive test for picking up hepatic dysfunction in congestive heart failure. Affected similarly in heart failure due to different types of heart disease.

Abnormal retention more common and greater in acute (14 days or less) than chronic failure. Most values are around 10-24% retention (19). Higher values with increased amount of right heart failure as vs left heart failure (as high as 60-70% retention in 45 minutes).

BSP retention seems to correlate fairly well with both rise in venous pressure (20, 19) and extent of centrizonal hepatic damage (4, 18) (Table 2).

TABLE II

Correlation of serum BSP, bilirubin and alkaline phosphatase and albumin levels with extent of hepatic damage

Extent of Necrosis	BSP (% retention at 45 min.)	Bilirubin (mg %)	Alkaline Phosphatase (KA Units)	Albumin (gm %)
A	11.3	1.1	9.3 (6-25)	4.1
B	18.0	2.0	10.3 (6-20)	3.5
C	24.6	3.3	12.3 (5-26)	3.5

A - Changes in region immediately around central vein.

B - Changes in region 1/3 distance to portal area.

C - Changes > 1/3 distance to portal area.

There is no relation to arterial saturation with O_2 (19, 20).

Improvement in BSP to or toward normal is usually seen within one week of clinical improvement.

Possible causes of BSP retention: 1) ↓ hepatic blood flow. 2) ↓ hepatic damage. Available evidence does not permit definite assessment of these two possibilities and both likely are or can be of importance. Some studies, however suggest that hepatic damage may be more important. Thus (a) in 5 patients with congestive failure BSP retention was observed despite relatively normal hepatic blood flow (20) and b) it appears that the maximal transfer of BSP from liver into bile (Tm) is depressed primarily rather than BSP uptake and storage (S) in the congested liver (20). These observations of ↓ Tm (but not storage) suggest either an abnormality of hepatic conjugation of BSP with glutathione or ↓ BSP transfer from liver into bile or both. Regardless of mechanism, the data suggest a significant contribution of hepatic damage per se to impaired BSP clearance from blood. The correlation of BSP retention with elevated venous pressure fits (but does not prove) this concept.

BILIRUBIN

↑ in 27%, 40%, 52%, 31%, 70%, (4, 21, 9, 19, 26). Increased serum bilirubin occurs in heart failure of all etiologies. It seems to be somewhat more severe in valvular heart disease with a significant right sided component and especially with acute onset. Most values are below 5 mg% and often below 3 mg%. The height of serum bilirubin does not correlate with arterial oxygen tension or cardiac output in failure. There seems to be a correlation between height of bilirubin (especially over 2 mg%) and increase in venous pressure (4, 18).

As shown in Table 2 there seems to be a positive correlation of height of bilirubin with the degree of liver damage, especially when mild liver damage is excluded. Much overlap in values is seen, however (4).

Highest values seen are 18.0, 21.5 and 22 mg% (4). With high values one should always consider a concomittant pulmonary infarction. The evidence for this is seen in Table III.

TABLE III (4)

The Relation of Serum Bilirubin Concentration and Pulmonary Infarction

	No. Pts.	Bilirubin	Liver Histology Grade A	B	C
No pulmonary Infarction	26	1.4	0.9	1.6	2.1
Pulmonary Infarction	14	3.2*	2.6*	3.1*	3.5*

* * Mean values of serum bilirubin.

Abnormal bilirubin values usually disappear in 3-7 days on improvement in clinical state.

Usually about 60-50% of total bilirubin elevated is in form of unconjugated pigment. At times patients with congestive heart failure manifest classical unconjugated hyperbilirubinemia (i.e., direct fraction is < 25% of total) (22). Heart disease was the single (86 patients) most common cause of unconjugated hyperbilirubinemia found in 366 patients with this syndrome but without overt hemolysis (23). Most of the total bilirubin values were between 1-2 mg% but some reached 3.7 mg%. In 10 of 17 such patients followed up for as long as a year, the ↑ bilirubin cleared with resolution of heart failure (23). The cause of the unconjugated bilirubinemia seen in these patients was not determined. There was no uniform correlation of ↑ unconjugated bilirubin and other liver function test abnormalities or liver histology.

Causes of ↑ bilirubin:

a) Obstruction (bile canaliculi destructed by distended veins and sinusoids): unlikely as bile noted in common bile duct and few bile plugs are found in liver.

b) Hemolysis: Overproduction would explain the unconjugated hyperbilirubinemia noted in some cases (23) and possibly the increased bilirubin levels seen in pulmonary infarction (4) where ↑ pigment may be generated in infarcted lung. However 50-100 cc of blood (generating up to 500 mg bilirubin) introduced into tissues of patients with congestive heart failure did not induce ↑ serum bilirubin (24). This is not likely then as the sole cause of ↑ bilirubin, but may contribute to jaundice.

c) Hepatogenic: Consistent with ↑ PT (not responsibe to Vit. K), abnormal BSP test and correlation with severity of cellular change. Hepatic hypoxia may be the critical factor. (This would also explain ↑ bilirubin with pulmonary infarction).

Conclusion: 1) Etiology not certain

2) Probably hepatogenic with contribution of hemolysis.

3) If hepatic hypoxia is the critical factor, our data in experimental animals suggest that the main defect is at the level of bilirubin transport from liver cells into bile (25).

SGOT

↑ in 12, 21, 25, 33% of patients (9, 18, 27, 28). May be seen with either right or left sided failure. Most common in acute failure. (In one study comparing acute and chronic right heart failure, the incidence of ↑ SGOT was 49 vs 5% (9)).

Most SGOT values are in the range of 40-80 units but about 20% are higher and may reach values of 1-2000 units or even higher. The highest values are seen with rheumatic heart disease, acute onset of failure and especially with hypotension or shock. The very high SGOT values generally correlate fairly well with degree of centrolobular necrosis and tend to be associated with ↑ serum bilirubin. SGPT in general follows the SGOT but the degree of elevation is often lesser. SGOT values return to or toward normal in 3-7 days (9).

The cause of ↑ SGOT is debatable (9, 18). All agree on hepatic necrosis and hypoxia. Some blame primarily venous congestion, others decreased hepatic blood flow. The data suggest that hepatic venous congestion may explain the lower elevations of SGOT (< 200) and perhaps very rarely values greater than that. Decreased hepatic blood flow of any etiology (trauma, sepsis, myocardial infarction (29)) may also cause an elevation of SGOT and probably is the main cause of all large elevations <> 200-300 and especially > 500 units (29).

Differentiation from Viral and Toxic Hepatitis

The very high SGOT values (> 1000 units) seen in some cases of congestive failure are noted in viral hepatitis and toxic hepatitis.(39).

Differential Clues: a) Diagnosis usually provided by persistence of ↑ SGOT, despite rapid improvement of heart failure or shock, in viral or toxic hepatitis.

b) ↑ SGOT due to heart failure usually falls with improvement in failure.

Differentiation from Myocardial Infarction

The modestly elevated SGOT (< 200 units) due to congested liver has to be differentiated from ↑ SGOT due to possible concomittant myocardial infarction.

Differential Clues: a) ↑ in SGPT (about 5 fold higher in liver than heart tissue (31) would suggest liver involvement but cannot rule out concomittant cardiac involvement.

b) No ↑ in SGPT does not prove that ↑ SGOT is derived from heart since some patients with liver impairment have ↑ SGOT but not ↑ SGPT.

c) Helpful clues may be:

1) Serum hydroxybutyric dehydrodegenase (SHBD)

SHBD is the LD_{1-2} isozyme. SHBD derives primarily from heart while LDH_{3-4} derive from liver. There is some SHBD in liver. Thus in a myocardial infarct SHBD is up (2-14 days after infarct) and the ratio of SHBD/LDH is high, > .8, since the heart is rich in SHBD. In severe liver disease (hepatitis) SHBD may

be ↑ but much LDH is of the LDH_{3-4} type hence the SHBD/LDH ratio is usually < .6. Some overlap however may occur and the presence of both liver and heart disease may confuse the issue (31, 32, 33, 34). Occasional false positive >.8 SHBD/LDH ratios are seen with skeletal muscle disorders and pernicious anemia.

2) Heat Sensitive LDH

Liver LDH is heat sensitive (destroyed on incubation at 60° C for 30 min.). Heart LDH is stable, falls only 25% on similar incubation (33). As shown in Table IV, heat stable LDH values (HLDH) are higher in myocardial infarction than in congestive heart failure or viral hepatitis and the ratio of HLDH/LDH is 0.70 in infarction and only .18 in hepatitis and .37 in congestive failure. Still some overlap in data in various diseases is seen and multiple causes of ↑ LDH may be hard to dissect.

TABLE IV

Peak Heat Stable LDH (HLDH) Levels and HLDH/LDH Ratios for Various Diagnoses (37)

Category	No. Pts.	HLDH Units Mean ± S.D.	HLDH/LDH Mean ± S.D.
Normal	55	42 ± 19	0.50 ± 0.16
Myocardial Infarct	73	252 ± 142	0.70 ± 0.16
Heart Failure	26	73 ± 32	0.37 ± 0.16
Hepatitis	7	51 ± 30	0.18 ± 0.13
Pulmonary Infarct	15	84 ± 33	0.36 ± 0.13

3) Serum Creatine Phosphokinase (SCPK) (35, 36, 26)

Increased in muscle injury (both cardiac and skeletal) and very low levels only present in liver. Disadvantages are technical problems in accurate assays, and brief ↑ in myocardial infarction (6-48 hrs.). Also high values of SCPK may be seen in a variety of other non-myocardial and non-hepatic problems (pneumonia, pulmonary embolism, diabetic ketoacidosis, etc., (26, 36).

Conclusion:

These laboratory techniques may help to identify the site of ↑ SGOT (Liver vs Heart) but no clinically tested invariably reliable method is yet available to differentiate these sites.

Alkaline Phosphatase:

↑ in 10%, 17%, 65% of patients (9, 4, 18, 19). Rise usually small - maximum ' X 2 normal. Does not correlate with severity of histologic changes (Table II). One study (18) of 224 patients reported a surprisingly high 65% incidence of increased values, most others run about 10-20%. Occasional values go up to 24 Bodansky Units (18).

Prothrombin Time:

↑ in 80-90% of patients (9, 6). In most instances 50-85% of normal values. Not influenced by Vit. K. and thus presumably reflects ↓ hepatic synthesis of prothrombin. Abnormalities seen more often in acute than chronic heart failure. Responds to clinical improvement rather slowly - over 2-3 weeks.

Albumin/Globulin:

Albumin: ↓ in 30-50% of patients (9, 21). Changes usually not marked (2.5 - 2.9 gm% in 3/4 of low values). No correlation with acuteness or chronicity and no definite correlation with degree of morphologic damage (Table II). Lower values, as expected, are seen more in patients with more severe ascites and edema and probably are responsible, at least partly, for them. Highest incidence of low values is seen in patients with rheumatic heart disease. Takes about one month to return to normal with improvement.

The cause(s) may be not only decreased hepatic synthesis of albumin in the congested liver but perhaps ↓ absorption by or ↑ leakage of protein by the congested intestine. Some ↓ in serum albumin may reflect ↑ plasma volume.

Globulins: ↑ in 17-50% of patients (9, 21). Usually mild - only 3.5 - 4.1 gm% in 3/4. Most common in rheumatic heart disease.

+ Cephalin Flocculation and Thymol Turbidity:

↑ in 2-33% (9, 21).

↓ Blood Sugar:

Important to remember that hypoglycemia may occur in the setting of congestive liver disease and may on occasion explain mental signs, palpitation and sweating usually attributed to heart disease (13, 9).

The exact incidence is not certain and will obviously depend on the intensity of search. The mechanism is also not certain but may involve both ↓ intake in the setting of congestive heart failure and ↓ hepatic function.

Overall Conclusions Regarding Clinical Setting:

1. Jaundice is rare and if present is usually mild.

2. Hepatic coma and effects of portal hypertension (varices) very rare.

3. Most sensitive test is BSP.

4. Bilirubin elevation usually under 5 mg% and sometimes primarily unconjugated. High bilirubin values should suggest pulmonary infarction.

5. Alkaline phosphatase seldom more than X2 normal.

6. SGOT usually < 100 but may reach values (> 1000), seen in diffuse hepatic necrosis (hepatitis). This usually seen with acute failure, right sided failure and hypotension.

7. SGOT, BSP and bilirubin levels correlate reasonably well (but not invariably) with histologic liver impairment.

Cardiac Cirrhosis (7, 8, 38):

Definition: Distortion of normal liver lobular pattern by fibrous septae bridging between central veins (reverse lobulation) and originating from centrolobular hepatic congestion associated with heart failure.

Incidence: a) In 4200 consecutive autopsies - 30 cases of cardiac cirrhosis (0.7%) (38). Other series 22 of 3000 autopsies (0.7%); 33 of 4000 autopsies 0.8%. All types of cirrhosis noted in about 4% of same autopsy series. Thus cardiac cirrhosis accounts for about 20% of all cirrhosis picked up at postmortem. This will obviously vary with the patient population studied.

b) Of 790 adults dead of heart disease, 35 or 4.4% had cardiac cirrhosis (38). In another series of 407 patients the incidence of cardiac cirrhosis was 1.7% (8). If fibrosis is used as a criterion of "cirrhosis", the incidence is higher - about 10% (7).

Clinical and Laboratory Considerations

a) Cardiac cirrhosis seems to occur most frequently (7) in:

1. Rheumatic heart disease
2. Constrictive pericarditis
3. With prolonged heart failure
4. With recurrent heart failure

b) It is generally agreed that there is no biochemical test to distinguish congestive cirrhosis (cardiac cirrhosis) from congested non-fibrotic liver (4). In addition, presence of cardiac cirrhosis alone may give no detectable biochemical abnormalities. There are well-documented cases where in the presence of cirrhosis plus centrolobular congestion and necrosis - definite impairment of liver function resulted and with improvement in cardiac status, cirrhosis alone remained but liver function returned almost to normal (4, 9).

c) There is both paucity of data (4, 8) and some difference of opinion as to whether splenomegaly and ascites are more common in the presence of cardiac cirrhosis as compared to centrolobular congestion. Most data support a primary effect of severe hepatic congestion and necrosis rather than fibrosis per se. There is no good evidence that cardiac cirrhosis as such increases the incidence of portal hypertension viz esophageal varices, increased superficial collateral veins (4, 9).

Findings in Favor of Presence of Cirrhosis:

1. Rheumatic heart disease or constrictive pericarditis
2. Prolonged or recurrent heart failure
3. Small liver in the face of ascites and splenomegaly
4. Lack of hepatic pulsation in the presence of tricuspid insufficiency.

Conclusion:

a) Cardiac cirrhosis has little functional significance as regards hepatic function in congestive failure. It is the status of centrolobular hepatic area which matters.

b) Liver biopsy for staging the degree of morphologic liver damage in a congested liver does not seem worthwhile. The main value of the biopsy is in making a diagnosis of the type of disease present i.e., viral hepatitis, alcoholic liver disease, etc.

Pathogenesis of Liver Dysfunction in Congestive Heart Failure:

Postulated mechanism(s) of hepatic changes in congestive heart failure may be related to:

a) Decreased arterial oxygen saturation with resultant hypoxia of liver.
b) Decreased hepatic blood flow with resultant decrease in hepatic O_2 supply.
c) Increased venous pressure with resultant -
   1) anoxia through edema of perisinusoidal area
   2) pressure atrophy of liver cells
d) Combination of above factors

Regardless of which factors are important - the critical final common mechanism is believed to be hepatic hypoxia (4).

This concept is based on the observations that:

1) Severe hypoxia alone (breathing low oxygen), in the apparent absence of decreased hepatic perfusion or of congestion, may induce centrolobular hepatic damage (40, 41) and impaired hepatic metabolism of BSP (42, 25) and bilirubin (42, 25, 43, 44)*.

2) Severe hypoxia alone decreases hepatic fluoroscein secretion, mostly in the centrolobular area (41).

3) The differential effect of hypoxia on the centrolobular area fits the relative remoteness of this site from the oxygen carrying blood supply which enters at the relatively normal-appearing portal areas.

4) The observation of similar centrolobular damage by decreased hepatic perfusion alone (as with myocardial infarction, and in trauma) (30, 45, 46), by hepatic congestion alone (experimental thoracic inferior vena cava ligation (47), and Budd-Chiari syndrome (48) or by breathing low oxygen (40, 41) - can best be explained simply as due to centrolobular hypoxia.

Individual Mechanisms

a) Decreased Arterial oxygen saturation in heart failure as cause of hepatic dysfunction:

This is not a likely primary factor since: 1) There is little significant arterial hypoxemia in these patients (19, 20); 2) There is essentially no correlation between liver dysfunction (19) or morphology (4) and degree of hypoxemia; 3) Studies in our laboratory indicate that arterial hypoxemia has to be very severe in experimental animals to interfere with liver function (25); 4) Studies in 28 patients with chronic lung disease and moderately severe hypoxemia (paO_2 63.2 ± 10.4 mm Hg (49) failed to show impaired hepatic storage or transport of BSP. These data suggest therefore that abnormalities in hepatic function reported previously in patients with chronic lung disease were primarily due to concomittant heart disease (not present in our patients) (40, 51).

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* In some studies inhaling 10% O_2 failed to effect BSP clearance from blood unless patients with previously damaged liver were studied (44).

Conclusion: Except in isolated cases where it may contribute, arterial hypoxemia is not likely cause of liver dysfunction in congestive heart failure.

b) Decreased Hepatic Blood Flow:

Normally liver perfused with a dual blood supply - 606-915 cc/min/m^2 (66-83% of total hepatic blood flow via portal vein and 142-418 cc/min/m^2 (17-34%) via hepatic artery (52). Some values of total hepatic blood flow are higher 1530 ± 300 ml/min (53) or 1400 cc/min (54). Normally about 50% of hepatic oxygen is delivered via the arterial circulation.

In congestive failure cardiac output decreases and hepatic blood flow is decreased on average by about 1/3 (Table V). The hepatic blood flow correlates well with the decrease in cardiac output so that the % of total cardiac output delivered to the liver is about the same, although the total quantity is obviously less. At rest, this decreased hepatic perfusion is compensated by increased O_2 extraction by the liver (Table V) so that total splanchnic (and presumably hepatic) oxygen consumption is maintained at normal levels (55, 57).

Table V

Splanchnic† Oxygen Consumption in Heart Failure at Rest (55)

	Normal* (14)	Heart Failure* (13)
Cardiac Output (liters/min/M^2)	4.1 ± 0.5	2.2 ± 0.5
Splanchnic Blood Flow (ml/min/M^2)	850 ± 170	535 ± 170
% of Cardiac Output	20 ± 4	24 ± 7
Splanchnic Oxygen Consumption (hepatic blood flow x hepatic A-V oxygen)	38 ± 10 ml	41 ± 11 ml
Hepatic A-V oxygen difference (Vol %)	3.9 ± 0.5	7.1 ± 1.4

* Mean ± S.D. of number of patients shown in brackets.

† Splanchnic oxygen consumption is the hepatic oxygen consumption plus that of viscera drained by the portal vein.

With exercise in normal individuals, splanchnic blood flow decreases (68). In patients with congestive heart failure, the decreased cardiac output may not be able to increase with exercise (56).

Measurements of hepatic A-V oxygen difference in both normal individuals and those with congestive heart failure were found to increase with exercise and the difference was greatest in those with most impaired cardiac output response to exercise. It is evident from data in Table VI that the hepatic venous oxygen saturation during exercise in the presence of severe congestive heart failure is very low.

Table VI (56)

Hepatic Venous Oxygen Saturation With Exercises in the Presence of Congestive Heart Failure

	Hepatic Venous O_2 Saturation
Normal (5)	60 %
Grade 1 Impairment (3)	44 %
Grade 2 Impairment (1)	29 %
Grade 3 Impairment (5)	18 %

Based on these observations and the known decreased cardiac output in congestive heart failure during rest, it has been estimated (not measured) that in severe congestive failure and with exercise hepatic blood flow may decrease to as low as 27% of normal resting cardiac output or about 350 ml/min/M^2. It is presumed that with this low hepatic blood flow the increased A-V oxygen extraction is insufficient to provide enough oxygen for the liver resulting in centrolobular hypoxia and damage (56).

Although such data are apparently not available for congestive heart failure, hepatic venous lactate/pyruvate ratio as an index of tissue anoxia (anaerobic metabolism) rises in concert with decreased splanchnic oxygen consumption in hemorrhagic shock (58) and endotoxin shock (59).

C) ↑ Venous Pressure:

Increased hepatic vein pressure (reflecting mainly ↑ systemic venous pressure) is well-documented (57, 61). This may cause cell atrophy although data in isolated liver perfusion system suggests a greater effect on production of perisinusoidal edema with probable decreased transfer of oxygen to cells in this area (60).

Clinical correlations with BSP retention (19, 20) also suggest this a as an important factor.

Overall Conclusion: Decreased hepatic blood flow and ↑ venous pressure result in hypoxia of liver. Pressure atrophy and arterial hypoxaemia are not primary factors but may contribute to hepatic damage.

ASCITES - MECHANISMS

1) Sodium and water retention due to heart failure

2) Low serum albumin, when present

3) Increased capillary permeability - ? from hypoxia

4) Hepatic lymph leakage. Supported by experimental studies with isolated perfused liver where amount of ascites formed correlated well (increased) with hepatic venous pressure. Factors 3 and 4 may explain the ascitic fluids which are high in protein. There are some suggestive data that high protein ascitic fluid may be more common in acute heart failure - reflecting high protein hepatic lymph leakage while prolonged heart failure gives an ascitic transudate reflecting leakage of low protein lymph from intestine, etc. (69).

5) Portal hypertension of much magnitude seldom present (57, 61). although some increase in wedged hepatic vein pressure is often present. This is usually almost equivalent to the free hepatic vein pressure and may mainly reflect "postsinusoidal extrahepatic obstruction" - i.e., the high systemic venous pressure (57, 61). However there is also in congestive heart failure about 2-fold increase in splanchnic volume and this may contribute to some portal hypertension (57). Actual measurements of splenic pulp pressure in congestive heart failure are difficult to find. In a few instances there was only a slight or no increase (62).

CONCLUSION: Multiplicity of Factors Account for Ascites. Their relative significance is difficult to assess.

SOME COMMENTS ABOUT THERAPY

1.. Treatment obviously primarily directed at the failing heart. Even with established cardiac cirrhosis, resolution of congestion in the liver results in marked improvement in hepatic function (4, 20). (The approximate time course of response of abnormal liver function tests is given under the individual tests).

2. Depression of mental state should suggest a cause other than hepatic coma which is very rare. One must consider among others - "hepatic" hypoglycemia and look for inadvertent or excessive use of NH_4Cl.

3. Anticoagulants have to be used with care since severe liver dysfunction increases the sensitivity to anticoagulants (63). One must keep in mind the rare occurrence of hypersensitivity hepatitis as a reaction to phenindione (64, 70).

4. Digitalis dosage obviously depends partly on its metabolism.
a) There are reasonable data that digoxin is metabolized normally in the presence of severe liver disease* (42) most likely because digoxin is excreted primarily by the kidneys in unchanged form (42, 65).

b) Partial or total hepatectomy in rats results in accumulation of oubain in blood and the LD_{50} rises, cited in (42). This is clearly related to large biliary excretion of oubain in rats (83-93% of injected load). Apparently in man oubain is not excreted significantly in bile but by the kidney (66) and oubain is tolerated well in patients with liver disease (personal communication - Marcus)*.

c) Digitoxin is also elevated in blood of hepatectomized rats. However in rats biliary ligation did not ↑ blood digotoxin and in man only 10% of administered digitoxin is excreted in bile. If digitoxin is more toxic in patients with liver disease, this would have to relate to impaired hepatic metabolism thus decreasing the renal excretion of digitoxin metabolites (79% of digitoxin excreted by kidneys in man; all but 8% as metabolites) (67). There are apparently no data at present on the effect of liver disease on the handling of digitoxin in man. (71).

* Obviously complicating renal disease alters the above comments.

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