The liver in heart failure

Cosmas C. Giallourakis, MD[a,b], Peter M. Rosenberg, MD[c],
Lawrence S. Friedman, MD[a,b,*]

[a]*Department of Medicine, Harvard Medical School, Boston, MA, USA*
[b]*Gastrointestinal Unit, Massachusetts General Hospital, Blake 456D, Boston, MA 02114, USA*
[c]*St. John's Health Center, Santa Monica-UCLA Medical Center, Santa Monica, CA 90404, USA*

As a result of a complex vascular supply and related vascular physiology, the liver is well buffered against hemodynamic alterations, even when a high level of metabolic activity is present, but can succumb to circulatory disturbances under a variety of circumstances. The resulting injury may take a variety of forms, depending on the blood vessels involved, extent of the injury, and relative contributions of passive congestion and diminished perfusion. Although processes as diverse as Budd-Chiari syndrome, hepatic veno-occlusive disease, and postoperative jaundice are part of the spectrum of circulatory disorders that affect the liver, this article focuses on the spectrum of clinical and pathophysiologic disorders that affect the liver as a result of primary cardiac disease, specifically congestive heart failiure.

Acute central necrosis of the liver first was described histologically by Kiernan in 1833, in association with severe congestive heart failure [1]. The clinical and biochemical features of necrosis in zone 3 that was associated with heart failure were described by Sherlock in 1951 [2]. The capability of measuring serum aminotransferase levels in 1954 increased awareness of the spectrum of clinical presentations, and in 1960, Killip and Payne described massive elevations of serum aminotransferase levels that resulted from cardiogenic shock [3].

Anatomy and physiology of hepatic blood flow

The liver makes up only 2.5% of total body weight but receives 25% of the total cardiac output [4]. Two thirds of the blood flow to the liver is supplied by

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* Corresponding author. Gastrointestinal Unit, Massachusetts General Hospital, Blake 456D, Boston, MA 02114.

E-mail address: friedman.lawrence@mgh.harvard.edu (L.S. Friedman).

the portal vein. Portal venous blood is rich in basic nutrients, including glucose, amino acids, and triglycerides, but is lacking in oxygen. By contrast, the hepatic artery, which supplies about one third of the total hepatic blood flow, carries oxygen-rich blood and accounts for more than 50% of the oxygen that is delivered to the liver; it also is the sole blood supplier for the major bile ducts. In humans, the hepatic artery can be ligated or occluded without adverse consequences; portal flow and arterial collateral flow by way of the subcapsular channels provide adequate perfusion [5,6]. Blood that flows through the liver is drained into the inferior vena cava by the right, left, and middle hepatic veins and then into the right side of the heart.

The functional unit of the liver is the hepatic acinus, which consists of a cluster of hepatocytes that are approximately 2 mm in diameter and are grouped around terminal branches of the hepatic arteriole and portal venule (Fig. 1). Blood from the portal vein and hepatic artery branches enters the acinus in the portal and periportal regions and flows through the hepatic sinusoids toward the periphery, where it drains into a terminal hepatic venule. According to the Rappaport classification, the center of the acinus (periportal region) is zone 1, the periphery (perivenular region) is zone 3, and the region in between these areas is zone 2 [7]. Zone 1 receives blood with the highest levels of oxygen and nutrients, whereas zone 3 receives relatively hypoxic blood that has passed through zones 1 and 2. The gradient is exaggerated in the setting of vascular collapse, when extraction of oxygen by hepatocytes in zone 1 is increased to compensate for the reduction
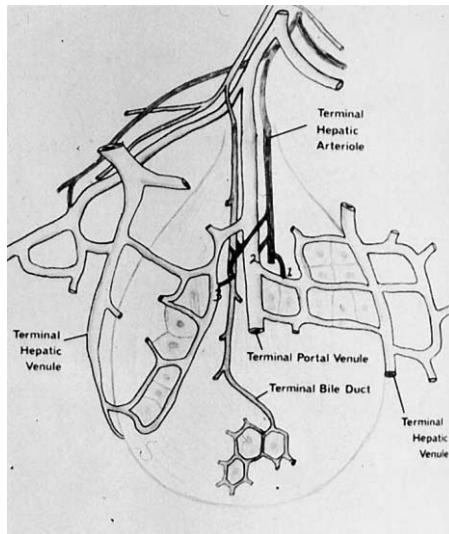

Fig. 1. Functional unit of the liver—the acinus. Blood flows through the terminal hepatic arteriole and terminal portal venule to the center of the acinus (zone 1) and then drains into the terminal hepatic venule at the periphery of the acinus (zone 3). (*From* Lautt WW, Greenway CV. Conceptual review of the hepatic vascular bed. Hepatology 1987;7:952–63; with permission.)

in hepatic blood flow, thereby resulting in a lower-than-normal oxygen tension in zone 3.

The hepatic sinusoids are suited for the primary function of the liver (clearance of toxins and metabolism of nutrients), which requires a constant rate of blood flow and close contact between the blood and hepatocytes. The sinusoidal endothelium lacks a true basement membrane and contains multiple fenestrae that measure 1 to 3 μm in diameter. These characteristics allow fluid, metabolites, toxins, and hormones to flow freely between the sinusoids and the space of Disse, which surrounds the hepatocytes.

Total hepatic blood flow is kept constant largely through the regulation of hepatic artery blood flow. Portal flow can vary significantly in response to a number of stimuli, although there is no evidence that the liver itself directly can regulate portal blood flow. A constant rate of hepatic blood flow is believed to be important for at least two major homeostatic reasons: (1) The maintenance of constant hepatic blood flow and the ability to stabilize intrahepatic pressures minimize alterations in venous blood flow over a broad range of conditions; however, this buffering capacity may not be sufficient enough to avoid damage caused by the poor hepatic arterial blood flow in acute cardiac decompensation. (2) A constant hepatic blood flow is probably important for hepatic clearance of compounds, such as hormones, that may depend on a certain rate of metabolism.

The mechanism by which total hepatic blood flow remains constant is under the control of two interrelated physiologic processes: (1) the hepatic artery buffer response (HABR), in which a change in arterial pressure leads to an inverse change in arterial flow, and (2) hepatic artery autoregulation, in which a change in portal blood flow leads to an inverse change in hepatic arterial flow (eg, reduced portal flow results in a rapid increase in arterial blood flow and vice versa). These two processes seem to be mediated by the local concentration of adenosine, a potent vasodilator. Adenosine is postulated to be produced at a constant amount and secreted by cells of an unknown type into the space of Mall, which surrounds the hepatic arterial resistance vessels and portal venules. The local concentration of adenosine is determined by its washout rate, as determined by sinusoidal blood flow [8]. When portal blood flow diminishes, the local adenosine concentration increases, resulting in compensatory arteriolar vasodilation. Similarly, a decrease in arterial pressure leads to decreased hepatic artery flow, which leads to the accumulation of adenosine (as result of a reduced adenosine washout rate) and hepatic artery dilation. In a rat model, graded obstruction of the left portal vein led to an increase in flow in the left hepatic artery but a decrease in flow in the right hepatic artery, suggesting that HABR can occur independently in each lobe of the liver as a result of the action of local factors rather than as a result of systemic hemodynamics [9]. In a rat model of carbon tetrachloride-induced cirrhosis, in which portal flow was compromised, HABR seemed to remain intact, as assessed by perivascular Doppler probes [10].

The presence of the HABR was examined in patients with cirrhosis using intravascular Doppler technology and simultaneous measurement of hemodynamic parameters after the patients received direct infusion of adenosine into the

hepatic artery [11]. This study showed that the HABR remains intact in patients with cirrhosis, although it may be blunted in patients with more severe disease. In contrast to the noncirrhotic rat model described earlier [9], systemic hemodynamics, rather than the degree of cirrhosis, seems to affect the hepatic artery blood flow in humans.

Clinically or biochemically significant hepatic ischemia that is caused by the disruption of hepatic arterial flow is not common but has been described in a number of settings, such as hepatic arterial thrombosis or stenosis after liver transplantation, injury during hepatobiliary surgery, occlusion during radiologic procedures, and injury caused by trauma. Anastomoses between hepatic arterial and portal venous branches at interlobar spaces and collateral pathways have been demonstrated in cadaveric livers; when the common hepatic artery is ligated, the pancreaticoduodenal and gastroduodenal arteries serve as the major collateral pathways. Ischemic changes after surgical ligation of the hepatic artery occur more frequently in the presence of risk factors, such as decreased portal blood flow, sepsis, biliary obstruction, cardiac failure, or chronic obstructive lung disease. In the nonhemodynamically compromised patient, it has been shown that the hepatic artery can be ligated to provide symptomatic relief to some patients with pancreatic neoplasms, without causing hepatic compromise [12]. The transition from hepatic ischemia to hepatic infarction has not been reported as a result of congestive heart failure or acute myocardial infarction alone, testifying to the relative protection of the liver from severe ischemia.

Pathophysiology

Passive hepatic congestion

The effects of congestive heart failure on the liver result from three pathogenic factors: decreased hepatic blood flow, increased hepatic venous pressure, and decreased arterial oxygen saturation. Unique to heart failure, as opposed to other causes of circulatory collapse, is the effect of passive congestion on the liver. Elevated central venous pressure is transmitted readily to the hepatic veins and then to the small hepatic venules that drain the hepatic acini. Electron microscopic studies of congested human livers have documented that this increased pressure can cause the atrophy of hepatocytes in zone 3 [13]. Elevated hepatic venous pressure also results in sinusoidal congestion and enlargement of the sinusoidal fenestrae, thereby allowing exudation of protein-rich fluid into the space of Disse. The resulting perisinusoidal edema may impair diffusion of oxygen and nutrients to hepatocytes [13,14].

Excess fluid in the space of Disse can be drained into hepatic lymphatics, but when the formation of lymph exceeds the capacity of the lymphatics, high-protein fluid may exude from the surface of the liver and drain into the peritoneal cavity. It is hypothesized that such exudation could contribute to the relatively high protein content of cardiac ascites; however, this phenomenon has not been

confirmed [14]. Measurement of hepatic lymph at autopsy in patients with acute congestive heart failure has not revealed a significantly elevated protein content, even though the ascites has a high protein concentration. The contribution of hepatic lymphatics to the development of ascites during cardiac dysfunction is unclear [15].

Continued ischemic insults or chronic passive congestion can result in liver fibrosis in the perivenular area (zone 3) and in the space of Disse, leading to further impairment of the blood-to-hepatocyte diffusion of oxygen and nutrients. The degree of fibrosis is variable from one region of the liver to another. This variability may be explained by the fibrogenic effects of focal thrombi within the sinusoids, hepatic venules, and portal veins as a result of chronic vascular stasis [16].

Passive congestion is not sufficient but may be necessary, along with decreased hepatic blood flow, to cause the hepatic necrosis seen in the histopathologic picture of ischemic hepatitis. Sherlock's observation that there is no correlation between right atrial pressure and the degree of necrosis in zone 3 in patients with congestive heart failure supports the concept that chronic passive congestion is not the sole determinant of hepatic necrosis in heart failure [2]. A significant degree of necrosis in zone 3 that is caused by acute left-sided heart failure has been documented in the absence of right-sided heart failure; this finding suggests that reduced cardiac output may be the predominant determinant of hepatic ischemia in some patients [17]. Passive congestion seems to be an important cofactor in most cases of clinically apparent hepatic ischemia. In one study, all patients with a clinical diagnosis of ischemic hepatitis were found to have clinically significant cardiac disease, and 94% had right-sided heart failure [18]. Seeto and colleagues compared this retrospectively collected series of patients with a clinical diagnosis of ischemic hepatitis with a prospective group of patients with trauma and documented hypotension. These investigators found that none of the patients with trauma had clinically significant elevations in serum levels of liver biochemical tests [18]. This observation argues strongly that the liver may need to be primed by hepatic congestion to sustain hepatic necrosis in patients with cardiac disease.

In patients with chronic passive congestion, atrophy of hepatocytes, rather than necrosis, is responsible for cell disappearance. This atrophy is likely the result of pressure, which flattens plates of hepatocytes between dilated sinusoids without causing significant ultrastructural changes of ischemia. The nutritional and metabolic status of the hepatocytes may be compromised, as suggested by similarities in hepatocyte morphology in passively congested livers and in starved animals. Undernutrition of hepatocytes is proposed to be the result of the impaired diffusion of nutrients between cells and blood that is caused by collagen deposition in the space of Disse. Nutritional status has an important influence on hepatocellular sensitivity to hypoxia. Fasted rats seem to be less prone to hepatic ischemia than are fed rats, possibly because their diminished glycogen stores provide less substrate for anaerobic glycolysis, resulting in decreased intracellular production of lactic acid [19].

The liver compensates for declining cardiac output by increasing the amount of oxygen that it extracts. As a result, the arteriovenous oxygen difference increases across the hepatic bed. The perivenular liver cells receive blood that has a lower oxygen content than that received by cells in the periportal zones. As cardiac output declines further, compensatory mechanisms become inadequate, and hypoxia ensues.

Hepatic ischemia

Hepatic ischemia, similar to ischemia involving other organs, results from an imbalance between oxygen supply and demand. Because the metabolic rate of the liver is relatively constant, oxygen supply, not demand, is the principal determinant of hepatic ischemia [20,21]. Hepatic oxygen delivery is a function of the oxygen content of blood and the total hepatic blood flow. It previously was believed that severe arterial hypoxemia is not likely to be an important pathogenic factor in liver damage because: (1) most patients with stable congestive heart failure do not have significant arterial hypoxemia; (2) there seems to be no correlation between the degree of hypoxemia and extent of liver damage; and (3) the degree of hypoxemia that is necessary to induce hepatic dysfunction in animal models is more profound than the degree needed to induce hepatic dysregulation in cases of presumed congestive heart failure [14]. More recent observations suggest that arterial hypoxemia may be the underlying cause of ischemic hepatitis in some patients with chronic obstructive pulmonary disease and obstructive sleep apnea, in whom there also is likely to be some passive congestion that is secondary to elevated right-sided cardiac pressures [22–24]. In 1999, Henrion and co-workers reported on the clinical and histologic diagnosis of 17 patients with hypoxic hepatitis (as opposed to ischemic hepatitis) [22]. These patients had significant hypoxemia (Pao_2, 27–45 mm Hg), preserved cardiac output, and only mild elevations in the pulmonary capillary wedge pressure (PCWP) or central venous pressure (CVP). In comparison, controls with congestive heart failure and ischemic hepatitis had mild hypoxemia, decreased cardiac output, elevated PCWP and CVP, and slightly decreased Pao_2. These observations suggest that hypoxemia, not ischemia, and elevated right-sided pressures can induce a clinical picture that is similar to that of classic ischemic hepatitis. The degree of hypoxemia likely needs to be severe in such cases, as supported by the fact that, at least in the mouse model, hepatocyte excretory function remains intact until extreme hypoxia is reached [25].

The most critical factor in hepatic ischemia is a reduction in total hepatic blood flow. As noted earlier, hepatic blood flow is determined primarily by cardiac output, and the splanchnic bed constantly receives 25% of the cardiac output [4]. In patients with cirrhosis or hepatic venous thrombosis (Budd-Chiari syndrome), however, the splanchnic circulation is not directed entirely through the liver because of collateral drainage into the systemic venous system (portosystemic shunting); as a result, the liver is more susceptible to ischemia. As hepatic blood flow declines in proportion to a reduction in cardiac output, the liver compensates

by increasing the extraction of oxygen. This process usually maintains oxygenation of hepatocytes in zones 1 and 2 but not of hepatocytes in zone 3.

Chronic congestive heart failure renders the liver vulnerable to acute ischemic injury. Reduced cardiac output in patients with this condition leads to an approximate threefold decrease in total hepatic blood flow [4,21]. In the resting state, increased extraction of oxygen by hepatocytes compensates for the reduction in hepatic blood flow. Under situations of systemic stress, such as sepsis or increased physical activity, in which cardiac supply cannot meet the extrahepatic metabolic demands and hepatosplanchnic perfusion decreases, extraction of hepatic oxygen may be unable to increase above its already elevated baseline, and hepatocellular hypoxia can result, especially in zone 3 of the hepatic acini.

Ischemia–reperfusion injury

Over the past decade, studies based on rat and mouse models have attempted to explain in molecular biologic terms the mechanism of hepatic damage in low- or no-flow states and to examine the relative contribution of ischemia–reperfusion in the pathogenesis of hepatic injury. These experimental studies can be subdivided into those that examine cold ischemia (preservation injury during liver transplantation) and those that examine warm ischemia (temporary vascular exclusion during liver surgery for trauma or tumors). The distinction between warm and cold ischemia is important, because the mechanisms of injury may differ, although they may share overlapping characteristics. Apoptosis seems to be critical in the development of cold ischemic injury, but its role in warm ischemic injury is less well defined [4].

These studies have established that most ischemic damage to the liver that is histologically apparent occurs during the reperfusion phase of injury, not the ischemic phase, and that the reperfusion phase of injury can be divided into two functionally distinct periods (Fig. 2). The initial phase is mediated by Kupffer cells and is not associated with infiltration of polymorphonuclear leukocytes (PMNs). Kupffer cells react to ischemia by producing a number of inflammatory factors, the most important of which may be tumor necrosis factor α (TNFα), which trigger a cascade of events that leads to the second phase of reperfusion injury. This phase is mediated by the recruitment and activation of PMNs. Kupffer cells also have been shown to produce reactive oxygen species after reperfusion, although the role of reactive oxygen species in mediating injury is unclear. When animals are treated before an ischemic insult with gadolinium chloride or methylpalmitate, which inactivate Kupffer cells, levels of glutathione (a surrogate marker of the production of reactive oxygen species) and serum alanine aminotransferase (ALT) are lower than those seen in the absence of Kupffer cell inactivation, suggesting that the Kupffer cell-induced oxidant stress contributes to the hepatic ischemia–reperfusion injury [26].

Tumor necrosis factor α triggers the secondary influx and activity of PMNs after reperfusion through a variety of mechanisms, including up-regulation of
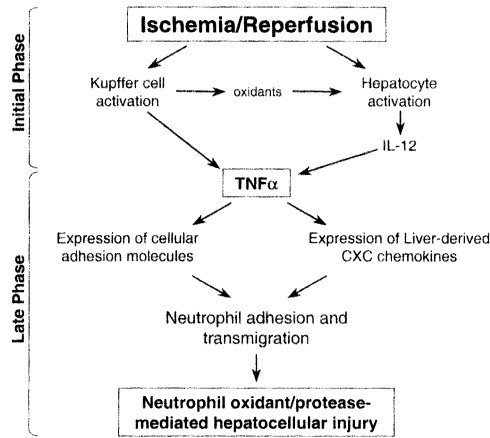
Fig. 2. Inflammatory pathogenesis of ischemic–reperfusion injury. (*From* Lentsch A, Kato A, Yoshimode H, McMasters KM, Edwards MJ. Inflammatory mechanisms and therapeutic strategies for warm ischemia/reperfusion injury. Hepatology 2000;32:169–73; with permission.)

adhesion molecules and chemokines, such as intracellular adhesion molecule 1, epithelial neutrophil-activating protein 78, and macrophage inflammatory protein-2 in the liver [27–29]. The importance of endothelial adhesion in reperfusion injury has been demonstrated in a model of a P-selectin knockout mouse with ischemia–reperfusion [30]. Mice deficient in P-selectin showed a wide range of protective effects, including decreases in PMN infiltration and platelet sequestration, lower levels of serum aminotransferase, and improved survival rates. Anti–P-selectin antibodies reduced reperfusion injury in ischemic heart, intestine, and kidney models. Recruitment of activated PMNs leads to oxidative damage and may lead to the so-called "no reflow" phenomenon by plugging blood vessels.

Evidence suggests that interleukin 12 (IL-12) may be a key mediator in up-regulating the expression of TNFα in the earliest phase of ischemia–reperfusion injury [31]. In this study, mice that were treated with neutralizing antibody to IL-12 and IL-12 knockout mice displayed reduced TNFα production. IL-12 was present immediately after reperfusion, whereas TNFα levels increased substantially 1 hour later and peaked at 8 hours, suggesting that the presence of IL-12 leads to TNFα production.

Organs that are remote from the liver, such as the lung, seem to be injured as a result of the accumulation of PMNs, triggered by the release of TNFα from the liver. It is hypothesized that because the pulmonary circulation is the first vascular bed into which cytokines from the liver, such as TNFα, are delivered, the pulmonary parenchyma is most likely to manifest the toxic effects of these cytokines. In rat models of liver ischemia–reperfusion injury, the lungs experienced significant dysfunction secondary to infiltration of PMNs and edema, with maximal increases in myeloperoxidase levels in the lung that were detected 1 hour

after hepatic reperfusion. Pretreatment with anti-TNFα blunts myeloperoxidase activity in the lung and may improve survival [32]. It is unclear whether patients with hepatic ischemia–reperfusion injury have actual lung damage.

The secretory leukocyte protease inhibitor (SLPI) has been shown to down-regulate a number of responses, such as TNFα production, aminotransferase elevations, and myeloperoxidase levels, in the lung and liver after hepatic ischemia [33]. SLPI is up-regulated in hepatocytes during ischemia and for up to 4 hours after reperfusion. Administration of an anti-SLPI antibody before the induction of ischemia leads to the potentiation of inflammatory responses, suggesting that endogenous production of SLPI attempts to blunt liver damage. SLPI may be an important endogenous negative regulator of the hepatic inflammatory response to ischemia–reperfusion injury. Pretreatment with IL-10 also has been shown to have a protective effect [34]. Although ischemic hepatitis typically is self-limited, patients whose disease deteriorates toward liver failure might benefit from immunomodulator agents. Extrapolation from animal studies to humans must be made with caution. Trials of IL-10 in patients with acute pancreatitis have not been promising [35]. On the other hand, anti-TNFα treatment has been effective in fistulizing Crohn's disease and rheumatoid arthritis [36].

Congestive hepatopathy

The term *congestive hepatopathy* refers to hepatic manifestations that result specifically from passive hepatic congestion, as opposed to those that result primarily from reduced cardiac output. As suggested earlier, this dichotomy is not absolute, because the two processes—passive congestion and reduced cardiac output—are intertwined.

Pathology

A congested liver often appears as an enlarged purplish organ with rounded or blunted edges and prominent hepatic veins. On sectioning, the liver often conforms to the classic description of the so-called "nutmeg liver." This appearance results from the contrasting combination of reddish hemorrhagic areas, where red blood cells have extravasated from the sinusoids into atrophic regions, and yellowish portal areas that represent normal or mildly fatty liver.

A number of studies have described the microscopic changes in hepatic congestion in autopsied livers and percutaneous liver biopsy specimens. Theoretically, liver biopsy involves an increased risk for bleeding because of the high venous pressure in the congested liver, but this increased risk has not been demonstrated. Microscopic examination of the liver may reveal sinusoidal engorgement, degeneration, and variable degrees of hemorrhagic necrosis in zone 3; fatty change; and variable degrees of cholestasis, sometimes with bile thrombi in the canaliculi. Bile thrombi tend to be present in patients with severe
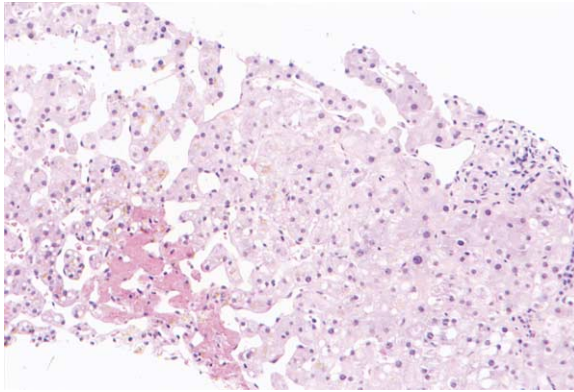
Fig. 3. Hepatic congestion in chronic heart failure showing dilated sinusoids in zone 3, hepatocyte plate atrophy, and extravasation of red blood cells, H & E, × 10. (*Courtesy of* F. Graeme-Cook, MD, Massachusetts General Hospital, Boston.)

jaundice, and it has been hypothesized that the thrombi result from excessive concentrations of bilirubin or stagnation of bile resulting from distortion of the canaliculi by hepatic congestion (Fig. 3) [2].

As the damage progresses with chronic or recurrent episodes of heart failure, there is collapse of the reticulin network that surrounds the central vein and the degenerating hepatocytes in zone 3, leading to a stromal reaction of fibrotic bands that radiate outward from the central vein. These bands of collagen ultimately reach adjacent central veins and encircle the relatively spared portal regions, generating the reverse lobulation pattern of cardiac fibrosis (cardiac cirrhosis) [2]. This pattern differs pathologically from that associated with other causes of liver fibrosis (Fig. 4). Reverse lobulation is not always found in patients with chronic
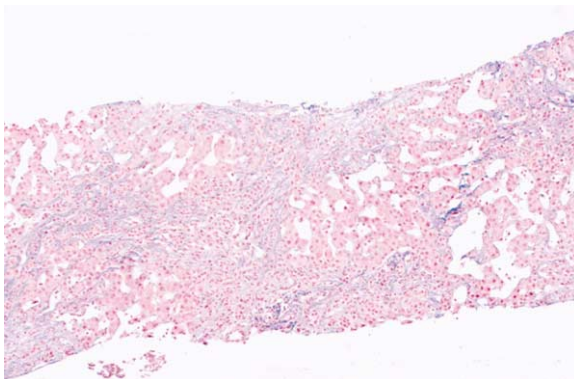

Fig. 4. Cardiac cirrhosis in a patient with chronic congestion, dilated sinusoids, and fibrosis H & E, × 10. (*Courtesy of* F. Graeme-Cook, MD, Massachusetts General Hospital, Boston.)

hepatic congestion [37]. The degree of functional reversibility of these changes is the subject of debate. Terblanche et al biochemically studied hepatic function in patients with constrictive pericarditis before and after therapy [38]. In this study, 32 of 38 cases were presumed to be secondary to tuberculosis pericarditis. The duration of heart failure ranged from 3 to 13 months, and most patients had stage III heart failure. These 38 patients showed a persistent increase in levels of total serum bilirubin and abnormal bromosulphalein retention years after their cardiac function had improved, suggesting that reversal of hepatic dysfunction is not 100% complete after relief of cardiac disease. Even though there was biochemical evidence of sustained liver dysfunction, this finding did not translate into the development of clinically significant liver disease.

Fibrosis that is caused by hepatic congestion may involve terminal hepatic venules (phlebosclerosis) [2]. The development of full-blown bridging fibrosis or true cardiac cirrhosis is variable, even in patients with similar degrees of cardiac decompensation, and the degree of fibrosis varies significantly from region to region within the same liver. There may be some correlation between the distribution of fibrosis and fibrous obliteration of hepatic veins and portal veins of various calibers secondary to thrombosis [17]. The degree of cardiac decompensation or its duration does not have any predictive value with regard to degree of hepatic fibrosis. Clinical manifestations, such as jaundice, splenomegaly, and ascites, do not correlate with histology [2,39]. It has been suggested that the safety of cardiac transplantation for heart failure in patients with evidence of mild liver dysfunction attributed to congestion, especially if ascites is present, may be best determined by a histologic assessment of the extent of hepatic fibrosis [40].

Clinical features

In a large series of 175 patients with both acute and chronic congestive heart failure, hepatomegaly was present in 90% to 95%, ascites in 17% to 25%, and splenomegaly in 7% to 20% [41]. A few patients experienced right upper quadrant pain that was caused by stretching of the liver capsule.

Runyon described characteristics of ascites that are clinically useful in differentiating cardiac ascites from ascites of other causes. Although ascites is present at autopsy in approximately 41% of patients with heart failure, clinically overt or compromising amounts of ascites occur in substantially fewer patients. In patients with ascites, the level of protein in the fluid is elevated (typically > 2.5 g/dL), and the serum albumin gradient is greater than 1.1. The level of lactate dehydrogenase (LDH) and the red blood cell count are higher in patients with ascites caused by heart failure than in patients with alcoholic or viral cirrhosis, presumably because of the leakage of red blood cells into the ascites through the lymphatic vessels and lysis [42]. The unique combination of parameters in patients with cardiac ascites is believed to reflect the relatively well-preserved liver synthetic function and the elevated venous pressures that are transmitted to the portal system. The extent of parenchymal liver damage and hemodynamic parameters do not seem to correlate with the amount of ascites [41].

In general, patients with passive congestion or cardiac fibrosis do not have stigmata of portal hypertension, such as spider angiomata, or evidence of portosystemic shunts, such as a caput medusae. In Sherlock's series, none of the 28 autopsies disclosed esophageal varices [2]. The absence of portal hypertension may reflect the relative sparing of the portal tracts from fibrosis.

Physical examination may reveal a pulsatile liver in patients with tricuspid stenosis, as first emphasized by Mackenzie in 1902. The normal hepatic pulse consists of the "A," or presystolic, wave and the "V" wave, representing atrial contraction and the increase in hepatic volume in early diastole, respectively. A positive systolic wave is considered abnormal and is termed *en plateau*. In patients with tricuspid regurgitation, the systolic wave results from retrograde transmission of the pulse wave caused by right ventricular contraction. In contrast, patients with tricuspid stenosis have a prominent A wave, although any process that results in overloading of the right atrium, such as pulmonary artery stenosis or atrial septal defect, may lead to a prominent A wave [43]. Loss of hepatic pulsatility in patients with long-standing congestive hepatopathy suggests progression to cardiac cirrhosis.

Jaundice is uncommon in congestive heart failure. Grob reported an overall incidence of 5% in patients with acute and chronic congestive heart failure [41]. Sherlock's original series of 50 patients with heart failure included eight patients (17%) who had marked jaundice and serum bilirubin levels that ranged from 4.5 to 22 mg/dL [2]. This series likely overrepresented patients with an acute exacerbation. Sherlock found that the serum bilirubin level correlated with the right atrial pressure but not with cardiac output. The exact mechanism of hyperbilirubinemia is unclear, and multiple factors are believed to contribute, including hepatocellular dysfunction, hemolysis, pulmonary infarction, canalicular obstruction caused by high hepatic vein pressures and bile thrombi, and medications.

In one series, right-sided cardiac hemodynamic measurements were correlated with the results of liver biochemical tests in 133 patients with ischemic cardiomyopathy; patients with primary valvular heart disease or pericardial disease were excluded [44]. (These latter patients had made up most of the patients in Sherlock's series.) These data revealed that, although the magnitude of changes in the test results correlated with the hemodynamic severity of heart failure, there was considerable variability among patients, and the researchers were unable to distinguish the relative contributions of passive congestion, as measured by atrial pressure and PCWP, from those of reduced hepatic arterial flow, as measured by cardiac index, using the observed laboratory changes. This analysis suggests that congestion and reduced cardiac output contribute to the pathology of congestive hepatopathy and ischemic hepatitis.

Liver dysfunction in congestive heart failure generally is mild and asymptomatic and often is noted incidentally on routine liver biochemical testing. Patients with severe, usually acute, right-sided heart failure rarely develop striking hyperbilirubinemia. In patients with chronic, severe heart failure, jaundice may be so deep as to suggest biliary obstruction [45]. When jaundice is accompanied by significantly elevated levels of serum aminotransferase in patients with acute

cardiac decompensation, the clinical picture may simulate that of acute viral hepatitis [46,47].

Although overt jaundice is uncommon, mild elevation of the serum bilirubin level occurs in up to 70% of patients. The total serum bilirubin levels are usually less than 3 mg/dL, with a predominantly unconjugated fraction. The level of serum alkaline phosphatase is typically normal, and elevations are noted in only 10% of patients [8]. Even in the presence of deep jaundice, the level of serum alkaline phosphatase is usually normal or minimally elevated, a finding that helps distinguish cardiac jaundice from obstructive jaundice. Serum amino-transferase levels are elevated mildly, usually two to three times the normal value, in up to one third of patients with chronic heart failure. In patients with severe acute heart failure, however, the serum aminotransferase levels may be elevated extremely, simulating acute hepatitis, especially when heart failure is complicated by hypotension. These high levels have been described in patients with heart failure and minimal or no hemodynamic instability, probably because of ischemic injury as a result of decreased cardiac output, because the degree of elevation of serum aminotransferase levels correlates with the extent of necrosis in zone 3 [17,46,48].

Serum albumin levels are decreased in 30% to 50% of patients with congestive heart failure but are rarely less than 2.5 g/dL. The degree of hypoalbuminemia does not correlate with the degree of histologic liver damage. The prothrombin time is mildly abnormal in 80% of patients with chronic congestive heart failure. The elevated prothrombin time usually fails to resolve with vitamin K therapy, suggesting that this impairment may be caused by impaired hepatic synthesis of coagulation factors II, V, VII, IX, and X [41].

Serum ammonia levels have been elevated in a minority of patients with congestive heart failure and may be associated with clinical encephalopathy in the absence of other clinical evidence of liver dysfunction.

Elevated serum levels of the tumor marker carcinoembryonic antigen (CEA) have been reported in a patient with cardiac decompensation in whom no malignancy was found. In this patient, a normal CEA level had been measured four months before an episode of acute cardiac decomposition had occurred, and the CEA level returned to normal after the cardiac disease was stabilized [49].

Two case series have described hypoglycemia in patients with acute or chronic passive congestion of the liver, but these series involved neonates with hypoplastic right hearts, adults with other reasons for hypoglycemia, and noncardiac causes of liver disease [50,51]. It is unlikely that, in the absence of full cardiac cirrhosis with decompensated liver disease, hypoglycemia is a clinically significant manifestation of cardiac failure. Another series has reported hyperglycemia in patients with ischemic hepatitis [52].

Clinical course

The outcome of patients with passive congestion of the liver relates to the underlying heart disease; liver disease rarely causes significant morbidity or

mortality in these patients. If heart failure can be controlled medically, the early histologic changes of passive hepatic congestion may resolve. Prolonged, persistent hepatic congestion may result in cardiac cirrhosis, as described earlier. Cardiac cirrhosis classically is seen in patients with constrictive pericarditis or prolonged mitral valve disease and secondary tricuspid regurgitation. Cardiac cirrhosis itself does not confer a poor prognosis. Sherlock found that jaundice and hepatic synthetic function were no worse in patients with cardiac cirrhosis than in patients with simple passive congestion [2]. As noted earlier, no patients with cardiac cirrhosis showed stigmata of chronic liver disease or evidence of portosystemic shunting, and esophageal varices have not been documented as a result of cardiac cirrhosis alone. Even after progression to cardiac cirrhosis, control of the heart failure can lead to regression of the histologic and clinical liver abnormalities, leaving only latent cirrhosis.

Several cases of fulminant hepatic failure with coma, some of which resulted in death, have been reported to occur secondary to congestive heart failure [11,53–55]. Most, but not all, of these cases occurred in the setting of super-imposed shock, and all cases seem to have been caused by hepatic ischemia rather than passive congestion alone. In such cases, it is difficult to attribute mental status changes to hepatic encephalopathy, because cerebral hypoxia from the underlying heart disease may lead to altered mental status.

Treatment

The cornerstone of management for congestive hepatopathy is treatment of the underlying heart disease. Jaundice, hepatic congestion, and ascites may respond dramatically to therapy with diuretics. In patients with severely impaired cardiac output, care must be taken to avoid excessive diuresis, which may impair hepatic perfusion and precipitate necrosis in zone 3 [55]. Maintaining an adequate cardiac output is of paramount importance.

Patients with cardiac disease often take medications that undergo significant hepatic metabolism, such as warfarin. Evidence of reduced demethylation activity of the liver has been suggested in studies of patients with heart failure (although not necessarily passive congestion). In a rat model of hepatic congestion and fibrosis, no alteration in the metabolism of intravenously administered morphine or pentobarbital was observed [56]. A decreased clearance of lidocaine has been reported in patients with congestive heart failure [57]. There is insufficient evidence in humans to assess whether hepatic congestion alters drug metabolism, but cautious use of these drugs is advisable, because the metabolism of some drugs may be altered in congested or fibrotic livers.

Ischemic hepatitis

Ischemic hepatitis refers to diffuse hepatic injury that results from acute hypoperfusion; common synonyms include shock liver, hypoxic hepatitis, and

occasionally (and erroneously) acute hepatic infarction. The use of the term *ischemic hepatitis*, as introduced by Bynum and colleagues in 1979, captures the potential clinical resemblance of this entity to viral hepatitis [48]. Even when, as in most cases, the presentation is distinct from that of viral hepatitis, the term *ischemic hepatitis* seems to be preferable to the alternatives, because it accounts for the occurrence of the syndrome in the absence of shock and distinguishes the diffuse pattern of injury from the focal nature of hepatic infarction. The clinical, laboratory, and histologic features of ischemic hepatitis overlap considerably with those of congestive hepatopathy; decreased cardiac output is a central component of both entities. Most cases of ischemic hepatitis occur with congestive heart failure, although there are many other potential causes.

Pathology

The histologic hallmark of ischemic hepatitis is necrosis in zone 3. Depending on the duration of ischemia, a variable degree of architectural collapse around the central veins can occur. With severe prolonged ischemia, necrosis can extend to the midzonal hepatocytes; necrosis rarely occurs predominantly in the middle zones [58]. Histologic changes that are indicative of passive congestion (discussed earlier) may be present concomitantly, especially in patients with cardiogenic shock (Fig. 5). There is a characteristic paucity of inflammatory activity. Recovery from the ischemic event is associated with regeneration of hepatocytes and restoration of normal architecture, because the reticular framework of the hepatic lobules is undamaged.

Clinical features

Because a significant decrease in hepatic perfusion is a prerequisite to ischemic liver injury, the hemodynamic insult is usually clinically apparent before evidence of liver injury appears. Occasionally, transient subclinical
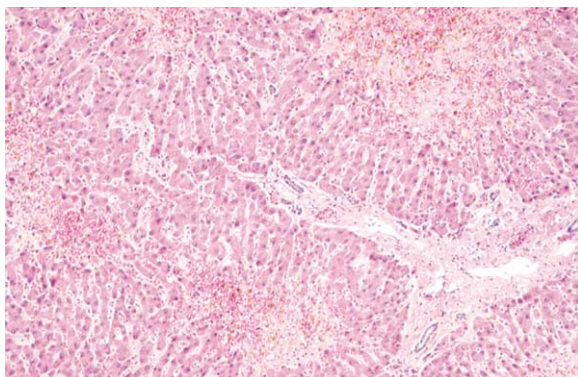

Fig. 5. The liver after acute circulatory collapse, characterized by necrosis without congestion in zone 3, H & E, × 20. (*Courtesy of* F. Graeme-Cook, MD, Massachusetts General Hospital, Boston.)

circulatory disturbances are undetected, leading to diagnostic uncertainty, especially in patients with chronic heart failure, in whom the liver is more susceptible to injury from transient reductions in hepatic arterial perfusion [17,41]. Clinical detection of hepatic injury almost always results from the seemingly incidental elevations in liver biochemical tests after a hypotensive episode. Rarely, ischemic hepatitis may present as symptomatic acute hepatitis, with symptoms of nausea, vomiting, anorexia, malaise, right upper quadrant pain, and jaundice [17,48]. Ischemia always should be considered in the differential diagnosis of acute hepatitis, along with more common causes, such as viral infection, drug use, toxins, autoimmunity, and metabolic disorders.

Routine use of liver biochemical test panels has been responsible for the increasing recognition of ischemic hepatitis as a clinical entity. The typical pattern in ischemic hepatitis consists of a dramatic and rapid rise in serum aminotransferase levels that is associated with an early massive rise in LDH levels (Fig. 6). Peak aminotransferase levels are typically 25 to 250 times the upper limit of the normal value and are reached within 1 to 3 days of the hemodynamic insult [52]. In the absence of ongoing hemodynamic instability, aminotransferase levels decline steadily, usually returning to normal within 7 to 10 days. The serum bilirubin level rarely increases more than four times the upper limit of the normal value, and its elevation usually occurs after the aminotransferase levels begin to decline. Levels of serum alkaline phosphatase are rarely higher than twice the upper limit of the normal level.

Although the diagnosis of ischemic hepatitis cannot be made definitively on the basis of the pattern of serum liver biochemical tests alone, several features suggest a diagnosis of ischemic rather than viral hepatitis. An early rapid
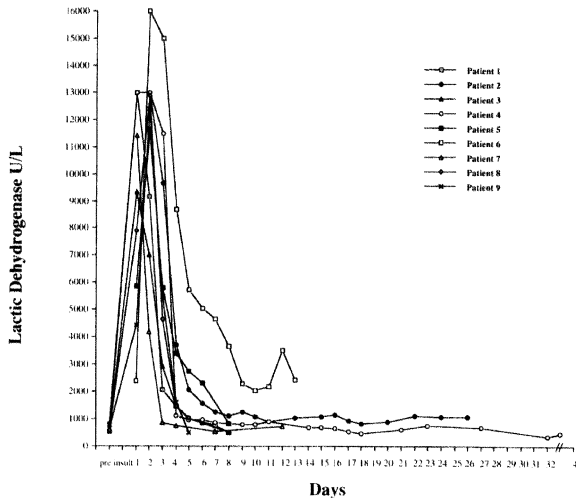

Fig. 6. Pattern of serum LDH levels in ischemic hepatitis after an acute hypotensive episode, showing characteristic rapid increase and decline in levels. (*From* Giltin N, Serio KM. Ischemic hepatitis: widening horizons. Am J Gastroenterol 1992;97:831–6; with permission.)

increase in the serum LDH level is unusual in patients with viral hepatitis, and a ratio of the serum alanine aminotransferase level to the LDH level of less than 1.5 early in the course of acute hepatitis has been reported to favor a diagnosis of ischemic hepatitis [59]. A rapid decrease in serum aminotransferase levels after their initial rise is characteristic of ischemic liver injury and atypical for other causes of hepatitis. Ischemic hepatitis often is accompanied by additional evidence of end-organ hypoperfusion, especially acute tubular necrosis of the kidney. A concomitant, early increase in the serum creatinine level favors a diagnosis of ischemic hepatitis [18,52].

Clinical course

Ischemic hepatitis usually is benign and self-limited. Hepatic synthetic function is impaired only mildly, if at all; specifically, the prothrombin time rarely is prolonged by more than 3 s. Changes in mental status, although frequent, reflect impaired cerebral perfusion that is caused by the underlying cardiac or systemic illness, and do not reflect hepatic encephalopathy. The severity of the liver injury correlates with the duration and extent of the hemodynamic compromise, but overall prognosis is related to the severity of the underlying systemic disease, not the severity of the liver disease [60]. As noted earlier, elevated levels of serum aminotransferase typically resolve spontaneously in 7 to 10 days in the absence of ongoing hypotension. Generally, the liver regenerates and recovers normal function.

Death may result from fulminant hepatic failure in patients with ischemic hepatitis and chronic congestive heart failure [17]. Fulminant hepatic failure also may result in patients with ischemic hepatitis secondary to cirrhosis; this combination is encountered most often in patients with variceal bleeding or sepsis. Because perfusion in a cirrhotic liver is impaired mildly at baseline because of intra- and extrahepatic portosystemic shunting and because hepatic reserve is limited, ischemic hepatitis that complicates cirrhosis is associated with high mortality rates, ranging from 60% to 100% [61,62]. Even in a previously healthy liver, sufficiently prolonged hypotension can result in clinically significant liver failure. In such cases, ischemic hepatitis usually is overshadowed by the underlying condition that led to catastrophic shock.

Treatment

The aim of therapy in patients with ischemic hepatitis is to restore cardiac output and reverse the underlying cause of hemodynamic instability. Overly aggressive diuresis should be avoided in patients with underlying congestive heart failure. Any patient with hemodynamic compromise that is sufficiently severe enough to cause ischemic hepatitis should be monitored for other signs of end-organ hypoperfusion (eg, acute renal failure, encephalopathy).

There is no specific therapy for ischemic hepatitis. Limited data suggest that intravenous administration of dopamine, at low or high doses, leads to preser-

vation, and perhaps augmentation, of hepatic blood flow. The clinical benefit of such therapy with regard to liver function has not been established [63]. Whether the effect on hepatic blood flow is caused by selective dopaminergic vasodilation of the mesenteric bed, increased cardiac output, or both is unclear. Similarly, augmentation of cardiac output with dobutamine, cardiac afterload-reducing drugs (eg, angiotensin-converting–enzyme inhibitors, hydralazine, sodium nitro-prusside), or an intraaortic balloon pump enhances hepatic perfusion, but the benefit of such therapies on liver function is uncertain. The choice of a pressor agent usually is dictated by the overall hemodynamic condition of the patient and not by the presence of ischemic liver injury. Strategies to minimize the generation of reactive oxygen species after ischemic liver injury have included vitamin C and vitamin E therapy, glutathione, and allopurinol; no data support the routine clinical use of these treatments.

A possible role for arachidonic acid metabolites in hepatic ischemic injury is suggested by the observation that arachidonic acid metabolites are produced and released in other organs during reperfusion injuries (eg, cardiac arrhythmias, sepsis, inflammation, asthma, arthritis). In rat models of liver ischemia–reperfusion, the severity of liver injury can be blunted by diets that include juniper berry oil and fish oil, compared with diets that include linoleic acid [64]. The salutary effect of juniper berry and fish oils is attributed to their ability to inhibit the conversion of linoleic acid to deleterious vasoactive eicosanoids by Kupffer cells, which results in improved hepatic microcirculation. Patients' diets after an episode of ischemic hepatitis may affect their overall clinical course.

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