

# Cardiovascular Diseases and the Liver

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## KEYWORDS

- Congestive hepatopathy • Ischemic hepatitis
- Cardiac cirrhosis

## MACRO- AND MICROCIRCULATION OF THE LIVER

The liver has a rich dual blood supply derived from both the portal and systemic vascular compartments and is well protected against ischemic injury during brief periods of systemic hypotension. Two-thirds of total hepatic blood flow originates from the portal vein and the remainder from the hepatic artery.<sup>1</sup> Blood from these 2 tributaries subsequently mixes within a complex delta of hepatic sinusoids before draining into the hepatic veins, inferior vena cava (IVC), and, ultimately, the right side of the heart. Because portal blood originates from the mesenteric veins, it is nutrient rich with high concentrations of glucose, water-soluble vitamins, amino acids, and triglycerides, but is relatively oxygen deficient. By contrast, blood originating from the hepatic artery contains little nutritive value but provides more than half of the oxygen delivered to the liver.<sup>1</sup>

Although the hepatic lobule is the classic architectural unit of the liver, the acinus model (also known as the Rappaport classification) is a functional hepatic unit that helps to define the complex microcirculation of oxygen and nutrient delivery.<sup>2,3</sup> The hepatic lobule is a hexagonal structure of hepatocytes and sinusoids flanked by 6 portal triads with a single central vein (**Fig. 1A**). By contrast, the portal triad occupies the center of the acinus, with terminal branches of the hepatic vein situated at the periphery (see **Fig. 1B**). In the acinus model, a 3-tiered oxygen and nutrient gradient exists in the hepatic parenchyma with the highest  $PO_2$  and nutrient concentration delivered to the periportal hepatocytes in zone 1. As blood percolates through the sinusoids toward the perivenular region of zone 3, oxygen is extracted and water-soluble nutrients are taken up by the zone 1 and 2 hepatocytes, resulting in the delivery of low-oxygen-tension blood to zone 3. Accordingly, zone 3 is the most susceptible to ischemic injury when hepatic blood flow is diminished.<sup>2,3</sup>

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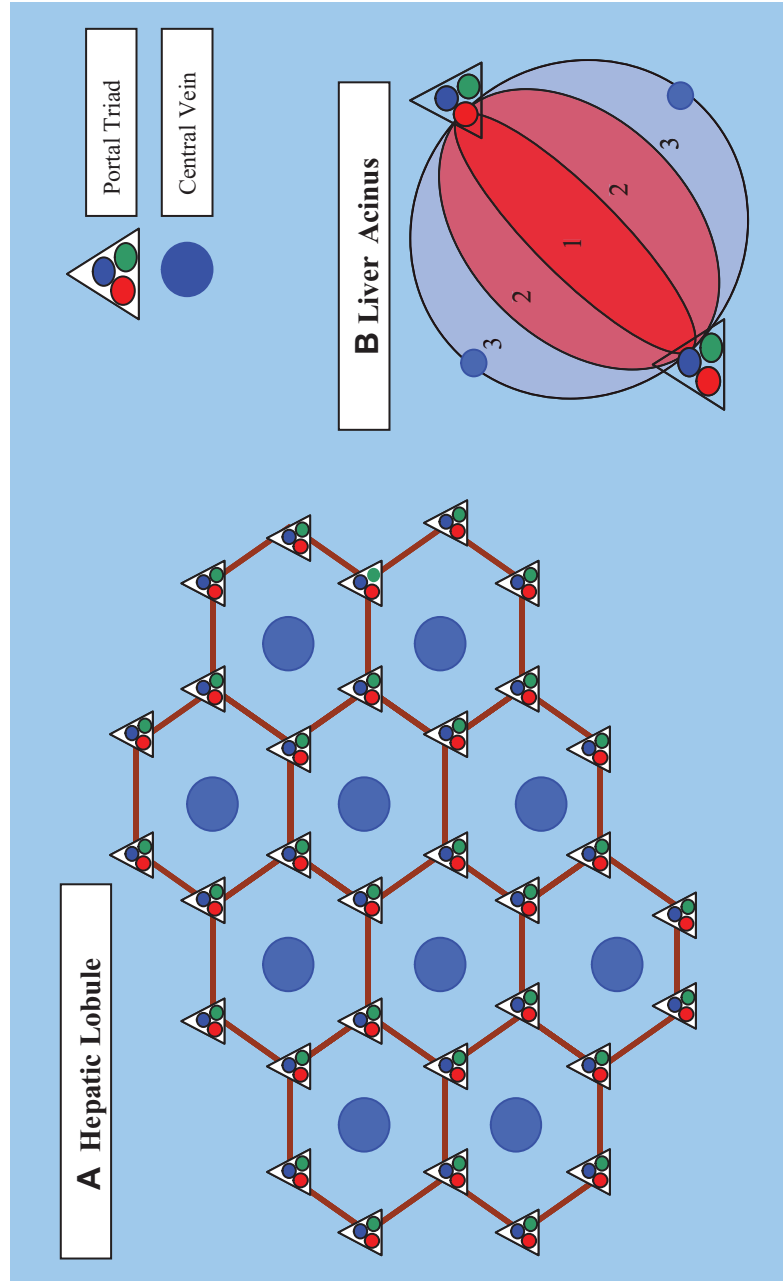
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**Fig. 1.** The hepatic lobule (A) and the Rappaport classification of the liver acinus (B). The portal triad is situated in the periphery of the hepatic lobule, whereas the central vein is located in the middle of the hexagonal structure. By contrast, the portal triad brings oxygen- and nutrient-rich blood to the central area of the acinus (zone 1). As blood flows toward the periphery of the acinus to the central vein, hepatic extraction leads to a nutrient and oxygen tension gradient between zones 1, 2, and 3. (Adapted from Danczyger H. Clinical hepatology: principles and practice of hepatobiliary diseases. Berlin, Heidelberg: Springer-Verlag; 2010, Figs. 3.2 and 3.4; with permission.)

The acinar gradient additionally explains the subdivision of the parenchyma into 3 hepatic microenvironments for specific metabolic and enzymatic activities.<sup>2,3</sup> Zone 1 hepatocytes contain abundant large mitochondria and are responsible for gluconeogenesis,  $\beta$ -oxidation of fatty acids, amino acid and cholesterol synthesis, and bile acid secretion. Dominant processes in zone 3 include glycolysis and lipogenesis.<sup>2</sup>

Total hepatic blood flow is tightly autoregulated by the hepatic artery to maintain a near constant delivery of oxygen and nutrients to the liver.<sup>4</sup> When portal venous inflow is diminished, adenosine levels in the portal triad accumulate, leading to nitric oxide-mediated smooth-muscle relaxation of the hepatic arterioles and increased arterial flow.<sup>5,6</sup> At times of increased portal flow, adenosine concentration is diluted, hepatic arterioles constrict, and arterial flow appropriately decreases. In animal models, infusion of adenosine has been shown to reduce ischemia<sup>7</sup> and attenuate reperfusion injury after liver transplantation.<sup>8</sup> In addition, this hepatic artery buffer system is preserved in patients with advanced liver disease and cirrhosis.<sup>9</sup> Despite this complex system for maintaining adequate blood flow to the liver, in times of cardiovascular compromise these regulatory systems can be overwhelmed and lead to hepatic ischemia, infarction, and congestion.

### ISCHEMIC HEPATITIS

Ischemic hepatitis, sometimes referred to as shock liver or hypoxic hepatitis, refers to the process of diffuse hepatocellular injury after impaired oxygen delivery to the liver. Most commonly, the condition arises in the context of profound systemic hypotension from acute cardiopulmonary collapse after myocardial infarction, exacerbation of congestive heart failure (CHF), or pulmonary embolism. In patients with chronic passive congestion or preexisting portal hypertension, even subclinical circulatory disturbances resulting in impaired hepatic perfusion can give rise to ischemic hepatitis.<sup>10-12</sup> Moreover, ischemic hepatitis in the absence of established hypotension has been shown in instances of severe hypoxemia, such as obstructive sleep apnea<sup>12,13</sup> or respiratory failure,<sup>14,15</sup> and in conditions of increased metabolic activity and oxygen demand, as seen in toxic/septic shock.<sup>12</sup>

The central role of systemic hypotension in the pathogenesis of ischemic hepatitis was recognized more than half a century ago.<sup>16-19</sup> However, because decreased cardiac output, and the reduction of hepatic blood flow that ensues, is a central feature of both ischemic hepatitis and passive congestion, considerable overlap exists between these 2 conditions.<sup>20</sup> Moreover, it is evident that long-standing passive congestion augments the risk of hypoxic injury to zone 3 hepatocytes by promoting edema and fibrosis of the sinusoids to further impair diffusion of oxygen and nutrients. It has been proposed that profound hypotension alone is insufficient to result in the constellation of findings seen in ischemic liver injury without some element of hepatic venous congestion. Seeto and colleagues<sup>21</sup> compared 31 cases of documented ischemic hepatitis with 31 control patients with hemorrhagic shock after major trauma and free of primary liver disease or traumatic injury, many of whom had no recordable blood pressure for greater than 20 minutes. No patients in the traumatic shock group developed ischemic hepatitis although mild increases in the aspartate aminotransferase (AST) ( $78 \pm 72$  IU) and alanine aminotransferase (ALT) ( $51 \pm 55$  IU) levels were observed. More importantly, all cases of ischemic hepatitis had underlying cardiac disease, with 29 of 31 (94%) showing evidence of right heart failure. These data reinforce the protective dual blood supply of the liver and further the suggestion that passive congestion may predispose hepatocytes to hypoxic injury.<sup>20,21</sup>

### ***Incidence***

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The term shock liver was first coined by Birgens and colleagues<sup>22</sup> in 1978 to describe just 5 cases accrued over 13 years from several Danish hospitals. Similarly, Bynum and colleagues<sup>10</sup> first used the term ischemic hepatitis in 1979 to describe only 7 cases identified in 5 years. These early reports created the false impression that this condition is a rare clinical entity. Contemporary studies have shown that the incidence of ischemic hepatitis approaches 0.3% of all inpatient admissions,<sup>23,24</sup> 1% to 2% of all intensive care unit admissions,<sup>12,24,25</sup> 3% of cardiac care unit admissions,<sup>26</sup> and 22% of cardiac care unit admissions with decreased cardiac output.<sup>26</sup> Recent evidence suggests that these numbers may be even higher in elderly patients.<sup>27</sup> Moreover, several studies evaluating the cause of massive increase in aminotransferase level in the inpatient setting have established ischemic hepatitis as the cause in more than 50% of cases.<sup>28,29</sup>

### ***Clinical Features***

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The diagnosis of ischemic hepatitis is largely clinical and is defined by well-established criteria: (1) appropriate clinical setting of cardiac, circulatory, or pulmonary failure; (2) massive, transient increase in aminotransferase levels, usually to more than 20 times the upper limit of normal; and (3) exclusion of other known causes of liver damage. Liver biopsy is not required, nor is it advised, if these 3 conditions are met.

Patients with ischemic liver injury tend to be older (mean age 71 years), predominantly male, and acutely ill in the intensive care setting.<sup>12</sup> The hallmark finding of ischemic hepatitis is a massive increase in AST, ALT, and lactate dehydrogenase (LDH) levels 1 to 3 days after an episode of systemic hypotension. With return of hemodynamic stability, these values peak 1 to 3 days later and return to normal within 7 to 10 days. Increases in LDH level tend to be massive and an ALT/LDH ratio of less than 1.5 often distinguishes ischemic injury from other forms of acute hepatitis.<sup>30,31</sup> Total bilirubin level is usually increased as well, rarely more than 4 times the upper limit of normal, and tends to peak after the transaminases and LDH levels begin to decline. Alkaline phosphatase levels may be normal or mildly increased, but rarely more than 2 times the upper limit of normal. Increases in international normalized ratio (INR), a marker of hepatic synthetic function, are uncommon yet seen in cases of severe ischemic injury. The effects of systemic hypoperfusion are not isolated to the liver, and increases in creatinine level from acute tubular necrosis are nearly universal early in the clinical course.

Although there are no unique physical examination findings, some patients show tenderness to palpation in the right upper quadrant. Changes in mental status, when present, more often represent cerebral hypoperfusion and hypoxia rather than hepatic encephalopathy, although cases of hyperammonemia have been described. Recently, it has been suggested that a proportion of patients show transient intrapulmonary shunting, similar to hepatopulmonary syndrome, which may contribute to or exacerbate arterial hypoxemia.<sup>32</sup>

It is critical to consider and exclude other common and potentially treatable causes of acute hepatitis, most importantly viral hepatitis and toxin- or drug-induced liver injury.<sup>10</sup> A reasonable evaluation includes taking a careful medical history, serologic testing for hepatitis A, B, and C, a serum acetaminophen level, and when clinically indicated, evaluation for Wilson disease and autoimmune hepatitis. Doppler sonogram of the right upper quadrant is easily performed to evaluate patency of the portal and hepatic veins.

### ***Histopathology***

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In the truest sense of the word, the term hepatitis is a misnomer because histologic evidence of inflammation is absent. Instead, the sine qua non of ischemic injury is centrilobular necrosis of zone 3 hepatocytes.<sup>12,16–18,20–22</sup> Simultaneous signs of sinusoidal congestion are common (see next section). In the absence of coexistent underlying liver disease or long-standing congestive hepatopathy, fibrosis is characteristically absent. The pattern of injury usually resolves spontaneously, with regeneration of hepatocytes and a return to normal histologic architecture in most patients.

### ***Treatment***

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No specific therapy exists for ischemic hepatitis, as such. Treatment is directed toward correction of the underlying circulatory or respiratory disturbance. To improve hepatosplanchnic blood flow, infusion of renal-dose dopamine has been suggested,<sup>33</sup> but to date no proven clinical benefit has been shown. Adenosine infusion has been used in animal models but there are no human data to support its use in patients. Similarly, other investigators have suggested a role for administration of antioxidants<sup>20</sup> or N-acetylcysteine.<sup>34</sup> However, these findings are limited to case reports and need to be corroborated before any general recommendations can be made.

### ***Prognosis***

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For most patients, ischemic hepatitis follows a benign and self-limited course, with complete resolution of the aminotransferase to normal values within 3 to 7 days of the inciting event.<sup>21,30,35</sup> However, because ischemic hepatitis mainly occurs in critically ill patients, survival in most series is expectedly poor. In the largest published series to date (142 episodes in 10 years of surveillance), the 1-month and 1-year survival was only 53% and 28%, respectively.<sup>12</sup> Similarly, in a recent survey of 31 historical case series published between 1956 and 2002, in-hospital mortality was 52%.<sup>12</sup> Recently, a report of 117 patients in Vienna documented a 72% overall mortality, with risk factors for death including underlying cause (sepsis), duration and severity of the ischemic event, and increased baseline sequential organ failure assessment scores.<sup>36</sup> Although increased values of aminotransferases, LDH, and INR were observed in nonsurvivors, nearly 80% of all deaths were attributed to septic shock, cardiogenic shock, or cardiac arrest, underscoring that survival is directly related to the severity of the underlying cardiopulmonary and circulatory disease.

Although fulminant hepatic failure has been reported after ischemic injury, it is rare and seems to be restricted to patients with long-standing CHF and cardiac cirrhosis<sup>11</sup> or other forms of chronic liver disease. In particular, patients with portal hypertensive bleeding after a variceal hemorrhage are at risk, and in this setting the mortality has been estimated to exceed 60%.<sup>37,38</sup>

## **CONGESTIVE HEPATOPATHY**

Congestive hepatopathy refers to the spectrum of chronic liver injury attributed to passive hepatic congestion that arises in the setting of right-sided heart failure or any cardiopulmonary disease leading to increased central venous pressure (CVP).<sup>39,40</sup> Sherlock's seminal work on the topic published in 1951<sup>39</sup> still holds as the standard reference on the condition. Common causes include right ventricular infarction, biventricular failure from cardiomyopathy, severe pulmonary hypertension, cor pulmonale, constrictive pericarditis, and valvulopathies such as mitral stenosis and tricuspid regurgitation (TR). Incompetence of the tricuspid valve is particularly prone to result in passive congestion because pressure from the right ventricle is

transmitted directly to the hepatic veins and sinusoids.<sup>39</sup> Untreated, long-standing congestion can lead to cardiac fibrosis and, ultimately, cardiac cirrhosis.

### ***Incidence***

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The incidence of congestive hepatopathy, significant fibrosis, or cardiac cirrhosis is difficult to estimate because the condition is often subclinical and typically remains undiagnosed. However, depending on the definition and type of abnormality considered, range estimates of 15% to 65% in patients with significant heart failure have been reported.<sup>41–44</sup> The few available histologic studies evaluating the incidence of fibrosis after long-standing congestion are replete with selection bias because only those patients with clinically apparent disease (ascites, lower-extremity edema) and severe perturbations in liver function tests, or those undergoing evaluation for cardiac transplantation, are likely to be investigated.<sup>41,45</sup> Nonetheless, by today's accounts, cardiac cirrhosis is rare. Meyers and colleagues<sup>41</sup> investigated liver histology in a diverse population of 83 patients with heart failure and found that the presence of congestive changes was apparent in nearly all specimens; however, significant fibrosis associated with architectural distortion was present in 19% and only one individual had cirrhosis. In a series of 59 patients with severe heart failure awaiting cardiac transplant or left ventricular assist device (LVAD) placement, congestive changes and sinusoidal dilation were near universal.<sup>45</sup> In addition, most (~80%) had evidence of hepatic fibrosis with 26%, 17%, 28%, and 19% showing stage 1, 2, 3, and 4 (cirrhosis), respectively. The capacity to generalize from these values to better-compensated patients with CHF is not clear, and additional studies are warranted to ascertain the true incidence and prevalence of congestive liver damage.

### ***Clinical Feature***

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Patients with congestive changes are typically asymptomatic and frequently identified only when routine laboratory analysis returns subtle abnormalities in liver function tests.<sup>20</sup> Occasionally, stretching of the hepatic capsule from congestion and hepatomegaly causes patients to report mild, dull pain in the right upper quadrant. Less frequently, patients present with signs of decompensation such as jaundice, ascites, and lower-extremity edema.

On physical examination, evidence of right heart failure is often evident, including jugular venous distension and a hepatjugular reflux. In addition, patients with constrictive pericarditis may display a pericardial knock or the classic Kussmaul sign. Abdominal palpation can reveal massive hepatomegaly with a firm, tender liver edge. In cases of TR, a pulsatile liver is sometimes appreciated and the loss of this pulsatility over time may suggest the progression from long-standing congestion to cardiac cirrhosis. Even in the presence of ascites and lower-extremity edema, splenomegaly is characteristically absent and varices are rarely identified on upper endoscopy.<sup>41,46</sup> This finding can be explained by the fact that varices typically form between the high-pressure portal system and the low-pressure systemic circulation, whereas in cardiac cirrhosis no pressure gradient exists because pressure is increased along the entire route of venous return to the right heart.<sup>41</sup>

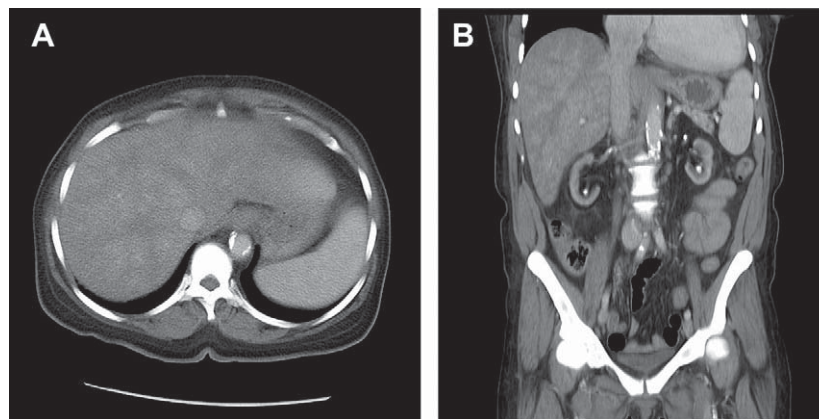
Routine laboratory testing typically reveals mild, nonspecific increase in the serum aminotransferase level, rarely greater than 2 to 3 times the upper limit of normal.<sup>39,40,47,48</sup> The total bilirubin level is only mildly increased (<3 mg/dL) and predominantly unconjugated. Increases in bilirubin level have been shown to correlate with the severity of right atrial pressure and passive congestion<sup>39,48</sup> and in patients with severe right ventricular failure can become jaundice.<sup>40</sup> Even with jaundice, alkaline phosphatase level is normal or only mildly increased, which helps distinguish

congestion from biliary tract disease. However, the investigators have seen exceptional cases in which more impressive increases in ALT or disproportionately increased alkaline phosphatase levels have been noted. Significant impairment of hepatic synthetic dysfunction is unusual. Although the INR is often increased to around 1.5, serum albumin level is usually normal or only slightly reduced. Although serum ammonia level is occasionally increased, hepatic encephalopathy is not a salient feature of congestive liver disease.<sup>49</sup>

Ascites, when present, should always be evaluated with a diagnostic paracentesis because its distinct profile can assist in the diagnosis of hepatic congestion. Like other conditions of portal hypertension, the serum ascites-albumin gradient (SAAG) is increased ( $>1.1$ ). However, in cardiac ascites the total protein is characteristically increased to greater than 2.5 g/dL.<sup>50,51</sup> This situation is caused by preservation of hepatic synthetic function and the contribution of hepatic lymph to the peritoneal fluid. Sinusoidal congestion leads to the accumulation of protein-rich fluid in the space of Disse, which overwhelms the normal lymphatic drainage system of the liver and leaks into the peritoneal cavity.<sup>1,40</sup>

Congestive changes can readily be seen on cardiac and abdominal imaging.<sup>52-54</sup> Echocardiography often details evidence of right ventricular dysfunction, incompetence of the tricuspid valve, and increase of the right ventricular systolic pressure. Hepatic ultrasound typically shows hepatomegaly with a homogeneous increase in echogenicity throughout the liver and dilation of the suprahepatic veins and IVC. Routine findings on computed tomography (CT) and magnetic resonance (MR) abdominal cross-sectional imaging include hepatomegaly, distension of the IVC and hepatic veins, early reflux of contrast material from right atrium to the IVC, and a heterogeneous mottled-appearing liver parenchyma, often referred to as a mosaic pattern, which corresponds to the nutmeg liver seen on gross inspection (**Fig. 2**). In addition, large patchy areas of poor enhancement are often seen in the periphery of the liver as a result of stagnant blood flow. Additional nonspecific findings such as ascites and pleural and pericardial effusions are frequently reported.

Transjugular assessment of hepatic hemodynamics in patients with congestive liver disease shows an increase in the right-sided cardiac pressures that are transmitted



**Fig. 2.** Typical CT findings associated with congestive hepatopathy seen on axial (A) and coronal (B) cross-sectional imaging include hepatomegaly, distension of the IVC and hepatic veins, and a heterogeneous mottled hepatic parenchyma, resulting in a mosaic pattern of enhancement. (Courtesy of Dr Sophia Kung, Weill Cornell Medical Center, New York.)

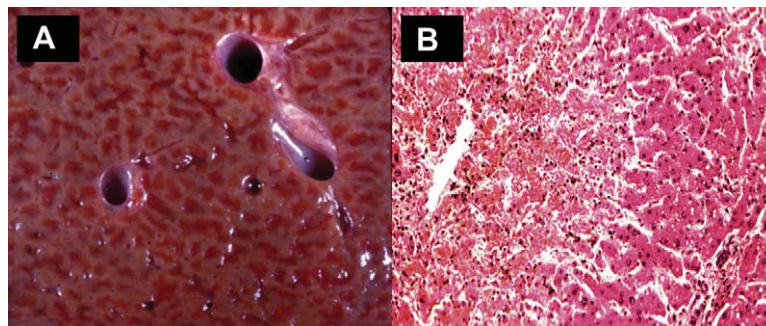
caudad to the hepatic and portal venous circulations.<sup>41</sup> The free hepatic venous and wedged hepatic venous pressures are increased, but characteristically the hepatic to portal venous pressure gradient, which reflects the intraparenchymal contribution to portal hypertension, is normal ( $\leq 4$  mm Hg).<sup>41</sup>

### **Histopathology**

On gross examination (**Fig. 3A**), the congested liver is enlarged, with a purple or reddish hue with prominent hepatic veins. The cut surface shows the classic nutmeg appearance, reflecting the alternating pattern of hemorrhage and necrosis of zone 3 (red in color) with the normal or slightly steatotic areas in zone 1 and 2 (yellow).

Microscopically (see **Fig. 3B**), the hallmark features of hepatic venous hypertension are prominence of the central veins, central vein hemorrhage, sinusoidal engorgement, and fibrosis of the terminal hepatic venules (phlebosclerosis).<sup>39,55,56</sup> Parenchymal fibrosis, when present, circumscribes the central veins and over time can form bridges with adjacent central veins to form discrete nodules (cardiac cirrhosis). Histologically, this is a unique form of cirrhosis because in all other causes of chronic liver disease, cirrhosis arises from portal-portal bridging fibrosis. In addition, the pattern of fibrosis is typically nonuniform, and it has been suggested from autopsy studies that the distribution of fibrosis may be influenced by thrombosis of the portal and hepatic vein branches.<sup>57</sup> Occasionally, discrete nodules can form in the absence of fibrosis as a result of regeneration of hepatocytes in zone 1 of the acinus, resulting in nodular regenerative hyperplasia (NRH).<sup>56</sup> Steatosis and zone 3 iron deposition from chronic hemorrhage<sup>41</sup> are commonly identified as well. Variable degrees of cholestasis are observed, with bile thrombi occasionally seen in cases associated with severe jaundice.<sup>39</sup>

The safety of liver biopsy in the evaluation of congestive hepatopathy has not been well studied and most of the histologic literature comes from older autopsy studies. However, 2 small reports suggest that tissue sampling, particularly when the transjugular route is used, can be performed effectively and safely. Parera and colleagues<sup>58</sup> successfully performed transjugular liver biopsy in 21 of 23 patients (91.3%) with advanced heart failure without any observed complications. Similarly, Gelow and colleagues<sup>45</sup> obtained adequate tissue for staging without any observed complications in all 35 patients in their series. Given the scarcity of organ availability and



**Fig. 3.** The cut surface of the congested liver shows the classic nutmeg appearance caused by passive congestion of central veins with hemorrhage and necrosis in zone 3 (**A**). Congestive hepatopathy results in hepatocellular necrosis surrounding central venules (*left*) and preservation of hepatocytes in zones 1 and 2 (**B**) (original magnification  $\times 200$ ). (*Courtesy of Dr Rhonda Yantiss, Weill Cornell Medical Center, New York.*)

convincing data that cardiac patients with cirrhosis perform poorly after heart transplantation, preoperative tissue diagnosis is likely an important component of operative risk stratification and organ allocation.<sup>59,60</sup>

### **Diagnosis**

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The diagnosis of congestive liver disease should be suspected in any patient with abnormal liver tests and a clinical picture of CHF or increased CVP. Routine serologic evaluation for other causes of viral and metabolic liver disease should be performed to exclude primary hepatic disease, as clinically indicated. An additional important consideration is to exclude those liver diseases commonly associated with cardiomyopathy, such as hemochromatosis, sarcoidosis, and infiltrative amyloidosis. Sources of additional supportive data include abdominal cross-sectional imaging and ascites fluid analysis. Liver histology and hepatic hemodynamic data can provide support in equivocal cases, establish the severity of fibrosis, and evaluate for concomitant hepatic disorders. The best support of the diagnosis is the improvement of liver function with treatment of the underlying cardiac condition.

### **Treatment**

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The cornerstone of management is to treat the underlying cardiac disease and improve forward cardiac output, which leads to improvement in liver function tests and reduce ascites. Diuretics should be used with caution to avoid dehydration, hypotension, and hepatic ischemia.<sup>61</sup> Serial large-volume paracentesis can relieve symptoms associated with tense ascites, but over time can lead to protein loss and exacerbate the protein malnutrition commonly seen in patients with advanced cardiac failure. Transjugular intrahepatic portosystemic shunts or peritoneal-venous shunts can worsen the underlying heart failure and are therefore contraindicated in this population. Cautious use of anticoagulants, when indicated, is advised because patients often have a baseline mild increase in INR and are especially sensitive to warfarin and other related compounds.<sup>62</sup>

In patients refractory to medical therapy who are suitable operative candidates, both LVAD implantation<sup>63,64</sup> and cardiac transplantation<sup>65</sup> have been shown to improve and reverse the congestive liver injury associated with the failing heart. In select patients with established cirrhosis, combined heart and liver transplant is a feasible option.<sup>60</sup>

### **Prognosis**

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Over time, hepatic function typically remains stable. Even with the development of cardiac cirrhosis and ascites, patients with congestive hepatopathy rarely develop the sequela of liver disease<sup>39,66</sup> and long-term mortality is dictated by the underlying cardiac disease. Fulminant liver failure has been documented but seems to be restricted to those cases with superimposed ischemic liver injury<sup>11,35,61,67</sup> rather than passive congestion alone. The mortality in such patients is high (>90%) and is nearly always attributable to the underlying heart failure.<sup>11,67</sup>

Several studies have addressed the prognostic importance of liver function abnormalities in predicting short- and long-term outcomes. Batin and colleagues<sup>68</sup> suggested that increases in bilirubin and AST levels correlate with increased mortality. Similarly, in a Japanese chronic heart failure study,<sup>69</sup> total bilirubin, alkaline phosphatase, and  $\gamma$ -glutamyl transferase (GGT) levels were all associated with worsened outcomes. In the subanalysis of a large multinational heart failure study,<sup>43</sup> total bilirubin level was independently associated with increased morbidity and mortality. However, only one study to date has evaluated the relationship between cardiac

hemodynamic parameters, abnormal liver function testing, and clinical outcome.<sup>44</sup> Although, like other investigators, these investigators found increases in AST, alkaline phosphatase, GGT, and LDH levels correlated with increased patient mortality, after adjusting for cardiac index (CI) and CVP, no association between liver function tests and survival was observed. These data reinforce the idea that it is the primary cardiac disease, rather than hepatic dysfunction, that predicts patient morbidity and mortality.

### CONGENITAL HEART DISEASE AND THE LIVER

With advances in pediatric cardiac surgery, many infants born with severe congenital heart defects are living into adulthood.<sup>70</sup> This is particularly the case for those children born with single ventricle malformations such as tricuspid or pulmonary atresia and the hypoplastic left heart syndrome, in which the Fontan procedure can result in near normal growth and development and good quality of life. This surgery diverts blood from the right atrium to the pulmonary arteries and is palliative but not curative because significant long-term complications are known to arise. The ensuing cavopulmonary anastomosis results in increased CVP 3 to 4 times normal, and passive hepatic congestion leading to fibrosis and cardiac cirrhosis is frequently observed. Moreover, reduction in CI and bradycardia leads to ischemic and hypoxic injury to the liver. As a result, these children often develop the same constellation of clinical findings, including abnormal liver function tests, ascites, and coagulopathy, as seen in adult patients with biventricular heart failure.<sup>71-74</sup> Management, as in adults, relies on restoration of cardiac output and relieving hepatic venous congestion and often requires cardiac transplantation. In addition, patients with cardiac cirrhosis should be surveyed at regular 6-month intervals with contrast-enhanced abdominal imaging of the liver and serum  $\alpha$ -fetoprotein, similar to other causes of cirrhosis,<sup>75</sup> because at least 3 cases of hepatocellular carcinoma have recently been reported in this population.<sup>70,76</sup>

### HEATSTROKE AND HEAT-RELATED DISORDERS OF THE LIVER

Heat stroke is the severe multisystem disorder that occurs with failure or overload of the thermoregulatory system of the body.<sup>77</sup> It is characterized by hyperthermia (core body temperature  $>40^{\circ}\text{C}$ ), neurologic impairment ranging from mild confusion to coma, and systemic hypotension. It represents the most serious of the heat-related disorders and without prompt and appropriate medical therapy can rapidly lead to multiorgan failure, disseminated intravascular coagulation (DIC), sepsis, and death.<sup>77-79</sup>

Broadly, heat stroke is classified into 2 categories that differ with regards to their cause and epidemiology, but are similar in terms of their clinical presentation and management.<sup>78</sup> Exertional heat stroke typically occurs in young, otherwise healthy individuals after intense exercise (ie, marathon runners, soldiers). The classic variety, by contrast, tends to involve elderly and chronically ill patients in times of extreme environmental heat exposure. Medications and illicit drugs that interfere with the thermoregulatory homeostasis of the body (eg,  $\beta$ -blockers, diuretics, cocaine) can augment the risk of heat stroke.<sup>77,78</sup>

#### *Incidence*

The reported incidence of heat stroke varies greatly by data source. Globally, outdoor laborers are the group most affected, but in the United States elderly inner-city residents with poor access to air conditioning and cognitive obstacles to self-care are at the greatest risk (10/100,000 individuals).<sup>78</sup> Each year, 240 deaths in the United States are attributed to heat stroke. In addition, epidemic heat stroke frequently arises

with dramatic increases in rates of emergency room (ER) visits, hospital admissions, and patient mortality.<sup>80,81</sup> For example, during the Chicago heat wave in 1995, more than 3300 excess ER visits and an excess of 600 deaths were attributed to heat-related disorders.<sup>81</sup>

### ***Clinical Features***

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In times of thermal stress, cardiac output and minute ventilation are markedly increased. However, to facilitate heat dissipation by the skin, splanchnic blood flow is reduced<sup>82</sup> and blood flow is shunted away from core vital organs to the peripheral vasculature, which leads to impaired visceral perfusion and hypotension. Ischemic injury to intestinal mucosa promotes bacterial translocation, leading to endotoxemia and sepsis, and may account for many of the hematologic changes resembling DIC that are commonly identified.<sup>83</sup> Renal failure from massive rhabdomyolysis is frequently observed.

Mild to moderate hepatic injury is a common feature in nearly all patients with heat shock and is explained by 2 distinct mechanisms.<sup>84,85</sup> The severe systemic hypotension results in classic ischemic/hypoxic injury to zone 3 hepatocytes in the liver. In addition, excessive body temperature leads to direct thermal injury and hepatic necrosis.<sup>84,85</sup> The result is a profound increase in serum aminotransferase values and LDH levels. Although the ALT level is rarely increased more than 20 times the upper limit of normal, the AST level can be massively increased as a result of concomitant injury to skeletal and cardiac muscle, brain, and kidneys. Rarely, massive hepatocellular damage and acute liver failure are observed.<sup>86–89</sup> As in ischemic hepatitis, the aminotransferase levels peak 1 to 2 days after the inciting event. However, recovery takes a more protracted course, occurring over several weeks. Total bilirubin level is frequently normal or only mildly increased.

Physical examination findings are nonspecific, and a high index of suspicion is required to promptly make a diagnosis of heat shock and initiate appropriate therapy.<sup>77,78</sup> Affected patients present with hyperpyrexia, with core body temperatures ranging from 40 to 44°C (104–111.2°F) and signs of central nervous system (CNS) dysfunction (irritability, ataxia, confusion, seizure, coma). Additional findings may include hot dry skin, variable degrees of tenderness in the right upper quadrant, bleeding from sites of venipuncture, epistaxis, melena, or hematochezia. As a result of systemic endothelial damage, peripheral and pulmonary edema is commonly observed.

### ***Histopathology***

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The pattern of liver injury suggests both direct thermal injury and hypoxic damage.<sup>79,90,91</sup> Evidence of ischemic hepatitis is apparent, with centrilobular dilatation of sinusoids and zone 3 necrosis, whereas heat-mediated degenerative changes to hepatocytes ranging from basophilia to necrosis are evident. Additional common features include steatosis, vacuolization, and cholangiolar proliferation. In survivors, these histologic features recover spontaneously without the formation of significant fibrosis.<sup>90,92</sup>

### ***Treatment***

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The mainstay of therapy is rapidly reducing the body temperature to prevent thermal injury to vital organs.<sup>78</sup> External cooling by wetting the skin to promote evaporative heat loss, immersion in an ice bath, or applying ice packs to the axilla and groin should be initiated immediately. After transfer to an intensive care setting, internal cooling with gastric, bladder, or rectal cold-water lavage should be instituted. Hypotension should be treated with appropriate fluid resuscitation with the goal of improving

end-organ perfusion. No pharmacologic therapies have shown any clinical benefit, including muscle relaxants, benzodiazepines, antipyretics, and dantrolene.<sup>77,78</sup>

Liver transplantation has been proposed for individuals with severe liver injury not responding to conservative medical therapy.<sup>85</sup> However, many of the features of acute liver failure are normal findings in heat shock (altered mental status, coagulopathy), making conventional prognostic algorithms such as the Kings College criteria difficult to apply in this clinical context. In addition, the long-term benefit of liver transplant has not been established. By way of example, 16 cases of fulminant liver failure after heat shock have been reported in the literature, only 3 of which were transplanted.<sup>85,88,93,94</sup> Amongst the 13 cases treated medically, 8 (61.5%) survived and 5 (31.5%) died, whereas all 3 of the transplanted patients died. Given these limited results and the fact that patients with massive hepatic necrosis have been shown to recover spontaneously,<sup>92</sup> caution should be applied before listing patients for liver transplant. Although further data are warranted, a single case report showing benefit with the molecular adsorbent recirculating system has been described, suggesting that, where available, liver assist devices may be a useful bridge to patient recovery.<sup>95</sup>

### ***Prognosis***

Heat shock is a true medical emergency, with mortality estimates of 10% to 25%. However, with early and aggressive therapy survival approaches 100%. Nonetheless, fulminant liver failure is observed in at least 5% of cases, and this may be an underestimate of the true risk.<sup>93,96,97</sup> In addition, permanent CNS dysfunction persists in up to 20% of survivors. Prognostic factors for morbidity and mortality have not been elucidated; however, some investigators have suggested that higher levels of aminotransferase and bilirubin,<sup>84</sup> extensive centrilobular necrosis, and persistent renal failure from rhabdomyolysis<sup>85</sup> portend increased risk of death and long-term morbidity. Prevention of heat-related injury is the most effective means to reduce the morbidity and mortality associated with this disorder.<sup>81</sup>

### **VASCULAR DISORDERS OF THE LIVER**

With the exception of portal vein thrombosis in patients with cirrhosis, vascular disorders of the liver are rare.<sup>98</sup> However, 2 uncommon systemic conditions, hereditary hemorrhagic telangiectasia (HHT) and polyarteritis nodosa (PAN), can present with severe hepatic involvement and deserve mention.

#### **HEREDITARY HEMORRHAGIC TELANGIECASIA**

Also known as Osler-Weber-Rendu disease, HHT is a rare autosomal-dominant genetic disease characterized by diffuse mucocutaneous and visceral arteriovenous malformations (AVMs). A mutation in one of 2 genes, endoglin (ENG) and activin receptorlike kinase type 1 (ALK-1), is identified in most affected families. These genes encode for a vascular endothelial transmembrane protein involved in the transforming growth factor pathway.<sup>99,100</sup>

#### ***Incidence***

HHT is said to affect only 10 to 20/100,000 individuals, with approximately 50,000 affected people in the United States. Although hepatic AVMs are observed in 75% of individuals with HHT, they are infrequently symptomatic (<10%)<sup>101-104</sup> and tend to be restricted to families and patients with ALK-1 mutations.<sup>98,105</sup> Fewer than 100 symptomatic cases of liver involvement by HHT have been documented in the English language literature.<sup>102,103</sup>

### ***Clinical Manifestations***

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Symptomatic patients can present with one or more of 3 phenotypic expressions of the disease, including high-output heart failure, portal hypertension, or biliary ischemia. Three distinct types of vascular shunting in the liver help explain the variability in clinical presentation of this disorder: arteriovenous, portovenous, and arterioportal.<sup>102,103</sup>

The most common presentation is heart failure secondary to arteriovenous and portovenous shunting and the resultant hyperdynamic circulation.<sup>98,102,103</sup> Symptomatic patients display typical signs and symptoms of cardiac dysfunction, including fatigue, shortness of breath, reduced exercise capacity, ascites, and extremity edema. Non-cirrhotic portal hypertension from arterioportal shunting or from NRH after variable blood flow to the liver leads to ascites, portal hypertensive gastropathy, and variceal formation. However, because hepatic synthetic function is preserved, hepatic encephalopathy is not a prominent feature. Shunting of hepatic artery blood flow can lead to complications of biliary ischemia, including cholestasis, strictures, and cholangitis. The term hepatic disintegration has been used to describe the extreme presentation of bile duct and liver necrosis that has rarely been documented.<sup>106</sup>

### ***Diagnosis***

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International consensus criteria, the Curacao Diagnostic Criteria, are used to establish a diagnosis of HHT and are based on 4 findings: spontaneous and recurrent epistaxis, multiple mucocutaneous telangiectasias, visceral involvement (gastrointestinal, pulmonary, cerebral, or hepatic), and an affected first-degree relative.<sup>107</sup> When more than 3, 2, or one of the criteria are met the diagnosis is considered to be definite, suspected, or unlikely, respectively. Confirmatory genetic testing for mutations in the ENG or ALK-1 genes is commercially available and can help confirm the diagnosis. Patients with HHT with a typical clinical history should be evaluated for hepatic involvement.

Although angiography is the gold standard, the diagnosis is readily established with noninvasive testing such as Doppler ultrasound and contrast-enhanced CT.<sup>98</sup> Sonographic findings of intrahepatic hypervascularization and a markedly dilated common hepatic artery (>7 mm) have been shown to be highly sensitive and specific for the diagnosis of hepatic HHT.<sup>108</sup> Similar characteristic findings on CT include a dilated hepatic artery and heterogeneity of the hepatic parenchyma.<sup>109</sup> Nodularity secondary to NRH is often misinterpreted as cirrhosis. Liver biopsy is not required to make the diagnosis and should be avoided because of increased risk of complications related to bleeding.<sup>98,102,103</sup>

### ***Treatment***

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No specific treatment is indicated for asymptomatic liver involvement by HHT and therefore screening for hepatic involvement in these individuals is not indicated. Symptoms of high-output cardiac failure should be managed like other patients with CHF from more typical causes (eg, salt restriction, diuretics,  $\beta$ -blockers). Similarly, complications from portal hypertension should be managed in accordance with guidelines for cirrhotic patients.<sup>98,102,103</sup> To avoid cholangitis, invasive biliary procedures should generally be avoided in patients with the biliary ischemic phenotype, and early initiation of antibiotics should be used for signs of biliary sepsis.

Case reports of surgical ligation and transarterial embolization of the hepatic artery have been described for control of medically refractory cases of high-output heart failure and portal hypertension. However, this approach is strongly unadvised because benefits are modest, transient at best, and associated with serious

morbidity and mortality from the ensuing biliary ischemia and necrosis.<sup>98,102,103</sup> Garcia-Tsao<sup>102</sup> recently reported that more than one-third of patients undergoing this intervention developed serious complications leading to rescue liver transplantation or death.

The only definitive curative treatment of hepatic HHT is liver transplantation. A recent report from the European transplant registry of 40 patients with HHT documented excellent overall 5-year survival (80%), although patients with the portal hypertensive phenotype seem to perform slightly worse (63% survival at 47 months).<sup>103,110</sup> Symptomatic patients with hepatic HHT should be considered for Model for End-Stage Liver Disease exception points and given priority for liver transplantation because their laboratory parameters may inadequately represent their risk of morbidity and mortality from heart failure and other complications.<sup>111</sup>

Medical therapies with thalidomide and hormone-based therapies have had mixed results in the management of gastrointestinal bleeding from HHT. Recently, case reports using bevacizumab, an antibody to vascular endothelial growth factor with antioangiogenic properties, has been shown to reduce complications of portal hypertensive bleeding<sup>112</sup> and reduce the need for liver transplantation in a patient with heart failure.<sup>113</sup> Although these initial results are promising, more experience with this agent is needed before general recommendations can be made for its use in symptomatic patients with HHT.

#### **POLYARTERITIS NODOSA**

PAN is a systemic necrotizing vasculitis that results in immune complex deposition in small and medium-sized arteries, resulting in segmental necrotizing lesions, arterial stenoses and aneurysms, and tissue ischemia. The kidneys, muscles, skin, peripheral nervous system, and gastrointestinal tract are the most commonly involved, but any organ can be affected. Although rare, case reports of hepatic involvement have been described.<sup>114–117</sup>

##### ***Incidence***

PAN is rare, affecting only about 2 to 33 cases per million individuals. The incidence increases with age and peaks in middle age. It is not possible to estimate the frequency of liver involvement because there are fewer than 20 reports in the literature of hepatic complications of PAN.<sup>114–117</sup> Although most cases of PAN are idiopathic, a clear association between chronic infection with hepatitis B virus (HBV) and hepatitis C virus exists, and universal HBV vaccination and improved blood donor screening have already led to a dramatic reduction in the frequency of this rare extra-hepatic manifestation.<sup>118</sup>

##### ***Clinical Manifestations***

Symptoms of PAN are nonspecific, with fever and lethargy being the most common presentation. Hepatic or gall bladder involvement is usually accompanied by abdominal pain, nausea, and vomiting. In more severe cases, patients can present with massive hepatic infarction,<sup>115,116</sup> hepatic abscess,<sup>114</sup> and cholecystitis.<sup>115</sup> In addition to laboratory values reflecting chronic hepatic ischemia, there is evidence of leukocytosis and the C-reactive protein and erythrocyte sedimentation rate are frequently increased. Diagnosis is confirmed when biopsy of affected tissues reveals necrotizing arteritis or when the typical pattern of arterial stenosis and aneurysmal dilation is seen on angiography. Noninvasive imaging with MR or CT arteriography may miss small vascular changes and may not be diagnostic.

### **Treatment**

The goal of treatment is to rapidly suppress inflammation and end-organ damage.<sup>118</sup> Without appropriate therapy, 5-year survival is less than 15%. For systemic disease, treatment with corticosteroids plus cyclophosphamide, methotrexate, or azathioprine is often used. In cases of HBV-associated PAN, plasma exchange to reduce antigenic excess and suppression of HBV viremia with antiviral agents facilitates induction and long-term maintenance of PAN remission.<sup>118</sup>

### **SUMMARY**

The dual blood supply of the liver provided by branches of the hepatic artery and the portal vein makes it relatively protected from ischemic injury. Nonetheless, minor or brief disruptions in cardiac output and hepatic perfusion, particularly in patients with underlying right or left heart failure, can result in ischemic liver damage. Similarly, conditions that lead to impaired venous return to the heart, when long-standing, may result in passive hepatic congestion, fibrosis, and rarely cardiac cirrhosis. Together, ischemic hepatitis and congestive hepatopathy represent 2 of the commonest indications for a hepatology consultation in the inpatient and outpatient setting and can serve as a framework to understand less common conditions such as heatstroke, congenital heart disease, and vascular disorders of the liver. Management is largely supportive, with care directed at correction of the inciting cardiac event. Although liver function typically resolves spontaneously in most cases, prognosis is dictated by the severity and reversibility of cardiac dysfunction.

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