Heart diseases affecting the liver and liver diseases affecting the heart

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Background The association of cardiac and liver disorders has not been extensively outlined in the literature.

Methods A survey of the MEDLINE database was performed to assess the current status of research regarding the association between cardiac and liver disorders.

Results Combined cardiac and hepatic disorders occur in 3 different settings: heart diseases affecting the liver, liver diseases affecting the heart, and cardiac and hepatic disorders with joint etiology. The spectrum of heart diseases affecting the liver includes mild alterations of liver function tests in heart failure, cardiogenic ischemic hepatitis, congestive liver fibrosis, and cardiac cirrhosis. The liver diseases affecting the heart include complications of cirrhosis such as hepatopulmonary syndrome, portopulmonary hypertension, pericardial effusion, and cirrhotic cardiomyopathy as well as noncirrhotic cardiac disorders such as high-output failure caused by intrathoracic arteriovenous fistulae. Cardiac and hepatic disorders with joint etiology include infectious, metabolic, immune, vasculitic, and toxic disorders. We propose a practical approach to a diagnostic workup of combined cardiac and hepatic disorders based on recognizing the sequence of appearance of the cardiac and liver disease, presence of features of a multisystem disease, and presence of pathognomonic features. The evaluation of combined cardiac and hepatic disorders takes into consideration the expected benefit of treatment and the risks related to invasive procedures. Accordingly, investigations can be limited to ancillary tests for patients with congested liver and mild alterations of liver function tests, in cardiogenic ischemic hepatitis, patients with cardiac cirrhosis who are proposed for conservative treatment, and multisystem disease involving the heart and the liver. Conversely, comprehensive investigations are recommended when invasive therapeutic interventions are considered for the treatment of hepatopulmonary syndrome, portopulmonary hypertension, or arteriovenous fistulae.

Conclusion Classification of a patient to any of the 3 categories—heart diseases affecting the liver, liver diseases affecting the heart, and cardiac and hepatic disorders with joint etiology—permits the physician to narrow the span of the possible diagnoses and allows for a more simple workup. (Am Heart J 2000;140:111-20.)

The association of cardiac and liver disease can occur in 3 different settings: hepatic complications of heart failure, cardiac complications of liver disease, and cardiac and hepatic damage with joint etiology. The association of cardiac and liver disorders has not been comprehensively outlined in textbooks of cardiology, liver diseases, or internal medicine. This paper provides an overview on disorders involving both the heart and the liver and proposes a practical and simplified way of diagnosis.

Heart diseases affecting the liver

Hepatic complications of heart failure comprise a spectrum of combined cardiac and hepatic disorders (Table I).

Mild alteration of liver function tests in congestive heart failure

The congested liver is usually enlarged and firm, often associated with slight enlargement of the spleen. Features of portal hypertension are usually not present. Modest elevations of aspartate aminotransferase (ALT), alanine aminotransferase (AST), lactate dehydrogenase (LDH), gamma-glutamyl transferase, alkaline phosphatase, and total bilirubin as well as small decreases in albumin levels are often noticed in patients with passive hepatic congestion, reduced hepatic perfusion, or both.1,2 Liver function abnormalities are most commonly seen in patients with a cardiac index less than 1.5 L/min per m2 (up to 80% of cases) and uncommon among patients with a higher cardiac index.2 In
In general, these enzyme abnormalities are not associated with clinically apparent hepatic disease, are fluctuating, and resolve with compensation of heart failure. Mild jaundice occurs in one third of the patients. Jaundice increases with prolonged and repeated bouts of congestive heart failure.1,2

**Cardiogenic ischemic hepatitis**

The rapid and marked elevation of serum transaminase levels in the setting of an acute fall in cardiac output is called cardiogenic ischemic hepatitis (IH).1,3 The term “ischemic” hepatitis is a misnomer because ischemic liver injury is characterized by centrilobular necrosis in the absence of inflammation. However, no other designation for this syndrome has been accepted in the literature. Cardiogenic IH does have similarities with IH precipitated by noncardiac causes.4,5

**Cause and pathogenesis.** The liver is a highly vascular organ receiving approximately 20% of the cardiac output. Seventy percent of the hepatic blood flow is derived from the portal system, and the other 30% is delivered by the hepatic artery, which expresses a linear relation between the blood pressure and blood flow. The liver can maintain normal oxygen uptake by increasing oxygen extraction, with as much as 95% of the oxygen from the blood being extracted in a single pass through the liver.6 This remarkable compensatory mechanism most probably accounts for the low incidence of liver damage in shock. Nevertheless, when hypotension is persistent, visceral flow is critically reduced, or severe hypoxemia develops, the mechanisms protecting the liver against hypoxic liver damage are overwhelmed. Accordingly, IH may occur in the setting of overt cardiogenic shock in patients without preexistent heart failure, or IH may occur because of an acute decline in cardiac output in the absence of hypotension if the patients have underlying severe heart failure. Only rarely does cardiogenic IH emerge in a patient with chronic congestive heart failure without an obvious triggering event. This could possibly be related to an unperceived arrhythmia, silent coronary event, or transient hypotension.7 Although the cardiac cause is as a rule evident, the appearance of the syndrome is, nevertheless, unpredictable. Among patients who had numerous episodes of pulmonary edema, the duration and severity of pulmonary edema was not related to the subsequent occurrence of IH. Likewise, neither antecedent hepatic or renal derangement, nor suspected triggering factors such as medications, hypovolemia, hyponatremia, and intercurrent infections, were more prevalent in the IH group.8

**Clinical presentation.** In the setting of the coronary intensive care unit, IH occurs during the course of myocardial infarction complicated by cardiogenic shock. More often, the diagnosis is established in a different clinical setting in patients admitted to the medical ward. The typical patient has a protracted course of congestive heart failure (New York Heart Association class III or IV). After recovery from an episode of pulmonary edema that seemed similar to many previous attacks, the IH is unexpectedly revealed after a latency period of 2 to 24 hours. Symptoms at the onset of IH include weakness and apathy; in a minority of cases, mental confusion, jaundice, oliguria, flapping tremor, and hepatic coma may be present. Laboratory abnormalities at the time of IH include a sharp elevation of the serum ALT, AST, and LDH (usually more than 10 times the normal values), elevation of serum bilirubin, and prolongation of the prothrombin time. In addition, a minority of patients have consumption coagulopathy developed, which is more often clinically silent and is diagnosed on the basis of laboratory abnormalities: prolonged partial thromboplastin time and prothrombin time, low fibrinogen levels, elevated fibrin-fibrinogen degradation products, and thrombocytopenia. Occasionally, a functional renal impairment, with or without oliguria, appears with the IH. It shows an abrupt increase in blood urea nitrogen, creatinine, and potassium, low urine volume, and a normal urinary sediment.7 In survivors, the abnormalities of the hepatic, coagulation, and renal function tests reach their peak 1 to 3 days after the onset of the cardiogenic IH and return to normal within 5 to 10 days from onset of the disorder.4,8

**Diagnostic testing.** The diagnosis of IH is made when, in the appropriate context, a sharp increase in serum aminotransferase activity between 10 and 20 times the upper limit of normal occurs and is followed by a more than 50% decrease within 72 hours if the causative disturbance has been eliminated. This characteristic time course of the biochemical alterations differentiates IH from viral, alcoholic, or drug-induced hepatitis (Table II).4,9 Currently, there is no specific test to differentiate IH from drug-induced liver damage. It may have practical importance that the ALT/LDH ratio in IH and viral hepatitis is significantly less than for acute acetaminophen hepatitis. When the fold increase (fi) of the enzymes was
Congestive liver fibrosis and congestive cirrhosis (cardiac cirrhosis)

Congestive liver fibrosis (CLF) is a clinically silent disorder characterized by a spectrum of morphologic alterations in the liver ranging from mild deposition of sinusoidal collagen to emergence of broad fibrous septa. The presence of extensive fibrosis in association with the formation of regenerative nodules is called cirrhosis. Focal cirrhosis, incomplete cirrhosis, and complete cirrhosis are variants of cardiac cirrhosis (CC). CC is currently quite rare in the United States. The chief causes of CC include cardiac cirrhosis (31%), cardiomyopathy (23%), valvular heart disease (23%), restrictive lung disease (15%), and pericardial disease (8%).

Pathogenesis. CLF and CC are thought to be the reaction of the hepatic stroma evoked by increased venous pressure, hypoxia, or hepatocellular necrosis. Still, it is not clear why the degree of fibrosis varies from one region of the liver to the other and why similar degrees of heart failure cause CLF in some patients but not in others. Recently, the role of thrombosis in the pathogenesis of CLF and CC was demonstrated. On the basis of a study of autopsy livers, it was shown that the distribution of liver fibrosis correlates with the distribution of fibrous obliteration of hepatic and portal veins caused by organized thrombosis. It has been suggested that propagation of thrombosis into medium-sized hepatic veins causes necrosis of the hepatic parenchyma and intensifies stasis in the hepatic sinusoids that, in turn, promotes the sinusoidal thrombosis, fibroblast activation, and collagen deposition.

Clinical presentation. The presentation of CC is usually masked by symptoms and signs of right-sided heart failure. In the majority of patients, ALT, AST, alkaline phosphatase, bilirubin, and albumin levels are within the normal range. Occurrence of cardiac ascites is the hallmark of CC. An occasional patient has ascites of unknown cause while the existence of a cardiac disease has not been previously recognized. The ascitic fluid protein content is usually ≥2.5 g/dL and is probably a manifestation of the relatively high serum protein level in these patients. The high serum ascites albumin gradient of 1.1 g/dL or more in cardiac ascites is common with other disorders characterized by portal hypertension (Table III).

However, cardiac ascites is relatively unique in that it is characterized by high protein content and a high serum ascites albumin gradient. In the case of infected cardiac ascites, the high serum ascites albumin gradient is preserved. The ascitic fluid, LDH, and red cell count are significantly higher than in cirrhotic ascites of other

<table>
<thead>
<tr>
<th>Table II. Differential diagnosis of hepatitis in patients with congestive heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mild, asymptomatic, reversible increase of one or several liver function tests: AST, ALT, bilirubin, alkaline phosphatase</td>
</tr>
<tr>
<td>2. Cardiogenic IH, mainly a “laboratory syndrome”; Abnormalities within a few hours of an acute cardiac event, sharp increase in AST and ALT to 10- to 20-fold normal levels followed by a &gt;50% decrease within 72 hours</td>
</tr>
<tr>
<td>3. Shock liver—similar to IH, complicates severe arterial hypotension of various causes</td>
</tr>
<tr>
<td>4. Common variants of hepatitis: drug-induced hepatotoxicity, alcoholic hepatitis, viral hepatitis</td>
</tr>
<tr>
<td>5. Jaundice after cardiac surgery: very high levels of AST and ALT may occur by the second postoperative day</td>
</tr>
</tbody>
</table>
High serum ascites albumin gradient (≥1.1 g/dL)
- Cardiac ascites
- Budd-Chiari syndrome
- Alcoholic hepatitis
- Fulminant hepatic failure
- Hepatic veno-occlusive disease
- Massive liver metastases
- Myxedema

High ascitic protein level (≥2.5 g/dL)
- Cardiac ascites
- Cirrhotic ascites after diuretic treatment
- Malignant ascites
- Peritonitis
- Infected ascites occasionally

High serum ascites albumin gradient and high ascitic protein
- Cardiac ascites
- Cirrhotic ascites after diuretic treatment
- Infected cirrhotic ascites occasionally

causes, although cardiac ascites is not visibly bloody.\textsuperscript{19} Hepatic synthetic function is usually preserved with normal plasma albumin and prothrombin time.

**Diagnostic testing.** Right heart failure, restrictive cardiomyopathy, or constrictive pericarditis may induce hepatic congestion with or without CC. In either situation, cardiac ascites may be present.\textsuperscript{18,21} Portal flow studies and liver biopsy may help establish the diagnosis of the hepatic disorder associated with any of the cardiac disorders mentioned. Clinically, the diagnosis of CC is suggested by the triad of right heart failure with hepatomegaly, ascites with high protein content, and high serum ascites albumin gradient, along with refractoriness of ascites to diuretic treatment that contrasts with resolution of peripheral edema with diuretics.\textsuperscript{16,18}

Esophageal varices and splenomegaly may also be present. Under the latter circumstances, a presumptive diagnosis of the hepatic disorder may suffice because there is no evidence that CC worsens the prognosis of patients with congestive heart failure; instead the mortality rate is determined by the severity of the underlying cardiac disease. Yet when a heart transplant candidate has ascites, performing a liver needle biopsy is requested to rule out the presence of cirrhosis.

**Treatment.** There are no prospective studies on the management of CC. Empirically, CC is treated similarly to heart failure, along with paracentesis for refractory ascites. There is no need to regularly replace the albumin lost during paracentesis because synthetic function is preserved in CC.\textsuperscript{1,6} Peritoneovenous shunts have not been accepted as an alternative for the treatment of resistant ascites in CC. Transjugular portosystemic shunt has been used to relieve portal hypertension and ascites in postinfectious cirrhosis, alcoholic cirrhosis, and hepatic veno-occlusive disease but is contraindicated in cardiac ascites. Indeed, shunting of the portal blood to the right heart may increase the pulmonary arterial pressure and precipitate heart failure.

**Liver diseases affecting the heart**

The resting cardiac output, left ventricular diastolic diameter, and mean velocity of left ventricular wall contraction may all be increased in patients with liver cirrhosis and are reversible after liver transplantation.\textsuperscript{1,22} The hemodynamic consequences of liver disease, in the systemic and pulmonary circulation, hereafter called liver diseases affecting the heart, include: hepatopulmonary syndrome in cirrhosis, plexogenic pulmonary hypertension in cirrhosis, pericardial effusion in cirrhosis, cirrhotic cardiomyopathy, and noncirrhotic high-output heart failure caused by hepatic arteriovenous shunts.

**Hepatopulmonary syndrome**

Although the association of chronic liver disease, cyanosis, and digital clubbing was first described more than 100 years ago, and the term hepatopulmonary syndrome (HPS) was suggested in 1977,\textsuperscript{23} this entity has generated interest only recently.\textsuperscript{24} HPS is characterized by the triad of chronic liver disease, intrapulmonary shunts, and hypoxemia.\textsuperscript{25} A mild, asymptomatic variant of HPS is present in 5% to 29% of patients with chronic liver disease. Symptomatic HPS occurs in approximately 15% of patients with end-stage liver disease.\textsuperscript{22,25}

**Pathogenesis.** The pathogenesis of intrapulmonary shunting in HPS is dominated by liver disease. An imbalance between vasoconstrictors and vasodilators and between hepatic factors stimulating and inhibiting endothelial cell growth eventuate in development of intrapulmonary vascular dilation. The vasodilator substances that may have a role in the pathogenesis of HPS are prostaglandins E\textsubscript{1} and I\textsubscript{2}, vasoactive intestinal peptide, calcitonin, glucagon, substance P, nitric oxide, atrial natriuretic factor, and platelet activating factor. A blunted hypoxic pulmonary vasoconstriction could contribute to the unbalanced pulmonary vasodilation. Growth factors originating in the liver, such as hepatic growth factor and vascular endothelial growth factor, stimulate growth of pulmonary small vessels.\textsuperscript{22,26} Dilation of pulmonary capillaries may be diffuse (type I) or discrete (type II).\textsuperscript{25} Consequently, intrapulmonary shunting through dilated vascular channels, ventilation-perfusion mismatching, and restriction of oxygen diffusion ensue and result in hypoxemia. The fact that HPS is reversed after liver transplantation is consistent with the understanding that the intrapulmonary vascular dilations of HPS are caused by the hepatic disorder.\textsuperscript{25} Nevertheless, the degree of intrapulmonary shunting and hyperdynamic circulation correlates poorly with the degree of liver disease.\textsuperscript{25,26}

**Clinical presentation.** Most patients with HPS have
symptoms and signs of liver disease, but up to 18% of patients have predominantly pulmonary symptoms.\textsuperscript{25} Pulmonary features include digital clubbing, cyanosis, dyspnea, platypnea, and orthodeoxia. Platypnea is defined as dyspnea induced by the upright position and relieved by recumbence. Orthodeoxia is defined as arterial deoxygenation accentuated in the upright position and relieved by recumbence.

**Diagnostic testing.** Dyspnea in a cirrhotic patient is composed of a range of diagnostic possibilities,\textsuperscript{22} one of which is HPS (Table IV). Failure to recognize HPS can be serious because progressive decline in oxygenation can occur despite stable hepatic function. A 41% mortality rate has been reported a mean of 2.5 years after onset of dyspnea.\textsuperscript{25} Intrapulmonary shunting of blood can be evaluated with contrast echocardiography, technetium 99m–labeled macroaggregated albumin scanning, computerized tomography, and pulmonary arteriography. Technetium 99m–labeled macroaggregated albumin scanning is one of the modalities used to demonstrate the intrapulmonary vascular dilation. Injected peripherally, the majority of the labeled albumin is normally trapped in the pulmonary capillary bed. If the bubbles appear in the left side of the heart, a shunt is implied. Intracardiac and intrapulmonary shunting can be differentiated on the basis of timing of the bubble appearance in the left atrium. In intracardiac right-to-left shunts, the bubbles appear in the left side of the heart within 3 heartbeats after their appearance in the right side of the heart, whereas the interval is 4 to 6 beats in intrapulmonary shunts.\textsuperscript{25} The proportion of patients with chronic liver disease with a positive contrast-enhanced echocardiogram has ranged from 13% to 47%.\textsuperscript{23} Approximately half of the patients with a positive contrast echocardiogram also exhibited hypoxemia and were classified as having HPS. The remaining patients may have had the forme fruste of HPS.\textsuperscript{26,29} A recent study demonstrated the higher sensitivity of transesophageal echocardiography with the use of gelatin contrast solution in detecting intrapulmonary shunting.\textsuperscript{30} Computerized tomography permits measurement of the diameter of the peripheral pulmonary arteries. The ratio of segmental arterial diameter to bronchial diameter in patients with HPS is increased (2.0 ± 0.2 mm compared with 1.2 ± 0.2 mm in normoxic cirrhosis), a finding that may be helpful in the diagnosis of HPS.\textsuperscript{31} Pulmonary angiography permits visualization of intrapulmonary vascular dilations and measurement of pulmonary arterial pressures.\textsuperscript{25} Normal or low pulmonary artery pressures and resistance are found in HPS,\textsuperscript{31} and the cardiac output often exceeds 7 L/min.

The diagnosis of HPS is established when 3 criteria are met: evidence of chronic liver disease usually complicated by portal hypertension (with or without cirrhosis), arterial hypoxemia with partial pressure of oxygen in arterial blood (PaO\textsubscript{2}) <70 mm Hg or alveolo-arterial oxygen tension gradient >20 mm Hg, and intrapulmonary vascular shunting documented on contrast-enhanced echo-cardiography or technetium 99m–labeled macroaggregated albumin scanning.\textsuperscript{25} Quantifying hypoxemia with the patient breathing room air permits determination as to which patients with HPS require supplemental oxygen.\textsuperscript{25} Interpretation of PaO\textsubscript{2} measurements in the laboratory should be cautious because PaO\textsubscript{2} may be worse when the patient is standing. Furthermore, determining the patient’s ability to increase PaO\textsubscript{2} while breathing 100% oxygen is prognostically useful. It has been suggested that adult patients with a PaO\textsubscript{2} >150 mm Hg while breathing 100% oxygen are potential candidates for liver transplantation. Patients with HPS who are being considered for a liver transplant should have right heart catheterization and pulmonary angiography to rule out intracardiac shunt, assess for shunts amenable to embolization, and rule out pulmonary hypertension.

<table>
<thead>
<tr>
<th>Table IV. Differential diagnosis of chronic hypoxemia in patients with liver diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Restrictive lung disease</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
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<tr>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Impaired diffusion capacity</td>
</tr>
<tr>
<td>Left heart failure</td>
</tr>
<tr>
<td><strong>Uncommon: liver diseases affecting the heart</strong></td>
</tr>
<tr>
<td>HPS characteristics</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
</tr>
<tr>
<td>Platypnea and orthodeoxia</td>
</tr>
<tr>
<td>Severe when PaO\textsubscript{2} &lt;150 mm Hg while breathing 100% oxygen</td>
</tr>
<tr>
<td>Low or normal pulmonary arterial pressure</td>
</tr>
<tr>
<td>Intrapulmonary vascular dilation visualized on angiography</td>
</tr>
<tr>
<td>PPHTN</td>
</tr>
<tr>
<td>Liver cirrhosis associated with primary pulmonary hypertension</td>
</tr>
<tr>
<td>High-output failure from intrahepatic arteriovenous fistulae in noncirrhotic liver</td>
</tr>
<tr>
<td>Hyperdynamic circulation</td>
</tr>
<tr>
<td>Right-to-left shunt (extracardiac and extrapulmonary)</td>
</tr>
<tr>
<td>Treatment with estrogen</td>
</tr>
<tr>
<td>Intrahepatic shunt diagnosed with selective arteriography</td>
</tr>
<tr>
<td>Immune alveolitis as extrahepatic manifestation of hepatitis C, primary biliary cirrhosis, or autoimmune hepatitis</td>
</tr>
</tbody>
</table>
Table V. Differential diagnosis of combined cardiac and hepatic disorders

<table>
<thead>
<tr>
<th>Sequence of appearance and presence of multisystem disease</th>
<th>Clues</th>
<th>Further tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac disease first, no multisystem disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild alterations of liver function tests in congestive heart failure</td>
<td>No hepatic symptoms, mild increase of one or several: AST, ALT, GGT, alkaline phosphatase, bilirubin</td>
<td>Serologic tests for viral hepatitis B and C</td>
</tr>
<tr>
<td>Cardiogenic IH</td>
<td>[1] Chronic congestive heart failure, [2] precipitating event such as pulmonary edema, acute coronary event, hypoxia, or hypertension, [3] sharp increase in AST and ALT to 10- to 20-fold normal followed by &gt;50% decrease within 72 h</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Chronic congestive heart failure with incidental hepatitis</td>
<td>New medication, alcohol consumption, blood transfusion, drug addiction, travel</td>
<td>Discontinuation of suspected medication, serology for hepatic viruses</td>
</tr>
<tr>
<td>Chronic congestive heart failure with hepatic vein thrombosis</td>
<td>Acute onset or unexplained aggravation of hepatomegaly and cardiac ascites,* simultaneous or past thromboembolism (occasionally)</td>
<td>Ultrasound of hepatic veins, testing for thrombophilia†</td>
</tr>
<tr>
<td>Slowly evolving multisystem disease</td>
<td>By exclusion</td>
<td>Tests according to the clinical setting</td>
</tr>
<tr>
<td><strong>Liver disease first, no multisystem disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPHTN</td>
<td>Liver cirrhosis with hypoxemia</td>
<td>Echocardiography showing pulmonary hypertension, normal left cardiac anatomy and function; tests to exclude secondary pulmonary hypertension</td>
</tr>
<tr>
<td>Cirrhosis incidentally associated with secondary pulmonary hypertension</td>
<td>Raynaud’s phenomenon in systemic sclerosis, CREST syndrome, clubbing in primary biliary cirrhosis, typical findings on cardiac examination in congenital heart diseases</td>
<td>Tests according to the clinical setting</td>
</tr>
<tr>
<td><strong>Simultaneous onset and/or presence of multisystem disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute onset: shock, infection, multiorgan damage syndrome, poisoning</td>
<td>Diagnosis mostly obvious, but may be elusive in form fruste</td>
<td>Tests according to the clinical setting</td>
</tr>
<tr>
<td>Usually insidious onset: vasculitis, immune and metabolic disorders</td>
<td>Hyperpigmentation: consider hemochromatosis, elevated purpura or cutaneous ulcers; consider vasculitis lupus pernio, erythema nodosum; consider sarcoidosis</td>
<td>Tests according to clinical setting, consider liver needle biopsy</td>
</tr>
<tr>
<td>Intrahepatic arteriovenous fistulae in the noncirrhotic liver</td>
<td>Hyperkinetic heart failure: hemangiomias in infants, Osler-Weber-Rendu disease in adults</td>
<td>Doppler ultrasound, selective angiography</td>
</tr>
</tbody>
</table>

SAAG, Serum ascitic albumin gradient; CREST syndrome, calcinosis, Raynaud phenomenon, esophageal involvement, sclerodactyly, and telangiectasia.

*Serum ascitic albumin gradient ≥1.1 g/dL and ascitic fluid protein ≥2.5 g/dL.

†Especially homocystinemia, activated partial thromboplastin time resistance, and polycythemia vera; pulmonary rather than hepatic symptoms may dominate the initial presentation.

**Treatment.** Long-term oxygen therapy is the simplest approach to improving symptoms in these patients.32 Case reports have documented improvement of arterial oxygenation from HPS with prostaglandin-F2α,33 steroids, and cytoxan,24 and a pilot trial suggests that garlic preparations may be effective.34 Selected patients with type II HPS may have improved oxygenation after coil embolization of dilated vessels, but the subsequent history in these patients is unknown.35 Progressive hypoxemia may be an indication for liver transplantation. HPS is reversible after liver transplantation in many, but not all, patients.25,26 In a large series of patients treated with liver transplantation, 70% had successful transplantation and resolution of hypoxemia, but patients with a PaO₂ of ≤50 mm Hg from HPS had a 30% mortality rate within 3 months of the liver trans-
Portopulmonary hypertension

Pulmonary hypertension associated with cirrhosis and without demonstrable primary pulmonary or cardiac disease is called portopulmonary hypertension (PPHTN).

Pathogenesis. PPHTN is not a common disorder, reported in less than 1% of patients with chronic liver disease in most studies. However, when cardiac catheterization was performed in patients with liver cirrhosis, 2% had pulmonary hypertension defined as a mean arterial pressure more than 25 mm Hg, with more than half being asymptomatic. These data show that primary pulmonary hypertension occurs at least 6 times and perhaps as much as 20 times more frequently in patients with cirrhosis than in the general population. The risk in developing pulmonary hypertension increases with the duration of portal hypertension, without any clear relation to the degree of portal hypertension, hepatic failure, or amount of blood shunted. Histologically, PPHTN resembles idiopathic pulmonary hypertension. Microscopic examination shows hyperplasia of the muscular pulmonary arteries and arteries with thickening of the intima and the media and stenosis of the lumen. Vascular wall necrosis, aneurysmal dilation, local thrombosis, recanalization of the vascular lumen, and cellular proliferation are the sequence of events leading to plexogenic arteriopathy. The mechanisms of PPHTN are unknown. Investigators have hypothesized that humoral factors derived from the splanchnic blood, which normally would be cleared by hepatic metabolism, reach the pulmonary circulation because of portosystemic shunting and impaired hepatic reticuloendothelial function. The latter substances modify endothelial cell function, promoting vasoconstriction, thrombosis, and mitogenic activity in the pulmonary circulation. Cell proliferation induces medial hypertrophy, plexogenic lesions, and formation of new blood vessels. Vasoconstriction, excessive clot formation and remodeling of blood vessels augment resistance to blood flow, and pulmonary hypertension ensues.

Clinical presentation. Subclinical portal hypertension precedes the onset of symptomatic pulmonary hypertension by months or years. The symptoms associated with PPHTN are exertional dyspnea, syncope, and precordial pains. Accentuation of the pulmonic component of the second heart sound and a systolic murmur along the left sternal border may be heard. The mean survival after diagnosis of PPHTN has been 15 months, with a 6-month mortality rate of 50%.

Diagnostic testing. Among noninvasive studies, transthoracic echocardiography is the most widely used. The presence of a dilated right ventricle or atrium, pulmonary valvular insufficiency, or shifting of the inter-ventricular septum into the left ventricle on transthoracic echocardiography raise suspicion of pulmonary hypertension. Pulmonary systolic pressures can be estimated in the presence of a tricuspid regurgitant jet. Patients with PPHTN exhibit an exaggerated respiratory alkalosis, more profound than is characteristic of patients with either primary pulmonary hypertension or liver cirrhosis. The combination of a suspicious blood gas result with an abnormal echocardiogram has been a useful screening regimen to identify patients with PPHTN. The diagnosis is confirmed on right heart catheterization when values of mean pulmonary artery pressure >25 mm Hg, pulmonary vascular resistance >120 dynes · s · cm⁻⁵, and pulmonary capillary wedge pressure <15 mm Hg are encountered.

A perplexing diagnostic problem may be present when the cirrhotic patient has a combination of features that resemble both HPS and PPHTN. The literature cites 2 cirrhotic patients who received long-term β-blockade for the treatment of portal hypertension and had severe hypoxemia develop. Pulmonary hypertension was recognized as well as a right-to-left shunt through a patent foramen ovale. The intracardiac shunt and pulmonary hypertension regressed after discontinuation of β-blocker therapy.

Treatment. Patients with mean pulmonary artery pressure <40 mm Hg can safely undergo orthotopic liver transplantation for PPHTN. Assessment of right ventricular function after fluid challenge and evaluation of left ventricular and pulmonary functions are essential for selection of the appropriate candidates for transplantation. Seven of 10 liver transplant recipients selected according to the last mentioned criteria had improved or normalized pulmonary artery pressures within 6 months after transplantation. In contrast, patients with mean pulmonary artery pressure greater than 40 mm Hg are at unacceptable risk for surgery. Yet the latter group of patients may benefit from long-term treatment with intravenous epoprostenol designed to control pulmonary hypertension. When on repeat right heart catheterization the mean pulmonary artery pressure is less than 40 mm Hg, liver transplantation may be considered. Currently, a prospective trial of the use of long-term epoprostenol as a bridge to orthotopic liver transplantation is underway. Epoprostenol treatment should be avoided in postcapillary pulmonary hypertension because of the risk of pulmonary edema.

Pericardial effusion in cirrhosis

Fluid retention in patients with decompensated cirrhosis is accompanied by edema, ascites, pleural effusion, and pericardial effusion. Pericardial effusion was revealed on echocardiography in 63% of patients with decompensated cirrhosis, was related to fluid retention, and often remitted after resolution of ascites.
Cirrhotic cardiomyopathy

In patients with cirrhosis, hyperkinetic circulation characterized by increased cardiac output is common and induces an increased left ventricular work. Cardiac troponin I concentrations were elevated in 32% of patients with cirrhosis and are the expression of subclinical myocardial damage. Cirrhotic cardiomyopathy refers to abnormal left ventricular function, which is manifested under conditions of physiologic or pharmacologic stress. Therefore cardiovascular status should be carefully evaluated in patients undergoing liver transplantation, surgical portosystemic shunts, or intrahepatic portosystemic shunts.

High-output heart failure caused by intrahepatic arteriovenous fistulae in the noncirrhotic liver

Systemic arteriovenous fistulas, as well as intrahepatic arteriovenous fistulas, are well-known causes of high-output cardiac failure. In early infancy, hepatic hemangiomas or hemangioendotheliomas result in hemodynamically significant arteriovenous shunting of blood with resultant hyperkinetic heart failure. Such hemangioendotheliomas have been treated with hepatic artery ligation. In adulthood, Osler-Weber-Rendu disease may manifest with intrahepatic arteriovenous fistulas and the resultant hyperdynamic circulatory state, heart failure, and pulmonary hypertension. Treatment with selective arterial embolization in a few patients was followed by remission of the hyperdynamic circulatory state. Furthermore, long-term use of estrogens may aggravate a preexistent vasculopathy or may induce peliosis hepatitis and sinusoidal dilation.

Joint causes of hepatic and cardiac disorders

The heart and liver can both be targets of a common pathogenic process, which may be infectious, metabolic, immune, vasculitic, or toxic. Detailed inventory of these disorders is beyond the aim of this paper. Clues to their distinction from heart diseases affecting the liver and liver diseases affecting the heart may be found in the patient history and clinical examination. First, the simultaneous onset of a cardiac and liver disease during the course of an acute disorder may hint to a common cause or a joint underlying mechanism. Examples are conjoint cardiac and hepatic damage in shock, sepsis, and the systemic inflammatory response syndrome. Second, in patients having a multisystem disease, the cardiac and the hepatic disorders could be part of the systemic disease. This is possible even if the cardiac and hepatic disorders make their appearance at different points of time. Such situations are hemochromatosis with myocardial, hepatic, pancreatic and cutaneous involvement; glycogen storage diseases; hepatitis C virus infection with hepatitis, myocarditis, cutaneous vasculitis, and nephritis; amyloidosis or sarcoidosis with pulmonary cardiac, hepatic, articular, neurologic, and cutaneous involvement; AIDS with hepatitis and myocarditis; and acetaminophen overdose with hepatitis and myocarditis. Third, pathognomonic features occasionally allow for a quick presumptive diagnosis. Such is the case with melanic pigmentation of the skin in hemochromatosis, lupus pernio, or bilateral mediastinal and hilar lymphadenopathy in sarcoidosis, and periorbital purpura in amyloidosis.

Diagnostic approach

The approach to the diagnosis of combined cardiac and hepatic disorders is based on recognizing the sequence of appearance of the cardiac and liver disease, presence of features of a multisystem disease, and presence of pathognomonic features. Consideration is given to the expected benefit of treatment and the risks related to invasive procedures in patients with advanced cardiac and liver disease. In most instances investigations can be limited to ancillary tests, as exemplified by mild alterations of liver function tests accompanying liver congestion, cardiogenic IH, incidental viral or toxic hepatitis in a patient with heart failure, cirrhosis incidentally associated with pulmonary hypertension caused by disorders other than liver disease, and multisystem diseases either acute or chronic involving both the heart and the liver (Table V). Conversely, thorough evaluation of the heart and liver is recommended when patients are considered for invasive therapeutic procedures. To this latter category belong patients with HPS, PPHTN, and intrahepatic arteriovenous fistulae. Furthermore, when patients with heart failure and cardiac ascites are considered for heart transplantation, a liver needle biopsy is requested to rule out the presence of cirrhosis. In patients considered for liver transplantation, the cardiovascular status should be carefully evaluated because covert cirrhotic cardiomyopathy may become evident and menacing under conditions of the operative stress or postoperative period.

In conclusion, a multitude of disorders may involve both the heart and the liver. The lengthy list of diagnoses to be considered may appear as a difficult task to the physician. However, the diagnostic approach can be facilitated by establishing, from the onset, the time sequence of appearance of the cardiac versus the hepatic syndrome, the presence of a multisystem disease, and the presence of pathognomonic signs in certain disorders. Classification of a patient to any of the 3 categories—heart diseases affecting the liver, liver diseases affecting the heart, or cardiac and liver disorders with joint etiology—permits to narrow the span of the possible diagnoses and allows for a more simple workup.
References


**Objective**

We analyzed the effect of the pharmacologic combination of 2 indirect antithrombin drugs—enoxaparin (low-molecular-weight heparin) and unfractioned heparin—versus enoxaparin alone on the recurrence of ischemia.

**Background**

Blocking some key factors of the coagulation cascade supports the concept that an antithrombin effect is needed during the acute phase of ischemia.

**Methods**

This was a prospective, randomized, pilot trial in patients with an acute coronary ischemic event occurring within the previous 24 hours. A total of 126 patients were allocated to receive aspirin (200 mg/day orally) plus 1 mg/kg subcutaneous enoxaparin at 8 AM and 12,500 IU of subcutaneous unfractioned heparin at 8 PM (group A) or subcutaneous enoxaparin 1 mg/kg (group B).

**Results**

Severe recurrent ischemia provoking urgent coronary revascularization occurred in 12 patients (9.5%), 3 (5%) in group A and 9 (13%) in group B (P = .1). Refractory angina was present in 27 patients (21%), 10 (17%) in group A and 17 (25%) in group B (P = .45). The combination of severe recurrent ischemia and refractory angina occurred in 23% of group A, and 37% of group B (odds ratio 0.49; 95% confidence intervals, 0.21-1.15; P = .07). A total of 7 patients (5%) had acute nonfatal myocardial infarction develop, 3 (5%) in group A and 4 (6%) in group B. Two (1.6%) deaths were observed in the study, both in group B. The incidence of the double end point (death plus nonfatal myocardial infarction) was 5% in group A versus 9% in group B (P = .5) and the triple end point (death, nonfatal myocardial infarction, and severe recurrent ischemia) was 10.5% in group A vs 22% in group B (odds ratio 0.42, 95% confidence intervals, 0.13-1.29; P = .09).

**Conclusions**

The combination of 2 indirect antithrombin drugs capable of intermittently blocking the coagulation system is not associated with a significant loss of safety. (Am Heart J 2000;140:e3.)