ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Pulmonary Complications of Cirrhosis

Norman L. Sussman, MD
Associate Professor of Surgery
Baylor College of Medicine
Houston, Texas

G&H What types of pulmonary complications are linked to cirrhosis?

NS There are several major pulmonary complications of cirrhosis that clinicians need to be aware of. The most common such problem is hepatic hydrothorax, the accumulation of fluid in the pleural space related to portal hypertension. Two less common, and poorly understood, complications are pulmonary hypertension and hepatopulmonary syndrome (HPS).

G&H What occurs in hepatic hydrothorax?

NS In hepatic hydrothorax, fluid leaks into the abdomen, and defects in the diaphragm enable that fluid to move into the pleural cavity. If the pleural cavity fills with fluid, the lungs are compressed and the patient cannot breathe.

G&H What occurs in HPS?

NS HPS is a condition in which the blood vessels in the lungs dilate. Blood passing through the lungs is inadequately oxygenated, leading to hypoxemia (a low oxygen level in the blood) and dyspnea (shortness of breath). The classic finding is that blood oxygen levels decrease and shortness of breath increases when patients change position from lying to sitting or standing, a condition known as platypnea-orthodeoxia (for increased dyspnea and hypoxemia, respectively).

G&H What occurs in pulmonary hypertension?

NS Pulmonary hypertension is caused by narrowing and/or obstruction of the pulmonary arteries and arterioles. When pulmonary hypertension is associated with portal hypertension, it is known as portopulmonary hypertension (POPH). In patients with POPH, the right ventricle may fail if it is unable to overcome the increased pressure required to drive blood through the pulmonary circulation. Excess pressure is also associated with a high mortality after liver transplantation, so pulmonary pressure must be controlled prior to liver transplantation.

G&H What are the common signs that a patient with cirrhosis might have one of these complications?

NS Early pulmonary disease may be asymptomatic, so clinicians should look for evidence of pulmonary disease in all patients with cirrhosis. Significant hepatic hydrothorax will be obvious on physical examination and may be confirmed with a chest radiograph or other imaging such as an ultrasound or a computed tomography scan. HPS is associated with hypoxemia, which may be suspected if pulse oximetry shows an oxygen saturation lower than 97% (sensitivity of 96% and specificity of 76% for detecting mild hypoxemia, defined as a partial pressure of oxygen [PaO_2] <70 mmHg). We therefore recommend pulse oximetry at every office visit. The diagnosis of POPH is rarely suspected clinically; it is usually detected on an echocardiogram. We do not recommend an echocardiogram on every patient with cirrhosis, but echocardiography is routinely performed on patients who are being evaluated for liver transplantation.

G&H How does cirrhosis lead to pulmonary complications?

NS We do not fully understand the connection. The pulmonary artery pressure is much lower than the systemic blood pressure, so the right ventricle does not require the

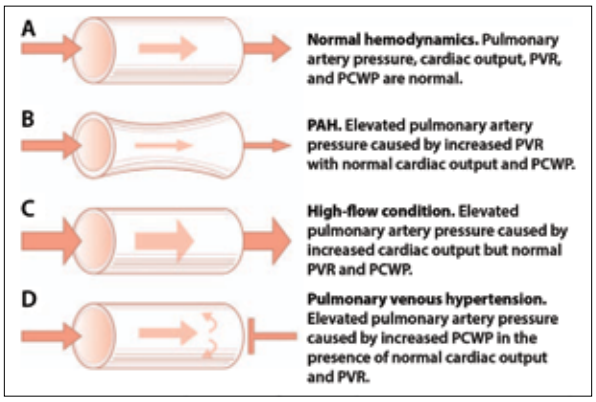

Figure. Potential causes of mean pulmonary artery pressure elevations in patients with portopulmonary hypertension.

PAH, pulmonary artery hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

Adapted with permission from Safdar Z, Bartolome S, Sussman N. Portopulmonary hypertension: an update. *Liver Transpl.* 2012;18(8):881-891.

muscle mass of the left ventricle. This makes the right ventricle vulnerable to failure in the setting of high pulmonary artery pressure. As shown in the Figure, pressure is related to vessel diameter, blood flow, and left heart pressure. During liver transplantation, the cardiac output and pulmonary artery pressure increase abruptly when the new liver is first perfused. In the setting of uncontrolled POPH, the right ventricle is unable to cope with the increased load and fails, usually with disastrous consequences.

Equally puzzling is the opposite scenario, in which the blood pressure drops extremely low. In order to maintain pressure, the muscles in the blood vessels constrict—the degree of constriction is described as vascular tone. In HPS, the pulmonary vessels lose tone and dilate. These wide-open blood vessels lead to very low blood pressure. As a result, the blood bypasses the lungs, leading to hypoxia.

We do not know why some patients with cirrhosis develop high pulmonary artery pressure, others develop low pulmonary artery pressure, and others retain normal pulmonary artery pressure. Most patients do not have any of these complications.

G&H Can these complications arise at any time during the course of cirrhosis?

NS These complications can occur at any time, and they are not related to the severity of the liver disease. They increase the risk of early death regardless of the state of the liver. A person with milder cirrhosis who has any of these complications is at a greater risk of dying than someone with a similar level of cirrhosis but none of these complications. HPS and POPH are so serious that they may be indications for liver transplantation, regardless of the severity of the liver disease.

G&H How do pulmonary complications factor into the decision regarding liver transplantation?

NS All patients with cirrhosis are assigned a Model for End-Stage Liver Disease (MELD) score. Patients with HPS or POPH are eligible to get MELD exception points, which account for the fact that the risk of death is higher than the MELD score would otherwise indicate. Patients with recurrent hydrothorax who require frequent thoracentesis also may be eligible for MELD exception points under certain circumstances.

G&H How is hepatic hydrothorax treated?

NS Hydrothorax that causes shortness of breath is usually treated with urgent thoracentesis, in which the fluid is removed by inserting a needle directly into the chest cavity. Hydrothorax may be treated with transjugular intrahepatic portosystemic shunt (TIPS) in some patients. Those in whom TIPS is contraindicated may require regular thoracentesis.

G&H What are the potential side effects of treatment for hydrothorax?

NS Thoracentesis always carries a risk of a collapsed lung. The potential risks associated with TIPS include blood vessel damage and hepatic encephalopathy, which can impair concentration and mental function. Rarely, the procedure can lead to coma.

G&H Is there a treatment for HPS?

NS There is no medical therapy for this condition. The key to solving this issue is early recognition and transplantation, before patients become too ill for the procedure. MELD exception points may apply once the patient falls below a certain level of hypoxia. HPS invariably improves after liver transplantation.

G&H Is the same true for POPH?

NS POPH is a different story altogether because it is frequently asymptomatic. Often, it is first recognized during an echocardiogram and must be confirmed with a right heart catheterization.

Once the condition is diagnosed, it is usually treated with one or more vasodilator drugs. If the patient

responds to vasodilators, then a liver transplant may be performed safely. The patient requires specialized care during and after liver transplantation, and the pulmonary pressure usually decreases over the following weeks to months. Some patients may still require medication after transplant, but the problem is usually much easier to control at that point.

In 2006, our group published a study in the *American Journal of Transplantation* in which patients with POPH were treated medically with continuous intravenous epoprostenol followed by liver transplantation. This study demonstrated that POPH could be treated and that these patients could then safely undergo liver transplant. Before this study, many patients with cirrhosis and POPH would not be considered for liver transplant because the risk of death following the procedure was too high. Since then, liver transplantation after medical control of POPH has become accepted practice in many transplant centers.

G&H Have the results of this study held up in long-term follow-up?

NS Yes. In 2014, we published long-term follow-up data in *Liver Transplantation* on POPH patients after liver transplantation. Seven patients were followed for a median of 7.8 years after liver transplantation. One patient died of cirrhosis caused by recurrent hepatitis C. Four of the remaining 6 patients required oral medication to control pulmonary hypertension.

G&H Are there any serious side effects associated with vasodilators?

NS Some of these drugs can cause liver toxicity. It is also important to not overdilate the patient because that can lead to a drop in blood pressure, which can then lead to heart failure and kidney failure.

G&H Is there any ongoing research on potential treatments for HPS?

NS Several investigators continue to work on the problem, but medical therapy has remained elusive.

Dr Sussman has no relevant conflicts of interest to disclose.

Suggested Reading

Khaderi S, Khan R, Safdar Z, et al. Long-term follow-up of portopulmonary hypertension patients after liver transplantation. *Liver Transpl*. 2014;20(6):724-727.

Koch DG, Fallon MB. Hepatopulmonary syndrome. *Curr Opin Gastroenterol*. 2014;30(3):260-264.

Krowka MJ, Miller DP, Barst RJ, et al. Portopulmonary hypertension: a report from the US-based REVEAL Registry. *Chest*. 2012;141(4):906-915.

Norvell JP, Spivey JR. Hepatic hydrothorax. *Clin Liver Dis*. 2014;18(2):439-449.

Safdar Z, Bartolome S, Sussman N. Portopulmonary hypertension: an update. *Liver Transpl*. 2012;18(8):881-891.

Sussman N, Kaza V, Barshes N, et al. Successful liver transplantation following medical management of portopulmonary hypertension: a single-center series. *Am J Transplant*. 2006;6(9):2177-2182.

Sussman NL, Kochar R, Fallon MB. Pulmonary complications in cirrhosis. *Curr Opin Organ Transplant*. 2011;16(3):281-288.

(continued from page 124)

treatment with the idea to consider surgery or pneumatic dilatation if the initial therapy fails. However, this therapy is rarely successful in the long term. If the first injection is not successful, the second or third injection is rarely successful. It also tends to wear off, with few people experiencing more than a year or two of improvement. Many people who initially receive this therapy are candidates for more definitive treatment, creating an unnecessary delay.

In addition, although onabotulinumtoxinA is safe, repeated injections cause inflammation and sometimes fibrosis in the sphincter region. Although there is no definitive evidence that the injections negatively affect the outcomes of the more definitive treatments, it is my belief that pneumatic dilatation is not as effective in people who have had multiple injections and that surgery may be more difficult or at least more time-consuming.

G&H Are there any other new treatment options?

PK There is some evidence in the laboratory that phosphodiesterase type 5 inhibitors, such as sildenafil, can decrease esophageal contraction amplitude and lower esophageal sphincter pressure and, thus, may be of use in patients with achalasia. However, the experience with these drugs is anecdotal; there have been no clinical trials to date.

Dr Katz has no relevant conflicts of interest to disclose.

Suggested Reading

Boeckxstaens GE, Annese V, des Varannes SB, et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med*. 2011;364(19):1807-1816.

Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol*. 2013;108(8):1238-1249.