Jacqueline Modock, BSN, RN

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Acute Pulmonary Hypertension After Transjugular Intrahepatic Portosystemic Shunt

A Potentially Deadly but Commonly Forgotten Complication

ABSTRACT

Hepatitis C virus (HCV) is a common cause of chronic liver disease and is the most common indication for liver transplantation in the United States. As increasing numbers of the population experience complications from chronic liver disease, management of these complications comes into focus. One such management technique is a transjugular intrahepatic portosystemic shunt (TIPS). As the number of patients with HCV cirrhosis increases, the proportion of TIPS procedures performed will also increase. It is, therefore, paramount to understand the potential adverse effects of this increasingly used procedure. This case report focuses on a 52-year-old man with HCV cirrhosis who developed the complication of acute pulmonary hypertension after receiving a TIPS procedure. In this case report, we discuss this important but commonly missed complication of TIPS, including incidence, diagnosis, and treatment.

As a disease, Hepatitis C is the most common indication for liver transplantation in the United States. It is estimated that 3.2 million Americans are infected with the virus. The Centers for Disease Control and Prevention (CDC) identified these patients at increased risk for hepatitis C infection: injection drug users, recipients of clotting factor concentrates made before 1987, recipients of blood transfusions or solid organ transplants before July 1992, chronic hemodialysis patients, HIV-infected patients, and children born to HCV-positive mothers (2009). While there are recommended treatment options for Hepatitis C virus (HCV) infection, the majority of infections remain undiagnosed and untreated leading to approximately 75%–85% of HCV infections becoming chronic (CDC, 2009).

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About the author: *Jacqueline Modock, BSN, RN, is Adult Gerontology Acute Care Nurse Practitioner, Lake Tahoe Regional Hospitalist, Carson City, Nevada.*

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Correspondence to: *Jacqueline Modock, BSN, RN, Case Western Reserve University, 1685 Murrieta Ct., Reno, NV 89521 (jmm286@case.edu).*

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Background

A serious complication associated with chronic Hepatitis C infection is the development of chronic liver disease. The CDC (2013b) reports that the fifth leading cause of death in individuals 45–54 years old in 2009 was liver disease. During 2005–2010, the number of annual chronic liver disease deaths attributable to Hepatitis C infection was 12,000 (CDC, 2013a). The CDC predicted that "the number of deaths attributable to HCV-related chronic liver disease could increase substantially during the next 10–20 years as this group of infected persons reaches ages at which complications from chronic liver disease typically occur" (CDC, 1998). As increasing numbers of the population experience complications from chronic liver disease, the need for medical management of these complications will also rise. One such management technique is a transjugular intrahepatic portosystemic shunt (TIPS).

Transjugular intrahepatic portosystemic shunt has been a procedure performed in cirrhotic patients for more than 20 years to treat the often-deadly complications of portal hypertension (Boyer & Haskal, 2009). Although successful outcomes have been achieved with the TIPS procedure, the American Association for the Study of Liver Disease continues to have very narrow

indications for the performance of a TIPS procedure (Boyer & Haskal, 2009). It is only after medical management has failed for abdominal ascites and variceal bleeding that the morbidity and mortality associated with a TIPS procedure no longer outweighs the benefits of the procedure (Boyer & Haskal, 2009). As the number of patients with HCV cirrhosis increases, the proportion of TIPS procedures performed will also increase. Therefore, it is becoming even more imperative for clinicians to be able to recognize the complications associated with a TIPS procedure and then be able to respond with appropriate interventions.

Case Study

This case study focuses on a 52-year-old Caucasian man with end-stage liver disease secondary to Hepatitis C infection who presented for an elective TIPS procedure due to refractory abdominal ascites, which required three paracenteses per week. The Model for End Stage Liver Disease score is a model that helps predict survival of patients with end-stage liver disease. The model scores a patient based on the patient's risk of dying while waiting for a liver transplant. Originally developed at the Mayo Clinic, the model currently approved by the Organ Procurement and Transplant Network and the United Network for Organ Sharing has been modified to include the patient's international normalized ratio, bilirubin, creatinine, and whether the patient has had dialysis twice in the past week.

At the time of the procedure, the patient's Model for End Stage Liver Disease score was 17. Prior to the procedure, the patient underwent an outpatient transthoracic echocardiogram that was unrevealing for any heart disease. The patient's medical history was significant for diabetes mellitus and cirrhosis. Following the TIPS procedure, the patient was admitted to the hepatology floor at the hospital for overnight observation and discharge was planned for the next day. Over the course of his stay, the patient developed shortness of breath and required transfer to the medical intensive care unit for closer observation. The patient remained stable over the next several hours, requiring only 2 L of oxygen support via a nasal cannula when he acutely developed worsening dyspnea.

At this time, an arterial blood gas (ABG) was obtained and electrocardiogram (ECG) was ordered. A prior chest x-ray demonstrated no pulmonary edema or pleural effusions, but a slightly enlarged cardiac silhouette was noted. Data obtained from the ABG revealed a partial pressure of oxygen in arterial blood (Pao2) of 60 mmHg. The ECG showed a normal sinus rhythm. The thoughts of the intensive care team were that the patient was experiencing an acute decompensation post-TIPS related to pulmonary hypertension.

Although a pulmonary embolism (PE) could not be fully ruled out, the patient's risk factors for PE were minimal given that he was ambulating prior to the procedure, had no history of blood clots, did not smoke, and was receiving low-dose heparin for deep vein thrombosis prophylaxis while hospitalized. Consideration of his potential for coagulopathy related to his cirrhosis was noted. The decision was made to intubate the patient, place a Swan-Ganz catheter, and start him on inhaled epoprostenol.

After the patient was intubated, readings from the Swan-Ganz catheter were obtained. The readings revealed an elevated right ventricular systolic pressure and pulmonary artery pressure consistent with a diagnosis of pulmonary hypertension. Epoprostenol was then delivered via aerosol by the endotracheal tube. Serial measurements were obtained from the pulmonary artery catheter and the epoprostenol was able to be titrated off after 2 days and the patient was successfully extubated on Day 5.

Pathogenesis of Hepatitis C Cirrhosis–Pulmonary Hypertension and the TIPS Procedure

The development of cirrhosis from Hepatitis C infection is thought to be a complex process with the virus itself not believed to be cytopathic (Pawlotsky, 2004). The exact role of the virus factors remains unclear in the disease progression from fibrosis to cirrhosis, but certain exogenous factors have significant influences with the most important factor being alcohol consumption. Other factors include co-infection by HIV or other hepatitis viruses, diabetes, obesity, and various causes of immunosuppresion (Pawlotsky, 2004).

The liver damage seen in HCV infection is thought to be mediated by inflammation and fibrosis. The inflammation is caused by a local immune response that results in portal lymphoid infiltration, necrosis, and degenerative lesions primarily composed of $CD4^+$ T cells (Pawlotsky, 2004). Pawlotsky states that "fibrosis progression appears to result directly from chronic inflammation of the liver, which is associated with chronic destruction of liver cells and local production of cytokines and growth factors."

Fibrosis leads to increases in collagen and other extracellular matrix products in the liver parenchyma. Throughout the entire process, the remaining hepatocytes are stimulated to regenerate as spherical nodules within the fibrous covering of the liver. The overall effect is severely compromised delivery of blood to the hepatocytes and reciprocal reduction in secretion of substances by the hepatocytes into the blood (Kumar, Abbas, Fausto, & Aster, 2010).

Resistances to portal flow and hyperdynamic circulation interact in the complex process of portal

hypertension (Kumar et al., 2010). The clinical consequences of ascites, portosystemic venous shunts, congestive splenomegaly, and hepatic encephalopathy then arise from the portal hypertension (Kumar et al., 2010). As a treatment option, the TIPS procedure involves entering the right internal jugular vein and passing a catheter down through the superior vena cava and inferior vena cava and into the hepatic vein. From there, a needle is then inserted through the liver into the portal system, the needle tract is dilated with a balloon, and a stent is placed in the dilated track (Mettler, 2005).

Discussion

There are many known complications associated with a TIPS procedure and these include thrombosis and occlusion of the shunt, transcapsular puncture, intraperitonel bleed, infection, fistulae, hemobilia, and encephalopathy (Boyer & Haskal, 2009). Despite the long list of complications, Ripamonti, Ferral, Alonzo, and Patel (2006) report that the major complication rate of the procedure is less than 5%. Of the fatal complications (e.g., intra-abdominal hemorrhage, laceration of the hepatic artery or portal vein, and right-sided heart failure), the prevalence was only 1.7% (Boyer & Haskal, 2009). If a patient acutely decompensates after the procedure, one must consider these potential fatal complications as part of the differential diagnosis.

The initial work-up of a patient presenting with acute dyspnea post-TIPS procedure should include ordering complete blood cell counts to rule out hemorrhage, an ECG, chest x-ray, ABG, and transthoracic echocardiograph to evaluate for right-sided heart failure, pulmonary hypertension, or PE. Table 1 provides an overview of key diagnostic findings for pulmonary hypertension following TIPS.

One of the most efficient and least invasive tests to begin with is the ECG. Guidelines for the diagnosis and treatment of pulmonary hypertension published by the European Society of Cardiology and the European Respiratory Society state that the ECG may demonstrate right ventricular and atrial hypertrophy and strain and a right axis deviation. The recommendations point out that the ECG is only supportive evidence because of the low sensitivity (55%) and specificity (70%), which does not allow the clinician to exclude pulmonary artery hypertension if a normal ECG is obtained (Galie et al., 2009).

Similar to the ECG, the chest x-ray obtained can also support the diagnosis of pulmonary hypertension by demonstrating right atrial and right ventricular enlargement and central pulmonary artery dilatation. A study looking at the ability of a chest x-ray to confirm a diagnosis of heart failure found the chest x-ray to have a sensitivity of 57% and a negative predictive value of 83%. Twenty-five percent of the patients with heart failure had a normal ECG or chest x-ray (Fonseca et al., 2004). Thus, while the data provided by chest x-rays and ECGs can lend support to the diagnosis of pulmonary hypertension, further studies are still warranted.

TABLE 1. Key Diagnostic Findings of Pulmonary Hypertension Following Transjugular Intrahepatic Portosystemic Shunt

Electrocardiogram	Right ventricular hypertrophy
	Right axis deviation
	Supraventricular arrhythmias
Chest x-ray	Central pulmonary arterial dilation
	Right atrial and ventricular enlargement
Transthoracic echocardiography	Tricuspid regurgitation velocity $>$ 3.4 m/s
	Pulmonary artery systolic pressure $>$ 50 mmHg
Right-sided heart catheterization	Mean pulmonary artery pressure $\geq$ 25 mmHg
	Pulmonary wedge pressure $\leq$ 15 mmHg

Note. Data from "Guidelines on Diagnosis and Treatment of Pulmonary Arterial Hypertension," N. Galie, A. Torbicki, R. Barst, P. Dartevelle, S. Haworth, T. Higenbottam, … G. Simmonneau, 2009, *European Heart Journal, 30*, pp. 2493–2537.

A transthoracic Doppler-echocardiogram (TTE) is an additional test that can not only assess the size of the right atrium and ventricle, but also estimate the pulmonary artery systolic pressure, which is equivalent to the right ventricular systolic pressure. The sensitivity of the TTE for diagnosing pulmonary hypertension has been found to be 79%–100% with a specificity from 60% to 98% (the correlation between TTE and a right-sided heart catheterization is 0.57–0.93) (Barst et al., 2004).

After these initial fast and relatively noninvasive tests have been performed, support for a diagnosis should become clear. A decision to treat as a hemorrhagic, embolic, or hypertensive cause of dyspnea will guide further interventions. Each treatment path will require different therapies to correct the underlying cause. If at this interval the data support a diagnosis of pulmonary hypertension, then more invasive interventions may be required.

A systematic review and meta-analysis performed to assess the diagnostic accuracy of echocardiography for pulmonary hypertension concluded that "echocardiography is a useful and noninvasive modality for initial measurement of pulmonary pressures but due to limitations, right heart catheterization should be used for

diagnosing and monitoring pulmonary hypertension" (Janda, Shahidi, Gin, & Swiston, 2011, p. 612). Both the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and the American College of Cardiology state that a right-sided heart catheterization is the gold standard for the diagnosis of pulmonary hypertension (Galie et al., 2009; McLaughlin et al., 2009). The clinician may determine that the clinical condition of the patient may warrant emergent right-sided heart catheterization for diagnosis and to guide treatment or that further follow-up may be performed as an outpatient.

Pathophysiology of Pulmonary Hypertension and the Cirrhotic Patient

The association between pulmonary hypertension and chronic liver disease is well recognized. It is estimated that 1%–2% of patients with cirrhosis and portal hypertension will develop pulmonary hypertension (Galie et al., 2009). It is postulated that the pathophysiology leading to pulmonary hypertension in the cirrhotic patient is related to toxic substances from the GI tract that are not eliminated by the liver due to portosystemic shunts, which lead to lung endothelium damage (Galie et al., 2009).

A contraindication to having a TIPS procedure performed is evidence of pulmonary or heart disease. The question raised, therefore, is why patients experience pulmonary hypertension after a TIPS procedure if they have been properly screened prior to the procedure for cardiac or pulmonary diseases. Several hypotheses have been proposed to explain the development of pulmonary hypertension after a TIPS procedure.

The first hypothesis is that the dramatic fluid shift post-TIPS exacerbates a subclinical case of pulmonary hypertension. Other explanations support the role of neurohumoral factors. In a study conducted by van der Linden, Le Moine, Ghysels, Ortinez, and Deviere (1996), the researchers demonstrated that the increase in mean pulmonary artery pressure after a TIPS procedure is not only attributable to increased cardiac output caused by increased preload after the shunt placement. The researchers hypothesized that the release of neurohumoral mediators, such as norepinephrine and endothelin, in response to either hypoxia, puncturing of the portal endothelial wall, or bypassed filtering of the liver with the shunt contributed to the vasoconstriction of the pulmonary artery (van der Linden et al., 1996). An additional study performed by Schwartz et al. (2003) concluded that "PAP [pulmonary artery pressure] increases after TIPSS [TIPS] and cardiorespiratory complications are common, yet unrelated to increased PAP" and that the exact mechanism is not yet well understood. Further research is needed to describe the exact mechanism related to pulmonary hypertension after a TIPS procedure.

Treatment of Pulmonary Hypertension Post-TIPS

Although pulmonary hypertension is a well-known complication associated with a TIPS procedure, the recommendations for treatment are less developed. Review of current literature reveals a gap in information available to the clinician about treating acutely decompensating pulmonary hypertension associated with a TIPS procedure. A single-case report describes the clinical course of a patient who developed pulmonary hypertension 1.5 years after a TIPS procedure (Van der Heijde et al., 1996).

Given the paucity of information available, the clinician must extrapolate treatment options from current recommendations for the treatment of pulmonary hypertension. The following discussion summarizes the current therapies for pulmonary hypertension, the limited studies involving portopulmonary hypertension, and how this information could be used in the acutely decompensating cirrhotic population. However, it must be emphasized that further research is needed to investigate the most appropriate therapies for patients with chronic liver disease experiencing an acute decompensation after a TIPS procedure.

The foremost goal in any rapidly decompensating patient with dyspnea is airway protection. The primary intervention is to maintain arterial oxygen saturations more than 90% with supplemental oxygen. Because of the rapid change in intravascular volume and the large change in preload associated with a TIPS procedure, the use of diuretics to reduce intravascular volume is recommended (Galie et al., 2004). Continuous assessment of the patient's volume status and response to treatment must be performed with special concern for blood pressure and electrolyte abnormalities.

An additional factor to consider when deciding on treatment interventions is the hypothesized increased resistance to pulmonary flow related to released substances from the GI tract or the liver itself after a TIPS procedure. The increased vascular constriction caused by these released substances may be affected by administration of vasodilatory medications.

The therapeutic effect of endothelin receptor antagonists and prostanoids is well supported in current literature for pulmonary hypertension (Galie et al., 2009). The beneficial vasodilation of the vascular system induced by these medications has been demonstrated in the long-term treatment of patients with portopulmonary hypertension and may prove to be beneficial to the acutely decompensating post-TIPS patient. There are limited case reports of patients being started on intravenous or inhaled prostacyclin drugs such as epoprostenol

or iloprost; however, these studies looked at long-term treatment of portopulmonary hypertension unrelated to a TIPS procedure. The results of these studies revealed improved symptom management and safe administration of these medications in the cirrhosis patient (Hoeper et al., 2007; Kuo et al., 1997).

Additional studies and case reports have been published on the use of oral endothelin receptor antagonists and prostanoids in the cirrhotic patient. Given the respiratory compromise of the acute decomensating TIPS patient, the use of oral medications is not advised but may become a beneficial treatment option if long-term treatment is warranted (Cartin-Ceba, Swanson, Iyer, Wiesner, & Krowka, 2011). Adverse effects experienced with the long-term administration of these medications include increased incidence of ascites and splenomegaly (Galie et al., 2009).

Other medications such as calcium channel blockers, digoxin, and warfarin are typically considered in the treatment algorithm of pulmonary hypertension (Galie et al., 2009). The initiation of these medications necessitates careful consideration of the individual patient. If the patient is at increased risk of bleeding, anticoagulation should be avoided and the use of calcium channel blockers requires the assessment of vasoreactivity during right-sided heart catheterization (Galie et al., 2009). The use of β-blockers may worsen the patient's clinical condition and may need to be discontinued in the acute period (Galie et al., 2009). While proven to be beneficial in pulmonary hypertension, the use of these treatments in acutely decompensating patients after a TIPS procedure requires further studies to determine the most therapeutic and beneficial treatment options for these patients.

Hepatitis C virus-related cirrhosis and associated complications, including ascites and variceal bleeding, will continue to be frequently observed in the healthcare field. As the number of patients experiencing complications of the disease increases, so will the occurrence of procedures to decrease these complications such as a TIPS procedure. To effectively treat the patient, the clinician must first be aware of the potential complications following a TIPS procedure.

Special attention should be afforded to the most life-threatening potential complications post-TIPS such as hemorrhage and pulmonary hypertension. Inability to diagnose and respond quickly could result in life-threatening consequences for the patient. Although pulmonary hypertension is well recognized as a potential complication, the lack of evidence-based data in this population makes the current treatment based upon clinician preferences, anecdotal experience, and extrapolation of data from pulmonary hypertension studies. Further studies are needed to guide interventions and treatment in this population.

Summary

Important signs and symptoms that may be suggestive of pulmonary hypertension after a TIPS procedure include dyspnea, fatigue, syncope, lightheadedness, chest pain, palpitations, edema, jugular vein distention, loud pulmonic component to the second heart sound, parasternal lift, tricuspid murmur, early systolic click, pulmonic murmur, hypotension, diminished pulse pressure, and cool extremities (Goldman & Schafer, 2012). Key diagnostic evaluation involves rapid assessment of electrocardiography, chest x-ray, ABG, and complete blood cell count. If there is a continued suspicion of pulmonary hypertension, obtaining a transthoracic echocardiography and placement of a pulmonary artery catheter may provide further information. ✪

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