Evaluation of liver transplant candidates: A pulmonary perspective

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Abstract:

Chronic liver disease is one of the leading causes of mortality and morbidity in the worldwide adult population. Liver transplant is the gold standard therapy for end-stage liver disease and many patients are on the waiting list for a transplant. A variety of pulmonary disorders are encountered in cirrhotic patients. Pleura, lung parenchyma, and pulmonary vasculature may be affected in these patients. Hypoxemia is relatively common and can be asymptomatic. Hepatopulmonary syndrome should be investigated in hypoxic cirrhotic patients. Gas exchange abnormalities are common and are generally correlated with the severity of liver disease. Both obstructive and restrictive types of airway disease can be present. Abnormal diffusion capacity is the most frequently observed pulmonary function disorder in patients with cirrhosis. Hepatic hydrothorax is another finding which is usually seen in conjunction with, but occasionally without ascites. Portopulmonary hypertension is a complication of long standing liver dysfunction and when severe, is accepted as a containdication to liver transplant. Since respiratory disorders are common and have significant impact on postoperative outcome in patients undergoing liver transplant, a careful preoperative pulmonary assessment is important.

Key words:

Hepatopulmonary syndrome, liver transplant, respiratory disorders

Regardless of etiology, advanced liver disease affects respiratory function as well as other organ systems. A variety of pulmonary disorders have been identified in patients with chronic liver disease. It is so common that around half of patients with advanced liver disease have been reported to be hypoxemic.[1] Both lung parenchyma and pleural space might be affected in patients with chronic liver disease. The impairment in pulmonary function in cirrhotic patients is multifactorial. In addition to preexisting lung diseases such as chronic obstructive pulmonary disease (COPD), bronchiectasis and asthma, cirrhotic patients may suffer from compromised lung function as a result of many reasons associated with liver disease. Edema, tense ascites, pleural effusion, interstitial lung edema, intrapulmonary vascular disorders, and respiratory muscle wasting are among such factors that contribute to development of respiratory dysfunction in these patients.[2]

Since respiratory disorders are common and have a significant impact on postoperative outcome in patients undergoing liver transplant (LT), a careful preoperative assessment is of paramount importance. In this paper, we aim to review the main respiratory disorders and preoperative pulmonary assessment of LT candidates. Pulmonary disorders related to liver disease are examined under three main headings.

Hepatopulmonary Syndrome and Gas Exchange Abnormalities

Hypoxemia is a very common clinical entity in patients with advanced liver disease.[3] Many factors are proposed to contribute to development of hypoxemia in cirrhotic patients such as hypoventilation, restrictive factors resulting from respiratory muscle wasting, the presence of ascites, pleural effusion, pulmonary edema, or changes in the ventilation–perfusion relationship as well as in the diffusion and abnormal vasoconstricting responses.[3]

Hepatopulmonary syndrome (HPS) is among the increasingly recognized complications of liver cirrhosis in patients suffering from hypoxemia. It is defined as a triad of hepatic disease, hypoxemia, and abnormal dilatation of intrapulmonary vasculature [Table 1].[4] Typically capillaries near the alveolar areas are dilated. Alveolar–arterial oxygen gradient [P(A-a)O$_2$] is elevated which is an early and sensitive indication of this syndrome. Further characterization might be established by documenting the intrapulmonary shunt using technetium-99m macroaggregated albumin labeled lung-perfusion scintigraphy, or contrast-enhanced echocardiography.[5] Contrast echocardiography is considered as the method of choice. It is a widely available and a noninvasive modality that can be used to document the dilatation of intrapulmonary vessels.[6] In normal persons with no cardiopulmonary disease intravenously injected microbubbles obtained

Table 1: Main characteristics of hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax

	Hepatopulmonary syndrome	Portopulmonary hypertension	Hepatic hydrothorax
Definition, Diagnostic criteria	A triad of: 1. Liver disease 2. Hypoxemia, abnormal P(A-a) > 15 mmHg 3. Intrapulmonary vascular dilatation	Pulmonary hypertension in patients with liver disease and portal hypertension Mean PAP > 25mmHg, PCWP or LA pressure <15 mmHg and other causes excluded	Pleural effusion in cirrhotic patients in the absence of cardiac, pulmonary/ pleural disease Usullay seen in conjunction with ascites
Symptoms	Progressive dyspnea Platypnea Cyanosis	Dyspnea on exertion Fatigue Palpitations Orthopnea Syncope-near syncope (rarely)	Dyspnea Chest pain Cough
Chest X-ray	Usually normal	Hilar enlargement Cardiomegaly	Pleural effusion (mostly right sided)
Diagnostic tools	Contrast echocardiography (method of choice) Technetium-99-labeled macroaggregated albumin scanning Pulmonary angiography (rarely indicated for this aim)	Doppler echocardiography Right heart catheterization (gold standard)	Chest X-ray Computed tomography Ultrasonography
Therapy	Oxygen supplementation Liver transplant (curative)	Vasodilators (epoprostenol, iloprost, sildenafil) Liver transplant for mild-to-moderate PPHT (partial improvement)	Salt restriction and diuretics Thoracentesis Pleurodesis TIPS Liver transplant

PPHT = Portopulmonary hypertension, LA = Left atrium, PCWP = Pulmonary capillary wedge pressure, TIPS = Transjugular intrahepatic portosystemic shunt

from agitated saline do not pass through the pulmonary microvasculature. Opacification of left atrium and left ventricle indicates the presence of intrapulmonary or intracardiac shunting. In that case timing of the appearance of microbubbles in the left heart chambers determines the place of shunting. If microbubbles appear early in the left heart chambers, within three heartbeats, it indicates the presence of intracardiac shunting. In the case of intrapulmonary shunting, which is the case in HPS, bubbles are seen in the left side of the heart within four to six cycles. On nuclear imaging the uptake of radionucleotide in brain and kidney suggests the presence of intrapulmonary shunt. In a normal person, technetium-99-labeled macroaggregated albumin is large enough to be trapped in the pulmonary vascular bed. In the case of abnormally dilated pulmonary vasculature, it can pass through the lungs and appear in the kidneys and brain. Intrapulmonary vascular dilatation can also be shown by pulmonary angiography which is rarely indicated for this purpose.

It is reported that HPS is prevalent in around 20% of patients awaiting LT.[5] Schiffer *et al.* reported that the presence of HPS is a predictor of prognosis in cirrhotic patients.[7] The cause of death in these patients is usually as a result of the complications of hepatic disease rather than hypoxemic respiratory failure. The main complaint is progressive dyspnea. Spider naevi, finger clubbing, dyspnea, severe hypoxemia, and cyanosis are of the more common symptoms and signs in cirrhotic patients with HPS than those without this syndrome. Although not pathognomonic, the presence of platypnea and orthodeoxia in a patient with advanced liver disease should alert us about the presence of HPS. Platypnea is defined as dyspnea provoked by a erect position which resolves with recumbency. Othrodeoxia is diagnosed as arterial deoxygenation (a decrease in $PO_2 \geq 5\%$ or ≥ 4 mmHg) developed by upright position and relieved by lying down. Hyperventilation is common in these patients and hypocapnia and respiratory alkalosis are among the characteristic findings on arterial blood gas analysis.

Diffusion capacity (DLCO) is consistently decreased in patients with HPS. A 100% oxygen shunt study might be performed to discriminate between anatomical and functional shunts. Arterial PO_2 is measured when the patient breathing in room air in the supine and erect positions. Then, these measurements are repeated while breathing 100% oxygen. If arterial PO_2 is below 200 mmHg on 100% oxygen it indicates the presence of severe pulmonary vascular dilatations or intracardiac shunt.

Although the precise link between chronic liver failure and intrapulmonary vascular dilatation/shunt is not entirely clear, several mechanisms are proposed. Failure of removal of the vasodilator substances from the pulmonary vascular bed and increased production of circulatory vasodilators by the diseased liver such as prostacyclin, nitric oxide, and vasoactive intestinal peptide may contribute to pulmonary vascular dilatation. In animal models, it was demonstrated that upregulation of the nitric oxide synthase in the pulmonary arteries of rats lead to development of HPS.[8,9]

Except for supportive measures and oxygen administration there is no effective medication to treat HPS. Liver transplant, which provides a significant survival benefit, remains the only effective way of treating patients with this syndrome. Although mortality might be increased if preoperative hypoxemia is severe, the presence of HPS is a well-defined indication for LT. Swanson *et al.* from the Mayo Clinic reported that outcome after LT is similar between patients with and without HPS with a 5-year survival of 76%.[10] The European Respiratory Society Task Force proposed a classification system that uses PaO_2 to stage the severity of HPS. It is classified as mild when PaO_2 is 60–80 mmHg, moderate when 50–60 mmHg, and severe when <50 mmHg.[11] Although there is no association between the severity or presence of HPS and the severity of liver disease, staging the severity of HPS might be important for predicting prognosis and preparing the patient for LT.[10] In the above mentioned study by Swanson *et al.*, the strongest predictor

of death following LT were severe preoperative hypoxemia ($PO_2 < 50$ mmHg) and large intrapulmonary shunt identified on a lung scan with a brain uptake of 20% or more.[10] For this reason, we believe that when defining the postoperative risk, such factors should be taken into account. Although severe HPS is not considered a contraindication for transplant, when assessing patients with severe hypoxemia for LT candidacy the decision may be individualized. Since hypoxemia can be asymptomatic in patients with cirrhosis, hypoxemic patients, regardless of symptoms, should be evaluated for HPS because of the risk of mortality in the pre-transplant period.

Gas exchange abnormalities are quite common in patients with advanced liver disease and are generally correlated with the severity of liver disease. A decrease in total lung capacity, airway obstruction, an increase in $P(A-a)O_2$ gradient, impairment in DLCO are of commonly reported pulmonary function test (PFT) abnormalities in patients with advanced liver disease.[12-15]

Abnormal DLCO is the most frequently observed pulmonary function disorder in patients with advanced liver disease which was reported to occur in more than half of these cases.[13,15] Several mechanisms are proposed to be involved in the reduced diffusing capacity, including an abnormal ventilation/perfusion ratio (VA/Q), the presence of arterial venous shunts, interstitial edema, ascites, and changes in the alveolar-arterial membrane. Yigit *et al.* documented that there is a relationship between the severity of liver disease and diffusion tests and suggested that diffusion tests should be performed in addition to the PFT in LT candidates.[16]

Both obstructive and restrictive types of airway disease are observed. The reported prevalence of obstructive airway disease in cirrhotic patients varied between 7 and 18%.[13,17] As in the general population, smoking is the main risk factor for development of obstructive airway disease. In a study by Ehlers *et al.*, smoking has been shown to affect the postoperative outcome adversely in patients who underwent LT.[18] As a result, it is our belief that specific attention should be paid to those patients who smoke in the pretransplant pulmonary evaluation. Coexisting restrictive type of airway disease is also common in patients with advanced liver disease. Ascites, pleural effusion, atelectasis, and hepatomegaly are some of the causes of decreased lung compliance. This in turn, may lead to an underestimation of the actual presence of obstructive airway disease in these patients because of an increase in FEV1/FVC ratio.

Portopulmonary Hypertension

One of the major effects of long standing liver disease is on the pulmonary vasculature. Pulmonary hypertension that develops in patients with liver disease and portal hypertension is called portopulmonary hypertension (PPHT) [Table 1]. It is diagnosed by an increase in mean pulmonary artery pressure (PAP) of ≥25 mmHg, with an elevated pulmonary vascular resistance (>240 dyn/s/cm) and a normal pulmonary capillary wedge pressure (<15 mmHg).[1] It is classified as severe when mean PAP ≥ 45 mmHg, moderate when mean PAP is between 34 and 44 mmHg and mild when mean PAP is between 25 and 34 mmHg.[19] Around 20% of

patients with cirrhosis have been shown to have an increase in PAP.[20] However, the prevalence of true PPHT is reported to range from 2 to 10%.[21]

Accumulating data indicate that hepatosplenic schistosomiasis is a common condition associated with pulmonary arterial hypertension. It may account as one of the most prevalent form of PPHT worldwide, primarily in endemic areas. A recent study from Brazil showed elevated PAP in 7.7% of the patients with hepatosplenic schistosomiasis.[22] Physiopathologic mechanisms of the development of pulmonary arterial hypertension in patients with schistosomiasis is not clearly known, but probably multifactorial. Portal hypertension develops as a consequence of granuloma formation and periportal fibrosis in the liver. The eggs of this microorganism can pass through portacaval shunts to the vessels of the lungs leading to vascular inflammation and obstruction in affected cases. Additional factors such as changes in vascular tonus may also contribute to development of PPHT. Pulmonary hypertension in this setting has been demonstrated to occur at pre-or postcapillary levels. The clinical manifestations of this form of pulmonary hypertension are similar to those of the idiopathic form of pulmonary arterial hypertension.

Histopathological examination of pulmonary vessels in patients with PPHT reveals similar findings to those with other forms of pulmonary arterial hypertension.[23] Intimal proliferation, smooth muscle cell hypertrophy, and fibrosis are evident in the histological sections obtained from small pulmonary arteries.[23] Along with these changes, thrombus formation might also be noted. The exact pathogenesis of PPHT is not known. Activation of vasoconstrictor systems such as endothelin and serotonin, vasoproliferation, inflammation, thromboembolism, and genetics are among the proposed physiopathological mechanisms that play a role in the development of PPHT. Increased shear stress because of high cardiac output may also lead to an elevation in PAP.

As in other patient populations, elevation of PAP in patients with chronic liver disease is a poor prognostic indicator.[24] If left untreated, the course is usually fatal.

The affected cases might be asymptomatic at early stages of the disease. The most common symptom is dyspnea on exertion. Chest pain, palpitations, near syncope–syncope are some of the other less common complaints. Findings on physical examination may include, a louder second heart sound, a systolic murmur because of tricuspid regurgitation on the left sternal border, right ventricular heave, jugular venous distention, and peripheral edema. Transthoracic Doppler echocardiography is the most widely used noninvasive test for the initial evaluation and diagnosis of PPHT [Figure 1]. It has a very high sensitivity and specificity for the diagnosis of elevated PAP.[25] Right heart catheterization is the gold standard test for the diagnosis and further evaluation of PPHT. In this way, quantification may be established and therapy can be guided.

The prognosis of patients with PPHT is poor in the pretransplant era.[26] Regarding pharmacotherapy there is not much data in the literature with adequate follow-up periods that assist in guiding therapy in these patients. Since thrombocytopenia and
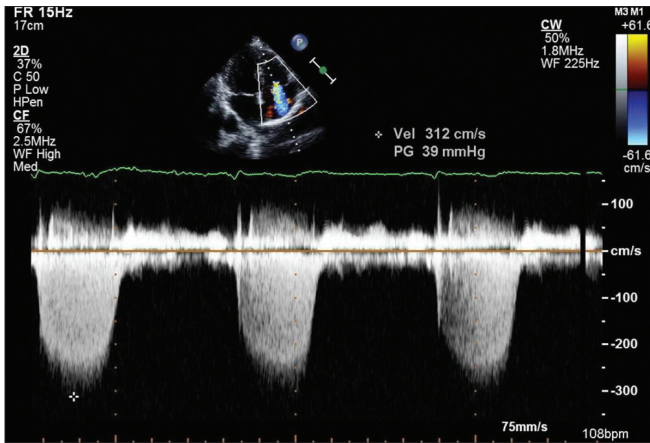
Figure 1: Determination of pulmonary artery pressure using Doppler echocardiography. Using the modified Bernoulli equation the systolic PAP (=4[TR]^2 + RA) can be calculated. Systolic PAP is equal to the right ventricular systolic pressure in the absence of pulmonary stenosis. In this case, estimated systolic PAP is 4 × (3.12)^2 + 10 = 49 mmHg. (PAP: Pulmonary artery pressure, TR: Tricuspid regurgitation velocity, RA: Right atrial pressure)

an increase in the prothrombin time are common, anticoagulant therapy, unlike in other patient subsets with elevated PAP, is not recommended in cirrhotic patients with PPHT. Along with supervised rehabilitation, oxygen, diuretics, digoxin might be administered as supportive therapy. Considering the specific drug therapy, as in other patient populations, basically three classes of agents are available.

The first group is prostanoids. Epoprostenol, iloprost, treprostinil, and beraprost are among the prostacyclin analogues that can be used for the treatment of PPHT in the pretransplantation period. Because of short half-life (3–5 min) epoprostenol is administered as a continuous intravenous infusion. It is a potent vasodilator that can be used in the pretransplant period. Abrupt discontinuation may lead to rebound vasoconstriction and a sudden elevation in PAP. Headache, jaw pain, diarrhea, flushing, leg pain, and nausea are among the common adverse effects. More serious complications are usually experienced because of problems with the delivery system (infection, catheter thrombosis). Iloprost is another available prostacyclin analogue. It can be given orally, intravenously, or as an inhaler. Data with oral use are limited. A 9–12 times per day inhaler has shown to be advantageous. Intravenous administration appears as potent as epoprostenol. Treprostinil is another agent in the same group that can be administered as an intravenous or subcutaneous formulation.

The second group is endothelin receptor antagonists. With regard to the significant role of endothelin system in the pathogenesis of elevated PAP, medications that inhibit this system were developed. Owing to the concerns regarding the hepatic side effects of endothelin receptor antagonists, data with these agents in cirrhotic patients with elevated PAP are limited. In one study, Bosentan has been shown to be an effective medication in the treatment of PPHT.[27] It decreased pulmonary vascular resistance and improved exercise capacity without resulting in serious side effects.

The third group is phosphodiesterase type-5 inhibitors.

Inhibition of this enzyme results in vasodilatation through the cAMP and nitric oxide pathway. Sildenafil, Tadalafil, and Vardenafil are among the available agents in this group that can be used for the treatment of elevated PAP. Data with this group of medication in cirrhotic patients are limited. Sildenafil is a lung tissue selective phosphodiesterase 5 inhibitor that prevents degradation of nitric oxide. Data from small clinical studies show that Sildenafil is effective in reducing PAP in patients with chronic liver disease.[28] Finally, a combination therapy with 2 or all three of these agents might be considered in patients with severe PPHT.

Since mortality is associated with an increase in PAP and PVR the presence of severe PPHT is considered as a contraindication to LT. A mean PAP value of >50 mmHg is regarded as a contraindication to surgery by many transplantation centers.[29] The increased mortality in these cases following transplantation is attributed to progressive right heart failure. However when PPHT is not severe, LT serves as a therapy to reduce PAP in these patients. A study from the Mayo Clinic showed that 28% 5-year survival without LT (n=66) and 56% with LT ($n = 28$).[30] In an our previous study, compared to pretransplant values, a significant reduction in systolic PAP following LT was detected.[31] Of the 114 adult LT patients, 24 (21.1%) had PPHT on Doppler echocardiographic examination. The mean systolic PAP in these patients was 46.6 ± 7.6 mmHg on preoperative assessment which decreased to 37.8 ± 15.5 mmHg in the postoperative follow up. Although the rate of pulmonary complications was higher in patients with PPHT, mortality rate did not differ between patients with and without PPHT. Therefore, we concluded that the presence of PPHT, if not severe, should not be regarded as a contraindication to LT. Rather, LT serves as a therapy for such cases. In line with our findings, other papers also report improvement in pulmonary hemodynamics following LT.[32-33]

Available data clearly re-inforce the role of Doppler echocardiography as the screening test of choice for determining PAP in LT candidates. Since it has great prognostic importance, cirrhotic patients experiencing any form of dyspnea should be evaluated for PPHT. In the case of significantly elevated PAP on Doppler echocardiography (systolic PAP > 50 mmHg), right heart catheterization should be considered. The severity of the disease can be assessed and additional parameters that assist in guiding therapy and establishing LT candidacy might be obtained. Pulmonary vascular resistance is calculated and the vasoreactivity test is performed. The result of vasoreactivity assists as a guide when prescribing pharmacotherapy. If PVR is not elevated, the prognosis after LT is good.[34] If PVR is high, LT should be cancelled owing to the high probability of failure of the donor organ.

Hepatic Hydrothorax

Hepatic hydrothorax is another manifestation of advanced liver disease with a reported prevalence of 10%.[35] It is defined as development of pleural effusion in cirrhotic patients in the absence of cardiac, pulmonary, or pleural diseases [Table 1]. It is usually seen in conjunction with ascites however, occasionally it can occur without ascites.[36] Although the exact mechanism is not clearly defined, it is thought to occur as a result of the passage of fluid from peritoneal cavity

to the pleural space through small defects on the tendinous portion of the diaphragm. More interesting is the occurrence of hepatic hydrothorax without detectable ascites. Here again, the proposed mechanism is the shift of fluid from the peritoneal cavity to the pleural space.[37] The negative intrathoracic pressure in conjunction with diaphragmatic openings permits the passage of fluid as soon as ascites occurs. It is thought that in these cases the reabsorption capacity of the pleura is equal to the production of ascites; so that ascites accumulation will not occur.

Dyspnea, coughing, and chest pain are of the common but nonspecific symptoms. It is mostly right sided and transudative in character. The use of thoracentesis is advised for two reasons: to confirm the diagnosis and exclude other possible causes such as infection and malignancy; and to relieve symptoms (therapeutic thoracentesis). Computed tomography is a useful tool in excluding other lesions of the lungs and pleura. Patency of the portal and hepatic vessels should be evaluated by Doppler ultrasonography.

Therapeutic approach is basically similar to that of ascites. Sodium restriction is advised, and diuretics are started as the first-line treatment. The objective should be to relieve symptoms and prepare the patient for LT. Meanwhile careful attention should be paid to prevention of pulmonary complications and infections until LT is performed. Therapeutic thoracentesis, pleurodesis, transjugular intrahepatic portosystemic shunt (TIPS), splanchnic vasoconstrictors, and thoracoscopic repair of diaphragmatic openings are of the other management options in hepatic hydrothorax.

The Impact of Preoperative Findings on Postoperative Outcome

With regard to the impact of preoperative pulmonary findings in relation to postoperative outcome, we analysed our patient data. Of the 341 patients with chronic liver disease evaluated for LT, 141 underwent surgery (94 from living donor and 47 from deceased donor) (unpublished data). Postoperative pulmonary complications were observed in 60 patients (pneumonia in 28, pleural effusion in 26, right heart failure and respiratory insufficiency in 2, alveolar hemorrhage in 1, hemothorax in 1, pulmonary thromboembolism in 1, and acute respiratory distress in 1). With regard to preoperative assessment findings, smoking history, emphysema, restrictive pattern or combined restrictive and obstructive pattern on PFT, high systolic PAP on Doppler echocardiographic examination, hypoxia on arterial blood gas analysis, and orthodeoxia were found as the factors associated with increased postoperative pulmonary complications. Portopulmonary hypertension was detected in 100 patients and in 17 of them systolic PAP was above 50 mmHg. Seven of these patients with severe PPHT underwent LT and four died following the operation; three due to sepsis and one due to right heart failure.

On a mean of 72.4 months of follow-up, 34 patients died (24.1%). Mortality was significantly higher in patients who developed a postoperative pulmonary complication than those without (38.7% vs. 13.8%). For this reason, during preoperative assessment, factors should be identified carefully to determine the most appropriate candidates who would

benefit most from LT surgery, and to take the necessary precautions in preparing those patients for LT with the least possible risk.

Conclusion

Since LT is a high-risk surgery and respiratory dysfunction is common and affects prognosis, the precise identification of pulmonary disorders is of great importance. In the assessment of an LT candidate, a careful pulmonary evaluation should be carried out, even if the patient is asymptomatic. A thorough history and physical examination provide detailed information, and combined with appropriate laboratory tests, respiratory disorders can be identified. Routine preoperative evaluation should include chest radiography, arterial blood gas analysis, PFTs, and transthoracic Doppler echocardiography. Any abnormal findings on these tests should warrant further study as necessary.

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