Review Article

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Pulmonary complications in patients with liver cirrhosis

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ABSTRACT

Patients with advanced chronic liver diseases, particularly with decompensated liver cirrhosis, can develop specific pulmonary complications independently of any pre-existing lung disease. Especially when dyspnea occurs in combination with liver cirrhosis, patients should be evaluated for hepato-pulmonary syndrome (HPS), porto-pulmonary hypertension (PPHT), hepatic hydrothorax and spontaneous bacterial empyema, which represent the clinically most relevant pulmonary complications of liver cirrhosis. Importantly, the pathophysiology, clinical features, diagnosis and the corresponding therapeutic options differ between these entities, highlighting the role of specific diagnostics in patients with liver cirrhosis who present with dyspnea. Liver transplantation may offer a curative therapy, including selected cases of HPS and PPHT. In this review article, we summarize the pathogenesis, clinical features, diagnostic algorithms and treatment options of the 4 specific pulmonary complications in patients with liver cirrhosis.

Key words: chronic liver diseases, decompensated liver cirrhosis, dyspnea, hepatopulmonary syndrome (HPS), porto-pulmonary hypertension (PPHT), hepatic hydrothorax, spontaneous bacterial empyema

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INTRODUCTION

Cirrhotic transformation of the liver is the characteristic outcome in the long run of chronic hepatic inflammation. Liver cirrhosis might occur as an end stage consequence of manifold infectious, toxic, metabolic, or autoimmune conditions such as viral hepatitis, alcoholism, non-alcoholic steatohepatitis (NASH), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), or a variety of storage disorders like hemochromatosis, Wilson's disease and alpha-1-antitrypsin deficiency.[1] The functional and anatomic consequences include: 1) hepatic insufficiency with restricted synthesis and metabolic functions of the liver, 2) portal hypertension, and 3) consecutively formation of intrahepatic porto-systemic shunts between portal vessels and hepatic veins.[2,3] If clinically relevant complications and sequelae of portal hypertension occur (*e.g.*, ascites, variceal bleeding, splenomegaly, hepatorenal syndrome) as well as deteriorating liver function (*e.g.*, limited formation of coagulation factors, limited degradation of ammonia with development of hepatic encephalopathy), this is called decompensated liver cirrhosis.[2,3]

Pulmonary complications may occur in patients either with or without decompensation of liver disease. These specific disorders need to be distinguished from primary lung diseases, such as chronic obstructive pulmonary disease (COPD), which may occur in patients with liver diseases as well, but are not pathogenically related to the liver cirrhosis. The most frequent and clinically specific relevant pulmonary complications are hepatic hydrothorax, spontaneous pulmonary empyema, hepato-pulmonary syndrome, and portopulmonary hypertension. In the present manuscript, we aimed to give an overview of pulmonary complications of liver cirrhosis and highlight possible treatment strategies.

HEPATIC HYDROTHORAX

Hepatic hydrothorax (HH) is defined as a pleural transudate in patients with liver cirrhosis and/or portal hypertension,

whenever other etiologies of pleural effusion (*e.g.*, renal or cardiac decompensation, or primary pulmonal disorder) have been ruled out (Table 1).[4,5] The presence of an HH is associated with higher morbidity and mortality when compared to ascites alone.[6] A recent study showed that the appearance of HH is associated with a median survival of 8–12 months.[7]

The exact pathophysiological mechanisms involved are yet not completely understood. Since most patients have coexisting ascites and hydrothorax, the currently favored hypothesis is based on a transdiaphragmatic fluid shift from the peritoneal into the pleural cavity via diaphragmatic defects. Patients may present microscopic or even macroscopic diaphragmatic lesions,[8] which are observed more frequently in the right hemidiaphragm, being thinner and less muscular than the left side. A study including 1038 patients with advanced liver cirrhosis described the incidence of HH with 5%, mostly right-sided (70%), less frequently left-sided (12%), or bilateral (18%).[9] Nevertheless, isolated occurrence of HH without ascites may be conditioned by the negative intrathoracic pressure generated during inspiration, promoting fluid accumulation in the pleural space rather than in the abdominal cavity.[10] Ascites is coexisting in 80% of cases with HH but is not required for diagnosis.[11]

Patients may present severe clinical symptoms, even with only a little amount of pleural effusion due to the restrictive pattern of pulmonary function. Clinical symptoms are not very specific and patients may report dyspnea at rest (34%), increased dyspnea after exertion (7%), non-productive cough (22%), pleuritic chest pain (8%), or dizziness and fatigue as a consequence of hypoxemia (7%). Respiratory failure and tension hydrothorax with consecutive cardiac failure have been described.[7,12,13]

Diagnostic thoracentesis to distinguish between transudate and exudate should be performed at initial diagnosis and if recurrent.[7] Complications of diagnostic pleural puncture are scarce (*e.g.*, pneumothorax < 5%, bleeding <1%, vasovagal reactions < 1%)[14,15] and can be further diminished by using sonographic guided puncture techniques. Prophylactic substitution of blood products (platelet concentrates, fresh frozen plasma, or coagulation factors) should only be considered in patients with grave coagulation disorders (INR > 3, platelets < 25,000/mm³).[16]

HH is characterized by a total cell count of polymorphonuclear cell (PMN) < 250/μL, a total protein concentration < 2.5 g/dL, an albumin gradient (serum - pleural fluid) > 1.1 g/dL, or an albumin quotient (pleural fluid/serum) < 0.6. Further optional parameters indicating HH are protein quotient < 0.5 (pleural fluid/serum), a LDH gradient < 0.6 (serum - pleural fluid), and similar pH value as well as glucose concentration in serum and pleural fluid.[17,18] As already mentioned above, renal, cardiac, and primary pulmonal causes of pleural transudate must been ruled out. Useful tools can be echocardiography, urine analytics, computed tomography angiography, cytological or microbiological work-up (in case of suspected malignancy or tuberculosis, respectively)

Table 1: Important clinical, diagnostic and therapeutic options for hepatic hydrothorax and spontaneous bacterial empyema

	Hepatic hydrothorax	Spontaneous bacterial empyema
Definition	Transudative pleural effusion + liver cirrhosis and/or portal hypertension + exclusion of other reasons of pleural effusion (*e.g.*, primary renal, cardiac and pneumological disease)	Spontaneous infection of a preexisting hepatic hydrothorax
Prevalence	5% to 15% in patients with cirrhosis	In 2% of cirrhotic patients, and 10%-16% among cirrhotic patients with hepatic hydrothorax
Diagnostic	Sonography, chest X-ray, diagnostic thoracentesis	diagnostic thoracentesis
Diagnostic criteria of the pleural effusion	1. a total cell count of PMN < 250/μL 2. a total protein concentration < 2.5 g/dL 3. an albumin gradient > 1.1 g/dL between serum and pleural fluid or an albumin quotient (pleura/serum) < 0.6. Optional: a protein quotient < 0.5 (pleura/serum), an LDH gradient < 0.6 (pleura/serum) and comparable values for pH and glucose in serum and pleural fluid.	Total cell count of PMN of > 250/μL + a positive pathogen detection or Total cell count of PMN > 500/μL + a negative pathogen detection
Clinical features	(depending on the amount of pleural effusion) dyspnea at rest/after exertion, non-productive cough, pleuritic chest pain, signs of hypoxemia, respiratory failure and acute tension hydrothorax with cardiac failure	Fever, encephalopathy, hepatorenal decompensation
Therapy options	Sodium restriction, diuretic therapy (furosemide, spironolactone), large-volume paracentesis, thoracentesis, TIPS, liver transplantation, pleurodesis	Intravenous antibiotic and albumin substitution, thoracic drainage

PMN: polymorphonuclear cell; TIPS: transjugular intrahepatic portosystemic shunt.

or specific laboratory tests when chylothorax (triglyceride level) or pancreatitis (amylase concentration) are considered likely differential diagnoses.

Ultra-sonography and X-ray are valid diagnostic tools. Nevertheless, a computed tomography of the thorax should be performed in order to rule out mediastinal, pulmonary, or pleural malignancies. Complementary abdominal imaging including Doppler sonography of splanchnic veins is recommendable. In some cases, intraperitoneal injection of 99mTc-sulphur colloid or 99mTc-human serum albumin may be helpful and confirms the diagnosis of HH when radioisotopes migrate from the peritoneal cavity into the pleural space.[19,20]

Therapy of HH is based on the therapeutic principles of ascites treatment. Sodium restriction, diuretics, and large-volume paracentesis improve respiratory function and may sufficiently relive symptoms.[21,22] In view of higher complication rates of therapeutic thoracentesis (as compared to paracentesis), it should only be performed if symptoms persist.[23] In order to avoid the development of re-expansion pulmonary edema, pleural puncture volume should not exceed 1.5–2 L/puncture. Substitution of 6–8 g albumin per liter may be beneficial, although no clear evidence for this practice exists. Complications of thoracentesis include pneumothorax, hemothorax, vasovagal episodes, pain at puncture site, laceration of liver or spleen, empyema and subcutaneous emphysema.[24,25]

A transjugular intrahepatic portosystemic shunt (TIPS) may be beneficial in cases of therapy resistant HH. Decreasing portal hypertension, this approach eliminates a major pathophysiological cause of HH.[26] A meta-analysis of 198 patients showed complete recovery in 56% and a partial improvement in 18%.[27] Contraindications for TIPS in HH are similar to those for other indications including severe liver dysfunction, poorly controlled hepatic encephalopathy, right-sided heart failure, pulmonary hypertension and complete portal vein thrombosis.

When TIPS is not feasible, pleurodesis (*e.g.*, applying talcum, OK-432, picibanil, minocycline) may be performed.[28,29] Meta-analysis showed an initial success rate of 70–75%, nevertheless, relapse occurs in up to 25% and complications (especially empyema and renal failure) were observed in up to 80%.[29] If diaphragmatic lesions are identified, surgical treatment with pleural flaps or mesh reinforcement have been described.[30,31] Liver transplantation is the only curative therapeutic option for HH. However, higher rates of postoperative infections and reduced survival rates were described, emphasizing the relevance of HH as an adverse prognostic factor in cirrhosis.[32]

A continuous transcutaneous thoracic drainage is not recommended because of massive protein and electrolyte depletion, risk of infection, renal failure and bleeding.[33,34] Furthermore, studies show increased risk of mortality in patients who did receive a continuous thoracic drainage when compared to patients who underwent (recurrent) thoracentesis.[35]

SPONTANEOUS BACTERIAL EMPYEMA

Spontaneous bacterial empyema (SBEM) is a specific complication of HH, analogous to spontaneous bacterial peritonitis (SBP) in the context of ascites (Table 1).[36]

An observational study following 3390 patients with cirrhosis over four years described SBEM in 2.4% of the overall population and in 10–16% of patients with pre-existing hydrothorax, with an associated mortality of 38%.[37] Recently, it was demonstrated that approximately 50% of patients with HH and pre-existing SBP develop SBEM.[38] Further risk factors associated with SBEM are poor liver function, low total protein and albumin concentrations in serum and/or pleural fluid, and low C3 complement in pleural fluid.[39,40] Mortality rate is described with 20–38%. Germ spectrum associated with SBEM is comparable to that with SBP and frequently includes Escherichia coli, Klebsiella, Streptococcus, or Enterococcus.[36] Of note, cirrhotic patients, particularly patients with a history of frequent hospitalizations, are often affected by infections with multidrug resistant bacterial strains,[41] which account for approximately one third of bacterial infections in hospitalized patients with liver cirrhosis.[42] Clinical symptoms are non-specific, a cardinal symptom is fever with the clinical picture of decompensated liver cirrhosis.

When suspected, a diagnostic thoracentesis should be performed. Diagnosis of SBEM is based on a total polymorphonuclear (PMN) cell count > 250/μL in combination with positive microbiological finding, or a total PMN cell count > 500/μL when cultures of pleural fluid remain negative. However, microbiological work-up remains negative in about two third of the cases.[39, 40] Imaging procedures, especially contrast-enhanced computed tomography, can support the diagnosis and identify pleural abscess formation that may require immediate drainage.

Therapy of SBEM, similar to that of SBP, consists in intravenous administration of 3rd generation cephalosporins (such as ceftriaxone 2 g every 24 hours for 7 to 10 days) and albumin substitution.[37] In countries with high rates of antibiotic resistance, piperacillin/tazobactam or carbapenem should be considered.[43] Antibiotics should be adjusted

according to local resistances and should be initiated right after pleural fluid sampling.[44] In case of purulent SBEM thoracic drainage, local application of streptokinase, or video-assisted thoracoscopic surgery (VATS) in case of chambered effusion should be evaluated.[38]

HEPATO-PULMONARY SYNDROME

Hepato-pulmonary syndrome (HPS) is defined as gas exchange disorder resulting from intrapulmonary vascular dilatation in patients with advanced liver disease, portal hypertension or portosystemic shunting.[45] However, HPS may also occur in acute liver failure such as ischemic or viral hepatitis and portal vein thrombosis.[46,47] Intrapulmonary vascular dilatation can be diffused or localized, rarely pleural and/or pulmonary arteriovenous shunts occur.

Observational studies reported a correlation between the presence of HPS and more severe liver disease.[48,49] The prevalence of HPS among patients with end stage liver disease is about 5–32%.[48,50] Nevertheless, isolated intrapulmonary vascular dilatation can be found in up to 50–60% of patients with liver cirrhosis, but mostly without influencing arterial oxygenation.[51,52] Mortality seems to be doubled in cirrhotic patients with HPS compared to non-HPS cirrhotic patients, independent of age, MELD-score, hypoxemia, and comorbidities.[53]

Pathophysiologically, HPS develops due to changes in pulmonary vessels leading to a lack of arterial oxygenation. The potent vasodilators nitrogen (NO), endothelin-1 (ET1), and carbon monoxide (CO) seem to play a crucial role.[54] NO is increasingly produced in the pulmonary circulation after the activation of both endothelial nitric acid synthase (eNOS) and inducible NOS (iNOS).[55] The underlying liver cirrhosis and portal hypertension cause an increased hepatic production of ET-1.[56] ET-1 enhances the activation of eNOS and triggers monocyte accumulation through endothelin B receptor overexpression in the pulmonary vascular endothelium.[57,58] Monocytes and monocyte-derived macrophages express iNOS and produce heme oxygenase-1, leading to increased CO production and further vasodilation.[59] Additional vasoactive mediators are released by increased bacterial translocation due to portal hypertension (intestinal endotoxemia), whereas their clearance is hampered because of decreased liver function.[60,61] Circulating monocytes enhance neoangiogenesis by producing and upregulating CX3CL1 and vascular endothelial growth factor A (VEGF).[62,63] Histopathologically, these pulmonary changes are reflected by a significant dilatation of precapillary and capillary vessels (15 to 500 microns, normal range is 8 to 15 microns), the formation of arteriovenous and/or portopulmonary shunts.[64,65] Both, vasodilatation and neoangiogenesis play a crucial role and lead to a mismatch between increased perfusion and unaltered alveolar ventilation. This favors alveolar-capillary diffusion limitation, leading to a right-left shunt and ultimately causes hypoxia.[45]

Clinical symptoms of HPS are non-specific. More than 80% of HPS patients present dyspnea in the setting of chronic liver disease. Especially while sleeping, episodes of significant desaturation may occur, even if daytime hypoxemia is moderate.[66] Tachypnea, polypnea and signs of chronic hypoxia such as digital clubbing and cyanosis are found in up to 20% of patients at the time of diagnosis.[53] As vascular dilatation predominately affects basal lung sections, platypnea (= increased breathing difficulty when sitting with improvement when lying down) or orthodeoxia (= decrease in PaO2 of 5% or 4 mmHg when changing position from lying to sitting) is found in about 25% of patients.[67–69]

As an initial screening test, pulse oximetry with a cut-off of 96% saturation at room air can be used. SpO2 < 96% was found to be highly sensitive (100%) and specific (88%) for detecting HPS in patients with a PaO2 < 70 mmHg.[70] Patients with HPS generally present normal findings in spirometry and lung volume measurements (unless there is coexisting obstructive or restrictive lung disease), so that pulmonary function testing is usually not helpful in the diagnostic work-up but may be used to rule out differential diagnoses. The diffusion capacity for carbon monoxide (DLCO) is typically impaired.[71] In the arterial blood gas analysis, an increased alveolar-arterial oxygen partial pressure difference (AaDO2) ≥ 15 mmHg (at age ≤ 64 years) and ≥ 20 mmHg (at age > 64 years) can be found.[72] Based on the arterial PaO2 at sea level, HPS is categorized by the degree of hypoxemia into mild (PaO2 ≥ 80 mmHg), moderate (PaO2 60–79 mmHg), severe (PaO2 50–59 mmHg), and very severe (PaO2 < 50 mmHg).[45]

Transthoracic or transesophageal echocardiography may be used to detect intrapulmonary vascular dilatation.[45,51,65] For this purpose, a normally non-respirable ultrasound contrast medium (shaken 0.9% saline solution to produce sonographically visible microbubbles > 10 μm in diameter) is injected via a peripheral vein. In the presence of a functional shunt due to dilated pulmonary vessels, the detection of the contrast medium in the left heart usually takes place after 2–5 heartbeats (in the case of an intracardiac shunt, such as open foramen ovale or atrial septal defect (ASD), usually after 1–2 heartbeats).[73] Further techniques to detect intrapulmonary shunts are scintigraphy, computed tomography and pulmonary arteriography. Lung perfusion scintigraphy uses 99m-Technetium-macroaggregated human albumin (MAA) (20–50 μm size), which can only cross pulmonary circulation via a right-left shunt.[74] An increased

shunt fraction of > 6% supports evidence that HPS is the major contributor to hypoxemia.[75] Shunt fractions of > 20% indicate very severe HPS (PaO2 < 50 mmHg) and are associated with high mortality.[76] Computed tomography or invasive pulmonary arteriography can visualize vascular dilatations and differentiate diffuse shunts (HPS type I) from focal shunts (HPS type II).[75,77] Pulmonary angiography should only be performed in patients with severe forms of HPS, when arteriovenous shunts seem suitable for embolization.[43] Table 2 summarizes the features and diagnostic findings of HPS.

Currently, there is no established conservative drug therapy for HPS. Effectiveness of invasive reduction of portal hypertension by TIPS is controversially discussed.[78] Interestingly, smaller case series provide evidence that surgical cavoplasty or angiographic embolization of portosystemic shunts improve arterial oxygenation and HPS.[79,80] Upon this contradictory data, no clear recommendations can be given. Long-term supplemental oxygen therapy (LTOT) improves clinical symptoms of intrapulmonary vascular shunts (*e.g.*, dyspnea, fatigue, desaturation).[43]

Indications for initiation of LTOT in the setting of HPS are similar to those used in patients with other chronic pulmonary diseases, namely PaO2 ≤ 55 mmHg or SaO2 ≤ 88%. Patients with milder forms of HPS require periodic monitoring (pulse oximetry and arterial blood gas analysis) every 6 to 12 months to detect worsening of HPS and to evaluate treatment options in time. The only curative treatment option is liver transplantation (LT). Patients with HPS presenting PaO_2 < 60 mmHg should be evaluated for LT. Data from observational studies demonstrated resolution of HPS with improved oxygenation and reduced shunt volumes in about 80% of patients within 6 to 12 months after LT.[81,82] Only patients with severe hypoxemia (PaO2 < 45–50 mmHg) are associated with increased post-LT mortality, and thus, LT is contraindicated in those patients.[83]

PORTO-PULMONARY HYPERTENSION

Portopulmonary hypertension (PPHT) is a rare complication of end-stage liver disease and is defined as pulmonary arterial hypertension (PAH) that is associated with portal hypertension (Table 2).[45,84] Other etiologies of the PAH (*e.g.*, collagen vascular disease, chronic heart failure, human immunodeficiency virus, primary forms of PAH, or drug-induced PAH) and differential diagnosis of primary pulmonary disease (*e.g.*, chronic thromboembolism, chronic lung disease) must be ruled out.

The pathogenesis of PPHT is still unknown. A broad variety of pathophysiological hypotheses were proposed: 1) imbalance of vasoconstrictive and vasodilatory mediators due to impaired liver metabolization, 2) hyperdynamic pulmonary circulation with increased sheer stress on the pulmonary vascular wall, 3) increased local inflammation due to elevated cytokine levels associated with the cirrhotic liver, 4) thromboembolisms that originated from the portal venous system, 5) genetic predisposition. In summary, a remodeling process of the pulmonary vasculature leads to increased pulmonary vascular resistance. Ultimately, this conditions an increased afterload and, in the long run, right-sided heart failure.[85]

PPHT and PAH show a similar histopathological picture characterized by media hypertrophy, remodeling processes of the pulmonary artery's lamina muscularis, and in situ thrombosis.[86] These changes go along with a dysregulation of endogenous vasoregulators, increased endothelin-1 and reduced prostacyclin synthase from pulmonary endothelial cells, proliferation of smooth muscle cells, endothelial activation, and platelet aggregation.

Upon physical examination, an accentuated and split second heart sound, right ventricular heave, right-sided S3 gallop, jugular venous distention, and leg edema may hint at PPHT.[87,88] Electrocardiographic abnormalities include right atrial enlargement, right ventricular hypertrophy, right axis deviation, and/or right bundle branch block. Radiologically, a prominent main pulmonary artery (hilar enlargement) or cardiomegaly may be found. Golden standard for the diagnosis of PPHT is right heart catheterization (RHC). The following criteria are considered diagnostic for PPHT: 1) Elevated mean pulmonary artery pressure (MPAP) > 25 mmHg at rest, 2) normal or low pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg at rest, 3) elevated peripheral vascular resistance (PVR) > 240 dyn-sec-cm-5 and transpulmonary gradient (TPG) > 12 mmHg.[84] The right ventricular systolic pressure (RVSP) estimated by Doppler echocardiography correlates with the mPAP measured by RHC.[89] It is used as a screening test, because a RVSP > 30 mmHg in Doppler echocardiography has a negative predictive value of 100%, whereas its positive predictive value is 59%.[90] Based on the mean values of pulmonary artery pressure, PPHT is classified as mild (MPAP 25–35 mmHg), moderate (MPAP 35–45 mmHg), and severe (MPAP ≥ 45 mmHg).[91]

Among patients with cirrhosis, prospective catheterization studies have demonstrated a prevalence of PPHT between 2% and 10%.[92–94] Female and autoimmune hepatitis (AIH) are associated with an increased risk for PPHT.[88] Notably, similar to what has been demonstrated for HPS, no association between severity of PPHT and severity of liver disease has been found.[88,93] Especially in early PPHT stages 60% of patients do not present symptoms.[92]

Table 2: Features of hepato-pulmonary syndrome and portopulmonary hypertension

	Hepato-pulmonary syndrome	Porto-pulmonary hypertension
Definition	Trias: 1) a gas exchange disorder 2) resulting from intrapulmonary vessel dilatation 3) in the presence of advanced liver disease, portal hypertension or portosystemic shunting	Pulmonary arterial hypertension associated with portal hypertension
Prevalence	5–32%	2–10%
Pathophysiology	Vasodilatation, intrapulmonary shunts, neoangiogenesis	Vasoconstriction
Diagnostic for screening	pulse oximetry (cut-off < 96%), Contrast-enhanced transthoracic echocardiography	Doppler echocardiography
Diagnostic to confirm the diagnosis	Lung perfusion scintigraphy/pulmonary angiography	Right heart catheterization
Severity grades	based on PaO2: mild (PaO2 ≥ 80 mmHg) moderate (PaO2 60-79 mmHg) severe (PaO2 50-59 mmHg) very severe (PaO2 < 50 mmHg)	Based on mPAP: mild (mPAP > 25 to < 35 mmHg) moderate (mPAP ≥ 35 to < 45 mmHg) severe (mPAP≥ 45 mmHg)
Clinical features	Dyspnea (platypnoea, orthodeoxia), significant sleep-time oxygen desaturation	Dyspnea on exertion, chest pain, syncope
Physical examination	Cyanosis, digital clubbing, spider naevi	Rarely cyanosis, accentuated and split second heart sound, tricuspid regurgitation murmur, right-sided S3 gallop and jugular venous distention, leg edema
Electrocardiography	No specific abnormalities	right atrial enlargement, right ventricular hypertrophy, right bundle branch block, axis deviation to the right, signs of RV hypertrophy
Blood gas analysis	Moderate to severe hypoxemia	None to moderate hypoxemia
Chest X-ray	No abnormalities	Cardiomegaly, Hilar enlargement
Contrast-enhanced transthoracic echocardiography	Always positive contrast in the left atrium approx. 3–6 heartbeats to the right atrium	Usually negative (only positive within 3 heart heartbeats in case of open foramen oval or ASD)
99mTcMAA-Scintigraphy	Shunt fraction ≥ 6%	Shunt fraction < 6%
Pulmonary hemodynamics	Normal to lowered pulmonary vascular resistance	Increased pulmonary vascular resistance with normal pulmonary occlusion pressure
Pulmonary angiography	Normal/"spongy" appearance (type I) Discrete arteriovenous communications (type II)	Large pulmonary arteries Distal arterial pruning
Therapy options	Long-term supplemental oxygen Liver transplantation	Prostacyclin pathway agonists, endothelin receptor antagonists, phosphodiesterase inhibitors and guanylate cyclase stimulants, Liver transplantation

ASD: atrial septal defect.

When symptomatic, dyspnea at rest or during exercise, as well as clinical signs of right heart failure are most common. Orthopnea, chest pain, peripheral edema or syncope may develop in the course of disease progression,[87,88,95] often accompanied by symptoms of the underlying liver disease.

Treatment of PPHT focuses on reducing portal hypertension and preventing complications of pulmonary hypertension (*e.g.*, right heart failure, thromboembolism). Because of limited data from patients with PPHT, most of the therapeutic strategies are derived from patients with idiopathic PAH.[96] However, complications of cirrhosis (especially impaired liver function and portal hypertension) must be taken into account when making therapeutic decisions. Patients with PPHT should not routinely receive anticoagulants as thrombocytopenia, coagulopathy or esophageal varices increase the risk of bleeding.[96] Prostacyclin pathway agonists, endothelin receptor antagonists, and nitric oxide-cyclic guanosine monophosphate enhancers (phosphodiesterase inhibitors, guanylate cyclase stimulants) are widely used in PAH. In PPHT, phosphodiesterase-5 inhibitors such as sildenafil and tadalafil are commonly used since their metabolism is not affected by liver dysfunction. Endothelin receptor antagonists (ERAs), particularly bosentan, can be associated with liver toxicity (transaminitis, liver failure, cirrhosis) and should be avoided in moderate to severe liver disease or when aminotransferases are elevated. In contrast to patients with idiopathic PAH calcium canal blockers (CCB) are not useful in PPHT, as here vasoactive response only occurs in 1.7%.[97] Furthermore, hypotension and splanchnic vasodilation induced by CCBs can result in an increased hepatic venous pressure gradient. Patients with PPHT are particularly susceptible to hypotension as systemic vascular

resistance (SVR) is usually low in cirrhosis and CCB may further reduce SVR resulting in reduced right ventricular (RV) filling and RV failure.

Treatment of portal hypertension is delicate when PPHT coexists. Beta-blockers should be avoided as they reduce right ventricle cardiac output and increase pulmonary vascular resistance (PVR).[98] TIPS increases the right ventricle preload and must be avoided in patients with PAH and PPHT. Liver transplantation is a potential curative treatment option. However, retrospective studies showed increased post-LT mortality in patients with moderate to severe PPHT (mPAP > 35 mmHg).[99]

CONCLUSIONS

Dyspnea represents a frequent symptom in patients with liver cirrhosis, but can be related to very different etiologies. After exclusion of extrahepatic cardiopulmonary comorbidities (*e.g.*, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, pneumonia and others), specific pulmonary complications of advanced liver diseases must be ruled out. Importantly, the pathophysiology, clinical features, diagnosis and the corresponding therapeutic options differ between the lung-associated complications of liver cirrhosis. At any rate, pulmonary complications like HH, SBEM, HPS or PPHT indicate an adverse prognosis and should prompt to consider liver transplantation. Despite organ transplantation, various specific treatment options exist, which require thorough diagnostic work-up and a mindful patient stratification.

Conflict of Interest

None declared.

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