Review Article

Pulmonary Circulation

Liver abnormalities in pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a cardiopulmonary disease with high mortality. In recent years, it has been recognized that PAH is a multi-organ system disease, involving the systemic circulation, kidneys, skeletal muscles, and the central nervous system, among others. Right heart failure produces congestive hepatopathy, a disease state that has direct consequences on liver biochemistry, histology, and systemic glucose and lipid metabolism. This article aims to summarize the consequences of congestive hepatopathy with an emphasis on liver biochemistry, histology, and PAH-targeted therapy. Furthermore, PAH-specific changes in glucose and lipid metabolism will be discussed.

Keywords

pulmonary arterial hypertension, liver, venous congestion, lipid metabolism

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Introduction

Pulmonary hypertension (PH) describes a cardiopulmonary disease, in which elevated blood pressure in the lung circulation affects the right ventricle (RV) and can lead to RV failure. Currently, PH is categorized by hemodynamic and clinical schemes. Hemodynamically, PH is defined by a mean pulmonary arterial pressure (mPAP) above 20 mmHg. PH can be divided into a pre- and post-capillary component. Pre-capillary PH, or pulmonary arterial hypertension (PAH), is defined by an elevated mPAP in the absence of increased pulmonary venous or left-sided filling pressures. Whereas post-capillary PH is defined by an increased mPAP and increased pulmonary venous or left-sided filling pressures. A combined pre-and post-capillary state can be present, defined as elevated mPAP, and increased pulmonary vascular resistance (PVR), or increased diastolic pressure gradient.[1] In addition to the hemodynamic definition, PH is currently divided into five different clinical groups according to the underlying pathophysiology, clinical presentation, and treatment strategy. More recently, PAH has been recognized as a multi-organ systemic disease, with abnormalities in the systemic circulation, central and peripheral nervous system, kidneys, skeletal muscle, and immune system.[2,3] Due to its intimate anatomical and physiological relationship to the RV, the liver is one of the first organs impacted by RV failure from PH. RV volume- and pressure overload can lead to congestive hepatopathy that can be associated with a multitude of liver abnormalities.

The liver is the largest solid organ in the adult human body and performs multiple diverse biological functions. There is a bidirectional intricate relationship between the liver, heart, and lung. Liver disease can manifest in various pulmonary diseases. Malnutrition from advanced cirrhosis can lead to immunosuppression and increase the risk for pulmonary infections.[4] Primary biliary cholangitis can be associated with fibrosing alveolitis, pulmonary hemorrhage, and organizing pneumonia.[5] Monogenetic diseases such as hereditary hemorrhagic telangiectasia are associated with vascular malformations in the liver and lungs.[6] Similarly, abnormal pulmonary vasodilation and the formation of

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arteriovenous malformations can develop in patients with congenital heart disease in which the pulmonary circulation is depleted of hepatic venous return.[7] Cirrhosis is associated with pulmonary arterial hypertension (portopulmonary hypertension) or abnormal dilation of the pulmonary vasculature associated with severe hypoxia (hepatopulmonary syndrome).[8] Conversely, cardio-pulmonary disease can lead to liver pathology. Cardiogenic shock and congestive heart failure can be associated with ischemic hepatitis and congestive hepatopathy, respectively.[9,10] Venous congestion from RV failure can lead to a significant increase in hepatic blood volume with a substantial impact on liver function (Fig. 1).[11]

This review article is intended to inform the reader about the pathophysiology of liver abnormalities observed in patients with PAH without pre-existing liver disease. PH associated with liver disease, portopulmonary hypertension, or hepatopulmonary syndrome are not discussed.

Liver biochemical testing in PAH

The dual vascular supply and high metabolic demand put the liver at high risk for circulatory injury from heart failure. The main circulatory disturbances affecting the liver are congestion from right heart failure, ischemic injury from low cardiac output states, or a combination of both.

Acute heart failure with decreased cardiac output and shock can result in ischemic hepatitis.[12] This condition is characterized by a hepatocellular injury pattern with a rapid increase in serum aminotransferases (aspartate and alanine transaminase, AST/ALT), and lactate dehydrogenase (LDH), often above 10 times the upper limit of normal.[9]

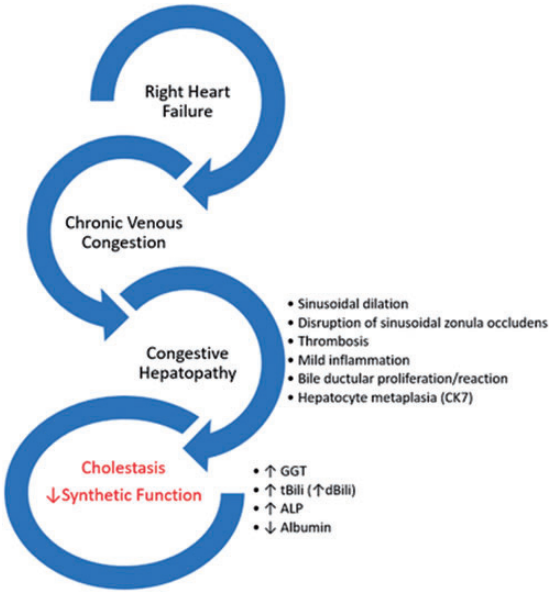

Fig. 1. Right heart failure and liver abnormalities in PAH.

In contrast, hepatic venous congestion from chronic heart failure is mainly characterized by cholestatic liver enzyme elevation (increased bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT),[12] and hypoalbuminemia[13]). Patients with acutely decompensated heart failure and decreased cardiac output can often show a mixed liver biochemical pattern with signs of hepatocellular injury (AST and ALT elevation) and elevation in cholestatic liver enzymes (bilirubin, ALP).[14,15] Cholestasis usually results from obstructed hepatic bile flow into the gallbladder, leading to the accumulation of bile acids in the liver.[16] Mild elevation in cholestatic biochemical testing, such as bilirubin,[15,17] GGT,[14,18–22] and ALP[17,18,20] are found in 17 to 77% of patients with stable congestive heart failure (CHF). Liver dysfunction in patients with chronic left heart disease is highly variable but closely related to right heart hemodynamics (central venous pressure and right atrial pressure), rather than left heart failure.[22] Interestingly, the exact pathophysiology of cholestatic chemistry in CHF is not clear, since there is usually no evidence of frank bile duct injury or obstruction on liver biopsy (see below). Disturbance of hepatic venous outflow can lead to interstitial and cellular edema that can impair the uptake and secretion of bilirubin, bile acids, and other substances. Dilatation of sinusoids can lead to extravasation of blood and increased serum levels of ALP and GGT. A decrease in hepatic congestion can reverse these processes and lead to improvement of cholestatic chemistry, as seen in patients with good treatment response to medical heart failure therapy or in patients undergoing heart transplantation for end-stage heart failure.[23–25]

Acute and chronic inflammation can disrupt hepatocyte and cholangiocyte homeostasis, leading to alterations in intracellular bile-acid transporters, impaired bile secretion, and therefore elevation in bilirubin, ALP, and GGT.[26,27] PAH is characterized by a chronic pro-inflammatory state with elevated levels of circulating cytokines and chemokines[28] that could contribute to impaired liver function and elevation in cholestatic biochemistry.

Impaired synthetic liver function is a well-recognized complication of chronic heart failure. Up to 25% of patients with chronic heart failure and up to 40% with acute heart failure present with low serum albumin levels.[13,29,30]

The etiology of hypoalbuminemia in heart failure is likely multifactorial and involves hemodilution,[31] malnutrition, chronic inflammation,[32] protein-losing enteropathy,[33] and proteinuria.[34] Hepatic congestion from right heart volume and pressure overload can also be associated with hypoalbuminemia.[35] Low albumin concentrations are associated with poor long-term outcomes in heart failure patients[36] but failed to predict response to therapy in acute-decompensated heart failure.[37]

Compared with left heart disease, the literature on liver test abnormalities in PAH is scarce. Similar to left heart disease, in the absence of acute decompensated heart failure,

the predominant biochemical pattern of liver injury in patients with PAH is cholestasis. Elevated total bilirubin levels in PAH patients have been observed in 15 to 20% of patients.[38] A study with 404 idiopathic PAH (IPAH) patients found that *direct* bilirubin was elevated in 37% of patients and was an independent risk factor of mortality.[39] Several smaller studies with well-characterized cohorts of PAH patients reported mildly elevated total bilirubin, ALP, and GGT.[40–44] Elevation in AST/ALT (transaminases) seems to be less common (~2%).

In most studies, bilirubin elevation at baseline is associated with poor prognosis in PAH patients.[38,39,44] In congestive hepatopathy, direct bilirubin is the predominant circulating form of bilirubin and shows a tight relation with central venous pressure.[15] In PAH, direct bilirubin outperformed total bilirubin in predicting survival in multivariate hazard analysis and decreased after response to PAH-targeted therapy or lung transplantation. Consequently, direct bilirubin failed to decrease in patients who did not respond to PAH-targeted therapy, indicating that direct bilirubin is a sensitive marker of venous congestion in PAH and responds to hemodynamic improvement.[39] These results are similar to patients with left heart disease, where decreased venous congestion is associated with a decrease in bilirubin levels and improved survival.[14] It is important to note that in the REVEAL registry, 15% of patients had elevated total bilirubin levels, compared to 4% with kidney dysfunction. However, elevated bilirubin levels were only significantly associated with survival in the univariate model, whereas kidney dysfunction remained a significant predictor of mortality in the multivariate model.[38] Liver and kidney dysfunction were only reported as qualitative variables and therefore need to be interpreted with caution.

Impaired synthetic liver function is common in PAH and decreased albumin levels (<3.3 g/dl) can have been found in up to 19 to 25% of patients.[41,45] Lower serum albumin concentrations were also shown in multiple studies to be a strong independent predictor of poor outcome in PAH patients.[40,41,45] Low albumin levels in PAH are likely multi-factorial (see above).

In addition, some of the commonly used members of a class of chronic pharmacologic pulmonary vasodilation in PAH, endothelin receptor antagonists, can be associated with elevations in AST and ALT which at times necessitates discontinuation (see below for more details).[46]

Despite its significant impact on mortality, and a close relationship to right-sided hemodynamics, liver dysfunction in PAH patients is likely underreported in clinical trials and large registries. This is certainly a component of the PAH field that will require more detailed research to better understand the relationship between PAH and liver dysfunction.

On routine blood work elevation of cholestatic markers with a mild increase in bilirubin, ALP, (GGT), and low albumin are common in PAH and should be monitored over time. Non-invasive biomarkers of liver pathology have low sensitivity and specificity for hepatic congestion. It is therefore important for the clinician to recognize that significant elevation in liver enzymes (2–4 times the upper limit of normal) should immediately prompt a dedicated workup.

Liver histology

Congestive hepatopathy shows a diverse clinical course, non-specific histologic manifestations that vary with the temporal progression and severity of cardiac dysfunction. Histopathological interpretation of liver biopsy samples can be limited by incomplete capturing of the venous outflow tract, consisting of terminal hepatic venules, intercalated veins, and hepatic veins when transcutaneous biopsies are performed. Histopathological characteristics of congestive hepatopathy are patchy distributed centrizonal sinusoidal dilatation and centrizonal fibrosis and mild portal inflammation.[47–50] In more advanced disease portal fibrosis, bridging fibrosis and liver cirrhosis can be seen. These changes correlate with the severity of right heart failure and liver congestion (central venous pressure, right atrial pressure), but not with markers of left ventricular function or cholestatic abnormalities in liver biochemical testing.[50–52]

On a histopathological level, the reason for a predominantly cholestatic liver test pattern in patients with chronic hepatic congestion remains controversial. ALP and GGT are mainly located in the biliary epithelium and the canalicular membranes of the hepatocytes;[53,54] therefore, congestive hepatopathy must be associated with some form of interruption of the hepatocyte-bile duct interface. Most biopsy and autopsy studies in congestive hepatopathy did not find evidence of frank bile duct injury or obstruction that could explain serum elevation in cholestatic liver testing.[47–49] Interestingly, the same observation was made in severe cases of long-standing hepatic congestion, as seen in patients with Fontan-circulation where over one-third of patients have evidence of cholestatic liver test elevation without signs of cholestasis on biopsy.[55–57] Using electron-microscopy on liver biopsy samples from patients with severe congestive hepatopathy revealed occasional dilation and rupture of bile canaliculi.[58] Furthermore, mechanical pressure from hepatic venous congestion can disrupt *the zona occludens* between hepatocytes and the bile canaliculus, exposing the biliary epithelium to circulating blood.[59] It was also observed that patients with congestive hepatopathy show signs of bile duct proliferation. Increased sinusoidal pressure from the hepatic veins can damage the canalicular bile system leading to biliary metaplasia, proliferation, and extravasation of bile salts, which could also explain the cholestatic enzyme profile seen in congestive hepatopathy.[48,49] In addition, two independent research groups found that in congestive hepatopathy, hepatocytes can express Cytokeratin 7 (CK 7), an intermediate filament predominately expressed in biliary epithelium.[47,60] In these studies, CK7 expression correlated with serum total bilirubin levels.

The authors suggest that CK7 expression in hepatocytes could indicate a metabolic transformation of hepatocytes into cholangiocytes that could explain increased serum levels of total bilirubin and AlkP in the absence of frank biliary disease. However, it is important to note that the expression of CK-7 in hepatocytes is likely non-specific and was also observed in NASH cirrhosis, viral and autoimmune hepatitis.[61]

Long-standing hepatic congestion from heart failure may result in cirrhosis. Regardless of the cause of heart failure, right-sided hemodynamics correlate closely with histopathological changes seen in the liver.[51] This is most evident in patients with Fontan-circulation, in which decades of increased venous pressure can result not only in liver cirrhosis but also in hepatocellular carcinoma.[62] Similarly, a biomarker of hepatic fibrogenesis (7S domain of collagen type IV) was found to closely correlate with elevated right-sided filling pressures, and time to clinical worsening in patients with PAH and CHF.[63,64]

Histologically, Budd-Chiari syndrome, a drug-induced liver injury (pyrrolizidine alkaloids, chemotherapy, immunodeficiency, and radiation damage), can cause hepatic outflow-tract obstruction at different levels and are important considerations in the differential diagnosis of congestive hepatopathy.[65]

Even though no comprehensive or detailed reports exist about liver histology specific to patients with PAH, most of the pathophysiological changes from right heart failure will apply to the PAH population. Whether or not PAH-specific therapies, hormonal changes, or alterations in specific metabolic, genetic, and inflammatory pathways are associated with additional or distinctive histologic liver abnormalities is therefore unknown and an area of research opportunity.

Although liver biopsy is not commonly performed in patients with PAH, it is important to recognize the microscopic features of congestive hepatopathy. On histology, a patchy distribution, non-specific centrizonal sinusoidal dilatation, and mild portal inflammation can be seen. These changes are closely linked to right-sided hemodynamics. Venous pressure can lead to micro-injuries at the level of the bile canaliculi, exposing biliary epithelium to circulating blood, leading to mild cholestatic enzyme elevation commonly observed in these patients. Long-standing congestive hepatopathy from chronic right heart failure can result in cirrhosis and in severe cases may lead to hepatocellular carcinoma. See Table 1 for a summary of liver function test abnormalities in patients with PAH.

Lipid metabolism in PAH

The liver is a central organ of carbohydrate, fat, and protein metabolism. Hepatocytes are a major source of triglycerides, many lipoproteins, and the major recipient of low-density lipoprotein (LDL). The liver is also a major regulator of glucose metabolism and plays an important role in insulin resistance and metabolic syndrome.

It is well established that patients with PAH have abnormal concentrations of circulating lipids and lipoproteins. The exact etiology of these changes and the clinical implications are less well defined. Several reports investigating lipoprotein levels in PAH found a reduction in circulating LDL, high-density lipoprotein (HDL), and chylomicrons.[70–74] The most consistent finding of lipid abnormalities in PAH however is a significant reduction of circulating HDL levels. When comparing 69 PAH patients (26% were treatment naïve), to 229 subjects *with significant cardiovascular disease* risk factors but without evidence of PH, a significant reduction in circulating HDL-C levels was found in the PAH group, that could not be explained by age, sex, or statin use. In addition, low HDL-C was associated with increased mortality.[72] These findings have been replicated by several other groups,[71,74,75] including a Chinese cohort of lean IPAH patients.[70] Another study with 227 PAH patients found that HDL levels were an independent predictor of survival after adjusting for comorbidities and right heart hemodynamics.[76] It was also suggested that the subclass of HDL particles modulates the association between HLD and mortality. In two independent PAH cohorts of 127 and 77 patients respectively, a reduction in small Apo A-2 rich HDL subgroup 4 (HDL-4) was independently linked to increased mortality in both cohorts. Based on HDL pleiotropic biological functions, including vasoactive and fibrinolytic activities, it was speculated that reduced circulating HDL levels might be associated with PAH pathophysiology.[77]

In one study with 177 treatment naïve patients, HDL levels were significantly reduced in the PAH cohort, compared with patients who did not have PH, and negatively correlated with PVR, mPAP, right atrial pressure, and positively correlated with cardiac index and mixed venous oxygen saturation.[67] In a cohort of 442 unselected patients with congestive heart failure, right ventricular end-diastolic diameter correlated with reduced circulating lipid levels, including TG, HDL, LDL, independent of LV function, age, gender, smoking status, comorbidities, and statin use. In addition, patients with severe TR had significantly lower lipid levels compared with patients who did not have TR.[78] The liver is the main source of HDL production[79] and it is possible that venous congestion from RV dysfunction can lead to reduced hepatic synthesis of lipoproteins, increased hepatic clearance, and decreased intestinal absorption. It was also suggested that there might be a mechanistic link between low circulating HLD levels and insulin resistance in PAH. Prior studies in non-PAH patients have suggested that insulin resistance correlates with an increased triglyceride to HDL ratio (TG/HDL) and TG/HDL ratios are used as a surrogate marker for pre-diabetic state.[80] One study found that PAH patients have higher TG/HDL-C ratios compared with a gender and age-matched NHANES cohort and concluded that PAH patients are therefore more likely to be insulin resistant.[75] In line with that,

Table 1. Biochemical liver abnormalities in PAH.

Reference	n	Patients	Lab	Summary of findings
Kawut et al.[40]	84	Treatment naïve, PAH (IPAH, HPAH, drug and toxin)	tBili, dBili Alb AST/ALT	↑ ALP, tBili, dBili, ↓Alb were associated with ↓survival in univariate analysis ↓Alb was associated with ↓ survival in multivariate analysis
Stepnowska et al.[43]	47	PAH (CHD, CTD, IPAH)	tBili ALP GGT AST/ALT	↑tBili was associated with ↓ survival
Haddad et al.[41]	119	PAH (IPAH, CTD, CHD, drug and toxin), hospitalized with acute RHF	tBili Alb	20% of patients had ↑tBili ↓Alb was associated with ↓survival
Hao et al.[42]	129	PAH (CTD)	tBili ALP	↑ALP was associated with ↓ survival
Xu et al.[39]	404	PAH (IPAH)	dBili	↑dBili in 37% of patients ↑dbili was associated with ↑WHO-FC and ↓survival
Takeda et al.[44]	37	PAH (IPAH, CTD)	tBili AST/ALT	↑tBili was associated with ↓survival in UV and MV analysis
Olsson et al.[66]	239	PAH (IPAH, CTD, CHD, PoPH, HIV, CTEPH)	tBili	↑tBili was associated with ↓survival in UV and MV analysis
Benza et al.[38]	2716	PAH (IPAH, HPAH, CHD, CTD, PoPH, drug and toxins, HIV)	tBili	↑tBili in 14% of patients ↑tBili was associated with ↓survival in UV analysis
Wang et al.[67]	177	PAH (IPAH, CTD, PoPH, CHD)	tBili	↑tBili was associated with ↓survival in UV analysis
Benza et al.[68]	773	PAH (IPAH, CTD, CHD, PoPH)	tBili	↑tBili was associated with ↓survival in UV analysis
Hu et al.[69]	173	PAH (IPAH)	tBili AST/ALT	↑tBili was NOT associated with ↓survival in UV or MV analyses
Snipelisky et al.[45]	163	PAH (IPAH, CTD, PoPH)	Alb	↓Alb in 25% of patients ↓Alb was associated with significant pericardial effusion ↓Alb was associated with ↓survival in MV analysis

PAH: pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; HPAH: hereditary pulmonary arterial hypertension; tBili: total bilirubin; dBili: direct bilirubin; Alb: albumin; ALP: alkaline phosphatase; AST/ALT: aspartate transaminase/Alanine transaminase; CHD: congenital heart disease; CTD: connective tissue disease; PoPH: porto-pulmonary hypertension; HIV: human immunodeficiency virus; ↑: increased; ↓: decreased; ↔: unchanged or normal.

another study with 41 PAH patients without a diagnosis of diabetes mellitus found that about half of the PAH patients showed signs of poor glucose control, based on Hemoglobin A1C levels.[81] Even though abnormal glucose homeostasis has consistently shown to be a clinical feature of PAH, the underlying mechanisms remain controversial. It has been shown in various studies with large numbers of different study subjects, that even though TG/HDL ratio correlates with insulin resistance (IR), it is an imperfect predictor of glucose homeostasis Cross-sectional longitudinal analyses with around 3000 patients from the Framingham heart study, found that IR predicts cardiovascular events independent of TG/HDL ratios, implying that lipid and glucose metabolism are not necessarily linked.[82,83] Interestingly, in the original publication investigating reduced HDL levels and outcomes in PAH, HDL levels did not correlate with IR measured by homeostatic model assessment of IR (HOMA-IR), an index of fasting plasma glucose and insulin levels.[72] The finding that triglyceride and HDL levels do not correlate with glucose homeostatic metrics in PAH was later confirmed by several studies using HOMA-IR or oral glucose tolerance testing (OGGT).[73,74,84] Two independent groups found that elevated TG/HLD levels showed a strong correlation with inflammatory markers in PAH patients, such as CXCL-10, IL-1b, IL-6, and MCP-1 [Heresi 2017, Jonas 2019], but not with adiposity or insulin levels.[73,84] This suggests that decreased HDL levels and other lipid abnormalities in PAH might in part be related to chronic inflammation or may have a biological role in the pathobiology of PAH, rather than simply be a consequence of obesity or the metabolic syndrome.

Using oral glucose tolerance testing (OGTT) in IPAH and healthy controls, two independent groups observed that PAH patients have lower baseline plasma glucose and insulin levels and decreased glucose-stimulated insulin secretion, suggestive of increased insulin sensitivity in PAH.[70,84] To further investigate this, one study group utilized the gold standard to define insulin secretion, the hyperglycemic clamp (blood glucose maintained at ~180 mg/dl for 3 h) in six PAH patients and six age- BMI and sex-matched

controls.[85] This study confirmed a decreased insulin response to hyperglycemia in PAH patients as found in other studies.[74,81,84] Surprisingly, the reduction in the insulin response was not due to reduced pancreatic insulin secretion or poor peripheral tissue insulin response, as expected in patients with insulin resistance and metabolic syndrome. The authors rather found an increased hepatic insulin extraction in PAH patients contributing to abnormal oral glucose homeostasis.[85] These findings underscore that abnormal glucose homeostasis in PAH patients is unlikely due to peripheral tissue level (skeletally muscle) insulin resistance and perhaps mediated by decreased systemic insulin circulation due to increased hepatic extraction of insulin. Here, the PAH pathophysiology of glucose homeostasis clearly differs from patients with diabetes mellitus or individuals with insulin resistance due to metabolic syndrome. In type 2 diabetes mellitus, there is an association between poor glucose control and decreased hepatic insulin extraction, contributing to hyperinsulinemia and metabolic syndrome.[86] To this effect, PAH patients behave more like patients with advanced left-sided heart failure. One study did not find a difference when comparing pancreatic insulin secretion in 140 patients with advanced systolic heart failure, compared to 21 sex- age and BMI-matched controls.[87] Worsening systolic heart failure was associated with a reduced insulin/C-peptide ratio that correlated with parameters of right heart function. The authors speculated that liver congestion from worsening right heart failure might cause an increase in hepatic insulin extraction leading to poor glucose control. Abnormal glucose homeostasis and reduced circulating HDL-C levels are also common features of patients with Fontan physiology and chronically elevated central venous pressure leading to congestive hepatopathy.[88,89] In these patients elevated central venous pressure correlated with poor oral glucose control using OGGT. These findings indicate that hepatic congestion independent of its etiology can result in reduced circulating HDL levels and abnormal glucose control.

Traditional cardiovascular comorbidities are increasingly recognized in an aging PAH patient population. Recent research revealed that the PAH metabolism might differ from patients with dyslipidemia, insulin resistance, and metabolic syndrome. This concept not only opens exciting research possibilities but might also have important clinical and treatment implications. It is important for the clinician to understand that the traditional interpretation of lipoprotein levels and hypercholesterolemia as risk factors for cardiovascular morbidity may not apply in the PAH patient population. In addition, there is emerging evidence that the pathophysiology of poor glucose control in PAH differs from patients with diabetes and metabolic syndrome. See Table 2 for a summary of metabolic liver abnormalities in PAH versus patients with metabolic syndrome.

Table 2. Liver in PAH and metabolic syndrome.

	PAH	Metabolic syndrome[90–93]
Lipid metabolism		
VLDL	↑[74]	↑
LDL	↓[71] or ↔[67,74]	↑↑
TG	↓ or ↔	↑↑
HDL	↓↓[94]	↓
TG/HDL	↑[72-75]	↑
Hepatic insulin resistance	No evidence of ↑	↑
Hepatic insulin extraction	↑[85]	↓
Hepatic fat content	No evidence of ↑	↑↑

PAH: pulmonary arterial hypertension; VLDL: very-low-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; HDL: high-density lipoprotein; ↑: increased; ↓: decreased; ↔: unchanged or normal.

Abnormal liver metabolism in patients with PAH is summarized in Fig. 2.

PAH-targeted therapy and the liver

Currently, five different drug classes are approved to treat PAH: prostanoids, prostacyclin receptor agonists, phosphodiesterase 5 inhibitors, (PDE-5i), soluble guanylate cyclase stimulators (sGCS), and endothelin receptor antagonists (ERAs). Except Epoprostenol,[95] most commonly used PAH-targeted therapies are – at least partially – metabolized by the liver. Significant liver toxicity from PAH-targeted therapy is rare. The most common finding of PAH-therapy related hepatotoxicity is a hepatocellular injury pattern with elevation in the transaminases. Among the three prostanoids used to treat PAH, Iloprost and treprostinil undergo hepatic metabolism and their clearance is impaired in patients with liver dysfunction. It is recommended to initiate Iloprost and treprostinil at a lower dose in patients with hepatic impairment and the use in patients with severe hepatic dysfunction (Child-Pugh C) is discouraged.[96,97] In subjects with mild hepatic impairment, oral treprostinil drug levels can increase 1.6- to 2.1-fold. The manufacturer, therefore recommends dose adjustments in patients with mild and moderate hepatic impairment (Child-Pugh class A, B) and recommends against use in patients with severe hepatic impairment (Child-Pugh class C).[98] Treprostinil drug levels can by influenced by inducers or inhibitors of the cytochrome pathway and drug–drug interactions should be reviewed before its use.

Selexipag is an oral prostacyclin agonist that is metabolized in the liver. There was no significant hepatotoxicity reported in clinical trials, but these trials did not include patients with pre-existing liver disease.[99] In patients with moderate hepatic impairment, selexipag levels can increase 2- to 4-fold, when compared to subjects with normal liver function.[100] The manufacturer recommends dose adjustments in patients with moderate hepatic impairment

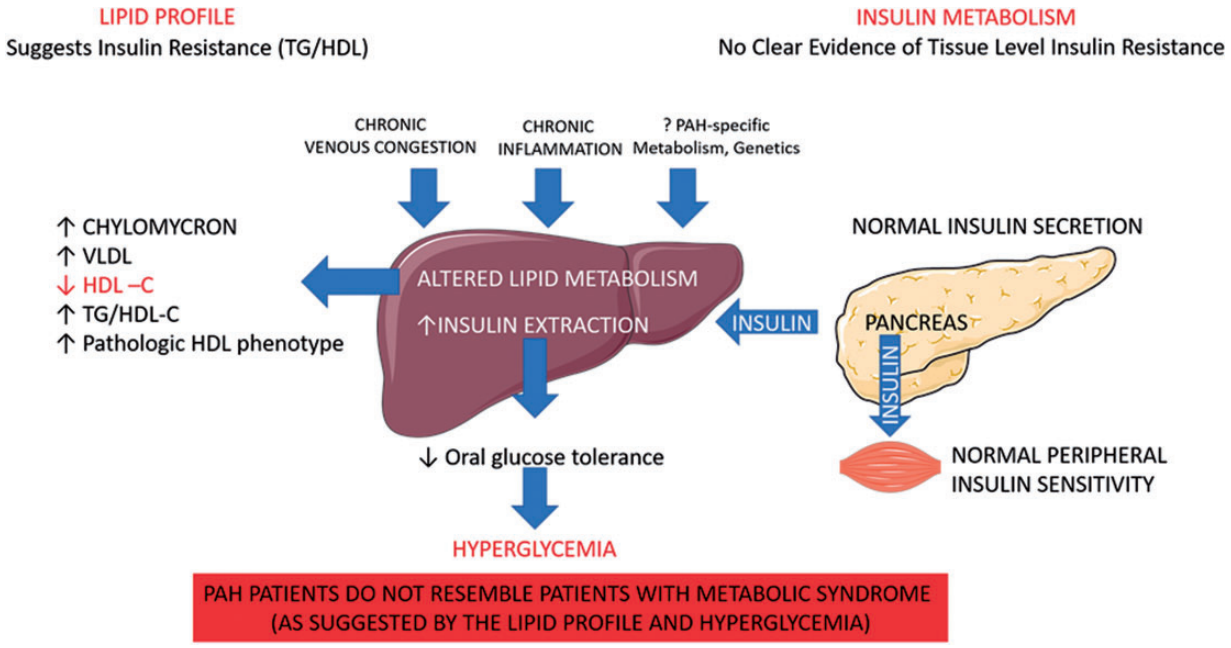

Fig. 2. Liver metabolism in patients with PAH.

(once-daily regimen versus twice-daily) and recommends against use in patients with severe hepatic impairment (Child-Pugh class C).[101] Selexipag is metabolized by the cytochrome system, which may lead to drug–drug interactions.

PDE-5i are metabolized by the liver. However, neither sildenafil nor tadalafil have been extensively evaluated in patients with severe liver disease (Child-Pugh class C) and their use in this patient population is discouraged.[102,103] In patients with mild to moderate hepatic cirrhosis (Child-Pugh class A and B), sildenafil clearance is reduced and can lead up to a 47% increase in maximum drug concentration. According to the manufacturer, it should be considered to adjust the starting dose of tadalafil to 20 mg per day (instead of 40 mg) in patients with mild to moderate hepatic impairment (Child-Pugh class A or B).[102] Both PDE-5i are metabolized by the cytochrome system and prone to drug–drug interactions.

ERAs are hepatically metabolized, but only bosentan is both a substrate and inducer of the cytochrome system.[104] According to a recent meta-analysis, bosentan was associated with the highest risk for hepatotoxicity, compared with ambrisentan[105] and macitentan.[106] In a post-marketing survey, 7.6% of patients taking bosentan developed an elevation in aminotransferases.[107] The bosentan-induced liver injury seems to be dose-dependent.[108,109] The most common liver injury during bosentan therapy is hepatocellular (AST/ALT), but cholestatic liver injury with increased ALP levels has been described. Compared to bosentan, ambrisentan seems to have less hepatotoxicity.[110] Macitentan has been linked to one case of fulminant hepatitis in a young patient with PAH.[111] However, in larger clinical trials, hepatotoxicity from macitentan was rare.[112] Macitentan is not a substrate of active drug transporters, possibly leading to its favorable liver safety profile.[113] Macitentan undergoes hepatic conversion into an active metabolite, and therefore drug levels can be *reduced* in patients with hepatic impairment.[106,114]

Currently, monthly monitoring of liver function test is only recommended in patients taking bosentan,[115] and baseline liver function test is recommended before initiation of ambrisentan and macitentan and repeated during treatment as clinically indicated. The exact mechanism of hepatotoxicity of ERAs is unknown, but likely involves interaction with bile salt transporters, glucuronidation, and cytochrome metabolism.[116] This could explain why the cholestatic potency of bosentan can be amplified by other bile-salt transporter inhibitors, such as glyburide.[108] All ERAs should be discontinued if there is evidence of significant hepatotoxicity.

Riociguat, a sGCS, is metabolized by the liver and hepatic impairment can be associated with higher drug levels.[117] The use of riociguat is discouraged in patients with severe hepatic impairment (Child-Pugh class C).[118] Patients should also be monitored closely for drug–drug interactions.

PAH patients are prone to hepatotoxicity and the practitioner should be aware of PAH-targeted therapy that is metabolized by the liver. Drug–drug interactions are common and need to be taken into consideration before starting PAH-targeted therapies. Even though liver toxicity from PAH-targeted therapy is uncommon, dose adjustments might be necessary. Only patients taking bosentan should be

Table 3. Liver metabolism and dose-adjustment of PAH-targeted therapy in patients with hepatic impairment.

Drug	Liver metabolism	Dose adjustments		
		Mild hepatic impairment (Child-Pugh class A)	Moderate hepatic impairment (Child-Pugh class B)	Severe hepatic impairment (Child-Pugh class C)
Iloprost, inhaled	Increased drug levels in patients with hepatic impairment; not CYP dependent	Consider a starting dose of 2.5 μg and increased dosing intervals (e.g., 3–4 h)	Consider a starting dose of 2.5 μg and increased dosing intervals (e.g., 3–4 h)	Not recommended
Treprostinil iv, sc	2- to 4-fold increase in maximum drug levels in patients with mild to moderate hepatic impairment; drug levels can be influenced by CYP inducer/inhibitors	Initiation dose should be reduced to 0.625 ng/kg/min, increase dose slowly	Initiation dose should be reduced to 0.625 ng/kg/min, increase dose slowly	Not recommended
Treprostinil, oral	1.6-fold increase in maximum drug levels in patients with mild hepatic impairment, 4-fold increase in maximum drug levels in patients with moderate hepatic impairment; drug levels can be influenced by CYP inducer/inhibitors	Start at 0.125 mg twice daily in patients with mild hepatic impairment; avoid in patients with moderate hepatic impairment	Not recommended	Not recommended
Selexipag	1.4-fold increase in maximum drug levels, 2- to 4.5-fold increase in AUC in patients with mild to moderate hepatic impairment; drug levels can be influenced by CYP inducer/inhibitors	No dose adjustment necessary	Start at 200 μg once daily; increase by 200 μg once daily at weekly intervals as tolerated	Contraindicated
Riociguat	Minimal increase in maximum drug levels, but 1.5- to 2-fold increase in AUC in patients with moderate hepatic impairment; drug levels can be influenced by CYP inducer/inhibitors	No dose adjustment necessary	Likely increased drug levels, monitor closely for adverse effects	Not recommended
Bosentan	5- to 12-fold increase in maximum drug levels and active metabolite, drug levels can be influenced by CYP inducer/inhibitors; Liver enzymes need to be monitored	Reduce dose if ALT/AST >3 and <5× ULN, stop Bosentan if >5× ULN.	Not recommended	Contraindicated
Ambrisentan	Likely increased drug levels in patients with hepatic impairment; drug levels can be influenced by CYP inducer/inhibitors	Discontinue if AST/ALT >5× ULN, or if AST/ALT>2× ULN and increase in total bilirubin	Not recommended	Not recommended
Macitentan	Production of active metabolite; associated with slightly reduced plasma levels of active metabolites in patients with hepatic impairment (clinically likely irrelevant); drug levels can be influenced by CYP inducer/inhibitors	Discontinue if AST/ALT >5× ULN, or if AST/ALT>2× ULN and increase in total bilirubin	Not recommended	Not recommended
Tadalafil	Likely increased drug levels in patients with hepatic impairment; drug levels can be influenced by CYP inducer/inhibitors	Consider starting dose of 20 mg	Consider starting dose of 20 mg	Not recommended
Sildenafil	1.5-fold increase in maximum drug levels in patients with mild to moderate hepatic impairment; drug levels can be influenced by CYP inducers/inhibitors	No dose adjustment necessary	No dose adjustment necessary	Not recommended

iv: intravenous; sc: subcutaneous; CYP: cytochrome pathway; AUC: area under the curve; AST/ALT: aspartate transaminase/alanine transaminase; ULN: upper limit of normal.

routinely monitored for hepatocellular liver injury. Hepatically metabolized PAH-targeted therapies and dose-adjustment recommendations are summarized in Table 3.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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Nils P. Nickel is responsible for the content of this manuscript.

Author contributions

Nils P. Nickel conducted the literature review, wrote the paper, and created the figures. Gian M. Galura created the table and wrote the manuscript. Marc J. Zuckerman wrote the manuscript. M. Nawar Hakim wrote the manuscript. Haider Alkhateeb reviewed and edited the manuscript. Debabrata Mukherjee reviewed and edited the manuscript. Eric D. Austin reviewed and edited the manuscript. Gustavo D. Heresi wrote the manuscript.

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