

The Liver-Lung Vascular Connection

Michael J. Krowka, MD

Division of Pulmonary and Critical Care, Transplant Research Center, Mayo Clinic, Rochester MN, USA

ABSTRACT

Since the 1950's and 1960's it is well known that liver dysfunction can induce two distinct lung vascular disorders. We commonly refer to these disorders as hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). This concise review is intended to update the clinician on the current understanding and management of HPS and POPH that has evolved over the last 10 years. Each disorder is discussed in 5 parts: 1) diagnostic criteria/screening/clinical presentation; 2) pathophysiology; 3) epidemiology/natural history; 4) medical management; and 5) implications for liver transplant (LT). A summary table is provided to compare these clinically significant pulmonary vascular disorders.

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Corresponding author: Michael J. Krowka, krowka@mayo.edu

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Correspondence to:

Michael J. Krowka

E-mail: krowka@mayo.edu

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INTRODUCTION

Liver dysfunction can result in two clinically significant lung vascular disorders – hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH)¹. These pulmonary abnormalities can be extremely debilitating, distinct in pathophysiology, treatment approaches and outcomes². The relevance of HPS or POPH is magnified in patients considered for liver transplant (LT) due to related/increased morbidity and mortality³. Although the vascular link between the liver and lung appears straightforward (all effluent from the hepatic veins drain into the pulmonary arterial/capillary bed), this pathway allows an unpredictable sequence of pulmonary vascular change presumably due to a myriad of circulating factors present in the setting of hepatic dysfunction. These factors, in combination with genetic predisposition, may cause pulmonary vascular dilatation and angiogenesis leading to arterial hypoxaemia (in HPS), or result in vascular obstruction due to endothelial/smooth muscle proliferation and platelet aggregation leading to pulmonary artery hypertension (in POPH)³.

Complicating the liver-lung interaction is the lack of correlation between the severity of clinical liver dysfunction and existence and severity of these pulmonary vascular syndromes³.

HPS

Diagnostic criteria/Screening/Clinical presentation

Specific diagnostic criteria for HPS proposed by the 2004 European Respiratory Society Task

TABLE 1. Diagnostic criteria^{1,2}

| Hepatopulmonary syndrome |
|---|
| Liver disease (usually cirrhosis with portal hypertension) |
| Intrapulmonary vascular dilatations <ul style="list-style-type: none"> – Positive contrast-enhanced transthoracic echocardiography*; or – Brain uptake following lung perfusion scan with ⁹⁹Tc macroaggregated albumin[†] |
| Abnormal arterial oxygenation <ul style="list-style-type: none"> – PaO₂ < 80 mmHg; and/or – AaPO₂ ≥ 15 mmHg (> 20 mmHg if age > 64)[‡] |
| Portopulmonary hypertension |
| Portal hypertension [§] <ul style="list-style-type: none"> – Right heart catheterization: <ul style="list-style-type: none"> • Mean pulmonary artery pressure (mPAP) > 25 mmHg • Pulmonary vascular resistance (PVR) > 3 wood units (240 dynes.s.cm⁻⁵) • Pulmonary artery wedge pressure (PAWP) < 15 mmHg |

*Microbubbles in the left heart ≥ 3 cardiac cycles after right heart microbubbles following 10 cc agitated saline injection in a peripheral arm vein.
[†]Brain uptake ≥ 6% following injection in peripheral arm.
[‡]AaPO₂ mmHg = PA_{alveolar} O₂ – PA_{arterial} O₂ = [FIO₂ × (Patm – PH₂O) – PaCO₂/8] – PaO₂
[§]A clinical diagnosis (gastroesophageal varices; splenomegaly, ascites) or portal pressure

AaPO₂: alveolar-arterial oxygen; FIO₂: inspiratory oxygen fraction; PaCO₂: arterial carbon dioxide pressure; PaO₂: partial pressure of oxygen; Patm: atmosphere pressure; PH₂O: water vapor partial pressure.

Force on pulmonary-hepatic disorders and the 2016 International Liver Transplant Society Practice (ILTS) Guidelines are shown in table 1.

HPS is characterized by arterial hypoxaemia due to intrapulmonary vascular dilatations (IPVD). Hypoxaemia is quantified by arterial blood gases that measure partial pressure of oxygen (PaO₂) and allow calculation of the alveolar-arterial oxygen (AaPO₂) gradient⁴. IPVD are documented by the presence positive contrast echocardiography (abnormal left heart opacification by microbubbles ≥ 3 cardiac cycles after right heart microbubble presence following peripheral vein injection of agitated saline) or abnormal brain uptake following lung perfusion after peripheral vein injection of ^{99m}Tc macro aggregated albumin (Fig. 1). Transoesophageal

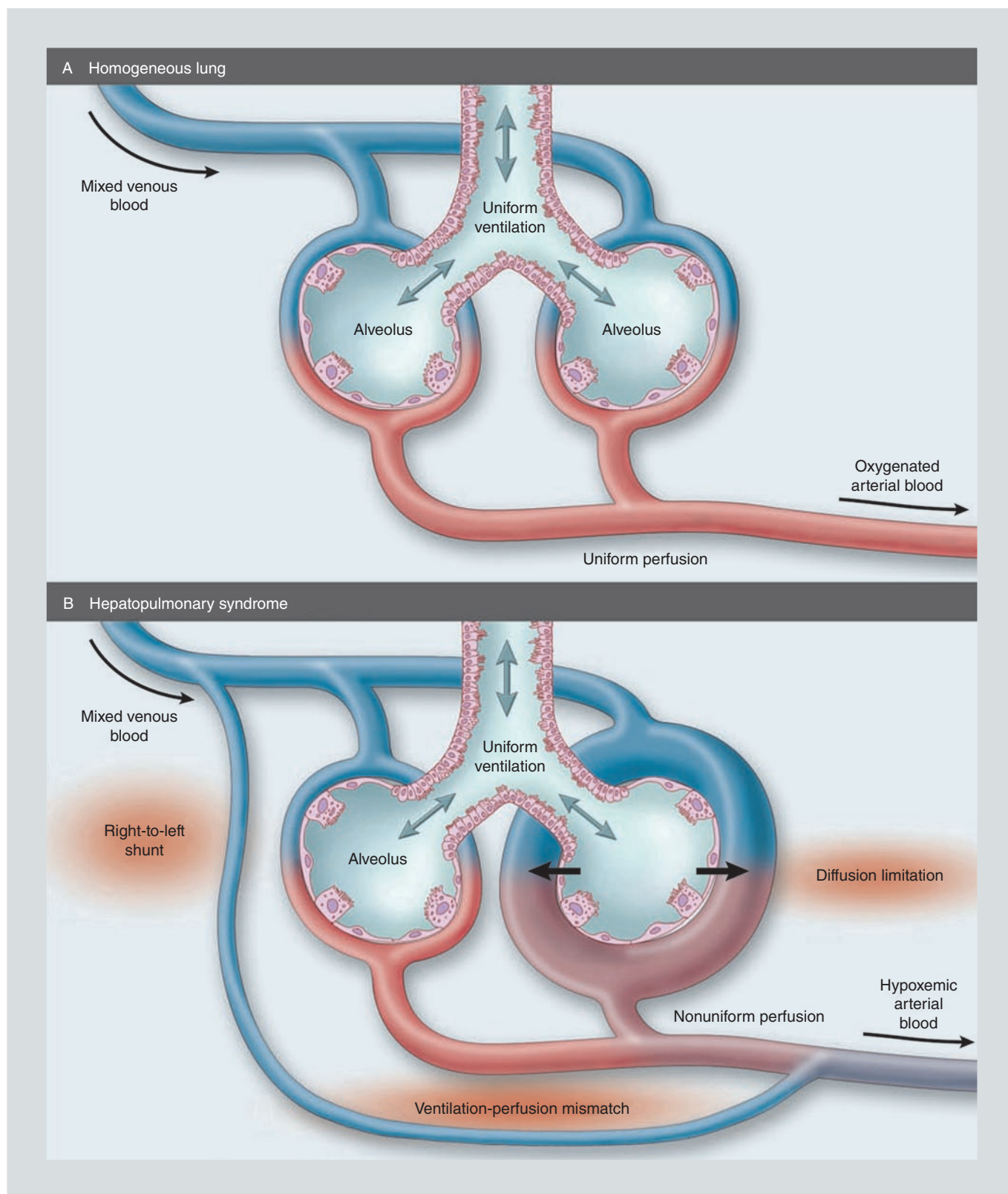


FIGURE 1. The mechanisms for arterial hypoxaemia in hepatopulmonary syndrome (HPS). **A:** normal alveolar-capillary ventilation-perfusion relationship. **B:** dilated capillary bed results in poor diffusion of O_2 into the blood flow. Fast pulmonary transit time due to high cardiac output, as well as uncommon existence of anatomic shunts contribute to hypoxaemia. In summary, the main reason for hypoxaemia in HPS is a mismatch of ventilation to perfusion (reproduced with permission from Rodriguez-Roisin R et al.²).

echocardiography is the non-invasive test of choice to exclude a possible patent foramen ovale or atrial septal defect right to left shunt contributing to “early” left heart opacification of microbubbles².

Screening and follow-up for HPS by finger pulse oximetry has been advocated. Oxygen saturations (SO_2) less than 96% have been associated with a high frequency of HPS⁵. However, many HPS patients have normal SO_2 , thus, the definitive diagnosis of HPS requires determination of PaO_2 and/or AaPO_2 gradient in adults and children⁶.

Clinically, the existence of spider angiomas of the skin, digital clubbing and cyanosis are frequent findings in HPS; exertional dyspnoea is the primary symptom, but dyspnoea can have many aetiologies in patients with advanced liver disease². Pulmonary function testing usually demonstrates a nonspecific, reduced single breath diffusing capacity. Lung volumes and expiratory airflow are otherwise normal. Increased exhaled nitric oxide (NO) has been well documented in HPS, however, reducing exhaled NO levels, may not be associated with improvement in hypoxaemia⁷.

Chest imaging may suggest an interstitial pattern in the lung bases due to a predominance of dilated precapillary and capillary blood vessels. Rarely, discrete arteriovenous communications can be seen on computed tomography (CT) scans of the chest. Pulmonary angiography is indicated if severe hypoxaemia exists and the response to 100% inspired oxygen (O_2) is poor ($\text{PaO}_2 < 300 \text{ mmHg}$)⁸. Angiography would be conducted for the purpose of embolizing discrete arteriovenous communications.

Pathophysiology

The HPS pathophysiology of IPVD causing arterial hypoxaemia at the precapillary and capillary levels (macro and microscopic) is based upon autopsy data and a common bile duct ligation (CBDL) rat model^{9,10}. The contributions of ventilation-perfusion mismatching, diffusion limitation and anatomic shunting noted in humans are variable and shown schematically (Fig. 2). Importantly, the usual response to 100% inspired O_2 in HPS patients may be excellent ($> 500 \text{ mmHg}$) reflecting the dominant ventilation perfusion mismatching in this syndrome.

From a mediator perspective, the factors that induce the predominant features of IPVD (vasodilatation and angiogenesis) are complex. Currently, the three mediators of greatest interest are endothelin (ET) -1, NO and vascular endothelial growth factor (VEGF)¹⁰.

In the CBDL model and humans, bile duct epithelium (cholangiocytes) is the source of increased circulating levels of ET-1. When ET-1 binds to upregulated ET-B receptors in the pulmonary vascular bed (up regulation noted in the setting of portal hypertension), pulmonary nitric oxide synthase (eNOS) is activated leading to NO-induced vasodilatation¹¹.

The activation of inducible nitric oxide synthase (iNOS), another route to cause NO-induced vasodilatation, results from endotoxemia, leading to the recruitment and activation of intrapulmonary vascular macrophages. The macrophages produce the cytokine tumour necrosis factor- α which in turn triggers iNOS activation. Another consequence of these macrophages, which may be increased by ET-1

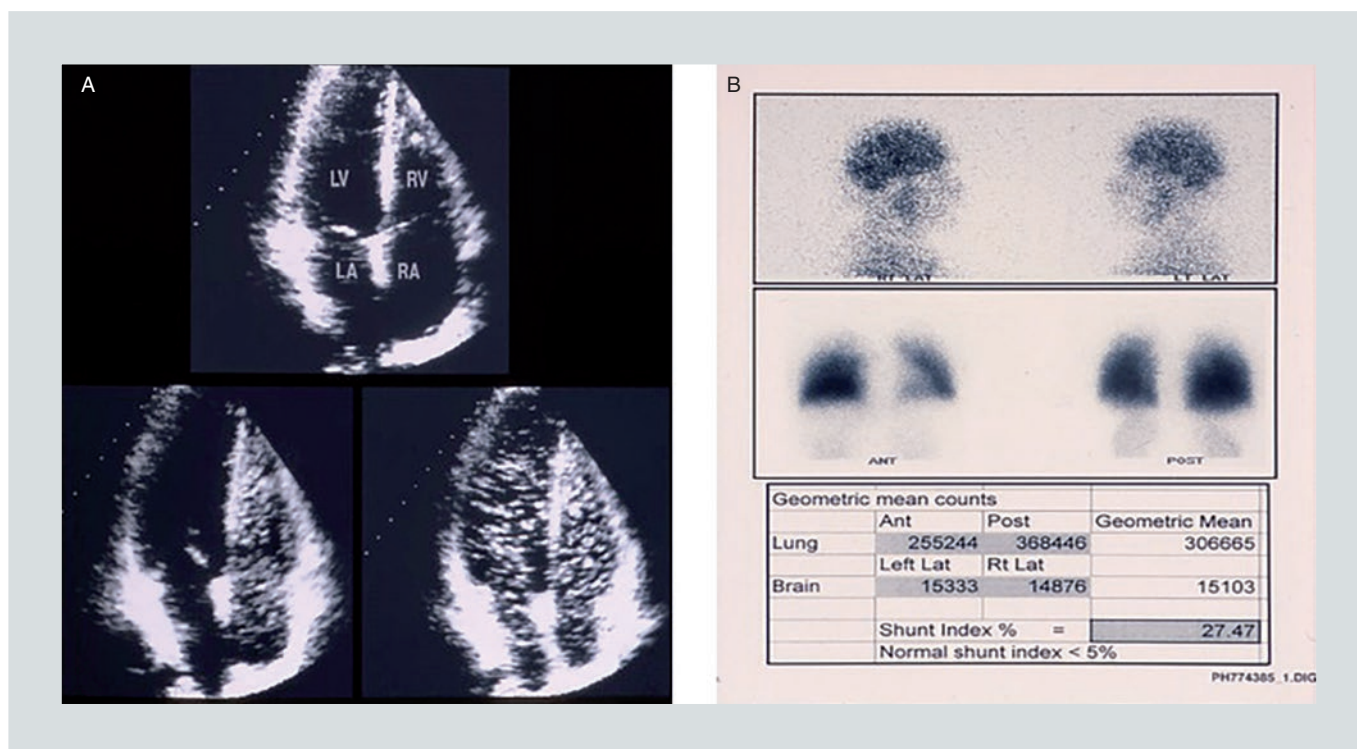


FIGURE 2. Imaging methods to demonstrate intrapulmonary vascular dilatation (IPVD) in a hepatopulmonary syndrome (HPS) patient with: partial pressure of oxygen (PaO_2) = 44 mmHg. **A:** “positive” contrast transthoracic echocardiogram - normal four-chamber view (top); microbubble opacification of right heart (left panel); delayed microbubble opacification of left heart (right panel). **B:** abnormal uptake in the brain (> 6%) after peripheral arm injection of technetium^{99m}-labeled TC macroaggregated albumin. LA: left atrium; LAT: latency; LV: left ventricle; RA: right atrium; RT LAT: right latency; RV: right ventricle.

levels, is to activate VEGF signalling pathways, thus inducing angiogenesis. Anti-angiogenesis therapy with sorafenib, a kinase inhibitor, can inhibit VEGF signalling, angiogenesis and improve gas exchange in the CBDL rat model¹¹.

Epidemiology/Natural history

HPS is not uncommon. Depending on the AaPO_2 and PaO_2 criteria used and the clinical setting, HPS frequency ranges from 4-32%². The frequency of IPVD *without* arterial hypoxaemia is common, occurring in approximately 50% in liver transplant candidates¹². It is important to recognize that approximately 30% of HPS patients may have additional pulmonary

reasons (pulmonary fibrosis, chronic obstructive lung disease, hepatic hydrothorax) for arterial hypoxaemia¹³. The use of macro-aggregated albumin lung perfusion scan (^{99m}Tc-MAA) with brain uptake can help to distinguish between HPS versus non-HPS causes of arterial hypoxaemia. Brain uptake is specifically seen in HPS and not in other hypoxaemia causes².

There is no relationship to any given hepatic disorder, but HPS most commonly occurs in chronic liver disease and portal hypertension. Quality of life is worse in HPS versus non-HPS patients¹⁴. Rarely, HPS has been documented in acute liver disease and extra-hepatic venacava obstruction. Genetic polymorphisms have been identified in HPS¹⁵.

Finally, 5-year survival in 64 HPS patients was approximately 20% for those who did not undergo liver transplant, survival being worse in Child-Pugh class severity liver disease^{16,17}.

Medical management

In HPS oxygenation can worsen over time, but the change is gradual with PaO_2 decreasing an average of 5 mmHg per year; therefore, annual monitoring is advised. Despite anecdotal reports of medications to improve oxygenation in HPS, there is no proven medical therapy, aside from supplemental O_2 to improve hypoxaemia³. Supplemental O_2 via nasal cannula (up to 5 litres/minute to maintain $\text{SO}_2 > 90\%$) at rest, with exercise, and during sleep improves arterial oxygenation (and symptoms of dyspnoea) in the vast majority of cases³. There is no proven role for transjugular intrahepatic portosystem shunting (TIPS) in treating HPS^{18,19}.

A current prospective, randomized National Institutes of Health (NIH) study is underway in the US using sorafenib, a kinase inhibitor to block angiogenesis (<ClinicalTrials.gov>). This study is based upon findings of sorafenib improving oxygenation and blocking angiogenesis in the HPS CBDL animal model.

Implications for liver transplant

In the early days of LT, the existence of severe HPS ($\text{PaO}_2 < 50$ mmHg) and $^{99\text{m}}\text{TcMAA} > 20\%$ were considered an absolute contraindication to LT and high risk for LT, respectively^{2,20}. This is no longer the case due to successful

patient selection and management strategies³. Clinically significant HPS ($\text{PaO}_2 < 70$ mmHg) is now considered an *indication* for LT³.

Because of poor outcomes in the setting of HPS without LT and lack of correlation to the severity of liver disease, a higher priority is given to HPS patients needing LT. The model for end-stage liver disease (MELD) score provides such a basis for LT priority in the United States²¹. Since the MELD score correlates poorly with the severity of HPS, “MELD exception” can be granted when PaO_2 is less than 60 mmHg due to HPS. The MELD score increases every 3 months as long as PaO_2 remains less than 60 mmHg.

In a study of 973 HPS patients given MELD exception (2002-2012), overall mortality was significantly lower (presumably due to earlier LT) compared to non-HPS patients awaiting LT. Overall 1, 3 and 5-year post-LT survival after HPS MELD exception was not significantly different from non-HPS post-LT survival²².

Despite being an indication for LT, there remains a higher risk of post-LT mortality in HPS, more so when very severe hypoxaemia ($\text{PaO}_2 < 44$ mmHg) exists²². Recently, centres with extensive experience in managing/transplanting HPS patients, have demonstrated excellent outcomes and syndrome resolutions when PaO_2 is less than 50 mmHg with no lower limit of PaO_2 that would preclude LT^{23,24}.

Guidelines for the pre- and post-LT management of HPS have been published³. Continual use of supplemental O_2 with a goal of $\text{SO}_2 > 90\%$ is strongly recommended. The intraoperative management of HPS patients is not affected by the type of anaesthesia³. Early

extubation is recommended and well tolerated. In the immediate post-LT period (24-72 hours) it is not unusual for oxygenation to worsen due to blood product/fluid administration and atelectasis. Rarely, the use of inhaled NO or prostacyclin has been used to alter the ventilation-perfusion mismatching post LT to improve oxygenation. The use of extracorporeal membrane oxygenation (ECMO) post-LT has been reported in the rare refractory hypoxaemia situations post-LT³.

Although complete resolution of HPS following successful LT occurs in most cases, the time to resolution varies and is correlated directly to the severity of pre-LT hypoxaemia; HPS resolution usually takes weeks to months to occur²⁵⁻²⁸. Rarely, pulmonary artery hypertension may evolve post-LT following successful resolution of HPS²⁹.

Living donor LT for HPS can have excellent outcomes^{30,31}. Comorbidities that complicate HPS such as common variable immunodeficiency (CVID), metastatic malignancy, or severe cardiopulmonary abnormalities may preclude LT candidacy³.

POPH

Diagnostic criteria/Screening/ Clinical presentation

All-cause pulmonary hypertension (PH) is defined haemodynamically by right heart catheterization (RHC) as a mean pulmonary artery pressure (mPAP) > 25 mmHg³². Distinguishing between pulmonary artery hypertension (PAH), precapillary PH and post-capillary pulmonary is very important in terms of therapy options

and outcomes. The key point to assess PH in liver disease (and establish the POPH diagnosis) is an accurate and complete pulmonary haemodynamic assessment obtained by RHC³. Other causes of PH must be excluded when making the clinical diagnosis of POPH. Specific diagnostic criteria for POPH proposed by the 2004 European Respiratory Society task force on pulmonary-hepatic disorders and the 2016 ILTS Practice Guidelines are shown in table 1. Examples of varying reasons for PH suggested by screening echocardiography, confirmed by RHC, that have occurred in the setting of liver disease are shown in table 2.

Screening for POPH is best accomplished non-invasively by a standard transthoracic echocardiogram (TTE)³³. The velocity of blood flowing back through the tricuspid valve during systole-tricuspid regurgitant (TR) velocity – reflects the pressure gradient between the right atrium (RA) and right ventricle (RV). RV systolic pressure (RVSP) is an estimate of the pulmonary artery systolic pressure assuming a normal pulmonic valve. This relationship between flows and RVSP is given by the modified Bernoulli formula:

$$RVSP \text{ (mmHg)} - RA \text{ (mmHg)} = 4 \times TR \text{ (m/sec)}^2$$

RA pressure can be estimated TTE determination of inferior vena cava collapse during inspiration (none; mild; moderate).

The practice at the Mayo Clinic is to proceed to RHC when RVSP ≥ 50 mmHg or the RV is enlarged with reduction in function. The latter is noninvasively characterized by tricuspid annular plane systolic excursion and longitudinal strain measurements (G. Kane, MD,

TABLE 2. Scenarios with increased mean pulmonary artery pressures

| | TTE RVSP (mmHg) | mPAP (mmHg) | PASP (mmHg) | PAWP (mmHg) | CO (L/min) | PVR (dynes.s.cm ⁻⁵) | Interpretation |
|---------|--------------------|----------------|----------------|----------------|---------------|------------------------------------|--|
| Case #1 | 69 | 33 | 48 | 7 | 11.9 | 2.2 (175) | High flow state |
| Case #2 | 50 | 34 | 49 | 23 | 14.9 | 0.6 (59) | Diastolic dysfunction (Pulmonary venous PH) |
| Case #3 | 68 | 52 | 72 | 11 | 4.0 | 10.2 (846) | POPH (Pulmonary artery PH) |

Case #1: represented a high flow state and required no pulmonary hypertension pulmonary artery targeted therapy. Case #2: had volume overload and diastolic dysfunction with normal renal function. Case #3: had severe portopulmonary hypertension (POPH) with severe right ventricle (RV) enlargement and dysfunction.

CO: cardiac output; mPAP: mean pulmonary artery pressure; PASP: pulmonary artery systolic pressure; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; POPH: portopulmonary hypertension; PVR: pulmonary vascular resistance; RVSP: right ventricular systolic pressure; TTE: transthoracic echocardiogram.

Mayo echocardiography laboratory; personal communication).

Pathophysiology

Unlike HPS, there is no animal model for POPH. The possible reasons for the development of clinical POPH are complex. Importantly, the resulting pulmonary artery hypertension does not correlate with the severity or aetiology of liver dysfunction³.

An obstruction to pulmonary arterial flow is the key feature of POPH. Such obstruction, quantifies at RHC, results in both increased mean mPAP and pulmonary vascular resistance (PVR). Although the literature describing the human pathology found in POPH is scant, the morphology of such a pulmonary vascular disorder has been described as either thromboembolic or plexogenic and, not uncommonly, co-existence of both³⁴.

The thromboemboli described have been usually microscopic. The origin of such emboli has been attributed to the portal venous system and its collateral channels. Organizing clot

in varicose oesophageal and gastric veins has been documented and portal vein thrombi reaching the lung via direct portacaval shunts have been reported³⁴.

Plexogenic arteriopathy refers to a disorganized proliferation of smooth muscle and endothelial cells of the small pulmonary arteries³⁴. Ranging from isolated medial hypertrophy to eccentric and concentric fibrosis, associated with a vasoactive component, these lesions may also be accompanied by vasodilatory pathways that may “off load” the constrictive component. The role of platelet aggregates further contributing to vascular occlusion has been proposed, releasing mediators such as serotonin (causing vasoconstriction) and platelet derived growth factor (stimulating growth of smooth muscles); platelet aggregates have been demonstrated at autopsy in association with severe POPH³⁴.

At the cellular level, three lines of evidence are important in understanding the pathophysiology (and subsequent treatment) of POPH; 1) a deficiency of endothelial prostacyclin synthase; 2) the effect of increased circulating ET-1 levels; and 3) mechanisms to block pulmonary artery vasoconstriction^{35,36}.

An important observation was the lack of prostaglandin synthase expression (by immunohistochemistry) in the pulmonary arteries and plexiform lesions in cirrhosis patients (3 autopsies; one explant)³⁷. Thus, a potent vasodilator (prostacyclin) is absent (or levels reduced) and forms the basis for synthetic prostacyclin replacement as a therapeutic option.

ET-1 is one of the most potent vasoconstrictors implicated in the pathogenesis of idiopathic pulmonary artery hypertension (IPAH). Not only is there a strong pathologic similarity between IPAH and POPH, but in cirrhosis, ET-1 levels are elevated compared to controls. As a corollary, it has been shown that a strong association exists between increased ET-1 blood levels in the pulmonary artery and the presence of POPH. This finding is the basis for a therapeutic approach using ET receptor antagonists³⁵.

Phosphodiesterase type 5 (PDE-5) enzymes normally function to metabolize cyclic guanosine monophosphate (cGMP). cGMP induces vasodilation through relaxation of arterial smooth muscle cells. The inhibition of PDE-5 thus favours vasodilation. Specifically related to POPH, since the pulmonary arterial bed has a high concentration of cGMP, it is theoretically useful to inhibit that enzyme. This approach has been successful in IPAH, and thus it is inferred, but not proven, that a similar pathophysiology may exist in POPH³⁵.

Finally, in nearly all patients with portal hypertension, a high flow state driven by the mesenteric vasodilation, results in a persistent elevation of cardiac output. This high flow state may contribute to a shear stress effect to damage the pulmonary circulation, contributing to pulmonary artery hypertension over time³⁶.

Overall in the setting of portal hypertension, circulating substances (aside from ET-1) may bypass the normal metabolism conducted by the liver, reaching the pulmonary circulation via portosystemic shunts (such as gastric/oesophageal varices or portacaval shunts) and affecting the pulmonary arterial bed. An imbalance of such factors (a lack of vasodilation; an excess of vasoconstrictors, such as thromboxane A-2, interleukins 1 and 6), along with a likely genetic predisposition to POPH, contributes to a complex pathophysiology which may or not be predictably reversible at a given stage of evolution³⁶.

Epidemiology/Natural history

The frequency of POPH depends upon the diagnostic criteria followed and the populations studied. Approximately 10% of the population in the French Registry of PAH had POPH³⁸. Variations in selecting cut-offs for normal PVR (120 versus 240 dynes/s/cm⁻⁵), have resulted in varying prevalence estimates.

In the largest POPH screening and RHC study conducted, it is notable that bias was introduced since only those with an echocardiographic RVSP greater than 50 mmHg went on to have RHC³³. In that study, out of the 1,235 who had echocardiograms, 101 (11%) underwent RHC. Using the criteria shown in table 1 (66%) had true POPH resulting in a POPH frequency of 5.6% in that time span of all liver transplant candidates. Patients with RVSP in the range 40-50 mmHg, mild POPH, may have been missed. Overall, 5.3-8.5% of liver transplant candidates are reported to have POPH³.

The 5-year survival in POPH (liver transplants excluded and uncontrolled for therapies) in a

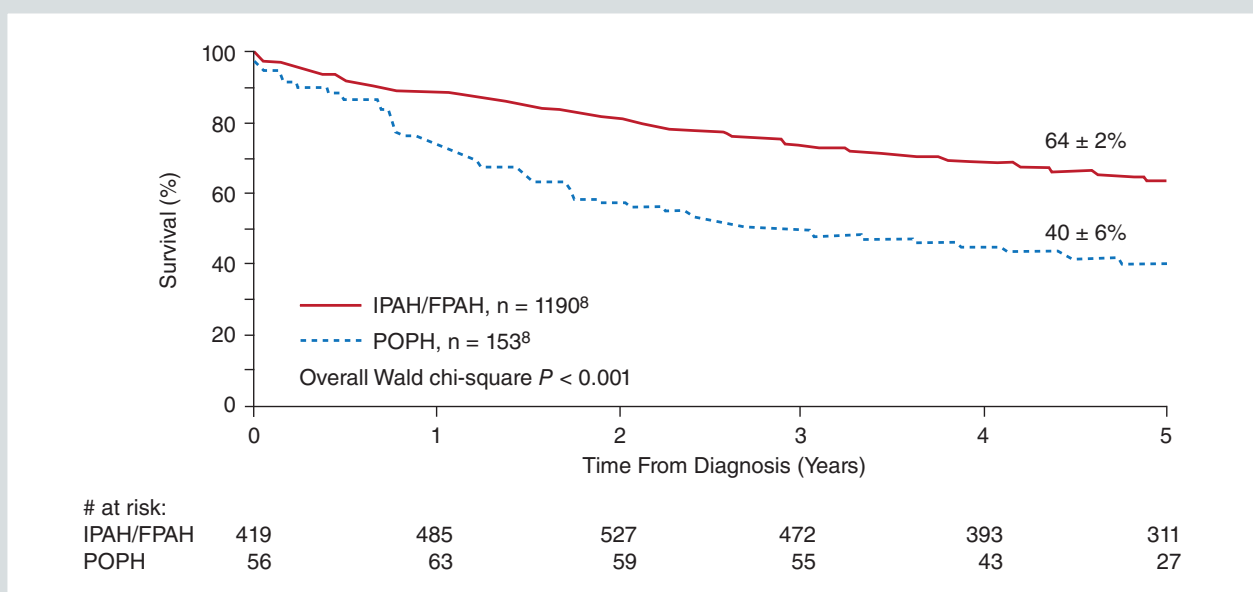


FIGURE 3. Portopulmonary hypertension (POPH) 5-year survival in the US-based REVEAL Registry. Patients with POPH were compared to patients with idiopathic/familial pulmonary artery hypertension (IPAH/FPAH). Patients with POPH who underwent liver transplant were excluded (reproduced with permission from Krowka MJ et al.³⁹).

cohort of 155 POPH patients was 40% in the largest multicentre experience to date³⁹. A 14% 5-year survival was reported in those with mPAP > 35 mmHg not treated and not transplanted⁴⁰. In a retrospective study of 80 POPH patients, unexpectedly, 20/34 (59%) who underwent contrast TTE had IPVD. Including 5 patients with IPVD (all died post-LT) transplanted, they had worse overall 5-year survival (9 versus 70%) compared to those without IPVD despite similar baseline arterial oxygenation, PVR and mPAP⁴¹ (Fig. 3).

Medical management

There have been no prospective controlled trials using current pulmonary artery target therapies to specifically treat POPH³⁵. The results of POPH treatment in the small series

and case reports have been favourable in many cases and are characterized by the following: reduction in mPAP, reduction in PVR, increase in cardiac output, improvement in right ventricular function by echocardiography and, in highly selected patients, improvement in pulmonary hemodynamics that would allow successful LT^{35,36}.

Since POPH is recognized as a subgroup of PAH (and indistinguishable from IPAH from a pathologic perspective), clinicians have cautiously used several medication approaches in the setting of POPH^{32,35}.

PROSTACYCLIN ANALOGUES

The lack of prostacyclin synthase in the endothelial cells of patients with IPAH, as well as

cirrhosis, led to the successful use of infusing continuous synthetic prostacyclin (epoprostenol via a central line 24/7) to treat POPH. Early IV epoprostenol experience in 48 POPH patients from 5 studies demonstrated a mean decrease in mPAP by -25%; decrease in PVR by -52%; and increase in cardiac output by 38%^{35,42}. Other studies have confirmed the long-term benefit of epoprostenol in POPH, as well as the successful use of other infused and inhaled prostanoids (treprostinil and iloprost)⁴³. Oral prostanoids and an oral specific prostacyclin receptor agonist are now available to treat PAH, but there has been no reported use in POPH to date. The optimal prostacyclin dose is usually what is tolerated in terms of drug-induced side effects (headache, bone pain, and diarrhoea). In addition, infusion rates of epoprostenol greater than 20 ng/kg/min have been associated with very cardiac outputs and progressive splenomegaly, which in turn, can worsen thrombocytopaenia^{44,45}.

ENDOTHELIN RECEPTOR ANTAGONISM

Documentation of a serum increase in the potent vasoconstrictor ET-1 in cirrhotic patients led to uncontrolled treatments of endothelin receptor (ER) blockade in POPH⁴⁶. Specifically, the pulmonary arterial bed has endothelium- ET-A and smooth muscle – ET-B receptors that produce vasoconstriction and vasodilation, respectively. Both oral bosentan (a non-specific ER antagonist) and oral ambrisentan (a more specific for the ET-A receptor) have demonstrated improvement in POPH pulmonary haemodynamics (reductions in mPAP and PVR) over a 12-48-week

period⁴⁶⁻⁴⁸. Liver toxicity has limited the use of bosentan; significant peripheral oedema has accompanied the use ambrisentan^{47,48}. A third ER antagonist, macitentan, is a significant addition for the treatment of POPH in that it is the first agent to be used in a multicentre trial (“PORTICO”) in only patients with POPH. This prospective, double-blind, placebo-controlled, international trial randomizes 48 patients to each arm; entry criteria includes mPAP > 25 mmHg and PVR > 320 dynes.s.cm⁻⁵. Primary outcome is a percentage reduction in mean (geometric) PVR at 12 weeks. Results are expected in 2018 (<ClinicalTrials.gov>).

PDE-5 INHIBITION

Treating POPH with a medication that causes pulmonary vasodilation via PDE-5 inhibition by locally increasing NO (preventing the breakdown cGMP) appears effective^{49,50}. Pulmonary haemodynamic improvement in POPH using the short-acting oral sildenafil (numerous reports) and long-acting oral tadalafil PDE-5 drugs have been published, with the latter described as reducing both portal (hepatovenous pressure gradient) and pulmonary artery pressures³⁶. It remains unclear if sildenafil can favourably alter portal pressures. Both drugs appear to be well tolerated in POPH and do not adversely affect hepatic function. In the large Canadian sildenafil series (n = 20 POPH), treatment was successful (PVR decreased by a mean of -236 dynes.s.cm⁻⁵ at 6 months) and the drug was used in 2 patients with increased pulmonary artery wedge pressure (PAWP), but their outcome data was not reported⁵¹.

GUANYLATE-CYCLASE STIMULATION

The only prospective PAH treatment study that included POPH patients was PATENT-1, using the riociguat, a soluble guanylate cyclase (sGC) stimulator³⁵. In that study, 11 POPH patients received riociguat. In this POPH subgroup the mPAP and PVR decreased, and 6-minute walk improved. The net effect of that drug is to induce vasodilation via sGC stimulation that is independent of any NO-sGC interactions that also cause vasodilation. Riociguat can also act synergistically with NO to cause vasodilation and antiproliferative effects, thus, the *combined* use of PDE-5 inhibitors and riociguat requires great caution in view of the possibility to induce significant systemic hypotension.

CAVEATS

Beta blockers. A French study described the withdrawal of beta blockers in the setting of moderate to severe POPH has resulted in improvement of exercise capacity, cardiac output (28%) and a decrease in PVR (19%) with no change in mPAP⁵². This study demonstrated the removal of a negative chronotropic effect and possible vasoconstrictive effect of beta blockers. Thus, caution is advised when considering the addition of a beta blocker in POPH patients, due to the possible adverse effect on RV function.

Transjugular intrahepatic portosystemic shunt (TIPS). An immediate increase in right heart filling pressures due to increased preload may occur following the placement of TIPS. The expected increases in cardiac output and pulmonary artery pressures are mild and

short lived (30 days)⁵³. There is no proven role in the treatment of POPH (by presumably relieving the degree of portal hypertension). An elective TIPS procedure in the setting of RV dysfunction could theoretically have an immediate, deleterious cardiac effect.

Implications for LT

Importantly, screening for POPH by TTE is current policy followed by all LT centres in the United States³. Confirmation of suspected POPH requires RHC. Unlike LT in the setting of HPS, the existence of moderate to severe POPH poses several unique challenges in the LT candidate. The two most important observations over the years have been 1) intraoperative death during LT can occur due to acute right failure – with or without pre-LT pulmonary artery targeted therapies (PATT)^{54,55}; and 2) successful LT, despite a successful (intravenous and/or oral PATT) and a successful transplant procedure, partial or complete resolution POPH is unpredictable⁵⁶⁻⁶³.

It has been thought to prevent progression of POPH and right heart failure, aggressive PATT combined with “early” LT would be prudent. To that end, and since the degree of POPH correlated poorly with severity of liver disease (and MELD score), MELD exception for POPH was introduced in 2006 in the United States LT programs⁶⁴. If specific pulmonary hemodynamic criteria can be met (reducing mPAP to less than 35 mmHg with therapy), additional MELD points are granted by the regional review boards in lieu of native MELD scores. A higher priority for LT is provided and granting MELD exception

TABLE 3. Outcomes following liver transplant in portopulmonary hypertension (POPH)

| Year - Author | # POPH transplanted | ATT stopped post-LT | Survival reported |
|------------------------------|---------------------|---------------------|-------------------|
| 2017 DeMartino ⁶⁷ | 6 | Not reported | 1-year 100% |
| 2017 DuBrock ⁶⁶ | 103 | Not reported | 1-year 87% |
| 2016 Verma ⁶⁰ | 28 | Not reported | 5-year 58%* |
| 2016 Legros ⁵⁹ | 5 | 60% by month 25 | 5-year 53% |
| 2014 Goldberg ⁶⁵ | 73 | Not reported | 3-year 64% |
| 2014 Khaderi ⁶² | 7 | 86% by month 8 | 86% at 7.8 years |
| 2012 Hollatz ⁶³ | 11 | 64% by month 7 | 1-year 100% |
| 2008 Swanson ⁴⁰ | 12 | 50% at one year | 1-year 58% |
| 2007 Ashfaq ⁵⁷ | 11 | 82% by month 9 | 5-year 67% |
| 2004 Krowka ⁵⁴ | 36 | Not reported | 30-day 67%† |

Studies selected/summarized if POPH $n \geq 5$.

DuBrock, Verma, and Krowka studies only required mPAP > 25 mmHg for the POPH diagnosis. All other studies required mPAP > 35 mmHg.

*POPH defined by mPAP > 25 mmHg and increased PVR.

†POPH defined by mPAP > 35 mmHg and increased PVR.

ATT: antitubercular treatment; LT: liver transplant; mPAP: pulmonary artery pressure; PATT: pulmonary artery targeted therapy; POPH: portopulmonary hypertension; PVR: pulmonary vascular resistance.

for POPH is re-evaluated every 3 months by RHC. Unfortunately, such specific therapeutic criteria (as well as diagnostic criteria) have not been rigorously followed, thus complicating LT outcome analysis in the setting of POPH. In the largest US *post LT survival analysis* to date ($n = 155$ patients granted POPH MELD exception from 2006 to 2012), only 73 (47%) actually fulfilled all MELD exception criteria⁶⁵. A similar difficulty was noted in a separate US pre-LT waitlist analysis ($n = 190$ patients granted POPH MELD exception from 2006 to 2014), where only 103 (54%) fulfilled correct POPH diagnostic criteria⁶⁶.

Despite these shortcomings several small series have reported successful LT (deceased donor and living donor) in the setting of treated moderate to severe POPH⁶⁷. Normalization of pulmonary hemodynamics and

discontinuation off all PATT post-LT has been reported in 50-82% of POPH patients post-LT (Table 3). Recent data suggest that POPH patients with mPAP > 35 mmHg at the time of LT can have successful outcomes up to 1-year post LT⁶⁸. Arguably, pre-LT normalization of PVR and RV function may be the best indicators for optimal post-LT outcomes and POPH resolution⁶⁶.

Finally, it should be stressed that POPH, regardless of treatments, poses a higher risk for LT and the mere existence of POPH (unlike HPS), is *not* an indication for LT at this time^{3,69}.

CONCLUSION

Comparisons between the two pulmonary vascular syndromes are summarized in table 4.

TABLE 4. Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) comparisons

| Clinical issue | HPS | POPH |
|--|---------------------------------|--|
| Pathophysiology | Vasodilatation/angiogenesis | Obstruction to flow |
| Presentation | Adults/children | Adults/children (uncommon) |
| Related to age/gender | No | No |
| Related to specific liver diseases | No | No |
| Related to severity of liver diseases | No | No |
| Genetic polymorphisms | Yes, documented | Yes, documented |
| Intrapulmonary vascular dilatations | Diagnostic | Not uncommon |
| Arterial deoxygenation | Mild → severe | Normal → mild |
| Chest radiograph | Normal | Hilar enlargement/cardiomegaly |
| TTE echocardiography | Diagnostic | Screening/not diagnostic |
| ^{99m} TcMAA lung/brain scanning | Estimates degree of IPVD | No diagnostic role |
| Right heart catheterization | No role | Diagnostic |
| Pulmonary angiography | If PaO ₂ < 300 mmHg* | No role |
| Pulmonary vasodilator therapy | No role | Advised if mPAP ≥ 35 mmHg |
| Liver transplant | | |
| Indication | Yes | No |
| MELD Exception | Yes | Yes |
| Risk | Higher than normal | Highest if mPAP ≥ 50 mmHg [†] |
| Intraoperative death | Never reported | Due to right heart failure |
| Outcome | Resolution expected | Resolution variable |

*Breathing 100% inspired oxygen.

[†]Contraindication to liver transplant.^{99m}TcMAA: Technetium macroaggregated albumen; IPVD: intrapulmonary vascular dilatation; mPAP: pulmonary artery pressure; PaO₂: partial pressure of oxygen; TTE: transthoracic echocardiography; Model for End-stage Liver Disease (MELD).

The understanding and management of these syndromes have evolved for quite different reasons. An animal model for HPS has led to the first randomized trial (sorafenib) in HPS. Experienced centres have successfully transplanted the most severe cases of HPS. Despite the lack on an animal model, the advent of effective pulmonary artery targeted therapies has improved the outcomes in POPH and facilitated successful LT in highly selected patients. The results of the first randomized, controlled trial in POPH will be welcome. Unravelling the pathophysiology of these entities remains a high priority for

those awaiting LT and those not appropriate for such surgery, yet debilitated by these syndromes. It is hoped that both of these liver-lung vascular problems will further benefit from innovative research and clinical approaches.

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CONFLICT OF INTEREST

Dr. Michael J. Krowka has no conflicts of interest to report. No funding.

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