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Review article: liver transplantation for the pulmonary disorders of portal hypertension

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SUMMARY

Background
Liver transplantation is potentially a life-saving therapeutic intervention for patients with portopulmonary hypertension and hepatopulmonary syndrome. However, due to limited data, listing criteria for patients with these conditions have not been clearly established. Indeed, this has led some to speculate that transplantation may not be appropriate in cases of moderate-to-severe portopulmonary hypertension and severe hepatopulmonary syndrome.

Aim
To critically discuss the utility of LT for the treatment of hepatopulmonary syndrome and portopulmonary hypertension.

Methods
A literature search was conducted in 2012 on PubMed, Ovid Embase, Ovid Medline and Scopus using the following search terms: hepatopulmonary syndrome, portopulmonary hypertension, pulmonary arterial hypertension, liver transplantation. Relevant manuscripts were included in the review.

Results
Liver transplantation has established itself as an effective treatment for selected patients with hepatopulmonary syndrome and portopulmonary hypertension. A multidisciplinary team approach incorporating focused strategies (both pre- and post-operatively) aimed at improving oxygenation in patients with hepatopulmonary syndrome has led to a dramatic improvement in patient outcomes. Additionally, careful patient selection and the use of targeted pulmonary vascular therapies are successfully being used to treat portopulmonary hypertension and 'bridge' patients to successful liver transplantation.

Conclusions
Liver transplantation is an effective therapy for patients with hepatopulmonary syndrome and portopulmonary hypertension. However, rigorous screening and early identification of these conditions allied with aggressive pre-operative optimisation of physiology and diligent post-operative care are imperative to ensuring a good outcome.

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INTRODUCTION

Pulmonary disorders associated with, or caused by, portal hypertensive change occur in a significant minority of patients with chronic liver disease. Of the two commonly recognised conditions, hepatopulmonary syndrome (HPS) is characterised by intra-pulmonary vascular vasodilatation, whilst portopulmonary hypertension (PoPH) is caused by hyperdynamic circulatory change and vascular proliferation leading to obstruction of the pulmonary vascular bed and increased pulmonary vascular resistance (PVR) (Figure 1). The two conditions, although pathologically distinct, can co-exist and usually it is PoPH that develops in a patient with pre-existing HPS. Both HPS and PoPH can become dominant indications for liver transplantation (LT), although many centres have adopted a conservative approach to transplantation in this setting due to the perception that these patients have worse outcomes. This is based on historical data, often derived from small, retrospective studies.

Of course, the infrequency of these disorders makes it difficult, if not impossible, to study these diseases in the setting of a controlled trial and there is a danger that transplant programmes may never progress with this group of patients. Nevertheless, developments in therapeutics, a better understanding of the mechanism of injury and improved intensive care techniques promise to improve patient outcomes and allow us to be more optimistic in our approach to these rare disorders. This review will examine the role of LT in both HPS and PoPH, and discuss the therapeutic options for the management of these conditions.

METHODS

A literature search was conducted in 2012 on PubMed, Ovid Embase, Ovid Medline and Scopus using the

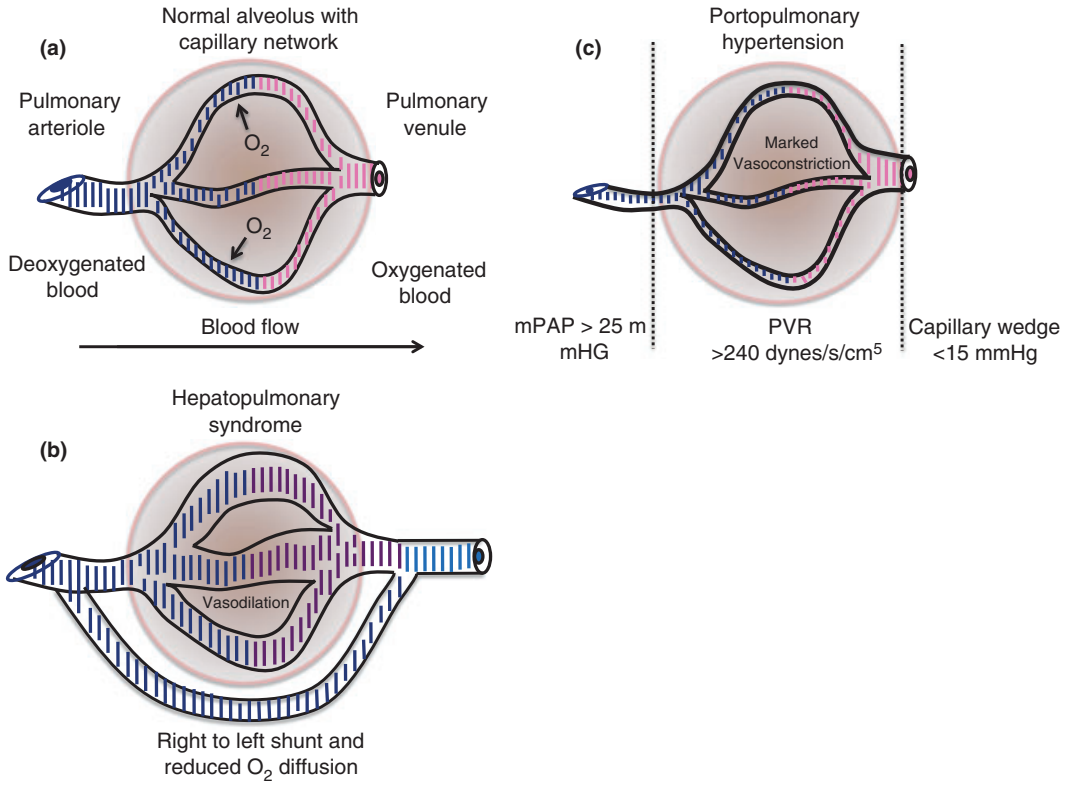

Figure 1 | Pathophysiology of HPS and PoPH shows (a) a normal alveolus surrounded by a capillary bed. The blood flow is regulated to ensure adequate oxygenation of haemoglobin prior to circulation around the body. HPS is characterised by abnormal intrapulmonary vascular dilatation. The increased blood flow causes a diffusion–perfusion mismatch and arterial hypoxaemia. In addition, arteriovenous co-lateral vessels (right to left shunt) may form bypassing the alveolus entirely compounding the hypoxaemia (b). Conversely, PoPH is characterised by abnormal intrapulmonary vascular constriction and pulmonary hypertension. It may therefore be defined by a resting mean pulmonary artery pressure (mPAP) >25 mmHg; a pulmonary capillary wedge pressure <15 mmHg; and a pulmonary vascular resistance >240 dynes/s/cm^5 (c).

Aliment Pharmacol Ther 2013; 37: 183-194

following search terms: Hepatopulmonary syndrome, Portopulmonary hypertension, Pulmonary arterial hypertension, Liver Transplantation. The references of all retrieved articles were reviewed. Abstracts of articles identified in literature search were reviewed, and the full-texts of articles considered eligible were examined. We have included 75 articles to complete this comprehensive review.

TRANSPLANTATION FOR PATIENTS WITH HPS

Definition

HPS is characterised by a defect in oxygenation secondary to pulmonary vasodilatation in the setting of liver disease. It is defined by a triad of liver dysfunction and/or portal hypertension associated with intrapulmonary vascular dilatations, which impair pulmonary gas-exchange, defined by an alveolar–arterial oxygen gradient (AaDO2) >20 mmHg.[1]

Prevalence

Although the term HPS was first used in 1977,[2] it was preceded by an autopsy series that demonstrated pulmonary vascular dilatation in patients with cirrhosis.[3] Studies from transplantation centres have suggested a prevalence of between 5% and 32% in patients with cirrhosis.[4] This variance reflects different cut-offs of alveolar gas exchange used to describe gas exchange abnormalities. At present, there are no prospective multi-centre prevalence studies available.

Pathophysiology

The key pathological features of HPS are dilatation of the pulmonary capillaries in conjunction with the formation of arteriovenous communications (Figure 1). These arteriovenous shunts cause ventilation–perfusion mismatching. Vessel dilatation also hampers oxygenation as rapid flow, and increased distance from the alveolar membrane to the centre of the vessel, means diffusion capacity of oxygen into the blood is reduced. This creates a 'Perfusion-Diffusion' defect resulting in hypoxia. The fixed, dilated pulmonary capillary circulation is less able to respond to gravitationally induced changes in blood flow, which exacerbates shunting at the lung bases when patients are upright leading to the characteristic orthodeoxia of HPS: a clinical state where hypoxia is accentuated by sitting or standing and improved by lying flat.

It is suggested that the vasodilatation of HPS is mediated by the increased production of nitric oxide (NO). Plasma concentrations of NO and its metabolites nitrite and nitrate are increased in patients with cirrhosis and ascites.[5] Moreover, the exhaled air of cirrhotic patients contains higher NO concentrations than normal subjects, which correlates with their cardiac output and Child-Pugh score.[6] These observations have led some to postulate that the increased generation of NO in cirrhosis is due to increased synthesis of inducible nitric oxide synthase (iNOS),[7] which is synthesised *de novo* in response to inflammation. Bacterial over-growth and failure of the gut mucosal barrier promote bacterial translocation and endotoxaemia in patients with cirrhosis, and several reports have demonstrated an association between NO release and endotoxinaemia.[8] Furthermore, the quinolone antibiotic, norfloxacin, has been reported to decrease iNOS synthesis by monocytes, improving oxygenation in patients with HPS; this protective effect is most likely to be mediated by downregulating expression of Toll-like receptors 2 and 4, which attenuate cirrhosis-associated priming of the innate immune system.[9] Indeed, bacterial translocation and increased expression of lipopolysaccharide binding proteins have been postulated as a potential mechanism underpinning cardiac disruption associated with advanced cirrhosis.[10] Clinical trials using norfloxacin for patients with HPS are currently under way.

Other factors including endothelin and tumour necrosis factor (TNFα) may also play a role in NO synthesis in HPS. Increased concentrations of endothelin in liver disease lead to NO overproduction via the ET-B receptor which in turn activates endothelial NO synthase. Interestingly, increased production of endothelin may be related to endotoxaemia. Indeed, endotoxin stimulates ET-1 synthesis *in vitro* and *in vivo* and correlates with plasma ET-1 concentrations in patients with liver cirrhosis.[11, 12] The observation that the nonspecific phosphodiesterase inhibitor, pentoxyfylline, can prevent the development of HPS in an animal model allied with more recent data suggests that there may be a role for TNFα in this condition.[13]

Investigation of HPS

Any patient with unexplained hypoxia and portal hypertension should be investigated for HPS. Classically, the patient will complain of platypnoea (shortness of breath that is relieved by lying down) and this is mirrored in blood gases demonstrating orthodeoxia. The chest film is often normal, but may show interstitial shadowing in the lower lobes due to capillary dilatation. Pulmonary function tests should demonstrate a reduced diffusion capacity.

Of course, there are many other causes of hypoxia in patients with liver disease, but bubble echocardiography and macro aggregated albumin (MAA) scanning should provide evidence of a right to left shunt in HPS.[14, 15] A bubble echocardiogram can help distinguish between intrapulmonary and intracardiac shunts. If the bubbles enter the left atrium 5 cycles after the right atrium, this suggests passage through an abnormally dilated pulmonary bed, whereas bubbles occurring immediately in the left atrium suggest an intracardiac shunt.[14] In an MAA scan, the large radio isotope-labelled particle, macro aggregated albumin, is injected into a peripheral vein. In a normal pulmonary vasculature, the majority (99%) of this large particle should be trapped within the lungs. In HPS, these particles can distribute to other organs as they can pass through the vasodilated pulmonary circulation. A greater than 7% extrapulmonary distribution suggests HPS.[15] Despite these advanced tests, clinical judgment is still necessary as other lung conditions can occur in up to 30% of patients with HPS.[16]

Survival without transplantation

The natural history of HPS is dismal, with the majority of patients suffering progressive hypoxemia over time. Interestingly, this deterioration often occurs on a background of stable liver function. Schenk *et al.* demonstrated a median survival of 10.6 months in patients with HPS and those patients with a PaO_2 <60 mmHg had an even worse outcome with only 25% being alive at 6 months.[4] More recently, the Mayo group compared survival in HPS patients with a matched control group of patients with similar liver function, but without HPS. The median survival was only 24 months (5-year survival of 23%) in the HPS group compared with 87 months (5-year survival of 63%) in the case control non-HPS group.[17] These figures do need to be interpreted with caution in view of the potential referral and selection bias associated by studying a population referred for transplantation. Furthermore, those patients not listed for transplantation with HPS had other comorbidities that may have led to an increased mortality.

Survival with transplantation

Transplantation is the only known effective therapy for HPS and most patients have an improvement in oxygenation at 1 year. However, a number of centres have described worse outcome in patients with HPS compared with other indications for transplantation and in particular, in patients with severe HPS (PaO_2 of $\leq$50 mmHg). In the largest series, the mortality was 16% and 30% at 3 months in the groups as a whole and the severe HPS group respectively.[18] This was an improvement on earlier series that had much higher mortality rates at the same stage. A recent paper suggests that outcomes are improving in HPS and that severity should not be a barrier for transplantation. Gupta *et al.* examined survival data from 2 large Canadian transplant centres between 2002 and 2008.[19] At 6 months, there were no deaths and at 12 months, the mortality was 7% and 14% in the group as a whole and the severe group respectively.[19]

Strategies to improve outcome of transplantation

Outcome for patients transplanted for HPS has improved over the last 20 years. There are many factors that may account for this change. Pre-operatively, patients should be managed in conjunction with respiratory physicians. They can optimise any concurrent pulmonary disorder and titrate oxygen therapy on a regular basis. This is particularly important in HPS, as the deterioration in respiratory function can be rapid whilst on the waiting list for transplantation.[20] In addition, adequate oxygen therapy can prevent a decline in functional status that is a key factor in survival from surgery. Figure 2 illustrates a diagnosis and management algorithm for patients with HPS.

During and after the operation, it is important to remember that most patients with severe HPS have adapted their haemoglobin in response to chronic hypoxia.[21] It is therefore not uncommon to find polycythaemia and raised levels of 2,3-bisphosphoglycerate. This needs to be taken into consideration if a large volume transfusion is required as the new blood will not be adapted and less efficient at carrying oxygen. During the patients' ITU stay, hypoxia can be problematic; we recommend an early prophylactic tracheostomy in the postoperative period to facilitate weaning (which is often very prolonged), and education of the nursing and medical staff about HPS including the requirement of nursing in the supine position. If the hypoxia becomes refractory to standard therapies, nitric oxide, trendelenberg positioning (supine position with feet elevated 15–30° higher than the head) and oscillator ventilation therapy have all been effective.[19] A close working relationship with the intensive care team is crucial as long periods of ventilation are often required.

A number of studies have demonstrated that these patients are at greater risk of developing both vascular and biliary complications.[19, 22] This is presumably due to tissue hypoxia at the point of both the biliary and vascular anastomoses. Indeed, rates of biliary leaks have

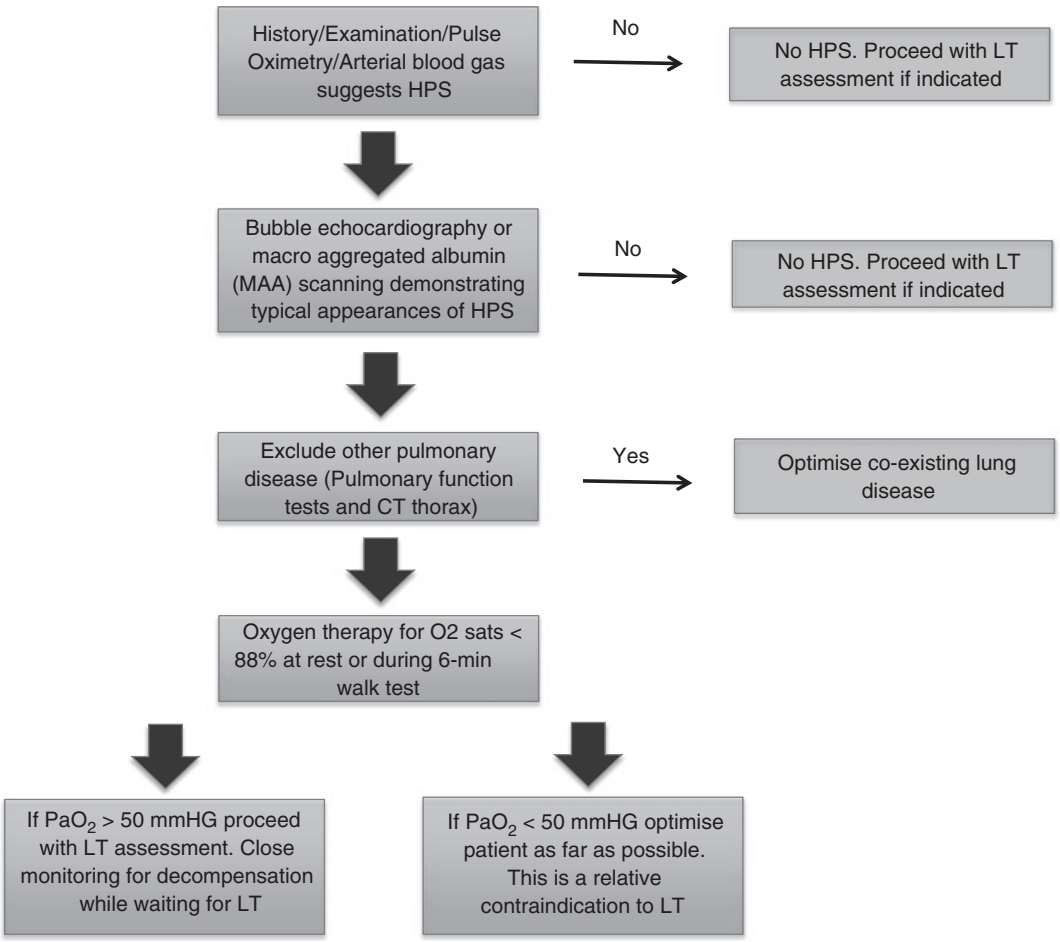

Figure 2 | Diagnosis and management algorithm for hepatopulmonary syndrome.

been described as high as 25% in some studies. We therefore recommend that these patients receive early prophylactic aspirin and low molecular weight heparin and that a high index of suspicion is adopted for biliary and vascular problems. Finally, it is important to educate the patients and their relatives that the recovery from HPS can be a long process and that some severe patients may not recover lung function until a year posttransplantation. Many will require oxygen therapy for some time post-operatively (range: 5–700 days),[19] and hospitalisations can last months post-transplantation. Although the mean rate of increase in PaO_2 has been described as ~3 mmHg per month, patients with more advanced disease (as predicted by a high MAA fraction) tend to have a lower rate of post-operative improvement.

Living donor liver transplantation for HPS

Potentially, living donor liver transplantation (LDLT) could be a sensible strategy for patients with HPS due to the rapid deterioration of lung function whilst on the transplant waiting list. Only a few case series exist of LDLT in this setting and the largest only describes 5 patients.[19] They found that the resolution of hypoxaemia and complication rates were similar to the cadaveric transplantation cohort.

TRANSPLANTATION FOR PATIENTS WITH POPH

Definition

PoPH is defined as the coexistence of pulmonary arterial hypertension (PAH) and portal hypertension, with or without liver disease, where no other cause of PAH has been identified. Exclusion of secondary causes of PAH is a prerequisite for the diagnosis to be made.[1] In such circumstances, PoPH is defined as a resting mean pulmonary artery pressure (mPAP) >25 mmHg, a pulmonary capillary wedge pressure $\leq$15 mmHg and a PVR >240 dynes/s/cm^{-5} (Figure 1).[1]

Prevalence

Reports on the prevalence of PoPH vary significantly in the literature. Postmortem examinations have indicated that less than 1% of patients with liver cirrhosis have histological changes compatible with PoPH,[23] whilst prospective studies estimate the prevalence at 2–6%.[24, 25] The postmortem figures are likely to be an underestimate of the true frequency of the condition, as the histological changes (vascular fibromuscular hyperplasia) of PoPH lag behind the clinical picture. The condition seems to be most prevalent in patients with longstanding and severe portal hypertension, particularly in the presence of refractory ascites,[26] often occurring in patients with cryptogenic cirrhosis or noncirrhotic portal hypertension. Registry data suggest that PoPH accounts for 7–10% of all cases of PAH.[27, 28] This considerable proportion may even be increasing with PoPH being the most common cause of non-idiopathic disease in the recent French PAH registry where it accounted for 20% of cases.[28]

Pathophysiology

Whilst the aetiological mechanisms that promote PoPH are beginning to be understood, its genesis remains unclear. PoPH shares the pathological features commonly seen with other causes of PAH such as medial hypertrophy, intimal proliferation and fibrosis with adventitial thickening. Several theories have been proposed to explain the causal relationship between portal and pulmonary hypertension. The most commonly accepted hypothesis has two pathways.[29] Firstly, as a direct consequence of portal hypertension, collateral porto-systemic vessels shunt venous blood from the splanchnic circulation directly into the vena cava. The increased venous return and vasomodulatory properties of portal blood induce a systemic hyperdynamic circulatory state, increasing stroke volume and cardiac output in response to a fall in systemic vascular resistance.[30] High flow rates in the pulmonary circulation induce shear stress in the pulmonary vascular tree, which promotes reactive medial fibro-muscular expansion and hyperplasia in the walls of pulmonary arterioles.[31, 32] Rarely, intrapulmonary anatomic shunts can occur in PoPH; more frequently, these abnormalities involve the heart and include right to left intracardiac shunting via atrial septal defects or through a patent foramen ovale. In such cases, the onset of symptoms may be sudden and cause such significant shunting that the hypoxia mimics the clinical appearance of HPS.[33]

This process is compounded by vasoactive components in portal blood, including ammonia, protein-adducts, inflammasome activation, cytokines and endotoxins absorbed from the gut, which, due to porto-systemic shunting, are permitted to enter the pulmonary circulation without protective first-pass hepatic metabolism.[34] The pulmonary vasculature is not normally exposed in this way and it is thought that these mediators lead to the changes seen PoPH.[1, 34] Some molecules directly induce smooth muscle vasoconstriction and, in a chronic setting, contribute to the medial hypertrophy of the pulmonary arteries, which characterises PoPH. Endothelins, serotonin and thromboxane B2 appear to be the most likely candidates as they are potent vasoconstrictors *in vitro* and their plasma concentrations are increased in patients with portal hypertension.[35, 36] Thromboembolic disease caused by micro-thrombi originating in the splanchnic circulation has also been proposed as a cause of PoPH.[37, 38] PAH is, however, characterised by *in situ* thrombosis and increased thromboxane A2 synthesis with resultant PDGF and EGF-mediated TGF-β secretion.[39, 40] This provides a potent stimulus for collagen synthesis and fibroblast proliferation within the arteriole, and induces microaggregation and thrombotic occlusion of small vessels.[41, 42] Therefore, *in situ* thrombosis seen in PoPH may represent this disease process rather than an embolic phenomenon.

A single genetic defect that predisposes patients to PoPH has yet to be discovered. Genome-wide association studies have identified a single nucleotide polymorphism in S100A4 (an intracellular binding protein) associated with the risk of PoPH in patients with liver disease.[43] While serum levels of S100A4 are raised in patients with PoPH, there was no significant difference when compared with liver disease controls, which makes the association less compelling.[44] A recent publication attempting to identify genetic risk factors for PoPH screened 31 patients with PoPH and 104 controls and identified genetic variation in oestrogen signalling and cell growth regulators in affected patients.[43] Consistent with these data, a multi-centre case–control study of prospectively recruited patients identified female gender and autoimmune liver disease as separate risk factors for developing PoPH.[45] Although incompletely understood, these findings may help elucidate the molecular mechanisms of PoPH.

Assessment

Patients may have clinical evidence of both portal hypertension and PoPH. Manifestations of portal hypertension typically precede those of PAH. The symptoms of PoPH

are often initially mild (or absent) and some can be non-specific such as fatigue and oedema, being easily attributed to the underlying liver disease. In addition, physical signs of PoPH (right ventricular heave, loud pulmonary second heart sound and elevated jugular venous pressure) may be subtle or only present in more advanced cases representing right heart failure. These factors contribute to the long interval between the first manifestation of portal hypertension and the documentation of PAH, which is highly variable ranging from 2 to 15 years.[29, 46] Often, PoPH is only diagnosed during LT assessment. In rare cases of rapidly progressive PoPH, patients may present with symptoms of dyspnoea on exertion, syncope, chest pain, fatigue, haemoptysis and orthopnea, which are likely to indicate severe pulmonary hypertension.

Patients suspected of having PoPH will require extensive diagnostic testing. Chest X-ray might demonstrate enlarged pulmonary arteries and right ventricle and atria as well as increased vascular shadowing in the upper lobes. Hypoxemia and hypocapnia (although often present and associated with an increased alveolar-arterial oxygen gradient) are always less pronounced that that observed in HPS. Echocardiography is regarded as the most practical screening tool in evaluating patients for the presence of PoPH. It is important to recognise, however, that pulmonary artery systolic pressure (PASP) estimation by echocardiography is an inexact science, as it is highly operator-dependent and may underestimate pulmonary pressures in the context of impaired right ventricular function. ECG changes consistent with right ventricular hypertrophy and strain are often seen in such cases.

Using doppler echocardiography, the estimated upper 95% limit for PASP among low-risk normal individuals within the population is 37.2 mmHg, although a PASP >40 mmHg is found in 6% of patients over 50 years of age and in 5% of obese individuals.[47] In cirrhotic individuals, a threshold estimated PASP of 30 mmHg demonstrated a positive predictive value of 59%, but a negative predictive value of 100% in identifying patients with PoPH.[25] Clearly, whilst such a low threshold will identify all true cases, a significant proportion of patients without PoPH would be compelled to undergo unnecessary invasive investigation. Given that doppler echocardiography often overestimates PASP in the presence of normal right ventricular function, and that many patients historically labelled with PoPH would not have met modified and more stringent criteria for its diagnosis, it seems reasonable to reserve invasive investigation for those patients with an estimated PASP >37 mmHg, or evidence of right ventricular impairment or other features that might suggest pulmonary hypertension (Figure 3). It is important to note that the discordance between PASP on echo and right heart catheterisation (RHC) increases as PASP rises, and that a tricuspid regurgitant jet is not seen in 10–20% of patients undergoing doppler echocardiography.[48] Particularly in this latter group, a low threshold for further investigation should be maintained if the patient appears to have any likelihood of PoPH.

Suspected PoPH is confirmed in patients who meet diagnostic criteria at RHC.[1] The transpulmonary gradient (mPAP-pulmonary capillary wedge pressure) is able to better characterise pulmonary hypertension in the common circumstance of a hyperdynamic circulation, whereupon a transpulmonary gradient >12 mmHg is regarded as typical of PoPH in the context of an elevated PVR.[49] These modified criteria effectively exclude those cirrhotic patients with elevated mPAP due to hyperdynamic circulatory changes associated with cirrhosis who would otherwise be erroneously diagnosed with PoPH. Such differentiation is important, as, in the context of transplantation, an elevated mPAP due to circulatory hyperdynamics does not portend the same outcome as true pulmonary hypertension.[50]

Full evaluation is required to confirm a diagnosis of PoPH. Patients should have clinical or biochemical evidence of portal hypertension, and where these are absent, portal pressure can be measured during hepatic vein catheterisation. It is important to exclude other causes of an elevated pulmonary artery pressure. Investigations performed include autoantibody testing and HIV testing, pulmonary function testing, ventilation–perfusion lung scanning, thoracic CT and CT pulmonary angiography.[51] Increasingly, cardiac MRI is being used in patients with suspected PoPH to establish its likelihood and severity by assessing the right ventricle and its function.

Survival without liver transplantation

Historical data, antedating the use of modern pharmaceutical intervention in PoPH, demonstrated a median survival from the time of diagnosis of approximately 15 months.[46] Indeed, some studies have shown that survival rates in PoPH are worse than those in idiopathic PAH, with projected 5-year survival rates of 38% (95% CI: 14–63) and 72% (95% CI: 54–85) respectively.[52] Notably, there were approximately equal proportions of IV Epoprostenol treated patients in each group (62% vs. 79% respectively); the mortality differences were

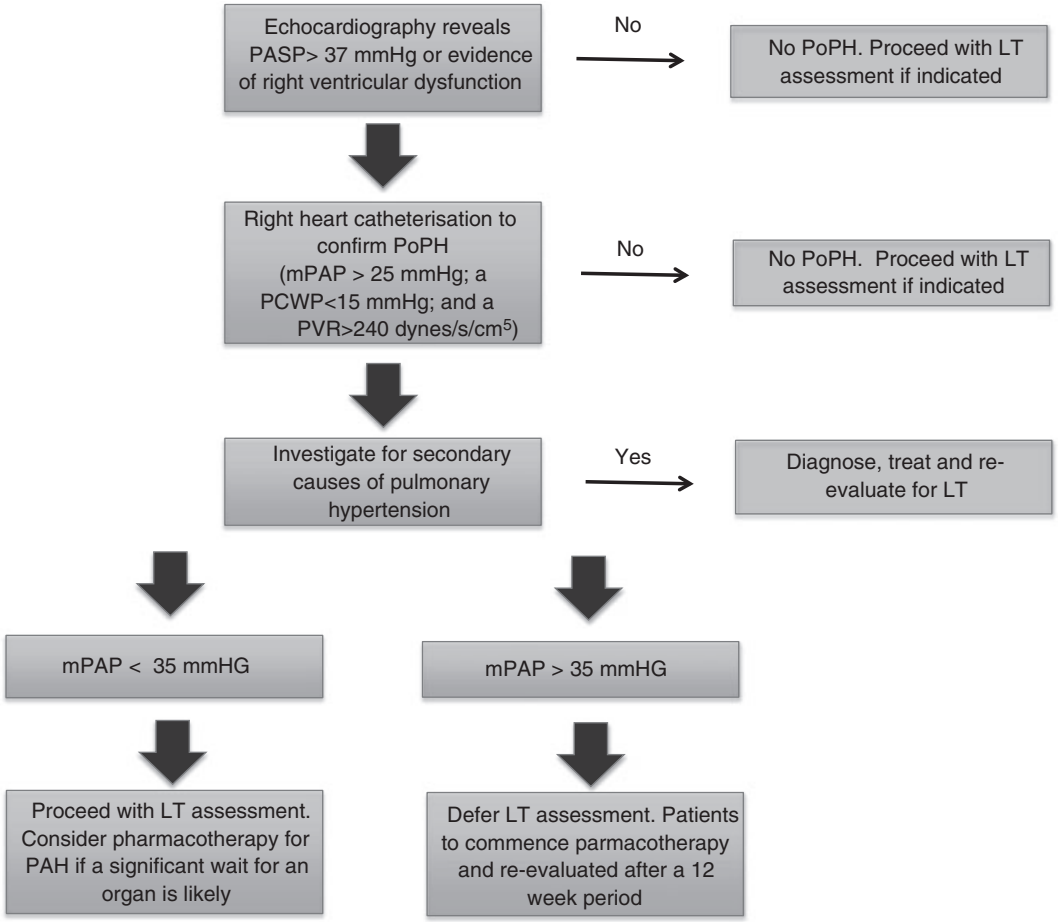

Figure 3 | Diagnosis and management algorithm for portopulmonary hypertension.

independent of whether patients were treated with anticoagulants and/or Epoprostenol, or the duration of therapy. Furthermore, a recent report from the US-Based REVEAL Registry supports the notion that patients presenting with PoPH have a worse outcome than those with idiopathic PAH and are less likely to be on specific therapy compared with other forms of PAH.[53] These data are particularly concerning as suboptimal management of these patients will further reduce their chances to be considered for LT.

Pharmacological intervention in PoPH

PoPH is a subtype of the broader group of conditions causing PAH, which share pathophysiology and have been treated in similar ways.[1] Notably, anticoagulation is avoided in patients with PoPH due to increased risk of gastrointestinal haemorrhage, and it has been demonstrated recently that withdrawal of beta blocker agents results in improved cardiac output.[54] In recent years, a number of agents used in the treatment of idiopathic PAH have been tested in patients with PoPH, which, by improving haemodynamics, allow a significant number of patients with advanced disease who would otherwise preclude liver transplantation to avail themselves of liver replacement.[55] Whilst experience with vasodilators such as prostacyclin has been tempered by the complexities of their administration, new oral vasodilator therapies promise to revolutionise our approach to PoPH.

Bosentan is a dual endothelin-A and endothelin-B receptor antagonist used to treat patients with idiopathic PAH.[56, 57] There are only limited experiences using endothelin receptor antagonists (ERAs) in patients with PoPH as patients are often excluded from randomised controlled clinical trials in PAH. Case reports and retrospective series suggest safety and benefit in this cohort as assessed by improved haemodynamics on right heart catheterisation studies and increased exercise capacity.[58–60] One study comparing the beneficial effects of Bosentan and Epoprostenol in patients with PoPH demonstrated superior survival in the former group (1-, 2- and

Aliment Pharmacol Ther 2013; 37: 183-194

3-year survival rates of 94%, 89% and 89% vs. 77%, 62% and 46% respectively).[61] This benefit appeared to reflect the substantial haemodynamic improvement in patients treated with Bosentan. ERAs can be associated with hepatotoxicity so careful monitoring is required, particularly in this patient population. There are limited data to support the use of Sildenafil (an oral phosphodiesterase inhibitor) in patients with PoPH. Individual case reports and case series suggest benefit; however, large studies using hard end-points including mortality have not been completed.[62, 63]

Survival with liver transplantation

Given the poor prognosis associated with PoPH and the limited medical therapies available, LT has been proposed as a means of potentially preventing disease progression and providing an opportunity for pulmonary haemodynamics to normalise. Early experiences of LT in the context of PoPH were disappointing due to an unacceptably high peri-operative mortality. Indeed, a multicentre prospective study investigating the patient outcomes following LT, demonstrated a post-operative mortality of 36%, with most deaths occurring in the immediate/early post-operative period.[64] The same authors previously identified cardiopulmonary failure as the major contributor to early post-operative death in these patients.[65] Specifically, in patients with an mPAP of 35–50 mmHg and PVR >250 dynes.s.cm^{-5}, the mortality rate was 50%. In contrast, no increase in peri-operative mortality was reported in patients with a pre-OLT mPAP less than 35 mmHg and a transpulmonary pressure gradient less than 15 mmHg. These data are similar to other retrospective studies, which demonstrated that patients with severe pulmonary hypertension (mPAP >60 mmHg) had mortality rates of 42% at 9 months and 71% at 3 years following surgery.[66] In summary, there is increased risk of death in patients with an mPAP of >40 mmHg, whilst an mPAP >50 mmHg is considered an absolute contraindication to transplantation by most liver centres.[65] Thus, the goal of therapy is to reduce pulmonary pressure as close as possible to 'safe' levels ($\leq$35 mmHg) whilst preserving cardiac function. Patients who maintain equivocal pressures despite therapy (35–45 mmHg) need to be considered on a case-by-case basis, although the presence of significantly elevated cardiac output in the face of high pulmonary pressure is likely to denote a better surgical candidate than a patient with only moderately elevated or normal cardiac output, as they are likely to have reduced cardiac reserve in the context of PoPH. Patients with mPAP >50 mmHg and elevated PVR in the context of an elevated transpulmonary gradient, and/or evidence of significant cardiac dysfunction should not be offered surgery, and are most likely to benefit from medical management as the predicted post-operative survival in this group is unacceptably low.

Survival with transplantation and targeted pulmonary vascular therapy

The early experiences of using targeted pulmonary vascular therapy for patients as a bridge to transplantation have been promising, but are limited to single centre reports.[67, 68] In Dallas, 16 patients with mild-to moderate-PoPH (mPAP >35 mmHG) were considered suitable for LT and received Epoprostenol/Bosentan as optimisation therapy. Twelve patients achieved mPAP <35 mmHG and 11 of these underwent LT. The 1- and 5- year survival in these patients was 91% and 67% respectively.[69] It is important to note that all patients included in this analysis were given a MELD exception of 25 and waited a mean of only 55 days for LT. These encouraging data are supported by the largest published single centre experience (Mayo clinic) examining the natural history of patients with PoPH.[70] The 5-year survival of patients receiving no pharmacotherapy or liver transplant (n = 19) was 14%, with over half the patients dying within 1 year of diagnosis. Forty-three patients received pharmacotherapy [i.v. Epoprostenol (n = 28), s.c. Treprostinil (n = 7), oral Sildenafil (n = 4), oral Bosentan (n = 1) and inhaled Iloprost (n = 3)], but no LT, and their median survival was 46 months with a 5-year survival of 45%. Three patients received LT without prior pharmacotherapy and 2 died intra-operatively. Finally, 9 patients received a combination of optimisation pharmacotherapy [i.v. Epoprostenol (n = 5), s.c. Treprostinil (n = 2), oral Sildenafil (n = 1), oral Amlodipine (n = 1)] and LT and had a documented 5-year survival of 67%. Notably, all patients with an mPAP <35 mmHg survived post-LT. Although limited, these data support the use of pharmacological optimisation therapy in PoPH patients before and after LT.

Evolution of PoPH after liver transplantation

The early experiences of LT in patients with PoPH were overshadowed by progressive right heart failure, circulatory failure and death. The evidence suggests that mPAP and PVR are important predictors of survival following LT.[65] Careful patient selection, as occurred in the Dallas series, allowed 9 of the 11 patients transplanted to discontinue all vasoactive medications within 1 year of

LT.[69] Similarly, in the Mayo clinic experience, all patients who survived transplantation discontinued prostacyclin therapy ($n = 6$) within 6 months of LT, and half of these patients were maintained on oral vasoactive agents.[70]

Strategies to improve outcome of transplantation

In addition to careful patient selection and the judicious use of pharmacotherapy to optimise patients pre-LT, there are a number of other strategies that may improve patient outcomes. First, LDLT has the potential to reduce the waiting times of such patients on the LT waiting list with improved survival. Reports of LDLT for patients with PoPH are limited to case reports; however, positive outcomes for both donor and recipient have been described.[71, 72] Whilst live donor procedures would seem ideally suited for patients with mild-to-moderate PoPH, the ethical judgement regarding whether it is appropriate to expose a donor to harm, to benefit patients with at best an equivocal prognosis, is challenging. Clearly, in such circumstances, both donor and recipient need to be counselled appropriately and it is recommended that ethical boards are consulted before listing. Secondly, we recommend a trial of targeted pulmonary vascular therapy for all patients with clinically significant PoPH. Earlier, more aggressive treatment of PoPH could facilitate successful LT. Finally, although MELD scores have proved useful for prioritising sick patients on LT waiting lists, there is evidence that it correlates poorly with the severity of PoPH.[73] This has led some to propose a MELD exception of 26 points for selected patients with PoPH.[74]

Proposed guidelines

Current clinical guidelines recommend that all patients undergoing evaluation for LT should be screened for PoPH using doppler echocardiography.[75] Patients with a positive screening echo should undergo RHC, with patients diagnosed with PoPH started on targeted pulmonary therapy unless contraindicated. If considering LT, we suggest that patients with mPAP >35 mmHG and pulmonary vascular resistance >240 dynes/s/cm^5 be commenced on PAH treatment for a minimum of 12 weeks prior to listing. Patients who respond positively to this intervention are suitable for LT, while nonresponders should raise prognostic concerns. For patients with a pulmonary pressure >40 mmHg, raised PVR and a modestly elevated or normal cardiac output outcomes are likely to be poor as the absence of circulatory hemodynamics might signify significant cardiac dysfunction. Formal evaluation of right ventricular function at cardiac MRI is mandated before any decision regarding liver replacement can be made. Conversely, outcomes in patients with moderately elevated pressures and resistance in the context of circulatory hyperdynamics are likely to be good. Vasomodulatory therapy is not indicated in the presence of a mild/moderate elevation in pressure due to a hyperdynamic circulation in the absence of raised PVR. All patients should undergo monitoring of mPAP by doppler echocardiography or right heart catheterisation every 3 months whilst they remain in the waiting list. Notwithstanding this, we suggest that LT is not undertaken in patients with severe PoPH (mPAP > 50 mmHG), unless they demonstrate a marked improvement in haemodynamics on therapy: evidence of significant cardiac dysfunction should remain an outright contraindication to transplantation.

Combined summary of HPS and PPH

Early studies demonstrated dismal outcomes for patients with HPS and PoPH. Although limited, the clinical studies over the past two decades have helped evolve therapy and improve outcome and prognosis in these patient groups. There is a wide variety of medications available and LT has established itself as an effective treatment for selected patients with HPS and/or PoPH. Our improved understanding of the pathology and outcomes associated with these conditions has helped to delineate patient sub-sets in whom LT is appropriate. For these patients, rigorous screening and early identification of the condition allied with aggressive preoperative optimisation of physiology and diligent post-operative care is imperative to ensuring a good outcome. All patients diagnosed with HPS and PoPH should be started on therapy and, where appropriate, considered for LT at an early stage in their assessment. Further research in both disorders is required to further improve patient outcomes and improve our understanding of the role and timing of disease-specific therapies.

AUTHORSHIP

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