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Dyspnoea in two children after paediatric liver transplantation

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Introduction

Liver transplantation has now become a standard treatment for children with end-stage liver failure. Even though survival in most centers are more than 90%, regular long term follow up for complications related to transplant and prolonged use of immunosuppressant is necessary. Dyspnoea can be a common complaint encountered in the follow-up of these patients. A variety of causes can account for these complaints, ranging from intrinsic cardiopulmonary disorders to unique diseases associated with chronic liver disease or portal hypertension. In this paper, we presented two children who underwent liver transplantation. They developed two unique and different pulmonary vascular disorders related to chronic liver disease.

Patient 1

Patient 1 had biliary atresia with Kasai operation performed at 2 months of age. Post-operatively there was persistent jaundice and deranged liver function. Living-related donor liver transplant was performed at 10 months of age. Post-operative course was complicated by acute rejection managed with pulse methyl-prednisolone and common bile duct stricture requiring percutaneous transhepatic biliary drainage and balloon dilatation.

The patient was found to have portal hypertension since 2 years old with recurrent gastrointestinal bleeding and esophageal varices, progressive splenomegaly and pancytopenia. There was an episode of massive gastrointestinal bleeding associated with aspiration pneumonia and shock at 7-year-old requiring ventilatory and inotropic support, somatostatin infusion, propranolol, and repeated blood transfusion. Splenectomy and spleno-renal shunt was performed at the age of 7 after the massive GI bleed.

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The patient was first noticed to have cyanosis and progressive deterioration in exercise tolerance at 8-year-old. SpO_2 at that juncture was 88% in room air. There was digital clubbing. Cardiovascular examination was normal. Chest examination was normal. Saturation improved to 98-100% with oxygen supplement via nasal cannula. Further workup showed arterial blood gas in room air to be – pH 7.4, PaO_2 7.4 kPa, $PaCO_2$ 3.9 kPa after administration of 100% oxygen, blood gas revealed – pH 7.35, PaO_2 10.8 kPa, $PaCO_2$ 4.9 kPa. Haemoglobin was 15.1g/dL with haematocrit was 0.432. Bilirubin was normal, ALT was 61U/L, and AST was 62U/L. Chest X-ray showed differential hyperinflation and decreased lung markings of right lung. Lung function test showed decreased FEV_1 and FVC e.g. 81% and 88% of predicted value respectively, TLC 87% of predicted value, decreased DLCO of 44% of predicted value, and normal DLCO/VA. Echocardiogram showed normal structured heart with no evidence of pulmonary hypertension. Contrast echocardiogram showed right to left shunt at the pulmonary level, compatible with hepatopulmonary syndrome.

Discussion

Hypoxaemia in patient with chronic liver disease

There are many causes of pulmonary dysfunction in chronic liver disease. They include intrinsic cardiopulmonary disease such as pneumonia, congestive heart failure, asthma, and ARDS. Other diseases specific to underlying liver disease include panacinar emphysema related to alpha-1-antitrypsin deficiency, and fibrosing alveolitis/pulmonary granuloma associated with primary biliary cirrhosis. Fluid retention in portal hypertension can result in hepatic hydrothorax and significant ascites. In ascites, increased abdominal pressure splint the diaphragm, resulting in reduced lung volume and atelectasis over the lung base. The more uncommon conditions are related to development of pulmonary vascular abnormalities resulting in hepatopulmonary syndrome and portopulmonary hypertension.

Differential diagnosis of hypoxaemia generally includes 1) ventilation-perfusion mismatch; 2) hypoventilation; 3) diffusion defects and 4) shunting. Different pathology would result in different blood gas analysis parameters (Table 1).[1]

Different diseases can be due to one or a mixture of the pathophysiologies. In our patient, there is partial but decreased response to 100% O_2, decreased $PaCO_2$, and increased Pa oxygen gradient of 65.7 mmHg, is more compatible with intrapulmonary shunting. Response to 100% oxygen has to be interpreted with caution since the method of administration of O_2 was not standardised in our case. Together with the positive echocardiogram finding, the picture is compatible with hepatopulmonary syndrome (HPS).

Hepatopulmonary syndrome was first reported in 1884 in a young woman with cirrhosis, cyanosis and clubbing in the absence of chronic lung and heart disease. In 1956, Rydell and Hoffbauer first documented the presence of pulmonary arteriovenous fistula and shunting in a patient in juvenile cirrhosis. Kennedy and Knudson first use the term 'hepatopulmonary syndrome' in 1977.[2]

The classical triad of hepatopulmonary syndrome consisted of: 1) chronic liver disease and/or portal hypertension, 2) hypoxaemia (increase in alveolar to arterial oxygen gradient), and 3) abnormal intrapulmonary vascular dilatations. Liver dysfunction needs not to be severe and intrinsic cardiopulmonary disease must be excluded.

Incidence

Reported incidence of hepatopulmonary syndrome in patients with liver disease was 4-29%. The variation in incidence can be related to difference in diagnostic criteria.[3] Hypoxaemia occurs in about one-third of patient with chronic liver disease. This proportion will change with different cut-offs – 19% with PaO_2 cut off at 80 mmHg and 15% with PaO_2 cut off at 70 mmHg. On the other hand, up to 40% of cirrhotic patients has detectable intrapulmonary vasodilatation, with only 8-15% diagnosed as hepatopulmonary syndrome. There is only slight association between severity of liver disease and degree of hypoxaemia. Prognosis of the disease is poor, with mortality rate of 41% within mean period of 2.5 years.

Pathogenesis

The cause of hepatopulmonary syndrome is multifactorial and modulated by extraneous factors at the same time. The major cause lies in the presence of abnormal pulmonary vascular dilatation. There are several types of vascular dilatation: 1) pre-capillary dilatation, 2) pleural based vascular dilatation and 3) direct arteriovenous communication. Many vasoactive mediators including VIP, calcitonin gene related peptide, glucagons, substance P, ANP, platelet activating factor and nitric oxide are responsible. This is either due to failure in clearance or increase in production of such mediators by the diseased liver. In portohypertension, the altered bowel perfusion is postulated to cause increased enteral translocation of gram negative bacteria and endotoxin, stimulating the release of vasocative mediators including tumour necrosis factor α, haem-oxygenase-derived carbon monoxide and nitric oxide.

Increased production of nitric oxide is proposed to be the most important mediator in the pathogenesis. Exhaled nitric oxide is increased in patients with hepatopulmonary syndrome and correlates with increase in PA-aO_2 gradient. The exhaled nitric oxide decreases after successful correction of hepatopulmonary syndrome by liver transplantation. However, the relationship of nitric oxide with degree of liver damage

Table 1. Differential diagnosis of hypoxaemia[1]

Finding	Response to 100% Oxygen	Partial pressure of Carbon dioxide	Alveolar-arterial oxygen gradient
Hypoventilation	Yes	Increased	Normal
Diffusion defect	Yes	Decreased	Increased
Intrapulmonary shunt	No	Increased or normal	Increased
Ventilation-perfusion mismatch	Yes	Decreased, increased or normal	Increased

and portal hypertension is still not very delineated. Increase in expression of the endothelial type B (ET_B) endothelin receptor seen in cirrhosis and portal hypertension may increase ET_B receptor-mediated ET-1-induced NO production.[3,4]

Clinical manifestation

The most common manifestation is progressive dyspnoea. Physical examination may reveal cyanosis, finger clubbing and signs of underlying liver disease. Platypnoea (increased dyspnoea from supine to upright position) and orthodeoxia (decrease in P_aO_2 ≥5% or 4 mmHg from the supine to upright position) is present in 88-100% of patient with hepatopulmonary syndrome.[3-5] This is due to predominant vasodilation over lung base leading to increased perfusion over lower lobes and worsening of diffusion-perfusion mismatch. Hyperdynamic circulation is present with increased cardiac output. These patients are also prone to systemic arterioembolisation.

Diagnosis

Lung function test (forced spirometric result and static lung volumes) is usually normal but moderate to severe DLCO reduction is common in hepatopulmonary syndrome. It is however not recommended for screening as the mechanism of this finding is unclear.[4]

Different centres have been using different definitions and cut-off values for hepatopulmonary syndrome. In hepatopulmonary syndrome, there is an increased age-corrected alveolar-arterial oxygen gradient (A-aPO_2) of greater than 15 mmHg in room air. This can be calculated using the simplified equation below: [$PAO_2 \sim FiO_2$ x 713 mmHg – $PaCO_2$].[4,6] For other centres and for elder patient aged >64 years, a cut off of ≥20 mmHg is used. Calculation of PA-aO_2 is the most sensitive for detection of early arterial deoxygenation.[4] The diagnostic criteria proposed by the ERS task force includes 1) liver disease; 2) PA-aO_2 ≥15 mmHg; and 3) positive contrast-enhanced cardiography.

Hypoxaemia and arterial deoxygenation is another key feature in pulmonary gas exchange. This should be measured at rest in room air with the patient in erect position.[2] A classification of HPS severity based on oxygenation abnormalities in 4 stages is proposed (Table 2).[4]

In blood gas anaylsis, hypocapnia may be present because of the usual hyperventilation in patients with portohypertension.

The presence of shunt fraction is assessed while patient is breathing 100% O_2 by using the formula:[2]

$$Q_s/Q_t = (PAO_2 - PaO_2) / [(PAO_2 - PaO_2)+1670]$$

In order to achieve accurate result, use of nose clip or mouth piece is required. Shunt fraction can distinguish between "anatomical" shunting from "functional" shunting by microvascular dilatation and is only positive in "anatomical" shunting. Normal study may be seen in hepatopulmonary syndrome with functional shunting.

Pulse oximetry is a rapid, noninvasive and inexpensive screening test for hepatopulmonary syndrome. There is no prospective study concerning the value of pulse oximetry. SpO_2 level of ≤97% has a sensitivity of 96% and specificity of 76% for detecting mild hypoxaemia i.e. PaO_2 of 70 mmHg. A lower SpO_2 level of ≤94% can identify all patients with moderate and severe hypoxaemia i.e. PaO_2 of 60 mmHg. Pulse oximetry is useful in following patients with moderate to severe HPS especially in children but it cannot replace routine arterial blood gas analysis.[4] A group reported that transcutaneous O_2 tension after 100% O_2 is reliable for characterising the severity of abnormal oxygenation in children.[7]

Modalities for demonstration of intrapulmonary vascular dilatation include contrast echocardiography, lung perfusion scan and pulmonary angiography/ catheterisation. The former two modalities are the most well accepted approaches. Contrast echocardiography is performed by injecting agitated saline or contrast medium intravenously and visualisation in the left atrium. Visualisation of contrast within 3 cycles is indicative of intracardiac shunt and visualisation at 4 to 5 cycles is

Table 2. Grading of severity of hepatopulmonary syndrome[4]

Stage	PA-aO_2 (mmHg)	PaO_2 (mmHg)
Mild	≥15	≥80
Moderate	≥15	<80-≥60
Severe	≥15	<60-≥50
Very severe	≥15	<50 (<300 on 100% O_2)

compatible with intrapulmonary shunt. Contrast echocardiography is more sensitive than lung perfusion scan but not as specific.[2] It can be positive in up to 40% of cirrhotic patients with normal arterial blood gas as mild intrapulmonary vasodilation is common but may be insufficient to be labeled as hepatopulmonary syndrome.

Another modality for evaluation of shunting is the lung perfusion scan. In normal condition, injecting aggregates of albumin (^{99m}TcMAA) greater than 20 μm should be completely trapped by the pulmonary capillary bed. In the presence of shunting, whole body scanning should show uptake in other organs such as the brain or spleen. It can be used for quantification of shunt fraction and is more specific for hepatopulmonary syndrome than contrast echocardiography even in the presence of co-existing lung disease. It complements the method of using 100% oxygen for estimation of shunt.[4] It is however unable to differentiate between intracardiac communications and intrapulmonary vascular dilatation.[4] The sensitivity is also lower than echocardiography.[4]

Pulmonary angiography is insensitive as a screening test and is invasive. It can however differentiate between microvascular (type I/ diffuse) or macrovascular (type II/ focal) shunting. In microvascular shunting, diffuse spider like branches ("minimal" pattern) or blotchy spongy ("advanced" pattern) appearance can be viewed. In macrovascular shunting, discrete vascular dilatations resembling arteriovenous communications can be seen. In the later type, there is poor response to 100% O_2 with PaO_2 <300 mmHg, hypoxaemia is less likely to resolve with liver transplantation and more amendable to embolisation therapy.

Computer tomography does not have specific diagnostic value in hepatopulmonary syndrome. High-resolution CT may be useful in exclusion of pulmonary condition.

Screening

For patient with chronic liver disease and post liver transplant with symptoms of dyspnoea, SpO_2 is useful screening test. The diagnostic cut off is SpO_2 of 97%. If SpO_2 ≥97% and chest radiograph is normal, regular follow-up for SpO_2 would be adequate. If SpO_2 <97%, arterial blood gas is indicated. ERS task force proposed a screening algorithm with arterial blood gas determination (i.e. PaO_2 and PA-aO_2) as the initial step (Figure 1).[4] Echocardiography and lung function test is performed in case of abnormal result.

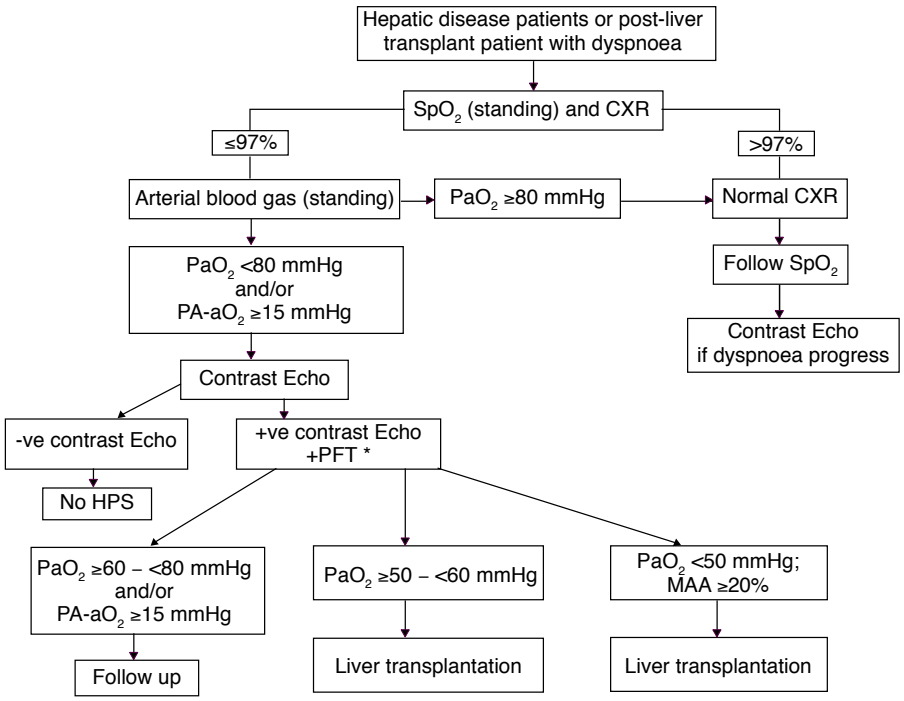
Management

Administration of oxygen can improve hypoxaemia in hepatopulmonary syndrome. Long term oxygen therapy should be given to patients with severe hypoxaemia (i.e. PaO_2 <60 mmHg).[4] In some cases, there will be spontaneous improvement either with the resolution of underlying hepatic disease or development of pulmonary hypertension. Increased nitric oxide production is a potential target, and medical therapy includes therapeutic nitric oxide inhibitors though this is not an established routine treatment yet. Nitric oxide inhibition can be achieved by low arginine diet, intravenous methylene blue and inhaled N(G)-nitro-L arginine methyl ester. Methylene blue is an inhibitor of guanylate cyclase which is a mediator of intracellular effects of nitric oxide. Other medical therapies on trial include indomethacin, octreotide, aspirin, antibiotics for reduction in enteral bacteria translocation, and *allium sativum L.* (garlic). β-blocker and nitrates, in an attempt to reduce portal venous pressure, does not have effect on hepatopulmonary syndrome.

Intervention techniques include embolisation by applying coil spring for closure of discrete arteriovenous dilatations. There has been reports of success in pre- and post- transplantation treatment. Transjugular portosystemic shunt may reduce portal hypertension and reduce progression of the syndrome, hence a palliative measure and a bridge to liver transplantation.

Complete resolution of hepatopulmonary syndrome with liver transplantation has been documented though it may take several months and years. Hypoxaemia improves in up to 80% of recipients.[2] Presence of hypoxaemia is considered an indication rather than contraindication to transplantation though severe hypoxaemia is a strong risk factor for morbidity after liver transplantation. Hepatopulmonary syndrome is viewed as an indication for transplantation especially in the paediatric population.[4]

Taille et al.[8] reviewed the result of liver transplantation in 23 adult patients with hepatopulmonary syndrome. The overall mortality was 30.5%. Mortality within 10 days after surgery was 8.5%. Recovery was achieved (defined as PaO_2 reaching 70 mmHg in room air) in 65% of the



SpO_2: Percutaneous oxygen saturation; CXR: Chest x-ray; PaO_2: arterial oxygen tension; $PA\text{-}aO_2$: alveolar-arterial oxygen tension difference; Contrast Echo: contrast-enhanced echocardiography; PFT: pulmonary function test; MAA: macroaggregated albumin. *MAA recommended especially if CXR and PFT abnormal. High-resolution CT recommended to rule out respiratory cormorbid conditions.

Figure 1. Algorithm for screening and therapeutic decisions in hepatopulmonary syndrome[4] (Adapted from Eur Respir J 2004;861-80).

patient. Some studies did not show clear association of isotopic shunt ratio or PaO_2 with mortality or long term survival.[8,9] In other reports, mortality has been shown to be higher in HPS with severe hypoxaemia and high shunt in lung perfusion scan.[10,11] Those with PaO_2 ≤50 mmHg and MAA shunt ≥20% has the highest risk.

Patient 2

The child was a case of idiopathic portal hypertension first presented with massive ascites, hepato-splenomegaly, gastrointestinal bleeding and shock at 15 months of age. Extensive investigations were performed. Liver function was normal. Ultrasound showed thickening of ligamentous teres with recanalisation of umbilical vein. Doppler ultrasound did not show any portal vein obstruction. Computer tomography of the abdomen showed hepato-splenomegaly. Liver biopsy was unrevealing. Repeated ultrasound liver in 1998 showed coarse parenchymal echogenicity compatible with cirrhosis, massive splenomegaly, patent portal vein with normal flow direction, small tortuous vessels at porta region and carvenous transformation which may be related to previous portal vein thrombosis. Magnetic resonance venogram (MRV) showed carvenisation of portal vein with lots of collaterals around the spleen. Patient had recurrent oesophageal and gastric varices bleeding, requiring repeated sclerotherapy.

The patient was first referred to our unit in March 2004 (14 years old) for dizziness and syncope. She also had retrosternal pain, reduced exercise tolerance and exertional dyspnoea. Physical examination showed a pink patient with normal SpO_2 in room air. Cardiac examination revealed right ventricular impulse, loud pulmonary component of second heart sound with no murmur. Chest X-ray showed clear lung field with no cardiomegaly. Electrocardiogram showed sinus rhythm and evidence of right ventricular hypertrophy. Echocardiogram showed right ventricular hypertrophy and dilated main pulmonary artery. Cardiac catheterisation showed severe pulmonary arterial

hypertension (pulmonary artery pressure of 130/65 mmHg and aortic pressure of 118/70 mmHg). There was no intracardiac shunt. There was mild decrease in pulmonary artery pressure on inhalation of 100% oxygen and nitric oxide of 40 ppm. Pulmonary angiogram did not reveal any thromboembolism. Overall picture was compatible with porto-pulmonary hypertension.

Definition

Portopulmonary hypertension (PPHTN) is defined by pulmonary arterial hypertension associated with portal hypertension. Diagnostic criteria include 1) raised pulmonary artery pressure i.e. mean pressure determined by right heart catheterisation of >25 mmHg at rest and >30 mmHg during exercise; 2) mean pulmonary artery occlusion pressure of <15 mmHg; 3) raised pulmonary vascular resistance of >240 dyne/sec/cm^5.[3,4] Arterial deoxygenation is not a diagnostic feature of PPHTN.[4]

Incidence and prognosis

In 0.7% of patient with cirrhosis, autopsy revealed pulmonary vascular changes compatible with pulmonary hypertension. Up to 10-20% of cirrhotic patient has pulmonary hypertension depending on the diagnostic criteria used.[3,4] It is as high as 16% among liver transplant candidates. In most cases, the diagnosis of portal hypertension was made before the diagnosis of PPHTN. There was however no definite co-relation between the aetiology of liver disease, severity of hepatic dysfunction, raised portal venous pressure and the severity of pulmonary hypertension. Porto-pulmonary hypertension is a poor prognostic sign. Reported 5-year survival rate ranges from less than 10% to 50%.[3,4] Mean and median survivals of 15 and 6 months respectively is reported.

Pathogenesis

In PPHTN, intimal proliferation and thickening, medial smooth muscle hypertrophy and fibrosis is seen in the small pulmonary arteries. The development of PPHTN is not dependent of the aetiology of portal hypertension. The mechanisms leading to pulmonary hypertension is not well understood. Hyperdynamic circulation is almost present in all patients with portal hypertension, increasing the shear stress on the pulmonary vasculature. This may trigger activation or repression of genes in endothelial/smooth muscle cells, leading to pulmonary vascular remodeling. In the presence of portosystemic shunts and impaired liver metabolism, escape of vasoactive substances from the hepatic circulation and subsequent imbalance of these substances can also be responsible for the pulmonary vascular lesions. Genetics factor and inflammation changes may also play a part in the pathogenesis. Abnormal regulation of neurohormones including serotonin and endothelin-1 is potentially important as well.

Clinical manifestations

The main feature of porto-pulmonary hypertension is progressive dyspnoea on exertion. Patients would also experience fatigue, palpitations, syncope and chest pain. Positive physical examination findings include raised jugular venous pressure, accentuated pulmonary component of the second heart sound, tricuspid regurgitation murmur, right ventricular heave and lower limb oedema.

Diagnosis

Chest X-ray may show prominent main pulmonary artery or cardiomegaly. Electrocardiogram reveals features of right axis deviation, right atrial enlargement and right ventricular hypertrophy. Pulmonary function test may show reduced DLCO. Computer tomography findings are not specific for PPHTN. Arterial blood gas shows often hypocapnia with $PaCO_2$ of <30 mmHg and hypoxaemia but at a degree much lesser than hepatopulmonary syndrome.

Echocardiography often provides the first clue to PPHTN including the presence of tricuspid regurgitation, pulmonary insufficiency, right ventricular hypertrophy and an increased right ventricular systolic pressure. The sensitivity, specificity, positive and negative predictive value of echocardiography for detecting PPHTN are 100, 96, 59, and 100% respectively.[12] It is useful as a screening test for PPHTN.

The gold standard for diagnosing pulmonary artery hypertension is right heart catheterisation.[13,14] Diagnostic criteria including pulmonary artery pressure (P_{pa}), mean pulmonary arterial occlusion pressure, and pulmonary vascular resistance are established by catheterisation. Vasodilator testing is performed with intravenous epoprostenol or inhaled nitric oxide (NO) to determine severity and expected therapeutic responses. Decrease in P_{pa} and PVR by 20% from baseline can be considered significant response.[15,16]

In the recommendation by the ERS task force, the classification of severity is based on P_{pa}.[4] This severity staging correlates with mortality after liver transplant. The severity of porto-pulmonary hypertension can be graded according to the New York Heart Association classification (Table 3).[3] The combination of a P_{pa} of <35 mmHg and a PVR of <250 dyne/sec/cm^5 is associated with excellent outcome post-liver transplant.[17]

Treatment

In mild portopulmonary hypertension, specific treatment is not required but follow-up with echocardiogram every 6 months to 1 year is advised.

Non-specific therapy includes diuretics which decrease hepatic congestion. Caution has to be exercised as it may decrease right ventricular pre-load.

Vasodilator therapy may reverse pulmonary artery vasoconstriction. However, they have no effect on the remodeling changes in PPHTN. Intravenous epoprostenol of the prostacyclin group is the most studied medication. Being a potent pulmonary vasodilator, improvement in terms of exercise capacity and changes in pulmonary artery pressure/pulmonary vascular resistance was reported. However, it cannot prolong the long term survival in most studies. The drug has to be administered continuously via a central venous access, with possible side effects including jaw pain, headache, diarrhoea, flush, leg pain, and gastrointestinal upset. Use of other prostacyclin analogues including subcutaneous treprostinil infusion, inhaled aerosolized iloprost and oral beraprost was also reported. Other vasodilators include endothelin receptor antagonist (bosentan and sitaxentan). Bosentan, a dual endothelin (ET_A and ET_B) receptor, has beneficial effect in primary pulmonary hypertension. It is however potentially hepatotoxic, though it is suggested to be safe and effective in selected group of patients with portopulmonary hypertension. Sitaxentan, a ET_A-receptor-selective, has been associated with fatal acute liver injury.

Phosphodiesterase-5 inhibitor, sildenafil, is another potentially promising treatment modality for pulmonary hypertension.[18] In animal study, sildenafil has been shown to modulate pulmonary gas exchange. Pulmonary artery pressure was decreased after high-dose sildenafil.[19] In adult patient with pulmonary arterial hypertension receiving inhaled iloprost, combination therapy with sildenafil has been shown to improve 6 min walking distance from mean of 256 m to 349 m (p=0.002) and decrease pulmonary vascular resistance from mean of 2494 to 1950 dyne/sec/cm^5 (p=0.036)[20]

Liver transplantation

Portopulmonary hypertension is not a contraindication for liver transplantation. Liver transplantation can lead to resolution of symptoms of portopulmonary hypertension although there is significant variability in survival and post-operative course, from improvement to deterioration. Pulmonary hypertension is reversible in mild to moderate cases but not severe ones, in which liver transplantation is associated with significant perioperative morbidity and mortality. Perioperative mortality is greater than 50% with P_{pa} of 35-45 mmHg and PVR of >250 dyne/sec/cm^5).[21] This is related to poor pulmonary status and compromised perfusion of liver graft associated with hepatic vein congestion. There are successful case reports of multi-organ transplantation.

Table 3. Criteria to distinguish between mild, moderate, and severe portopulmonary hypertension.[3]

	Normal	Mild	Moderate	Severe
NYHA class	-	I, II	II, III	III, IV
Mean pulmonary arterial pressure (mmHg)	15-24	25-34	35-44	>45
Cardiac index (L min^{-1} m^{-2})	2.5-4	>2.5	>2.5	<2
Pulmonary vascular resistance (dyne/sec/cm^{-5})	<240	240-500	500-800	>800
Right arterial pressure (mmHg)	0-5	0-5	5-8	>8
Prognosis	-	Favourable	Questionable	Poor
Specific treatment required	-	No	Questionable	Yes
Reversibility after liver transplantation	-	Yes	Questionable	No

Conclusion

With improved surgical technique, advance in immuno-suppressants and peri-operative care, immediate mortality has decreased significantly in liver transplantation. Care is now focus on monitoring and prevention of the long term morbidity. Both hepatopulmonary syndrome and portopulmonary hypertension commonly present with dyspnoea. Early detection and intervention is important towards successful treatment. However, the natural history, pathophysiology, diagnosis and management of these two diseases are still uncertain. Reports are mainly on adults and studies in children is lacking. Prospective large multicentre studies to formulate a better management guidelines are needed.

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