The Scientific Leadership Council of the Pulmonary Hypertension Association

The scientific program of the Pulmonary Hypertension Association is guided by the association’s Scientific Leadership Council. The Council includes the following health care professionals:

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For the first time in its history the Pulmonary Hypertension Association’s international conference will include a scientific program for physicians, researchers, and nurses. Featuring internationally known experts, the scientific program is entitled, From Puzzle to Picture—Mechanisms of PH: Identification of the Next Therapeutic Targets, June 24-25 in Miami, Florida.

Co-sponsored by the National Heart, Lung, and Blood Institute (NIH), the Centers for Disease Control and Prevention (CDC) and the Office of Rare Diseases (ORD), the program will include poster sessions, abstracts, and workshops as it consolidates recent basic and investigational advances to develop a consensus structure for further investigation. My colleagues and I on the Scientific Leadership Council are excited about the opportunity to meet in a forum that will bring together our peers from throughout the country in the spirit of scientific inquiry. After this meeting, physicians, researchers and nurses can take advantage of the patient-oriented conference, June 25-27 at which more than 50 meeting, physicians, researchers and nurses can take advantage of the areas to be discussed during the Scientific Session is part and parcel of his long-standing commitment to promoting research to find a cure for the disease. It began during his early years when he was a fel-

One of the catalysts behind that effort is Michael D. McGoon, MD, current chair of the Council, whose guidance and exemplary leadership has earned him wide recognition in the pulmonary hypertension community.

McGoon’s energy and enthusiasm for advancing treatment of the disease quickly become apparent as he speaks about the job that lies ahead. “There’s a paradigm shift in treatment, we’re moving beyond vasodilators to a different focus where we will be exploring having an impact on disordered angiogenesis and cell proliferation. We need to find ways of getting independently funded studies, through PHA, and optimize our sources of funding through government support. I anticipate we will focus more on genetic factors, the remodeling of blood vessels, the overgrowth of blood vessels, and the type of information being transmitted from one cell to another,” he said, providing a glimpse of some of the areas to be discussed during the Scientific Session of PHA in Miami, June 24-25.

For McGoon, the challenge underlying these discussions is part and parcel of his long-standing commitment to promoting research to find a cure for the disease. It began during his early years when he was a fel-

(continued on page 25)
Introduction
A relationship between the liver and lung was proposed by the Greek physician Galen (AD c. 126-216), who believed that venous blood was “concocted in the liver,” migrated via a tidal motion to the right ventricle of the heart, and divided into two blood streams, one to the lungs and one through the heart into the left ventricle. According to Galen (so say medical historians) the liver provided “natural spirit” to the body. It wasn’t until the 1500s that these pulmonary vascular teachings were questioned, and the first accurate description of the pulmonary circulation evolved from the Spanish theologian and physician Miguel Servetus.1

Nearly 500 years later we have witnessed both the remarkable success of orthotopic liver transplantation and a renewed interest in the seemingly mysterious relationship between the liver and the lung. Why do some patients with advanced liver dysfunction develop pulmonary vascular dilatations leading to severe arterial hypoxemia, which may totally resolve after liver transplantation (hepatopulmonary syndrome)? Why do patients with similar liver disorders experience a pulmonary vasoproliferative and vasoconstrictive process leading to pulmonary artery hypertension and right heart failure frequently not reversible by liver transplantation? Although these pulmonary vascular consequences of liver disease are relatively uncommon (up to 4% to 15% of transplant candidates), with 5000 transplants being done annually and another 18,000 patients on the Organ Procurement Transplant Network (OPTN) liver transplant wait lists, these clinical problems are no longer trivial.2

Definition of Portopulmonary Hypertension
First described in 1951, the coexistence of pulmonary arterial hypertension as a consequence of hepatic dysfunction has been well documented.3,4 The most important cause of increased mean pulmonary artery pressure (mPAP >25 mm Hg) in the setting of advanced liver disease remains the pulmonary arterial vasculopathy known as portopulmonary hypertension.4,5 Vasoconstriction, endothelial and smooth muscle proliferation, plexogenic arteriopathy, and in situ thrombosis and/or fibrosis characterize portopulmonary hypertension.6,7 Since a hyperdynamic circulatory state and the increased blood volume that accompany liver disease may raise mPAP (in addition to the pulmonary vasculopathy), specific hemodynamic criteria have evolved to define portopulmonary hypertension.5,8,9

Pathology and Pathogenesis
It is important to recognize that portopulmonary hypertension has pulmonary vascular pathology indistinguishable from that seen in primary pulmonary hypertension.4,10 A spectrum of pathology has been described from autopsy and lung explant specimens (open lung biopsy has been rightfully discouraged because of potential complications). Medial hypertrophy, endothelial and smooth muscle proliferation, in situ thrombosis, fibrosis, and classic plexogenic arteriopathy have been noted (Figure 1). Platelet aggregates lodged within the pulmonary vascular lumen have been reported and may contribute to acute right heart deterioration in the post liver transplant period.11,12 The lack of prostacyclin synthase within the pulmonary endothelium2,8,9 in portopulmonary hypertension has been documented, suggesting a lack of vasodilator capability.10 Recently the evolving “signaling” relationship between angiopoietin-1 and the TIE receptors within the pulmonary endothelium has received attention; this relationship in the setting of liver disease needs to be understood.13 To date there has been no relationship documented between portopulmonary hypertension and mutations in the bone morphogenetic protein receptor BMPR2 gene, as noted in other causes of pulmonary arterial hypertension such as primary pulmonary hypertension.

Epidemiology
Poor correlations with Childs-Turcotte-Pugh severity of liver disease, levels of liver enzymes, serum total bilirubin, and splanchnic hemodynamics such as the azygous blood flow and hepatic venous pressure gradient6,14,16 have been reported. An increased frequency of alcoholic cirrhosis has been noted.16,17 Noncirrhotic portal hypertension has been associated with portopulmonary hypertension.17,20 Two retrospective series have documented that surgical portosystemic shunt procedures preceded the diagnosis of portopulmonary hypertension in 30% to 76% of patients.16,20

In the pre-liver transplant era, the NIH pulmonary hypertension registry of 204 patients with primary pulmonary hypertension classified 17 (8%) of the patients as having cirrhosis-associated pulmonary hypertension.16 In the current era of liver

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transplantation, major transplant centers have reported the frequency of portopulmonary hypertension to be 4% to 15%. Remarking, a review of published portopulmonary hypertension cases through 1999 documented that 65% of diagnoses were first recognized during the liver transplant procedure.18

Clinical Presentation and Significance

The clinical presentation of portopulmonary hypertension is subtle; exertional dyspnea is the most common nonspecific symptom.4,16 Other symptoms and signs, including fatigue and leg edema, can be easily confused with those of underlying heart and/or liver disease so that making the diagnosis requires a high degree of suspicion. Chest pain and/or pressure and syncope are usually later manifestations of portopulmonary hypertension. The chest examination is quite unremarkable except for the usual cardiac findings of pulmonary hypertension.

In the pre-liver transplant era, survival from a French series reporting portopulmonary hypertension ranged from 72% mortality within 12 months of diagnosis14 to a US study from the Cleveland Clinic describing a 6 month (median)/15 month (mean) survival as determined from a literature review of 78 patents.15 Recent 2-year, single institution survival of portopulmonary hypertension patients (liver transplant patients excluded) ranged from 50% to 72%.4,17 The importance of pulmonary hypertension in the setting of advanced liver disease reflects the high risk of conducting liver transplantation in such patients.18,19,21 In 43 portopulmonary hypertension patients who underwent orthotopic liver transplantation, a 35% perioperative mortality was reported.18 Right heart failure and cardiopulmonary collapse caused most deaths; intraoperative death occurred in 5 patients.18 In a recent multicenter study, despite excluding 45% of 66 portopulmonary hypertension patients from liver transplantation consideration due to the severity of the condition, transplant outcome remained problematic. Transplant hospitalization mortality was 36%, with all deaths occurring within 18 days of transplant; intraoperative death was reported in 38%.19

Screening

Routine posteroanterior and lateral chest radiography and resting electrocardiography are insufficient for portopulmonary hypertension screening purposes. By the time enlarged pul-
Right Heart Catheterization

Right heart catheterization is necessary to explicitly delineate the pulmonary hemodynamic patterns that exist in the setting of hepatic dysfunction. In patients with advanced liver disease, increased pulmonary artery pressures can be found as a result of multiple underlying causes, including the high flow hyperdynamic state, excess volume, and the vasoproliferation and vasoconstriction pulmonary vasculopathy associated with portopulmonary hypertension (Figure 2). The current portopulmonary hypertension diagnostic criteria recently endorsed by the European Respiratory Society-European Association for Study of the Liver (ERS-EASL) task force on pulmonary-hepatic vascular disorders are summarized in Table 1.

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<th>Right Heart Catheterization Required</th>
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<td>• Portal hypertension (ie, ascites, esophagogastric varices, splenomegaly)</td>
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<tr>
<td>• Mean pulmonary artery pressure &gt;25 mm Hg</td>
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<tr>
<td>• Pulmonary capillary wedge pressure &lt;15 mm Hg</td>
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<td>• Pulmonary vascular resistance &gt;240 dynes.s.cm⁻⁵</td>
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Fig. 2—Via right heart catheterization, several hemodynamic patterns can be documented in the setting of advanced liver disease. The main patterns associated with increased mean pulmonary artery pressure (mPAP) are shown above. High cardiac output (CO) characterizes the hyperdynamic circulatory state that follows the development of decreased systemic vascular resistance. Excess central volume is reflected by increased pulmonary capillary wedge pressure (PCWP).

Slight increase in pulmonary vascular resistance (PVR) may be noted. The vasoconstriction and vasoproliferation that characterize portopulmonary hypertension initially result in marked increases in PVR, mPAP, and CO.

Transathoracic Doppler echocardiography (DE) is relatively sensitive in detecting increased right ventricular systolic pressure (RVsyst) as an estimate of pulmonary artery systolic pressure, as long as the pulmonary valve is normal. However, DE may not distinguish between causes of increased RVsyst such as seen in the hyperdynamic circulatory state, increased central volume, and the true pulmonary vasculopathy of portopulmonary hypertension. DE is the current screening procedure of choice if portopulmonary hypertension is suspected, but right heart catheterization is mandatory for the definitive diagnosis. However, although many screened patients have increased RVsyst (30 to 50 mm Hg by DE), they do not have increased pulmonary vascular resistance as determined via right heart catheterization. Using the more discriminatory screening criteria RVsyst >50 mm Hg to determine indication for right heart catheterization, 85% to 97% of patients with clinically significant portopulmonary hypertension (mPAP >35 mm Hg) were identified. In an unpublished series from the Mayo Clinic (N = 360 over the time period 2001 to 2003), approximately 10% of all orthotopic liver transplantation candidates had RVsyst >50 mm Hg; 20% had RVsyst >40 mm Hg. RVsyst could not be accurately measured in 20%. The clinical implications and/or benefits of vasoactive testing during right heart catheterization in the setting of portopulmonary hypertension are unclear, since...
Observe; repeat echo in 12 months if orthotopic liver transplantation candidate

Right heart catheterization for hemodynamic data

RA - right atrial pressure
mPAP - mean pulmonary artery pressure
PCWP - pulmonary capillary wedge pressure
CO - cardiac output
PVR - pulmonary vascular resistance

Characterize pulmonary hemodynamics

mPAP ≥25 mm Hg and PVR ≥240 dynes.s.cm⁻⁵

mPAP ≥25 mm Hg and PVR <240 dynes.s.cm⁻⁵

mPAP <25 mm Hg

Other patterns? See text

Portopulmonary hypertension diagnosis established

Probable high flow state

Portopulmonary hypertension does not exist

Go to portopulmonary hypertension management/treatment algorithm (see page 16)
the use of calcium channel blockers in this group of patients could theoretically worsen portal hypertension.

**Other Pulmonary Studies**

Although pulmonary function abnormalities are not specific for portopulmonary hypertension, arterial hypoxemia (mean PaO2 = 76±9; range, 53 to 97 mm Hg) was reported in 80% of patients with moderate to severe disease. Increased alveolar-arterial oxygen gradient and significant accentuation of respiratory alkalosis compared with cirrhotic patients without portopulmonary hypertension have been reported. Reduced diffusing capacity is frequent but nonspecific. In order to consider other possible causes of pulmonary hypertension in the setting of liver disease, recommended diagnostic assessments are summarized in the accompanying portopulmonary hypertension algorithm.

**Conclusion**

Recognition of the unique clinical associations and characteristics of portopulmonary hypertension has evolved rapidly over the last 15 to 20 years as a result of advances in medical therapies and implications for orthotopic liver transplantation (both cadaveric and living donor). Further understanding of the natural history and pathophysiology of portopulmonary hypertension is essential as our potential therapeutic interventions expand.

**References**

2. Organ procurement transplant network; accessible at www.optn.org
The perioperative management of patients presenting for orthotopic liver transplantation who have associated pulmonary hypertension still presents a challenge to the operative team. As a result of the limited amount of accurate data available, and because the conclusions reported are often conflicting, it has not been easy to develop an evidence-based strategy for the safe management of these patients through liver transplantation.1-13 This failure to reach a consensus opinion may be a result of the fact that patients have very different pathological presentations. When there are various associated comorbidities coupled with a lack of complete hemodynamic and echocardiographic data, it is difficult to make a precise comparative evaluation between transplant candidates.

Typically, patients with advanced liver disease experience a hyperdynamic circulatory state, with increased cardiac output and decreased systemic vascular resistance.14 In addition, some patients with pulmonary hypertension associated with liver disease have increased venous blood volume due to systemic volume overload, or they may have left, right, or biventricular cardiac dysfunction. Patients with portal hypertension have true portopulmonary hypertension when the measured pulmonary hypertension is accompanied by an increased resistance to pulmonary blood flow, as demonstrated by a calculated (pulmonary vascular resistance is a calculation based on the other measurements) increase in pulmonary vascular resistance, in the presence of a normal pulmonary capillary occlusion pressure or left ventricular end-diastolic pressure.

It is essential, therefore, to accurately characterize the pulmonary hemodynamics in these patients. The required hemodynamic data must be determined from right heart catheterization and must include the following values: mean pulmonary artery pressure (mPAP), cardiac output, pulmonary artery occlusion pressure, and calculated pulmonary vascular resistance, in the stable, resting state. Cardiac output is typically high in this patient group. If a normal or low value is obtained, volume depletion is usually present; however the diagnosis of cardiomyopathy should be considered. If the patient is volume depleted, the volume replenishment needed to restore homeostasis may lead to the demonstration of an even higher mean pulmonary artery pressure than initially measured, although the pulmonary vascular resistance is unlikely to change.

Pulmonary hypertension may be found in up to 20% of patients with cirrhosis of the liver. However, according to some studies, true portopulmonary hypertension has a prevalence of about 5% in patients presenting for orthotopic liver transplantation.9,14 High cardiac output, cardiac failure, cardiomyopathy, and volume overload account for a number of non-portopulmonary hypertension presentations, and the management of these patients is very different from those with true portopulmonary hypertension. In fact, some degree of cardiomyopathy (downregulation of beta receptors) has been reported to occur in all cirrhotic patients, thereby blurring the lines between true portopulmonary hypertension and pulmonary hypertension secondary to other causes.15

Portopulmonary hypertension is defined as the existence of portal hypertension with a resting mPAP >25 mm Hg, a pulmonary artery occlusion pressure <15 mm Hg, and pulmonary vascular resistance > 240 dynes.s.cm⁻⁵.

Essential hemodynamic measurements are calculated as follows: mPAP (mm Hg) = pulmonary artery systolic pressure + [(pulmonary artery systolic pressure – pulmonary artery diastolic pressure) / 3]; pulmonary vascular resistance (dynes.s.cm⁻⁵) = (mPAP – pulmonary artery occlusion pressure) x 80 / cardiac output. Cardiac index (cardiac output/body surface area) and pulmonary vascular resistance index allow body surface area to be taken into account so that true comparative measurements may be made. However, rarely does the portopulmonary hypertension literature provide this complete information.

The pathological changes in the microvasculature of the lungs of patients with portopulmonary hypertension include plexogenic arteriopathy, medial hyperplasia, thrombosis, and eventually fibrosis, quite similar to those findings found in idiopathic pulmonary arterial hypertension. Concomitant with these changes, vascular dilations and shunt formation may occur, such as that seen in patients with hepatopulmonary syndrome.21 This observation suggests that these changes may be balancing the physiological outcome until one predominates.22
after orthotopic liver transplantation, unless long-term pulmonary vasodilator therapy is instituted.\textsuperscript{1, 23} The shunt formations do resolve after transplantation, however, and this may reveal the underlying pulmonary hypertension. Therefore, transplantation may be considered an effective therapy for hepatopulmonary syndrome, in contrast to portopulmonary hypertension.

A calculated pulmonary vascular resistance >240 dynes.s.cm\(^{-5}\) is generally considered pathological, although some authorities\textsuperscript{16, 17} have defined pulmonary hypertension by a value >120 dynes.s.cm\(^{-5}\). Portopulmonary hypertension is further graded hemodynamically into mild (mPAP 25 to 35 mm Hg) moderate (mPAP 35 to 45 mm Hg) and severe (mPAP >45 mm Hg). Management of the patient with portopulmonary hypertension >35 mm Hg depends on the causative factors. Volume overload may be treated with diuresis or, if renal function is severely impaired, by utilizing continuous venovenous hemodialysis. If this treatment is effective and ventricular function is good, then transplantation may continue without extra risk. If cardiac function is poor as the result of a cardiomyopathy and filling pressures remain elevated, then the patient is at significant risk if transplantation is undertaken, unless significant improvement in cardiac function is achieved with inotropic agents. In most of the liver failure patients presenting for transplantation, pulmonary vascular resistance is low and left ventricular function appears enhanced, such that it takes experience in this group of patients to diagnose even moderate degrees of ventricular dysfunction. If reduced left ventricular function is noticed on echocardiography, it is likely that a severe cardiomyopathy exists and the transplantation should be deferred for further evaluation.

Reactive pulmonary hypertension may respond to anesthetic, adequate ventilation, and pulmonary vasodilators. Patients with fulminant liver disease who also have associated metabolic and respiratory acidosis may well have pulmonary hypertension that will respond to correction of the acidosis and adequate ventilation. Patients diagnosed with portopulmonary hypertension just prior to liver transplantation may respond to acute pulmonary vasodilator therapy. Inhaled nitric oxide (INO), the prostacyclin analogue iloprost, intravenous milrinone, epoprostenol, and oral sildenafil have all been administered to reduce mPAP with varied responses.\textsuperscript{18, 19} If the mPAP is lowered to 35 mm Hg or less, the pulmonary vascular resistance is <240 dynes.s.cm\(^{-5}\), and right ventricular function is good, there is no reported increased risk to proceeding with transplantation.\textsuperscript{17}

If the mPAP and pulmonary vascular resistance remain elevated, whether the patient will survive liver transplantation may depend on right ventricular function and the added stressors applied to it during the perioperative period. There are reports of successful transplantation in patients with an mPAP of 53 mm Hg and pulmonary vascular resistance as high as 639 dynes.s.cm\(^{-5}\). However, other reports demonstrate 100% mortality in patients with an initial mPAP >50 mm Hg.\textsuperscript{12, 20}

Moderate and severe portopulmonary hypertension places the liver transplantation patient at increased risk of perioperative morbidity and mortality.\textsuperscript{17, 20} The data available to date indicate a perioperative mortality of greater than 70% if liver transplantation were carried out with an mPAP of 45 mm Hg or higher and up to 100% if the mean pressure were >50 mm Hg. There is no increase in mortality risk if the mPAP is 35 mm Hg or less.\textsuperscript{20} A multicenter, national liver transplant database reported an overall mortality perioperatively of 36% for patients with portopulmonary hypertension undergoing transplantation.\textsuperscript{17}

Despite the realization that pulmonary hypertension may increase the morbidity and mortality of patients undergoing orthotopic liver transplantation, and the close attention to the cardiopulmonary system during the patient’s pretransplant assessment, it is not uncommon for patients to be diagnosed on the operating table at the induction of anesthesia.\textsuperscript{24} This is because the symptoms of end-stage liver disease are similar to those of severe pulmonary hypertension, and the time course for development of pulmonary hypertension is unknown. The risk to the patient with portopulmonary hypertension is based on two major outcomes that are very dependent on right ventricular function. First, an acute increase in pulmonary vascular resistance during transplantation may result in right ventricular dysfunction, which results in an elevation of right heart pressures, causing congestion and failure of the new liver graft. Second, a profound increase in pulmonary vascular resistance, as may be seen following reperfusion of the new liver graft, may cause the right ventricle to fail acutely, with resulting serious morbidity or mortality.

Right ventricular function should be assessed by echocardiography, whether the diagnosis of portopulmonary hypertension is made preoperatively or on the operating room table. Preoperatively, right ventricular systolic pressures >50 mm Hg and/or abnormal right ventricular chamber size, wall motion, or septal movement toward the left ventricle, require further analysis of hemodynamic data by right heart catheterization. The pulmonary vascular resistance that is calculated from the right heart catheter is very dependent on cardiac output. Typically elevated in cirrhotic patients, cardiac output is found to increase in most patients following reperfusion of the new liver graft. In a majority of patients, this increase in cardiac output is in the range of 5% to 10%. However, the increase is unpredictable and may reach 300% or greater in a small number of patients (3.8%).\textsuperscript{24} This massive unpredictable increase may stress a marginal right ventricle. Therefore, the key to survival in this patient population is good right ventricular function, and this must be assessed carefully before transplantation and during the procedure.

How rapidly portopulmonary hypertension can develop is uncertain, as reports vary from 3 weeks to 5 years.\textsuperscript{24, 25} Pulmonary thromboembolism may be the cause of an acute presentation of portopulmonary hypertension. As mentioned above, routine transthoracic contrast-enhanced echocardiography (CE-TTE) should be performed as part of the pretransplantation work-up. The symptoms of portopulmonary hypertension are too similar to those of end-stage liver disease to be able to differentiate without CE-TTE.

Echocardiographic findings of abnormal right ventricular function provide an indication for right heart catheterization, it
Endothelin (ET) concentrations are elevated in the plasma and lung tissue of patients with pulmonary arterial hypertension (PAH), suggesting a pathogenic role for ET in PAH.\(^1\)

The effects of ET are mediated by binding to \(\text{ET}_A\) and \(\text{ET}_B\) receptors. Only Tracleer is a specific and competitive antagonist for both ET receptors.\(^1\)

- Decreases rate of clinical worsening*  
- Improves exercise ability  
- Improves hemodynamics (CI, PAP, PVR, RAP)

**Liver and pregnancy warnings**

- Requires attention to two significant concerns  
  — Potential for serious liver injury: Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter  
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- Contraindicated for use with cyclosporine A and glyburide

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*Clinical worsening defined as combined endpoint of death, hospitalization or discontinuation due to worsening PAH, or initiation of epoprostenol therapy*\(^1\)
Carcinogenesis, Mutagenesis, Impairment of Fertility: Two years of daily administration of bosentan to mice produced an increased incidence of hepatoblastomas and carcinomas in males at doses of 8 times the maximum recommended human dose (MRHD) of 125 mg b.i.d. on a mg/kg basis. In the same study, doses greater than or equal to the MRHD were associated with an increased incidence of skin carcinomas. In rats, daily administration of bosentan for five years was associated with an increased incidence of brain astrocyes in males at doses of 4 times the MRHD. Impairment of fertility was observed in rats treated with bosentan at doses up to 50 mg/kg, which is 34 times the MRHD on a mg/kg basis. Impairment of fertility was observed in rats treated with bosentan at doses of 50 mg/kg, which is 34 times the MRHD on a mg/kg basis.

Genotoxicity: A two-year study of bosentan in rats did not show any evidence of genotoxicity. However, in vitro studies with human lymphocytes did not show any significant effects on the mitotic index or chromosomal aberrations.

Impairment of Fertility: Many endothelin receptor antagonists have shown evidence of impaired sperm motility and viability, although the extent and significance of this effect have not been fully characterized.

Adverse Events: Bosentan has been shown to be effective in reducing the symptoms of pulmonary arterial hypertension, but like other endothelin receptor antagonists, it may also have some adverse effects.

Long-Term Treatment: The long-term safety and efficacy of bosentan in patients with PAH have not been established. Patients should be monitored closely for any signs or symptoms of worsening disease, and treatment should be adjusted accordingly.

Drug Interactions: Bosentan can interact with a variety of other drugs, including statins, which may increase the risk of liver damage. Patients should be closely monitored for any signs of liver damage, and the dosage of bosentan may need to be adjusted if necessary.

Dosage and Administration: The recommended dosage of bosentan is 125 mg twice daily, with or without food. The dosage should be adjusted based on the patient's response and the severity of the disease.

Contraindications: Bosentan is contraindicated in patients with a history of severe liver dysfunction, as well as in patients with a history of severe pulmonary hypertension.

CYP3A4 metabolized statins should have cholesterol levels monitored after TRACLEER® is initiated to see whether the CYP3A4, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using Bosentan is also expected to reduce plasma concentrations of other statins that have significant metabolism by active Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotrans-
can be used to monitor the effectiveness of pulmonary vascular therapy, and it can be used as an assessment tool for determining the ability of the right ventricle to compensate for the increased pulmonary vascular resistance.\textsuperscript{26,27} If the right ventricle can adjust to the increased afterload over time by hypertrophy, this may provide a better chance of decreasing morbidity and mortality during transplantation. Perioperative risk to the patient is not only related to the absolute value of the mPAP and pulmonary vascular resistance but is also a function of the condition of the right ventricle. Once portopulmonary hypertension has been diagnosed, follow-up screening by CE-TTE to assess effectiveness of therapy and right ventricular function should occur at least every 6 months.

Right heart catheterization is the gold standard for the diagnosis of pulmonary hypertension, including portopulmonary hypertension.\textsuperscript{28} It not only provides accurate assessment of portopulmonary hypertension, pulmonary hypertension, and ventricular function, it can help sort out the differential diagnosis of hyperdynamic circulation, volume overload, and increased afterload. It also allows an evaluation of acute vasoactivity and can be used to monitor the effectiveness of therapeutic interventions.

Up to 60\% of patients with portopulmonary hypertension may not have their condition detected until reaching the operating room, undergoing the induction of anesthesia prior to liver transplantation.\textsuperscript{24} If diagnosed for the first time in the operating room, once an accurate diagnosis has been made and right ventricular function has been assessed by transesophageal echocardiography (TEE), a decision has to be made whether to proceed with surgery or delay transplantation to a future date after effective vasodilator therapy. Acute vasodilator testing should be considered when a diagnosis of moderate portopulmonary hypertension (mPAP >35 to 45 mm Hg) has been made. In the immediate preoperative setting, iNO, inhaled nitroglycerin, or inhaled iloprost are best suited to effect an immediate response. Intravenous vasodilators such as milrinone are somewhat limited by the systemic vasodilation that these agents may cause. The response to iNO is variable, with some patients responding well and others showing no vasoreactivity at all.\textsuperscript{18,19,29-32} Liver cirrhosis is associated with excessive production of endogenous nitric oxide and this may explain this unpredictable response to iNO.\textsuperscript{33}

The goal of vasodilator testing in the portopulmonary hypertension patient is to bring the mPAP down to 35 mmHg or less and to reduce pulmonary vascular resistance to <240 dynes.s.cm\textsuperscript{-5}. An accurate assessment of right ventricular function by TEE is also an essential part of patient examination. If acute vasodilator therapy is not effective, then surgery is postponed and long-term vasodilator therapy such as intravenous epoprostenol or in some centers oral bosentan is started. The use of bosentan, a dual endothelin receptor antagonist (A and B), is generally not recommended in portopulmonary hypertension as it may cause a rise in hepatic enzymes, although it has a potential advantage because it does not require long-term intravenous access. Most pulmonary artery hypertension experts are wary of using bosentan for portopulmonary hypertension patients because in a large multicenter study that excluded patients with liver disease at least a threefold upper limit of normal elevation of liver aminotransferases (ALT and AST) occurred in about 11\% of patients, accompanied by elevated bilirubin in a small number of cases. Epoprostenol generally produces a greater increase in cardiac output than does iNO. It is also a powerful systemic vasodilator that reduces systemic as well as pulmonary vascular resistance. It can be administered only by continuous intravenous infusion (central venous access via portable infusion pump) since its half-life in circulation is brief (3 to 5 min). Common adverse effects attributable to epoprostenol include jaw pain, headache, diarrhea, flushing, leg pain, and nausea or vomiting. More serious complications may occur because of the delivery system (catheter-related infections or thrombosis). Sildenafil has been used in managing portopulmonary hypertension, but no trials have been reported studying its efficacy in that condition.

Those patients with portopulmonary hypertension who undergo liver transplantation have a varied survival rate and change in pulmonary hemodynamics. One study reported a mortality of 71\% at 36 months after transplantation in patients with portopulmonary hypertension who did not receive postoperative epoprostenol.\textsuperscript{1} The same group reported 100\% survival in a group of patients with portopulmonary hypertension treated acutely with iNO followed by epoprostenol.\textsuperscript{23} Normalization of pulmonary pressures occurred in all patients, but took between 2 days and 18 months of postoperative epoprostenol therapy.\textsuperscript{23}

Reassessment of the patient at frequent intervals by repeat echocardiography can provide information not only on the progress of therapy but also on the condition of the right ventricle. With time, conditioning of the right ventricle may occur, and a widely dilated chamber may develop into a hypertrophied and well-contracting ventricle. If this occurs, then the patient may tolerate liver transplantation with a higher mPAP.\textsuperscript{34}

If pulmonary hypertension is diagnosed on the operating room table just before starting surgery, a decision has to be made to proceed or defer the procedure. This decision needs to be made rapidly, as another recipient may need to be admitted. The decision to proceed should be based on the level of the mPAP and systemic vascular resistance, the reversibility of the mPAP and systemic vascular resistance, and the condition of the right ventricle, as evaluated by TEE. It must include a careful rechecking of the hemodynamic data to ensure its accuracy and the elimination of other diagnoses, such as fluid overload, cardiomyopathy, and respiratory acidosis. The reversibility of the increased mPAP can be rapidly tested by the administration of iNO or another pulmonary vasodilator (see above). The function of the right ventricle may be evaluated by TEE surveillance while a one liter fluid bolus and a dobutamine infusion are administered. If the mPAP reduces to <35 mm Hg, pulmonary vascular resistance falls below 240 mm Hg, and right ventricular function is not severely impaired, a reasonable expectation exists that surgery can proceed safely. Inhaled nitric

(continued on page 17)
A message from the Scientific Leadership Council of the Pulmonary Hypertension Association

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As members of PHA’s Scientific Leadership Council and founding members of PH Doctor, we invite you to join us in this important new endeavor.

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Decision Tree: Management of Pulmonary Hypertension Diagnosed at Induction of Anesthesia for Liver Transplantation.

1. mPAP <35 mm Hg
   - Pulmonary vascular resistance <240 dynes.s.cm⁻⁵
   - Good cardiac output and right ventricular function
   - Continue with liver transplant

2. mPAP 35 to 40 mm Hg
   - Pulmonary vascular resistance >240 dynes.s.cm⁻⁵
   - Good cardiac function determined by TEE
   - Consider continuing with liver transplant
   - Attempt to reduce mPAP <35 mm Hg and pulmonary vascular resistance >240 dynes.s.cm⁻⁵
   - Irreversible, but right ventricular function is good (dobutamine and fluid challenge)
   - Continue with liver transplant

3. mPAP >40 mm Hg
   - Pulmonary vascular resistance >240 dynes.s.cm⁻⁵
   - Defer surgery; initiate vasodilator therapy
oxide may assist in the management of transient acute rises in pulmonary artery pressures associated with reperfusion of the new graft.35

An increase in cardiac output is frequently seen (5% to 18% of patients) after reperfusion of the new graft and is typically in the range of 5% to 10%. If there is a significant resistance to pulmonary artery pressure, then the laws of physics dictate that the pressure must increase. Occasionally (3.7% of patients), an increase in Qs of more than 100% of baseline may be seen (Figure).24

This massive increase in cardiac output with a fixed pulmonary vascular resistance may cause the development of systemic pulmonary artery pressures in patients with preexisting pulmonary hypertension and lead to acute right ventricular failure. Since this massive increase in cardiac output is unpredictable, it is prudent to reduce mPAP to a mild (>35 mm Hg) level before undertaking liver transplantation.

The increase in cardiac output is probably the result of the removal of the obstruction to portal blood flow by the extraction of the diseased liver, together with the systemic vasodilatation caused by the washout of acid metabolites and other vasodilator substances from the new graft. Why some patients have such an increase in cardiac output is not known, but if this occurs it clearly adds to the risk for the patient with pulmonary hypertension. The patient with the relatively fixed pulmonary vascular resistance can react to the increased flow only by an acute increase in pulmonary artery pressure and potential right heart failure.

If an acute elevation in mPAP occurs intraoperatively, an evaluation is made as to the etiology: increase in volume, increase in cardiac output, and increase in pulmonary vascular resistance or cardiac failure. Appropriate treatment is initiated. If right heart failure occurs, the new graft is immediately compromised, and the survival of the patient may be in jeopardy. If conventional measures fail, atrial septostomy and the insertion of a right ventricular assist device may be lifesaving.

Conditioning of the right ventricle has been seen in two of our patients who were awaiting orthotopic liver transplantation and were being treated with epoprostenol. The first was diagnosed on the operating room table with an mPAP of 49 mm Hg, pulmonary vascular resistance of 384 dynes.s.cm⁻⁵, and a cardiac index of 3.6 L/m². The TEE revealed a markedly dilated right ventricle and atrium, the left ventricular ejection fraction was 55% to 60%. An iNO response test reduced mPAP to 45 mm Hg. Liver transplantation was postponed. An epoprostenol infusion was started and the patient tolerated a maximum dose of 8 ng/kg/min. One year later, the patient was receiving epoprostenol at 34 ng/kg/min and mPAP was 47 mm Hg with a cardiac index of 6.9 L/m². At reevaluation after further therapy for 4 months, mPAP was 34 mm Hg with a cardiac index of 6.2 L/m². Finally, after another 8 months, the patient was admitted for liver transplantation. The mPAP was 39 mm Hg, systemic vascular resistance 130 dynes.s.cm⁻⁵, and cardiac index 5.1 L/m². On TEE, the right ventricle was now noted to be hypertrophied and contracting well; therefore transplantation was undertaken. At reperfusion there was an increase in cardiac output with a concomitant increase in mPAP to a peak of 55 mm Hg but the patient’s right ventricle tolerated this well. The patient recovered well and is continuing treatment with epoprostenol. The experience with the second patient was similar.34

Summary

The intraoperative management of pulmonary hypertension in the liver transplant recipient requires an accurate diagnosis of the etiology in order to classify the type of pulmonary hypertension that exists, which determines the subsequent course of action. A clear comprehension of the hemodynamic data and cardiac function is paramount. A TEE is essential in assessing the risk factors. Patients with an mPAP >35 mm Hg and pulmonary vascular resistance >240 dynes.s.cm⁻⁵ are at particular risk for orthotopic liver transplantation, and should undergo the procedure only after careful individual assessment of all these parameters. The available data provide a compelling reason to postpone transplantation when a patient is found to have an mPAP >35 mm Hg, and these data suggest that attempts be made to improve hemodynamics and right ventricular function. This may be accomplished in the operating room prior to transplantation or may require a prolonged (and sometimes indefinite) course of vasodilator therapy.

References


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This discussion was moderated by Ronald J. Oudiz, MD, Associate Professor of Medicine, David Geffen School of Medicine at UCLA, and Director, Liu Center for Pulmonary Hypertension, Division of Cardiology, Harbor-UCLA Medical Center, Torrance, California. The participants included Michael J. Krowka, MD, Professor of Medicine, and Russell Wiesner, MD, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, and Michael Ramsay, MD, FRCA, Chairman, Department of Anesthesiology and Pain Management, Baylor University Medical Center, and Clinical Professor, Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas.

**Dr Oudiz:** How are most patients diagnosed with portopulmonary hypertension? How many patients have their condition discovered “by accident” in the operating room as they’re being prepared for liver transplantation?

**Dr Ramsay:** Up until about 18 months ago we diagnosed about 60% of these patients on the operating room table just prior to transplant. Now, because everybody is looking for it, all our patients are being screened with echocardiography, so we’re diagnosing only about 15% to 20% on the operating room table. Those are the patients who have had normal echos sometime in the past year during the work-up, but developed portopulmonary hypertension since then.

**Dr Wiesner:** We’ve always been screening. Our pickup in the operating room is probably less than 15%, isn’t it?

**Dr Krowka:** It’s fairly low because we’ve been very aggressive with the screening. We’ve tried to screen so there are never more than 12 months between echos, but we still miss the few that get to the operating theater. But we have the back-up of their having a Swan-Ganz catheter placed at the time of the operation. So if we missed something during screening, we hope to pick it up at the time of operation.

**Dr Wiesner:** Most of these have been moderate cases. I don’t know if we’ve missed any severe ones.

**Dr Krowka:** We have not had to cancel any cases in the last 8 years that I’m aware of.

**Dr Ramsay:** We’re talking about pulmonary pressures of 40 mm Hg or so, or 35 mm Hg.

**Dr Krowka:** A mean pulmonary pressure certainly greater than 50 mm Hg. We screen routinely for portopulmonary hypertension—every case at our institution, symptomatic or not, gets a screening Doppler echo at the time of transplant evaluation. I’d say 10% of the candidates have a right ventricular systolic pressure estimate greater than 50 mm Hg, and all of those patients undergo a right heart catheterization.

**Dr Oudiz:** So if the right ventricular systolic pressure is less than 50 mm Hg, you don’t necessarily worry about significant pulmonary hypertension?

**Dr Krowka:** That is correct, but we follow through and probably repeat an echo in 6 months if, let’s say, the patient had a right ventricular systolic pressure of at least 40 mm Hg.

**Dr Ramsay:** That’s similar to what we do at Baylor, but I’d like to follow up on one comment about canceling patients on the operating room table. I’d like to change that to “delay” or “defer.” We bring everybody back later, having treated them with vasodilators for up to 18 months, and transplant successfully.

**Dr Oudiz:** So a good percentage of those who were initially found too risky for surgery were treated, and a good number of them were brought back and...
successfully underwent transplantation?

Dr Ramsay: Correct.

Dr Oudiz: Dr Krowka, does your experience match that of Dr Ramsay’s with respect to patients who might have had a normal echo a couple of years prior to their transplantation and then developed pulmonary arterial hypertension?

Dr Krowka: Absolutely. We found several cases where there was a normal screening echo, not only in terms of estimated right ventricular systolic pressure but also normal right ventricular size and function, and 12 to 18 months later at least moderate pulmonary hypertension developed by all recognized criteria. So this can change relatively quickly.

Dr Ramsay: We had one patient in whom severe pulmonary hypertension developed in 3 weeks. He had a normal echo 3 weeks prior to coming to transplant, and then had a mean pulmonary artery pressure of about 45 mm Hg at the time of transplant. We went back and reviewed the echo and, maybe in hindsight, we could look at it and say there may have been some signs that the right ventricle was under strain, but not definitely. It was basically a normal echo. There had to be some kind of acute thrombosis or thromboembolic etiology, you would think.

Dr Oudiz: It is fascinating that you have the opportunity to screen a relatively small group of patients that allows you a window into the development of pulmonary hypertension. In patients with connective tissue disease or primary pulmonary hypertension or drug-induced pulmonary hypertension, the denominator is too large to screen them all and assess development, so we don’t have a good feel for how quickly pulmonary arterial pressures rise from a baseline of normal. But here you’ve put a finger on the natural history of patients as they develop pulmonary hypertension, and sometimes catch it before it evolves. Three weeks is really strikingly quick. Even a year and a half is much quicker than what is generally thought to be the time course of pulmonary hypertension development. In portopulmonary hypertension patients we think it takes years to decades.

Dr Krowka: I agree that when these things occur this quickly a strong possibility exists that we’re dealing with some in situ thrombosis as opposed to their throwing clots or just obviously missing something on echo. Indeed, we’ve seen a spectrum of pathology at autopsy. There’s no question that platelet aggregates and in situ thrombi have been seen, at least in the setting of post-transplant pulmonary hypertension.

Dr Ramsay: That’s an interesting point, Mike. We certainly see 10% to 15% of liver transplant patients who come through for surgery who, despite having a significant coagulopathy on laboratory analysis, when you run a thromboblasiogram, they’re actually hypercoagulable. This is particularly seen in patients with primary sclerosing cholangitis (PSC) and in some with primary biliary cirrhosis (PBC). This may be a factor that sets them up to present more acutely with raised pulmonary artery pressures.

Dr Wiesner: When we look at our group, there’s no etiology that seems to stand out. We see it as often in alcoholic patients.

Dr Ramsay: The numbers of hypercoagulable patients are small. The number of patients with PSC who have the typical hypocoagulability compared with the number of patients who are found to be hypercoagulable in practice is not many.

Dr Oudiz: What happens when a patient is scheduled for liver transplantation and is found either on the operating room table or just with a screening echo? Clearly when the pressure is high, you’re going to send that patient to right heart catheterization. And those who by right heart catheterization have significant pulmonary hypertension that precludes surgery will likely be placed on treatment. What percentage of those treated patients with PPH-like disease can actually get their transplant?

Dr Ramsay: So far in our patients we’ve gotten very aggressive in treating them; we’ve performed transplantation in everyone we have deferred. We have not lost anyone on the list while they’ve been receiving therapy. But the thing that we look for is not just mean pulmonary artery pressure and pulmonary vascular resistance. We’re also looking at right ventricular function. So they’re getting right heart catheterization and echocardiography relatively frequently, every 3 to 6 months. We’ve had two patients in whom the right ventricle really toughened up. Instead of having a widely dilated ventricle and right atrium, we’ve seen that ventricle turn in a period of 18 months into a good contracting hypertrophied ventricle. So we took those patients on—we couldn’t get their pressures below a mean of 45 mm Hg, but the patients did fine.

Dr Wiesner: What are the ranges at the higher end? Are any of these in the 70, 80, or 90 mm Hg range?

Dr Ramsay: The highest mean pressure in the true portopulmonary hypertension patient (we’ve seen higher numbers in patients with cardiomyopathy and volume overload) we’ve seen that I can recall is probably 58 mm Hg. But that was pretransplantation. In that patient, after reperfusion of the new graft, we got a massive increase in cardiac output. That patient’s mean pulmonary artery pressure was equivalent to the mean systemic arterial pressure.

Dr Oudiz: The mean pulmonary pressure went up.
Dr Ramsay: Yes. With the increase in flow and relatively fixed pulmonary vascular resistance, the pulmonary artery pressure went up. That was several years ago. We eventually lost that patient. We probably in retrospect could have put a right heart assist device in that patient or something like an atrial septostomy would have been required.

Dr Krowka: We’ve had a few cases also where we identified during the evaluation the mean pulmonary arterial pressure being greater than 50 mm Hg on right heart catheterization and we initiated appropriate therapy with intravenous epoprostenol and had disappointing results. Either there was no significant improvement in hemodynamics over 6 to 12 months or a substantial adverse event occurred, usually related to the hepatic status. They had a bleeding episode, they got infected and died of a nonrespiratory or noncardiopulmonary complication. So not everyone we’ve seen previously has been a responder. Most of them have responded and we still have several on the waiting list for transplant, but unfortunately other bad things can happen.

Dr Ramsay: When you say they’re not responders, have they progressed or have they stabilized at whatever level you saw?

Dr Krowka: That’s a good point. They’ve stayed right where they are. We’ve not been able to dramatically improve their mean pulmonary artery pressure or their pulmonary vascular resistance. Now, recently we’ve noted when we followed B-type natriuretic peptide levels that the levels decrease, but the hemodynamic numbers stay about the same, and I’m not sure what that means—that could be favorable—but certainly the hemodynamics by number are not worsening.

Dr Ramsay: That’s not the natural history of the disease. If you don’t treat it, it’s going to continue to progress. Therefore, you have stabilized it. We’ve seen two patients now with that right ventricle over the course of 18 months that has looked a lot stronger, strong enough that we’ve elected to take them on and perform transplantation.

Dr Oudiz: Dr Ramsay, in the patients you are treating, are you also treating solely with intravenous epoprostenol?

Dr Ramsay: We have been administering intravenous epoprostenol as our primary therapy until this last year and a half. We have now looked at other therapies that don’t require the intravenous route. Some of the patients are getting bosentan despite the fact that it has a reputation for kicking up liver enzyme levels. We’ve got a pulmonologist who is administering it in preference to epoprostenol. We also have a limited experience with treprostinil.

Dr Krowka: We’ve used subcutaneous treprostinil rather than intravenous epoprostenol in four patients waiting for transplantation.

Dr Oudiz: Dr Ramsay, I think you mentioned that one of your end points in addition to the standard ones is right ventricular function.

Dr Ramsay: The right ventricle is the critical piece in this. If the pressure is high but the right ventricle is great, that patient ought to do fine.

Dr Oudiz: You will do a transplant in a patient whose right ventricular function has improved but the mean pressure is still over 50 mm Hg?

Dr Ramsay: Yes, but the right ventricle really has to be good, we have to see it really contracting well. In most of those patients, when you initially see them, the right ventricle is widely dilated and the right atrium is widely dilated. So even if they were to survive the surgery, that liver graft gets congested because of the right ventricular dysfunction. And the liver will fail. So we really must have good right ventricular function proven by preoperative and intraoperative transesophageal echocardiography.

Dr Krowka: I think we’ve used essentially the same criteria. A 50 mm Hg mean artery pressure is the number we’ve followed with our anesthesia group and we do want to see improvement with epoprostenol and the right heart function. I agree that right heart function is absolutely critical. Our anesthesiologists would follow right heart function in the operating room with transesophageal echocardiography. I don’t think there’s any patient we’ve let go to liver transplant if they were to survive the surgery, that liver graft gets congested.

Dr Ramsay: I think you mentioned that one of your end points in addition to the standard ones is right ventricular function. So not everyone we’ve seen previously has been a responder. Most of them have responded and we still have several on the waiting list for transplant, but unfortunately other bad things can happen.

Dr Oudiz and Dr Weisner, do you have the same criteria or do you have absolute cutoffs in terms of pressures?

Dr Krowka: At least not in recent times.

Dr Wiesner: At least not in recent times.

Dr Oudiz: Correct:

Dr Oudiz: What outcomes do you see on average when patients who had pulmonary hypertension were treated with, let’s say, intravenous epoprostenol, and had, for example, their mean pressure drop to 40 mm Hg? How do they do postoperatively and how do they do over the longer term?

Dr Ramsay: At Baylor, we’ve had one patient and this is the last one we lost postoperatively, someone who came in with a mean pressure in the mid to high 50 mm Hg range. We were able to reverse it on the table by just using inhaled
nitric oxide. We brought that patient’s mean pulmonary artery pressure down into the low 40 mm Hg range and we felt comfortable that we could transplant safely. The right ventricular function looked reasonable. We transplanted. However, in a very small number of transplant patients in our practice, in about 3%, on reperfusion the cardiac output increases up to 300%. That’s what happened in this patient. Cardiac output went up from 6 liters to nearly 18 liters per minute and with that massive increase in cardiac output, the mean pulmonary artery pressures went sky high and the right ventricle failed. So we’d rather back off and take some time to get that pressure down and make sure it stays down and that right ventricular function is good, before we go ahead.

Dr Krowka: At Mayo we would treat these patients with intravenous epoprostenol or subcutaneous treprostinil for several months before transplantation, continuing the medication through the procedure. After transplantation it’s a clinical judgment as to how quickly patients can be weaned off. With the last three patients that I am aware of, we were able to wean off over several months and within one year after the transplant. I’m not sure if we’ve cured portopulmonary hypertension. I think we’ve controlled it and improved it, but it’s unclear whether we actually normalized the hemodynamics after transplant in everyone. The other benefit pre-transplant was not only the pulmonary vasodilator therapy but some pulmonary vascular remodeling, hopefully, and an antiplatelet aggregating effect.

Dr Wiesner: We’ve had some deaths on treatment too. Early deaths. My feeling overall is that I’m not sure how often liver transplantation per se actually reverses the condition. I know it’s been reported. Mike, have we seen anywhere it’s been completely normalized?

Dr Krowka: We’ve dramatically improved patients’ hemodynamics, but I’m not aware of any patients at our institution that we’ve been able to take absolutely off all pulmonary vasodilator therapy, and that includes a calcium channel blocker, after transplantation. The patients we have post-transplant now are being treated either with a calcium channel blocker because they’ve had some systemic hypertension or with bosentan. No one is receiving intravenous epoprostenol or subcutaneous treprostinil post-transplant at least after a year. We’ve been able to wean everyone off it.

Dr Ramsay: It’s somewhat similar at Baylor. We’ve had to keep giving some patients intravenous epoprostenol for over a year, for almost 18 months, before we’ve gotten them off. But we’ve had a small number of patients whose condition reversed in a matter of days, and you just wonder if it is a different pathology that we are dealing with.

Dr Ramsay: Yes, before epoprostenol we did. They were mostly postoperative as the pulmonary artery hypertension continued to progress despite transplantation. But once we instituted epoprostenol therapy postoperatively until stabilization or normalization of pressures, we have not had a death as a result of pulmonary hypertension.

Dr Oudiz: That’s fantastic. The fact that you can get everyone off prostacyclin therapy, even if it takes a year and a half, is quite different from what we’ve seen with the pulmonary hypertension patients. That brings us to the last question. Dr Krowka, you had a concern and we all have concerns about what the future holds in terms of therapy. We mentioned bosentan, which is certainly off label in patients who have liver disease, and also sildenafil, which is looking promising and undergoing multicenter trials. What do you think about the use of these as primary agents with respect to initial treatment once the patient has been screened and found to have pulmonary hypertension?

Dr Krowka: There is substantial potential for bosentan if it’s given with careful attention to dosing and watching liver function. I would continue to use the prostacyclins, and perhaps combination therapy is going to be a good idea down the road. I have concerns about sildenafil mainly because some patients with liver disease probably have increased nitric oxide effect on the vascular bed already. If one thinks sildenafil is working because of increasing nitric oxide effect even further, I am not so sure that medication is going to be appropriate alone or in combination for portopulmonary hypertension. We would have to do the studies. I think combination management may well be an option and I would not exclude bosentan as Mike Ramsay said.

Dr Ramsay: I think the inhaled nitric oxide issue is interesting. In the first six patients we tried it on we got no response at all. We even looked at exhaled nitric oxide and in some of the patients it was very elevated, but in others it was normal. Then we had a series of five patients where inhaled nitric oxide helped. Inhaled nitric oxide in these patients clearly brought the pulmonary artery pressures down temporarily. I’m wondering if the same thing might be true of using sildenafil. You might find in some patients it works and in some it may not work.

Dr Krowka: That gets back to your comment on pathology. There is probably a spectrum of pathology that we are seeing, not just one pulmonary vascular pathology. And that is something we can hopefully learn more about over time.

Dr Oudiz: Is a heart-lung transplant a viable option in some patients?
Dr Wiesner: It is for certain people. For younger people I think it is a consideration.

Dr Krowka: There have been two adult heart-lung-liver transplants accomplished in the United States. Both were done in the Mayo Clinic system for primary biliary cirrhosis and severe pulmonary hypertension. We have not done any more because multiorgan transplantation is just such a major undertaking and it’s so hard to pick the right recipient. Our selection criteria have required that the patient had to be under 50 years of age. So right way you’ve narrowed such transplantation down to a very few patients.

Dr Oudiz: What are your thoughts on the possibility of a small, multicenter trial looking at initially the use of bosentan vs Flolan or Remodulin in patients who were screened and deemed to be inoperable because of their pulmonary hypertension?

Dr Krowka: I agree that it should be done. Anecdotally, several institutions are using the medication carefully but we’ve not been able to conjure up enough support to provide the medication in a multicenter trial. Perhaps we need to revisit this again as other investigators present their case-by-case successes. A case report from the United Kingdom will be published in *Transplantation* regarding the beneficial effects of bosentan after transplantation in a patient who did not respond to intravenous epoprostenol.

Dr Wiesner: Mike, are enough data published to put ours together with other groups? There are only anecdotes in this literature, right?

Dr Krowka: You’d really have to have a multicenter study where the inclusion criteria and outcome variables are well defined.

Dr Ramsay: I think now enough people are screening ahead of time that maybe we could get the numbers in a multicenter study and do this.

Dr Oudiz: Is there anything else that you think is critical or at least useful that we haven’t discussed?

Dr Ramsay: What’s the downside of going ahead? What happens to patients if you go ahead and transplant with significant portopulmonary hypertension? It’s twofold. One is that if you have acute right ventricular failure, you may lose the patient. Two, if you just have right ventricular dysfunction, you may lose the graft, which may mean losing the patient too. So there are two downsides to going ahead. It’s not just patient survival, it could be graft survival.

Dr Krowka: I think all the centers need to continue to be very aggressive with their screening because new medication options are coming down the road. Even inhaled iloprost may be a therapeutic option. The door is open for us not only to consider these options but also to initiate a multicenter approach toward therapy.
low in cardiovascular research at the Mayo Clinic, Rochester, Minnesota. He traces that interest in PH to the early 1980s, when he worked with Ron Vlietstra, MD, one of the consultants in cardiovascular disease whose work with hydralazine and ketanserin in patients with PH led McGoon to further explore the use of vasodilators in the disease. “While I was still a fellow, Dr Vlietstra introduced me to some of the great vascular biology researchers. This included spending a year in the laboratory of Dr. Paul Vanhoutte when he was at Mayo.” Following the development of prostacyclin, McGoon sought participation in the early trials of that drug.

A graduate of Harvard College, McGoon earned his medical degree at Johns Hopkins University School of Medicine and completed his residency at the Mayo Clinic College of Medicine where he is Professor of Medicine. He is also Consultant in the Division of Cardiovascular Diseases and Internal Medicine at the Mayo Clinic.

What pulled him into the clinical arena of PH? “It was a whole organism interest, the complexity of the disease, its impact on the patient’s overall health and ability to cope with life. Given the fact that there was no effective treatment at the time, it gave me the opportunity to participate in exploring what avenues might lead to better outcomes.” Through his work with prostacyclin, McGoon found like-minded clinicians similarly focused on finding an effective treatment for PH. “Clearly, the early investigational work on what became Flolan created a community both at Mayo and elsewhere of clinicians and investigators that now constitutes the core of much PH investigation. We all grew in our approach to the disease and I felt from the beginning that my involvement with the group and PHA provided a venue for my interest to solidify.

“Getting involved with PHA’s Scientific Advisory Board (now the Scientific Leadership Council) gave me and others the chance to make more of a tangible contribution on a day to day basis to patients within an organizational structure,” he added. As McGoon took on more of a leadership role within the Council, he was named chairperson and turned his attention to the upcoming PHA meeting where a scientific session will be held for the first time. This session will be held immediately prior to the patient-oriented sessions. “This will usher in greater participation by physicians and investigators.” It will be a departure from the previous meetings where physicians responded to questions from patients but did not have a venue per se for scientific presentations and discussions. Looking beyond the meeting to new multicenter clinical trials organized through the PHA Scientific Leadership Council, McGoon envisions a bright future where basic research concepts will be increasingly applied in the clinical arena. The Scientific Sessions will provide impetus to that effort. “The goal of the sessions is to hear from the experts about the main avenues of fruitful inquiry into mechanisms of the disease.” But, he emphasizes, the mission cannot be accomplished without funding—that “it has to be done in a collective fashion with a voice through PHA and the Council that will give validity to the need for research-based funding.”

Profiles
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