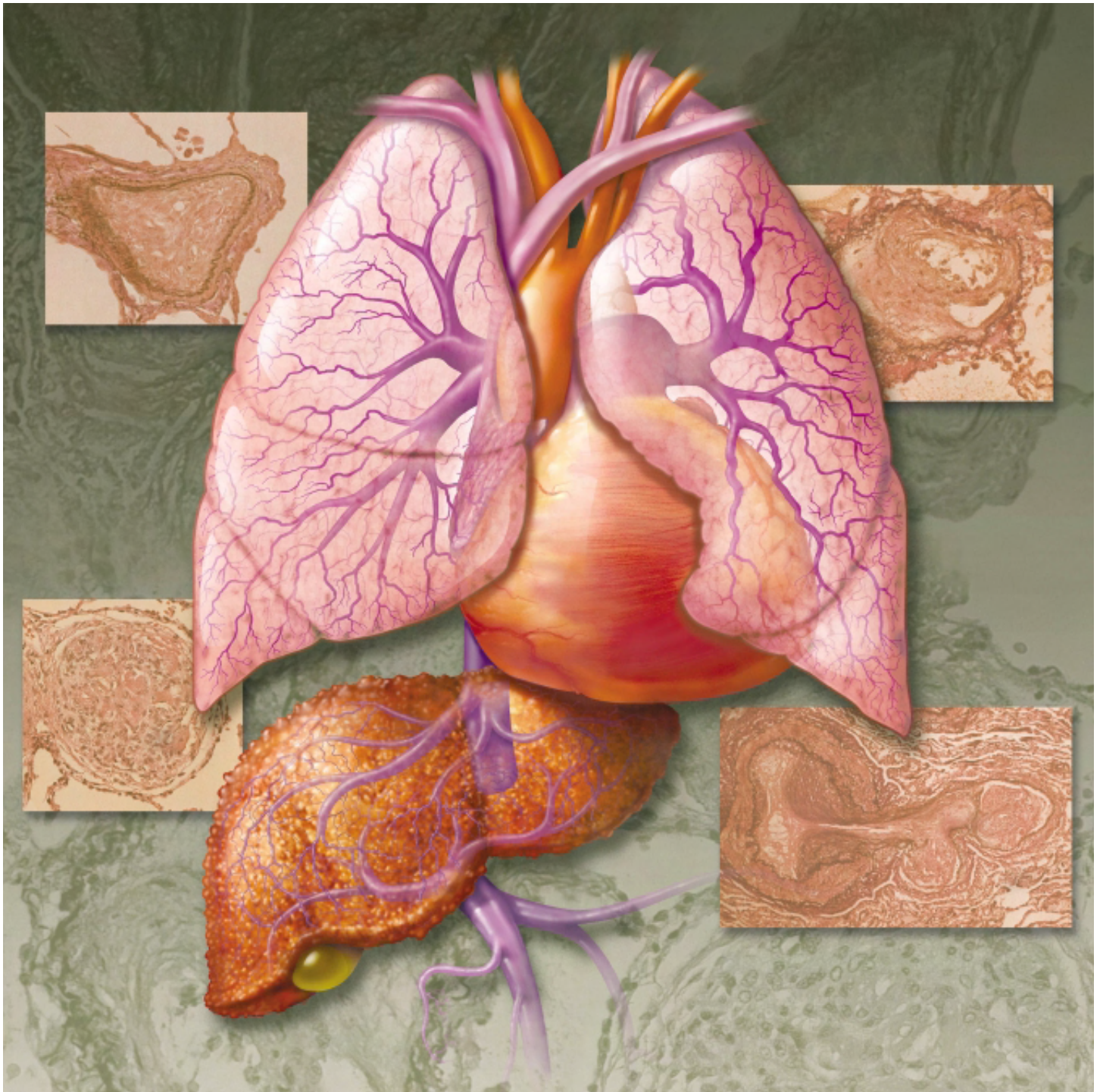


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Editorial Mission

Advances in Pulmonary Hypertension is committed to help physicians in their clinical decision making by informing them of important trends affecting their practice. Analyzing the impact of new findings and covering current information in the peer-reviewed literature, *Advances in Pulmonary Hypertension* is published four times a year. *Advances in Pulmonary Hypertension* is the official journal of the Pulmonary Hypertension Association.

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Cover photo: © Michael A King. The spectrum of pulmonary arterial vascular pathology in portopulmonary hypertension.

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Making History in Miami at PHA's 6th International Conference



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 medical and patient-led sessions will be held.

The establishment of the Scientific Sessions means that we have developed an exciting and much needed venue in which to carry on the dialogue with our peers, providing a connection for physicians and doctorate-level researchers with a special interest in PH to meet with key opinion leaders whose investigative work is paving the way for advances in identifying the mechanisms of PH, and hopefully appropriate therapeutic targets. The sessions will facilitate an improved exchange of

information, setting the stage for new multicenter clinical trials spearheaded by the Scientific Leadership Council.

For physicians unable to attend the conference, however, we will be providing comprehensive coverage of the highlights of the meeting in the next issue of *Advances in Pulmonary Hypertension*, including a Roundtable Discussion by members of the Editorial Advisory Board. The coverage will include topics such as the role of ion channels in pulmonary arterial hypertension (PAH), the role of serotonin in PAH, cellular biology of PAH, the genetics of PAH, the role of BMPR in PAH, whether genetic mechanisms can impact upon therapy and future directions in therapy.

As PHA has suggested in its literature in advance of the event, "Come to Miami for the Science. . . Stay for the Experience."

In This Issue

What You Need to Know About Portopulmonary Hypertension

The coexistence of pulmonary arterial hypertension as a consequence of hepatic dysfunction was first recognized more than 50 years ago. Within the last 15 to 20 years the unique clinical associations and characteristics of portopulmonary hypertension have reshaped concepts of diagnosis and treatment. Portopulmonary hypertension, however, remains a troublesome and complex disease.

Advances in Pulmonary Hypertension gratefully acknowledges the contribution of physicians who developed the superb content of this issue, including Ronald J. Oudiz, MD, Michael J. Krowka, MD, Michael Ramsay, MD, FRCA, and Russell Wiesner, MD. Their guidance and analysis provides us with timely and relevant information that will be helpful in determining appropriate strategies for portopulmonary hypertension.

Victor F. Tapson, MD
Editor-in-Chief



Michael D. McGoon, MD: Guiding Light for PHA Scientific Leadership Council and Proponent of New Research



Michael D. McGoon, MD

As the paradigm of treatment in pulmonary hypertension (PH) is poised to shift, the Scientific Leadership Council of the Pulmonary Hypertension Association (PHA) will drive advances in therapy. The Council plays an integral role in research efforts and has assumed the daunting task of spearheading new multicenter clinical trials as strategies to alter the course of disease move from the bench to the bedside.

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)

Portopulmonary Hypertension: Understanding Pulmonary Hypertension in the Setting of Liver Disease



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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.¹ 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 (portopulmonary hypertension)? 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 endothelium^{2,8,9} in portopulmonary hypertension has been documented, suggesting a lack of vasodilator capability.¹⁰ Recently the evolving “signaling” relationship between angiotensin-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 gradient^{6,14,16} 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

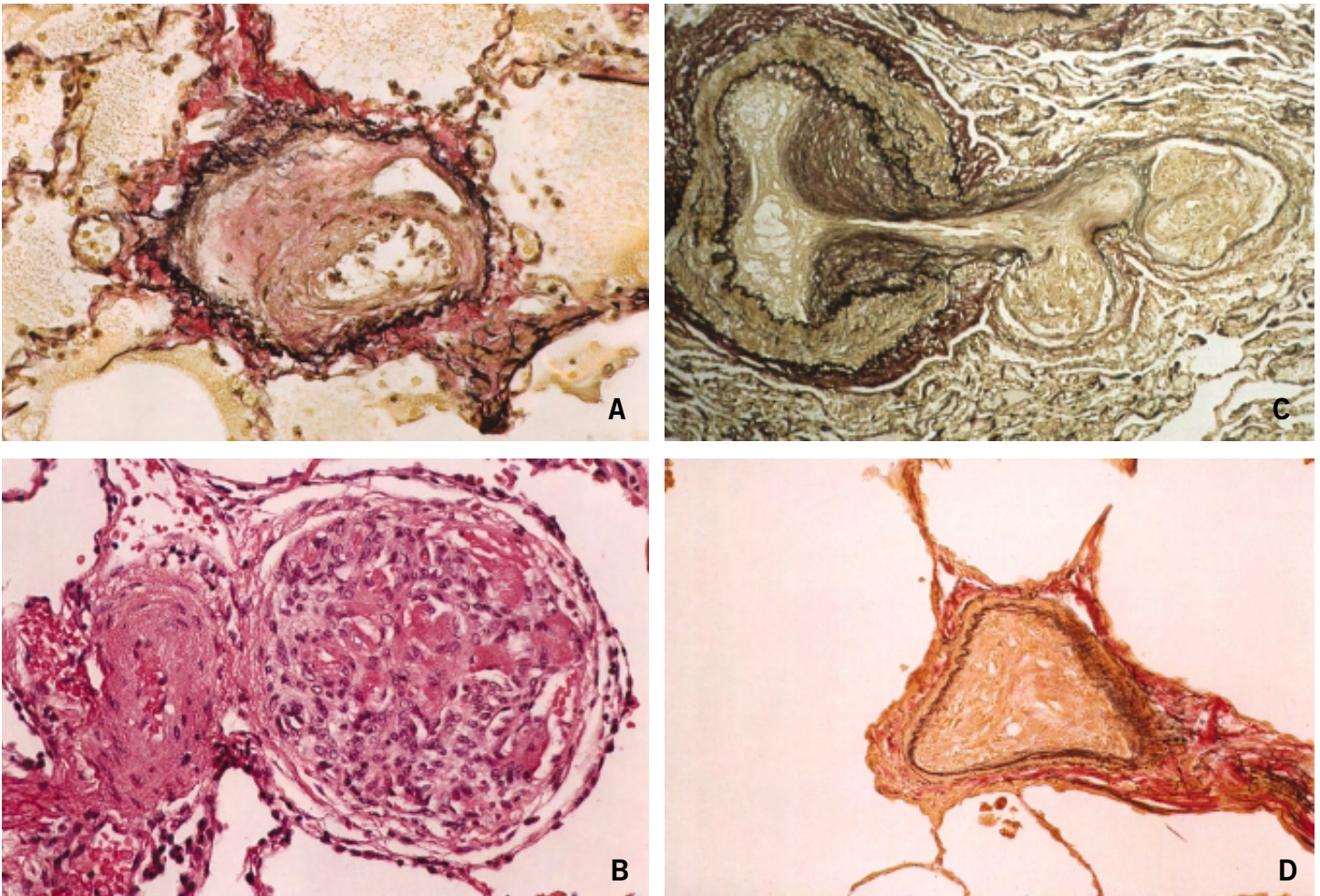


Fig. 1—The spectrum of portopulmonary hypertension. These color microphotographs of pulmonary arterial lesions, which also appear on the cover of this journal, show a) thrombotic type (autopsy), b) plexogenic type with platelet aggregates (autopsy), c) plexogenic type with microaneurysm (lung explant), and d) fibrotic type (autopsy). Reproduced with permission from *Liver Transplantation*. 2000;6:241-242.

transplantation, major transplant centers have reported the frequency of portopulmonary hypertension to be 4% to 15%.^{8,20-23} Remarkably, 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

patients.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-

Table 1—Current Diagnostic Criteria for Portopulmonary Hypertension.

- Portal hypertension (ie, ascites, esophagogastric varices, splenomegaly)
- Mean pulmonary artery pressure >25 mm Hg
- Pulmonary capillary wedge pressure <15 mm Hg
- Pulmonary vascular resistance >240 dynes.s.cm⁻⁵

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.^{4-6,18,19,28}

Consensus regarding “normal” pulmonary vascular resistance in the setting of advanced liver disease varies.²⁸ It is well documented that a reduced pulmonary vascular resistance exists in association with the hyperdynamic high-flow circulatory state in such patients.^{8,10,16,28} It is useful to describe evidence-based, clinically significant hemodynamic cutoffs as well as respect textbook-listed lower limits of normal in such patients. Data from the ERS-EASL task force on at least 200 patients with portopulmonary hypertension suggest that pulmonary vascular resistance >240 dyne.s.cm⁻⁵ is distinctly abnormal; it is always associated with mPAP >25 mm Hg, and it poses increased risk of right heart failure in the setting of liver transplantation.²⁸

A subgroup of liver disease patients with 120 < pulmonary vascular resistance <240 dynes.s.cm⁻⁵ and increased pulmonary capillary wedge pressure are of interest.^{8,19} If these patients have increased transpulmonary gradients (mPAP - PCWP >15 mm Hg), they should be considered to have mild portopulmonary hypertension and treated as such. The natural history of this subgroup is unclear and careful follow-up is required. It is also recognized that selected hemodynamic data (cardiac output and pulmonary vascular resistance) should be reported as indices that reflect body surface area in this subgroup. Rapid volume infusion during right heart catheterization (1.0 liter of saline over 10 minutes) has been suggested as a means to identify patients susceptible to ventricular failure during liver allograft reperfusion.²⁹ The clinical implications and/or benefits of vasoactive testing during right heart catheterization in the setting of portopulmonary hypertension are unclear, since

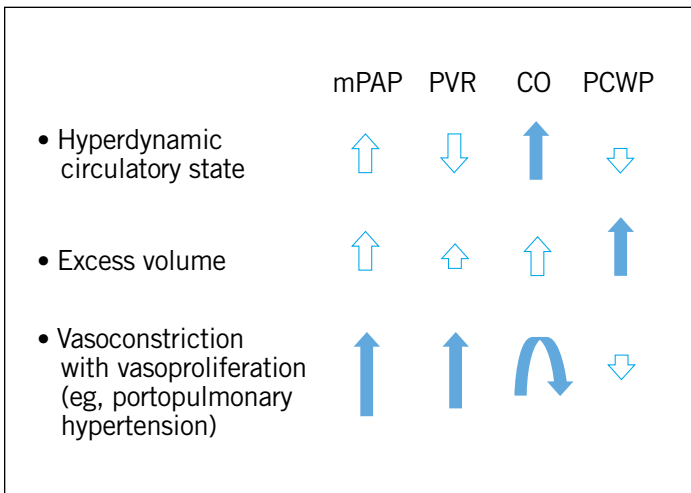


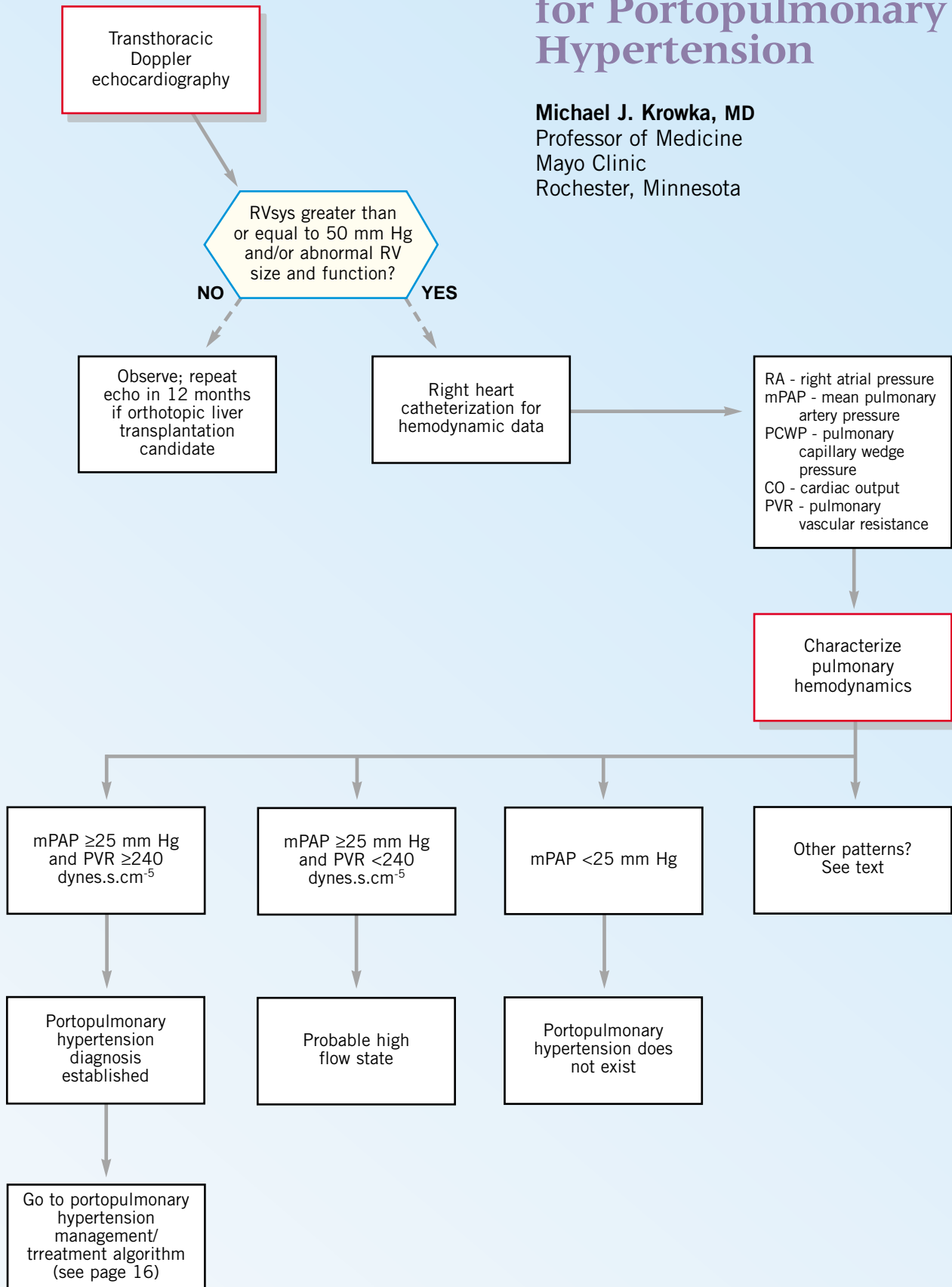
Fig. 2—Via right heart catheterization, several hemodynamic patterns can be documented in the setting of advanced liver disease. The main patterns associated with increased mean pulmonary artery pressure (mPAP) are shown above. High cardiac output (CO) characterizes the hyperdynamic circulatory state 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.

monary arteries and/or cardiomegaly are seen, pulmonary hemodynamics are markedly abnormal. Likewise, the electrocardiographic findings of right axis deviation, right bundle branch block, and t-wave inversions in the precordial leads are associated with advanced hemodynamic abnormality (mPAP >35 mm Hg), and thus these findings are not useful for detecting early disease.

Transthoracic Doppler echocardiography (DE) is relatively sensitive in detecting increased right ventricular systolic pressure (RVsys) 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 RVsys such as seen in the hyperdynamic circulatory state, increased central volume, and the true pulmonary vasculopathy of portopulmonary hypertension.^{4,5,25} DE is the current screening procedure of choice if portopulmonary hypertension is suspected,^{4,5,28} but right heart catheterization is mandatory for the definitive diagnosis.²²⁻²⁷ However, although many screened patients have increased RVsys (30 to 50 mm Hg by DE), they do not have increased pulmonary vascular resistance as determined via right heart catheterization.^{4,8,23,25} Using the more discriminatory screening criteria RVsys >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.^{23,25} 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 RVsys >50 mm Hg; 20% had RVsys >40 mm Hg. RVsys could not be accurately measured in 20%.

Screening and Diagnostic Algorithm for Portopulmonary Hypertension

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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.²⁶ Increased alveolar-arterial oxygen gradient and significant accentuation of respiratory alkalosis compared with cirrhotic patients without portopulmonary hypertension have been reported.⁹ Reduced diffusing capacity is frequent^{8,16} 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.

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Liver Transplant Considerations and Outcomes for the Portopulmonary Hypertension Patient



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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.^{9,1} 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 to balance the physiological outcome until one predominates.²²

The pulmonary vascular abnormalities may progress, even

after orthotopic liver transplantation, unless long-term pulmonary vasodilator therapy is instituted.^{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^{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 anesthesia, 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.^{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.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.^{12,20}

Moderate and severe portopulmonary hypertension places the liver transplantation patient at increased risk of perioperative morbidity and mortality.^{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.²⁰ A multicenter, national liver transplant database reported an overall mortality perioperatively of 36% for patients with portopulmonary hypertension undergoing transplantation.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.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%).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.^{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

Block Endothelin. Fight Pulmonary Arterial Hypertension WHO Class III or IV.



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 ET_A and ET_B receptors. Only Tracleer is a specific and competitive antagonist for both ET receptors.¹

- Decreases rate of clinical worsening*
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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
 - High potential for major birth defects: Pregnancy must be excluded and prevented by two forms of birth control; monthly pregnancy tests should be obtained
- Contraindicated for use with cyclosporine A and glyburide

Tracleer Access Program (TAP)

- Prescriptions can be filled only through TAP
- Call 1-866-228-3546 for a Patient Enrollment Form

Please see brief summary of prescribing information and full reference list on following page.

*Clinical worsening defined as combined endpoint of death, hospitalization or discontinuation due to worsening PAH, or initiation of epoprostenol therapy¹



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Brief Summary: Please see package insert for full prescribing information.

Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential damage to a fetus.

WARNING: Potential liver injury. TRACLEER® causes at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). To date, in a setting of close monitoring, elevations have been reversible, within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae. Elevations in aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin \geq 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances.

CONTRAINDICATION: Pregnancy. TRACLEER® (bosentan) is very likely to produce major birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER® and prevented thereafter by the use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER® (see Precautions: Drug Interactions). Monthly pregnancy tests should be obtained.

Because of potential liver injury and in an effort to make the chance of fetal exposure to TRACLEER® (bosentan) as small as possible, TRACLEER® may be prescribed only through the TRACLEER® Access Program by calling 1 866 228 3546. Adverse events can also be reported directly via this number.

INDICATIONS AND USAGE: TRACLEER® is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.

CONTRAINDICATIONS: TRACLEER® is contraindicated in pregnancy, with concomitant use of cyclosporine A, with administration of glyburide, and in patients who are hypersensitive to bosentan or any component of the medication.

Pregnancy Category X. TRACLEER® is expected to cause fetal harm if administered to pregnant women. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs. There are no data on the use of TRACLEER® in pregnant women. TRACLEER® should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for TRACLEER® should not be issued by the prescriber unless the patient assures the prescriber that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and to the fetus.

WARNINGS: Potential Liver Injury: Elevations in ALT or AST by more than 3 x ULN were observed in 11% of bosentan-treated patients (N = 658) compared to 2% of placebo-treated patients (N = 280). The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (\geq 3 x ULN) is a marker for potential serious liver injury. Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and to date have been reversible after treatment interruption or cessation. These aminotransferase elevations may reverse spontaneously while continuing treatment with TRACLEER®. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin \geq 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances. *Pre-existing Liver Impairment:* TRACLEER® should generally be avoided in patients with moderate or severe liver impairment. In addition, TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because monitoring liver injury in these patients may be more difficult.

PRECAUTIONS: Hematologic Changes: Treatment with TRACLEER® caused a dose-related decrease in hemoglobin and hematocrit. The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dl (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4-12 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment. *Fluid retention:* In a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with TRACLEER®. In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting TRACLEER®. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

Information for Patients: Patients are advised to consult the TRACLEER® Medication Guide on the safe use of TRACLEER®. The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases and urine or serum pregnancy testing and of avoidance of pregnancy. The physician should discuss options for effective contraception and measures to prevent pregnancy with their female patients. Input from a gynecologist or similar expert on adequate contraception should be sought as needed.

Drug Interactions: CYP Isoenzymes: Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER® is co-administered. Contraceptives: Specific interaction studies have not been performed to evaluate the effect of co-administration of bosentan and hormonal contraceptives, including oral, injectable or implantable contraceptives. Since many of these drugs are metabolized by CYP3A4, there is a possibility of failure of contraception when TRACLEER® is co-administered. Women should not rely on hormonal contraception alone when taking TRACLEER®, Cyclosporine A: During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. The concomitant administration of bosentan and cyclosporine A is contraindicated. Tacrolimus: Co-administration of tacrolimus and bosentan has not been studied in man. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and bosentan are used together. Glyburide: An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of TRACLEER® and glyburide is contraindicated, and alternative hypoglycemic agents should be considered. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A4. The possibility of worsened glucose control in patients using these agents should be considered. Ketoconazole: Co-administration of bosentan 125 mg b.i.d. and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered. Simvastatin and Other Statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A4 substrate), and its active β -hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that have significant metabolism by CYP3A4, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A4 metabolized statins should have cholesterol levels monitored after TRACLEER® is initiated to see whether the statin dose needs adjustment. Warfarin: Co-administration of bosentan 500 mg b.i.d. for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. Digoxin, Nimodipine and Losartan: Bosentan has been shown to have no pharmacokinetic interactions with digoxin and nimodipine, and losartan has no effect on plasma levels of bosentan.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses about 8 times the maximum recommended human dose (MRHD) of 125 mg b.i.d., on a mg/m² basis. In the same study, doses greater than about 32 times the MRHD were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses about 16 times the MRHD. Impairment of Fertility/Testicular Function: Many endothelin receptor antagonists have profound effects on the histology and function of the testes in animals. These drugs have been shown to induce atrophy of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Where studied, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear irreversible. In fertility studies in which male and female rats were treated with bosentan at oral doses of up to 50 times the MRHD on a mg/m² basis, no effects on sperm count, sperm motility, mating performance or fertility were observed. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as about 4 times the MRHD for two years but not at doses as high as about 50 times the MRHD for 6 months. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to about 75 times the MRHD or in dogs treated up to 12 months at doses up to about 50 times the MRHD. There are no data on the effects of bosentan or other endothelin receptor antagonists on testicular function in man.

Pregnancy, Teratogenic Effects: Category X

SPECIAL POPULATIONS: Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking TRACLEER® is not recommended. Pediatric Use: Safety and efficacy in pediatric patients have not been established. Use in Elderly Patients: Clinical experience with TRACLEER® in subjects aged 65 or older has not included a sufficient number of such subjects to identify a difference in response between elderly and younger patients.

ADVERSE REACTIONS: Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension, and other diseases. Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (5%; 8/165 patients) than on placebo (3%; 2/80 patients). In this database the only cause of discontinuations > 1%, and occurring more often on bosentan was abnormal liver function. In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily chronic heart failure), a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 6 months. For the adverse drug reactions that occurred in \geq 3% of bosentan-treated patients, the only ones that occurred more frequently on bosentan than on placebo (\geq 2% difference) were headache (16% vs. 13%), flushing (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg edema (5% vs. 1%), and anemia (3% vs. 1%).

Long-term Treatment: The long-term follow-up of the patients who were treated with TRACLEER® in the two pivotal studies and their open-label extensions (N=235) shows that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment with TRACLEER®. These estimates may be influenced by the presence of epoprostenol treatment, which was administered to 43/235 patients. Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival.

Special Considerations: Patients with Congestive Heart Failure (CHF): Based on the results of a pair of studies with 1613 subjects, bosentan is not effective in the treatment of CHF with left ventricular dysfunction.

OVERDOSAGE: Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 and 1000 mg b.i.d. of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed. There is no specific experience of overdose with bosentan beyond the doses described above. Massive overdose may result in pronounced hypotension requiring active cardiovascular support.

DOSAGE AND ADMINISTRATION: TRACLEER® treatment should be initiated at a dose of 62.5 mg b.i.d. for 4 weeks and then increased to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. did not appear to confer additional benefit sufficient to offset the increased risk of liver injury. Tablets should be administered morning and evening with or without food.

Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

ALT/AST levels	Treatment and monitoring recommendations
> 3 and \leq 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
> 5 and \leq 8 x ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 x ULN	Treatment should be stopped and re-introduction of TRACLEER® should not be considered. There is no experience with re-introduction of TRACLEER® in these circumstances.

If TRACLEER® is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin \geq 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances. Use in Women of Child-bearing Potential: TRACLEER® treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable or implantable contraceptives. Input from a gynecologist or similar expert on adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. Dosage Adjustment in Renally Impaired Patients: The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment. Dosage Adjustment in Geriatric Patients: Clinical studies of TRACLEER® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group. Dosage Adjustment in Hepatically Impaired Patients: The influence of liver impairment on the pharmacokinetics of TRACLEER® has not been evaluated. Because there is *in vivo* and *in vitro* evidence that the main route of excretion of TRACLEER® is biliary, liver impairment would be expected to increase exposure to bosentan. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. TRACLEER® should generally be avoided in patients with moderate or severe liver impairment. Dosage Adjustment in Children: Safety and efficacy in pediatric patients have not been established. Dosage Adjustment in Patients with Low Body Weight: In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg b.i.d. Discontinuation of Treatment: There is limited experience with abrupt discontinuation of TRACLEER®. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg b.i.d. for 3 to 7 days) should be considered.

HOW SUPPLIED: 62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62.5"; NDC 66215-101-06: Bottle containing 60 tablets. 125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125"; NDC 66215-102-06: Bottle containing 60 tablets.

Rx only.

STORAGE: Store at 20°C - 25°C (68°F - 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].

Reference

- Zimmerman HJ. Hepatotoxicity - The adverse effects of drugs and other chemicals on the liver. Second ed. Philadelphia: Lippincott, 1999.

Reference for previous page: 1. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. 2003.

Manufactured by:
Patheon Inc.
Mississauga, Ontario, CANADA

Marketed by:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA



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.^{26,27} If the right ventricle can adjust to the increased afterload over time by hypertrophying, 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.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 vasoreactivity 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.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.^{18,19,29-32} Liver cirrhosis is associated with excessive production of endogenous nitric oxide and this may explain this unpredictable response to iNO.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⁻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.¹ The same group reported 100% survival in a group of patients with portopulmonary hypertension treated acutely with iNO followed by epoprostenol.²³ Normalization of pulmonary pressures occurred in all patients, but took between 2 days and 18 months of postoperative epoprostenol therapy.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.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)

PH Doctor

A new professional section within the
Pulmonary Hypertension Association for physicians and MD/PhD-level
researchers interested in pulmonary hypertension

A message from the Scientific Leadership Council of the Pulmonary Hypertension Association

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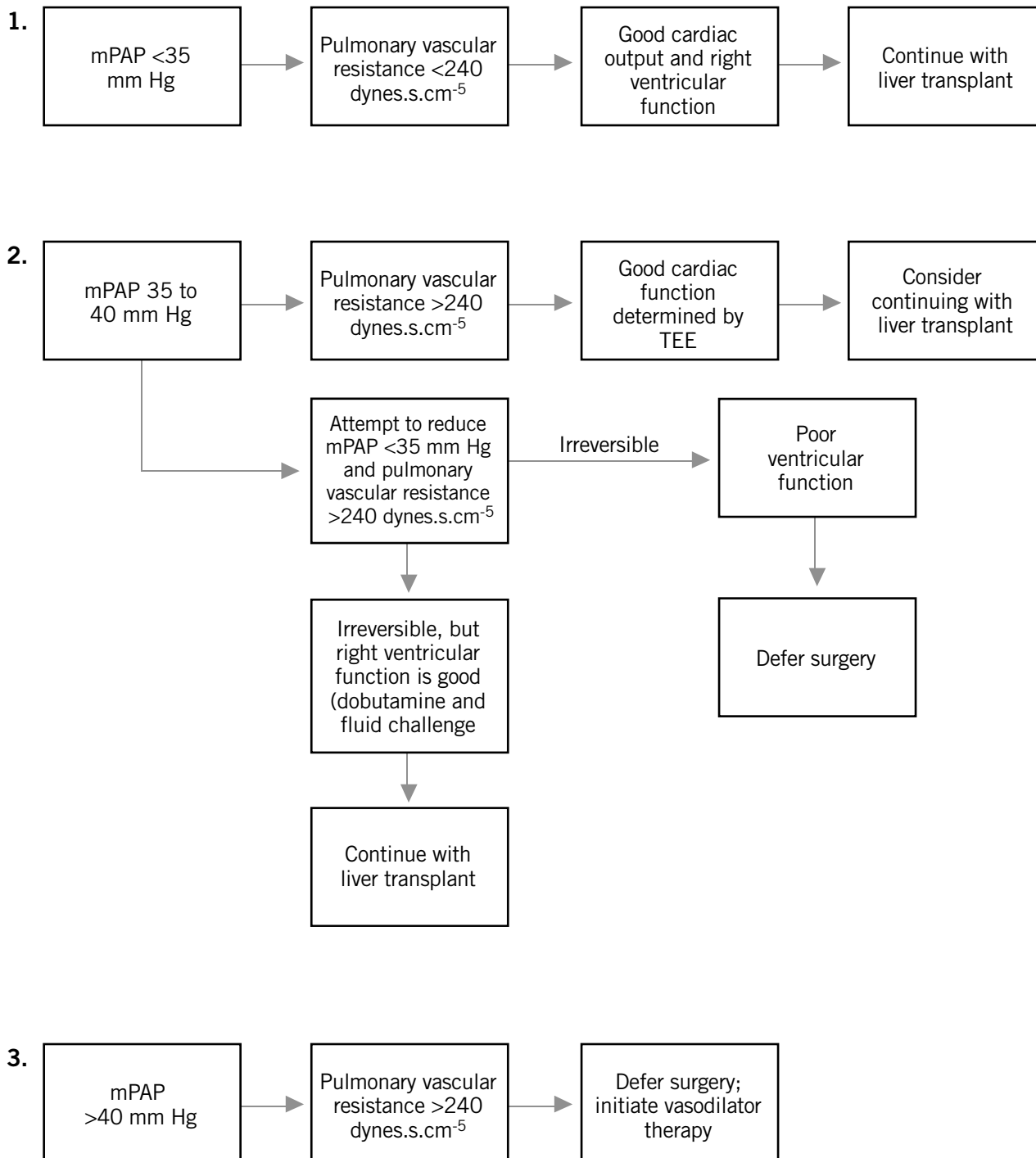
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Decision Tree: Management of Pulmonary Hypertension Diagnosed at Induction of Anesthesia for Liver Transplantation.



(continued from page 13)

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 blood flow, then the laws of physics dictate that the pressure must increase. Occasionally (3.7% of patients), an increase in Q_T 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

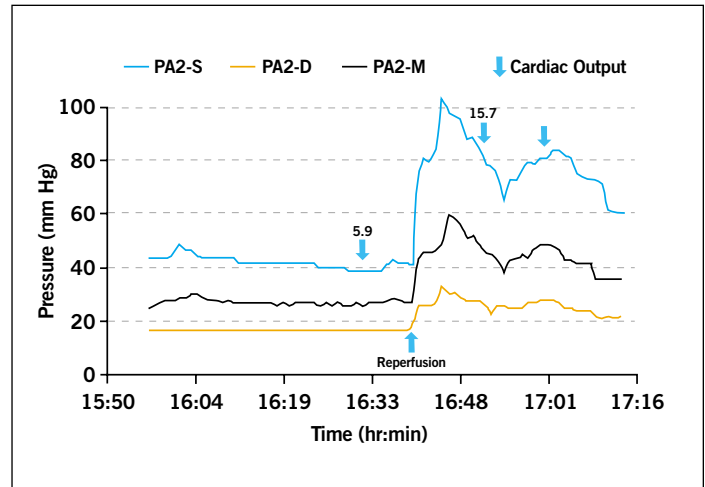


Fig.—Reperfusion of liver graft in patient with pulmonary hypertension.

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.

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Exploring the Spectrum of Pathology and Treatment in Portopulmonary Hypertension: Four Experts Address the Toughest Questions



Ronald J. Oudiz, MD



Michael J. Krowka, MD



Russell Wiesner, MD



Michael Ramsey, MD,
FRCA

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 Ramsey, 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 Wiesner: 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 thromboplas-



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 who has not been covered by at least intravenous epoprostenol, so we want to have a vasodilator on board for those who have a significant pulmonary hypertension situation.

—Dr Krowka

togram, 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 if 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



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 Ramsay

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

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 who has not been covered by at least intravenous epoprostenol, so we want to have a vasodilator on board for those who have a significant pulmonary hypertension situation.

Dr Wiesner: At least not in recent times.

Dr Krowka: 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 anybody where 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.



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.

—Dr Oudiz

Dr Wiesner: Have you had some deaths?

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.

Profiles

(continued from page 3)

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 multi-center 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.”

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***From Puzzle to Picture—Mechanisms of PH:
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