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Evaluation and Management of Pulmonary Hypertension in Patients with End-Stage Renal or Liver Disease

Preoperative Assessment and Management of Liver Transplant Candidates With Portopulmonary Hypertension
  Rodrigo Cartin-Ceba, MD
  Michael J. Krowka, MD

Perioperative Evaluation and Management of Patients With Portopulmonary Hypertension Aiming for Orthotopic Liver Transplantation
  José L. Díaz-Gómez, MD; Pablo Moreno Franco, MD;
  Juan M. Canabal, MD; Samuel Irefin, MD;
  Charles D. Burger, MD

Pulmonary Hypertension in Patients With Chronic Kidney Disease: Noninvasive Strategies for Patient Phenotyping and Risk Assessment
  Amresh Raina, MD

Hemodynamic Evaluation of Pulmonary Hypertension in Chronic Kidney Disease
  Ryan J. Tedford, MD
  Paul R. Forfia, MD

Pulmonary Hypertension Roundtable: The Challenging Spectrum of PH in Liver and Kidney Transplantation Patients

PHPN: Drug Interactions of Current Pulmonary Arterial Hypertension Therapies in Abdominal Organ Transplant Recipients
  Patricia A. Uber, BS, PharmD

Ask the Expert: Nutritional Assessment in Patients With Pulmonary Arterial Hypertension Facing Transplantation
  Beth Coplan, RD, CDE
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- Advocating for patients with pulmonary hypertension.
- Increasing involvement of basic and clinical researchers and practitioners.

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Clinical case studies
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While most articles are invited by the editorial board, the following submissions will be considered for publication:

• Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
• Letters to the Editor
• Clinical case studies

Submitted manuscripts are reviewed by the editorial board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision making.

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Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with AMA style.

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4. Conflict of Interest forms for all authors
5. List of approximately 5 key words for indexing purposes
6. Summary of the paper not exceeding 250 words in the format of Background; Objectives; Summary/Conclusions
Kidney and Liver Transplant and Pulmonary Hypertension: Navigating Through the Obstacle Course

Facing the news of needing kidney or liver transplant is a daunting prospect that many of our patients face. Indeed, according to the latest census by the Organ Procurement Transplant Network (OPTN) database, there are 15,841 patients on the waiting list for liver transplant and 97,511 for the kidney transplant. Among these, 6,256 liver and 16,485 kidney transplants were performed in U.S. in 2012. For those with end stage liver and kidney disease, transplant offers a second chance at life.

So being told by your physician that your echocardiogram shows pulmonary hypertension and that evaluation has to be on hold until further input can be obtained is devastating news. This is how patients are often referred to us, in the midst of confusion and dread hoping that we will be able to tell them that “all is well” and that they can proceed with the transplant that they desperately need. As any clinician who has been consulted for this reason can attest, this is a very difficult situation. On one hand, you do not wish to take away the chance for a life-saving measure but you also wish to avoid the prospect of a poor outcome for your patient as well as wasting a valuable resource.

Having experienced this difficult dilemma many times myself, it is my sincere pleasure to present to you this issue which focuses on evaluating and managing patients with portopulmonary hypertension and end stage kidney disease with PH who require a transplant. I am very grateful to our Guest Editors, Dr. Charles Burger and Dr. Paul Forfia, who have assembled a renowned group of experts to help answer the difficult questions that often arise such as: how do you manage patients with portopulmonary hypertension who have elevated pulmonary artery pressure and yet, normal pulmonary vascular resistance? how do you interpret hemodynamics in patients on hemodialysis with fistula? These questions and much more are discussed in the articles with lively and compelling dialogue in the Roundtable section.

I sincerely hope that you find this issue helpful the next time you are asked “I think this patient has PH. Can they undergo transplant?”

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We are excited about the current issue of Advances, as the authors have done an excellent job reviewing the challenges faced by patients with pulmonary hypertension (PH) in the setting of end-stage hepatic or renal disease. The selection of this topic is a result of the many challenges presented by these patient types, but also the need to contrast the differences between the 2 disease states—not only for our PH community but also for our transplant colleagues. The 4 primary articles have been designated to review the pretransplant evaluation and care of each disease state, followed by a review of the peri- and postoperative management, respectively.

Determination of the exact cause of the PH in patients with liver disease is critical, as the clinical implications and approach to treatment vary with the etiology. Drs. Carin-Ceba and Krowka have produced an outstanding update for the pretransplant evaluation, emphasizing an algorithmic approach and utilizing screening echocardiogram with diagnostic right heart catheterization. The priority is to maximize the patient's opportunity for safe transplantation; therefore, goal-directed pharmacological treatment for portopulmonary hypertension is reviewed. The immediate perioperative and postoperative care of portopulmonary hypertension can be equally if not more challenging and is nicely reviewed by Dr. Diaz-Gomez and his colleagues. A multidisciplinary team approach to care, utilization of bedside and intraoperative echocardiography, and current treatment experience are emphasized.

It is equally important to determine the cause of PH in patients with chronic kidney disease, as the implications, interventions, and impact of PH on transplant candidacy varies considerably. Simply diagnosing a patient with “pulmonary hypertension” does not suffice, as this diagnosis does not provide nearly sufficient detail to appropriately address patient management and transplant candidacy. Dr. Raina provides an excellent discussion on the approach to patients with PH and chronic kidney disease based on noninvasive assessment, with an emphasis on how to optimally use the echo-Doppler examination to determine the hemodynamic basis of the PH reliably and prior to invasive evaluation. Dr. Tedford explores the invasive hemodynamic evaluation of the patient with PH and chronic kidney disease, with a sophisticated discussion of PH hemodynamics and how to consider unique aspects of PH in this setting, ie, the role of an arteriovenous fistula in a patient with PH and end-stage renal disease.

In both the liver and renal disease articles, the authors appropriately emphasize the importance of the combined assessment of pulmonary vascular load (ie, pulmonary vascular resistance) and right heart function in order to gain the most insight into the impact of PH on any individual patient. We hope that this series of articles provides perspective and practical information about PH in the setting of advanced liver and kidney disease so that providers may be better informed on how to approach these complex patients.

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ADD MORE to your treatment strategy
+ PAH may be progressing even if patients seem stable1,2,5
+ Many patients plateau on oral therapy (PDE-5 inhibitor or ERA) within 12 weeks3,4

**ADD MORE:** Tyvaso is the only PAH treatment approved as an add-on to oral therapy6
+ After 1.7 years (mean) on oral monotherapy, adding Tyvaso for 12 weeks improved median 6MWD by 20 m (P<0.001)2,6
+ 4X daily dosing with short treatment sessions (2-3 minutes) approximately every 4 hours3,7

**Study design:** TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=235) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in a 4 daily treatment sessions with a target dose of 6 breaths (36 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, 6MWD at week 12 (obtained at least 4 hours after drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.2,6

**INDICATION**
Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor).

The controlled clinical experience was limited to 12 weeks in duration.

**IMPORTANT SAFETY INFORMATION**
+ Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System
+ The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.
+ Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants
+ In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension
+ Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn

Add More to Do More

For PAH (WHO Group 1) patients on oral monotherapy

ADD MORE to do more

**COULD YOUR STABLE PATIENTS ON ORAL MONOTHERAPY BENEFIT FROM ADD-ON THERAPY WITH TYVASO?**

+ The most common adverse events seen with Tyvaso in 24% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%)
+ Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women

Please see brief summary of Full Prescribing Information, Patient Package Insert, and the Tyvaso Inhalation System Instructions for Use manual. These items are available at www.tyvaso.com.

6MWD=6-minute walk distance. MLWHF=Minnesota Living With Heart Failure. NYHA=New York Heart Association. PAH=pulmonary arterial hypertension. WHO=World Health Organization

INDICATIONS AND USAGE

TYVASO is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

ADVERSE REACTIONS

The safety of TYVASO was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of 1 year. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo-controlled trial. Adverse Events Associated with Route of Administration—Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study occurred in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (TYVASO); however, some of such studies have been conducted with orally (treprostinil diethanolamine) and subcutaneously administered treprostinil (Remodulin®). Concomitant administration of TYVASO with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension. Anticoagulants—TYVASO should be used during pregnancy only if clearly needed.

USE IN SPECIFIC POPULATIONS

Pregnancy—No clinical studies of TYVASO have been conducted in pregnant women. Reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity. Animal reproduction studies are not always predictive of human response; TYVASO should be used during pregnancy only if clearly needed.

Labor and Delivery—No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether treprostinil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when treprostinil is administered to nursing women.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established. Clinical studies of TYVASO did not include patients younger than 18 years to determine whether they respond differently from older patients.

Geriatric Use—Clinical studies of TYVASO did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

Patients with Hepatic Insufficiency—Pharmacokinetics of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency.

OVERDOSAGE

In general, symptoms of overdose with TYVASO include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.
Recent Phase 3 Results

The Clinical Trials Update highlights new and ongoing research trials that are evaluating therapies for PAH. In this issue, Deborah Levine, MD, examines the PATENT-1 study results, findings from CHEST-1, and outcomes of the SERAPHIN trial.

Three important Phase 3 clinical trial findings have recently been published regarding treatment of pulmonary hypertension (PH): PATENT-1 described the results of treating patients with riociguat for pulmonary arterial hypertension (PAH); CHEST-1 reported findings on the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) with riociguat; and SERAPHIN discussed using macitentan for PAH.1-4

Riociguat is a soluble guanylyl cyclase (sGC) stimulator that, when bound to nitric oxide (NO), enhances synthesis of cyclic guanosine monophosphate (cGMP), which promotes vasodilatation, decreases proliferation, fibrosis, and inflammation. Riociguat has a dual mode of action: it sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding and it also directly stimulates sGC via a different binding site, independently of NO. Macitentan is a dual endothelin-receptor antagonist (ERA) that was developed by modifying the structure of bosentan to increase efficacy and safety. It is characterized by enhanced tissue penetration and receptor binding capability.

PATENT-1 (Pulmonary Arterial Hypertension sGC-Stimulator Trial) is a 12-week, double blind, randomized, placebo-controlled international multicenter trial. The inclusion criteria listed were: pulmonary vascular resistance (PVR) >300 dyn/sec/cm5, mean pulmonary artery pressure (mPAP) ≥25 mm Hg, and a 6-minute walk distance (6MWD) of 150-450 m. Patients were included if they had either been receiving no other PAH therapy or if they were receiving either ERAs or non-intravenous prostanoids for PAH (50% of patients were receiving no other therapy, 44% were receiving an ERA, and 6% of patients were receiving non-intravenous prostanoids). Patients were required to be on these medications at stable doses for at least 90 days. A total of 443 patients were randomly assigned to receive riociguat 3 times daily (TID) with dose titration to 2.5 mg TID, placebo TID, or riociguat TID with capped titration at 1.5 mg TID. The patients receiving the dose capped at 1.5 mg TID were not included in the efficacy analysis.

The primary endpoint was change in the 6MWD from baseline until the end of the study (12 weeks). Secondary endpoints included changes in the PVR, N-terminal pro-brain natriuretic peptide (NT-proBNP), World Health Organization (WHO) functional class, time to clinical worsening, Borg scores, and quality of life scores.

There was a statistically significant improvement in 6MWD at Week 12 in the riociguat group (+30 m) compared with the placebo group (-6m), for a total change of 36 meters. This effect was seen across both patients on and not on prior PAH therapy. Both PVR and NT-proBNP levels decreased significantly. The time to clinical worsening was increased and the Borg score improved in the riociguat group. These benefits of the riociguat group were maintained at 24 weeks, seen in the long-term extension study (PATENT-2). There was no increased frequency of adverse events or discontinuations in the riociguat group as compared to placebo.

These results reflect patients who were both on prior PAH therapy and those who were receiving no other therapy. In those patients not on prior therapy, the increase in 6MWD may be considered modest. However, in patients on prior therapy, improvements were similar to those in other trials (ie, PHIRST and BREATHE-1). The results also reflect that riociguat appears to be a safe therapy with a novel mechanism of action to add to the armamentarium of therapies for patients with PAH.

CHEST-1 CHEST-1 (A Study to Evaluate Efficacy and Safety of Oral BAY63-2521 in Patients With CTEPH) was a 16-week, multicenter, randomized, double blind, placebo-controlled international trial to evaluate riociguat in patients with CTEPH (Group 4 PH). Patients with either technically inoperable CTEPH or patients who had undergone pulmonary endarterectomy but had persistent or recurrent PH were included in the trial.

Inclusion criteria were: PVR >300 dyn/sec/cm5, mPAP ≥25 mm Hg, and a 6MWD of 150-450 m. Patients were excluded if they had received an ERA, phosphodiesterase type 5 (PDE-5) inhibitor, or NO donor 3 months prior to the study. The primary and secondary endpoints were identical to the PATENT-1 trial. A total of 261 patients (173 riociguat, 88 placebo) were randomly assigned to receive either placebo or riociguat (1, 1.5, 2, or 2.5 mg) TID, and the dose was titrated over the course of 8 weeks.

There was a statistically significant improvement in 6MWD at 16 weeks in the riociguat group compared to placebo (46 m difference). PVR and other hemodynamic parameters (mPAP, cardiac output) improved significantly when compared to placebo, as well as significant decrease in the level of...
NT-proBNP, and improvements in WHO functional class. There was no significant difference in the incidence of clinical-worsening events between the riociguat and placebo groups (2% vs 6%; P=0.17).

CHEST-1 demonstrates that riociguat appears to be a safe oral therapy for patients with inoperable CTEPH and for those with persistent PH after endarterectomy. Keeping in mind that patients should always be evaluated for CTEPH and that surgery must be the first option whenever possible, it would be a welcome additional treatment for these patients.

SERAPHIN

The SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve Clinical outcome) trial is the pivotal Phase 3 study designed to evaluate the efficacy and safety of macitentan. To date, SERAPHIN is the largest and longest conducted randomized, controlled study in PAH patients. SERAPHIN is unique among PAH trials in that it included a clearly defined primary endpoint of morbidity and all-cause-mortality of treatment vs placebo, making it the first event-driven Phase 3 trial in PAH.

The primary endpoint was a composite endpoint from the time of randomization to the first occurrence of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous (IV) or subcutaneous (SC) prostanoids, or worsening of PAH. Secondary endpoints included improvement in the 6MWD and improvement in WHO functional class at 6 months, death due to PAH or hospitalization for PAH up to the end of treatment, and death from any cause up to the end of treatment and up to the end of the study. Laboratory data were assessed at Months 3 and 6, and 6 months after until the end of treatment.

Seven hundred forty-two patients were randomized 1:1:1 into 1 of 3 treatment groups: placebo, 3 mg, and 10 mg a day of oral macitentan. Use of PDE-5 inhibitors, oral or inhaled prostanoids, calcium channel blockers, or L-arginine were all allowed. Any of these therapies had to be at a stable dose for at least 3 months. Any SC or IV prostanoids were excluded. Inclusion criteria were: patients 12 years of age and older who had idiopathic PAH, heritable PAH, or PAH related to connective tissue disease, repaired congenital systemic to pulmonary shunts, HIV, or drug or toxin exposure; 6MWD of 50 m or more, and in WHO functional class II, III, or IV.

In this study, macitentan showed a significant decrease in the morbidity and mortality endpoint. The composite endpoint of death due to PAH or hospitalization showed a significant treatment effect with macitentan (mostly driven by lower hospitalization in the macitentan groups). A trend in favor of the 10 mg dose was noted in all-cause mortality. The worsening of PAH was the most frequent primary endpoint event. The effect of macitentan on this endpoint was observed regardless of background therapy for PAH. The secondary endpoints, change from baseline to Month 6 in 6MWD, and WHO functional class were statistically significant at both dosages. Macitentan was well tolerated in the study. The overall incidence of adverse events reported and treatment discontinuations was similar across all groups. The incidence of serious adverse events was lower in patients treated with macitentan compared to placebo. Compared to placebo, a higher proportion of macitentan-treated patients had nasopharyngitis, headache, and anemia. There were no differences in liver function test abnormalities compared to placebo. In addition, no difference in edema was observed between macitentan and placebo.

This study is novel in its morbidity/mortality endpoint. The design, the duration of the study, and the results bring up the important issue of whether this trial establishes a new baseline of how we evaluate new therapies for chronically progressive diseases such as PAH.

All 3 of these important trials were published in the last 2 months in the New England Journal of Medicine. The FDA is currently reviewing the results of these studies for consideration for approval for treatment of PH.

References

Medication and Drug Exposure in PH Patients

Summaries and commentaries from the section editors and invited reviewers present a clinical context for practitioners’ application of the latest published research relevant to the care of patients with pulmonary hypertension. In this issue Kelly Chin, MD, discusses 2 recently published articles regarding medication and drug exposures in PH patients.


In this French pulmonary hypertension (PH) registry study, Montani and colleagues describe cases of dasatinib-associated PH among their cohort of patients. Patients were included in the study if they were diagnosed with catheterization-confirmed PH in the setting of either (or both) a diagnosis of chronic myeloid leukemia (CML) or treatment with dasatinib, imatinib, or nilotinib between 2006 and 2010. Nine PH patients met these criteria, all of whom had received long-term treatment with dasatinib over a median of 34 months (range 8-48 months); no patients receiving imatinib or nilotinib developed PH. Hemodynamics were consistent with precapillary PH (normal wedge pressure) with variable severity, including several patients who had evidence of right heart failure. No secondary causes of PH were identified, including left heart disease, lung disease, or chronic pulmonary embolism. Treatment included an endothelin-1 receptor antagonist in 2 patients and a calcium channel blocker in 1 patient who responded to a vasodilator challenge, and dasatinib was discontinued in all 9 cases. Among dasatinib-exposed patients. In addition to their 9 cases, 5 cases of PH associated with dasatinib were reported to the French pharmacovigilance agency, resulting in a total of at least 13 cases of PH over the study period. This was out of 2,900 patients receiving dasatinib during these years, resulting in an incident rate of 0.45% among exposed individuals. Based on this and other reports, the French, European, and US drug agencies have published a warning on the risk of PH in patients treated with dasatinib. These results suggest that dasatinib is capable of causing pulmonary arterial hypertension (PAH), at least in a subset of patients, and that increased awareness and close follow-up of exposed patients is indicated. Strengths of this study include the comprehensive clinical and hemodynamic evaluation, the long-term follow-up, and the use of multiple data sources to identify cases within France. Montani and colleagues also provide a nice overview of the various kinase and nonkinase targets, including future targets that they suggest are worth exploring in PH.


Cocaine has been suspected of causing PAH, based on case reports and on inconclusive results from diet-pill and other case-control studies. However, the mechanism through which this could occur has not yet been definitively determined, particularly because cocaine, as a monoamine reuptake inhibitor, is different mechanistically from the diet pills and other stimulants that have been associated with PAH. In this review article by Karch and colleagues, an alternative potential link between cocaine and PAH is described, based on recent work from their own laboratory. They propose that cocaine could be associated with PAH because it is often adulterated with levamisole, a drug whose metabolites include aminorex. Aminorex was associated with an epidemic of PH in Europe in the 1960s.

This unexpected metabolite was first identified after several dozen racehorses tested positive for aminorex, a banned stimulant in racing, and it was ultimately linked to the use of levamisole as an anthelmintic. Follow-up studies confirmed that levamisole could be converted to aminorex in both horses and humans. In their own recent work, Karch and colleagues report identifying levamisole and aminorex in over half of all cocaine-positive urine samples (62 of 154). Levamisole has also been identified in a majority of cocaine seized in the United States in recent years, and in many samples of cocaine in other countries. As a result, these authors raise a very valid concern: could aminorex exposure from cocaine lead to PAH?

They conclude their review by stating that: “The key issue to be addressed now is not whether humans convert levamisole to aminorex (we know they can), or whether aminorex can cause [PAH] (it does). The question that urgently requires answering is whether chronic users of levamisole-tainted cocaine actually convert enough levamisole into aminorex to cause [PAH].” This does appear to be the key question, but unfortunately, it is not one that is going to be easy to answer, both because it is not clear what minimum levels of aminorex exposure might be required to cause PAH, and because of
the widely varying dose and composition of drugs taken illicitly.

In summary, these 2 articles suggest that medication and drug exposures in PH patients are not just concerns of a prior era, but should remain a focus of both clinical assessment and future research in PH.

References
The goals that matter to you matter to patients

Go to www.letairis.com to learn more.

Please see accompanying brief summary of full Prescribing Information, including BOXED WARNING on the risk of serious birth defects.
LETAIRIS® (ambrisentan) Tablets, for oral use

Brief Summary of Full Prescribing Information. See Full Prescribing Information. Rx only.

**BOXED WARNING: CONTRAINDICATIONS IN PREGNANCY**

Do not administer LETAIRIS to a pregnant woman because it may cause fetal harm [see Contraindications]. LETAIRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals [see Contraindications]. Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T380A IUD or LNG 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests [see Warnings and Precautions]. Because of the risk of birth defects, LETAIRIS should be administered only through a restricted access program under a Risk Evaluation and Mitigation Strategy (REMS) called the LETAIRIS Education and Access Program (LEAP). As a component of the LETAIRIS REMS, prescribers, patients, and pharmacies must enroll in the program [see Warnings and Precautions].

**INDICATIONS AND USAGE:** LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

**DOSE AND ADMINISTRATION:** Healthcare professionals who prescribe LETAIRIS must enroll in the restricted program called LEAP and must comply with the required monitoring to ensure safe use of LETAIRIS [see Warnings and Precautions]. Because of the risk of birth defects, LETAIRIS should be administered only through a restricted access program under a Risk Evaluation and Mitigation Strategy (REMS) called the LETAIRIS Education and Access Program (LEAP). As a component of the LETAIRIS REMS, prescribers, patients, and pharmacies must enroll in the program [see Warnings and Precautions].

**CONTRAINDICATIONS:** Pregnancy: LETAIRIS may cause fetal harm when administered to a pregnant woman. Ambrisentan was teratogenic at oral doses of ≥25 mg/kg/day in rats and ≥2 mg/kg/day in rabbits; it was not studied at lower doses. In both species, there were abnormalities of the lower jaw and hand and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. Teratogenicity is a class effect of endothelin receptor antagonists. There are no data on the use of LETAIRIS in pregnant women. LETAIRIS is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pregnancy must be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment [see Usage and Administration, Warnings and Precautions].

**Idiopathic Pulmonary Fibrosis:** LETAIRIS is contraindicated in patients with idiopathic pulmonary fibrosis (IPF) including IPF patients with pulmonary hypertension (WHO Group 3).

**WARNINGS AND PRECAUTIONS:** LETAIRIS Education and Access Program (LEAP): Because of the risk of birth defects, LETAIRIS is available only through a restricted program called LETAIRIS Education and Access Program (LEAP). Required components of LEAP: Healthcare professionals who prescribe LETAIRIS must complete the LEAP Prescriber Enrollment and Agreement Form, enroll in the program, and comply with the REMS requirements. To receive LETAIRIS, all patients must complete a patient enrollment form and be re-enrolled annually by their prescriber. For women of childbearing potential, this test must be ordered and re-mediated by the prescriber prior to LETAIRIS treatment and monthly during treatment, (2) she must agree to be contacted prior to each shipment to confirm that a pregnancy test was completed, (3) she must agree to be counseled on the requirements of the REMS program and the risks of LETAIRIS, and (4) she must agree to be contacted by Gilead if she becomes pregnant while on LETAIRIS or within 30 days of treatment discontinuation. Physician compliance to the REMS must be monitored by Gilead. Physicians receiving LETAIRIS must enroll in the program and agree to comply with the REMS requirements. Further information is available at www.letairisrems.com or 1-866-664-LEAP (5327).

**Fluid Retention:** Peripheral edema is a known class effect of endothelin receptor antagonists, and it is also a clinical consequence of PAH and worsening PAH. In clinical trials in patients with PAH, fluid retention occurred in an estimated 12% of patients (PDE5) inhibitor therapy. More than 25% patients had pre-existing fluid retention, and about 35% of those patients who developed peripheral edema required diuretics. Although peripheral edema occurring in patients with PAH may be managed with diuretics, proper attention to fluid retention is indicated to avoid exacerbation of other PAH symptoms and worsening of functional class and clinical worsening. Fluid retention can be managed with the use of diuretics or angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). In clinical trials with LETAIRIS, patients who did not have pre-existing fluid retention required diuretic therapy at an increased rate compared to placebo. Patients treated with Sildenafil alone or Sildenafil with LETAIRIS had an increased rate of fluid retention compared to placebo. The rate of fluid retention was increased in patients receiving LETAIRIS alone compared to placebo. Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent. Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving LETAIRIS (44%, 29/205) or placebo (28%, 22/78), in elderly patients (≥65 years) receiving LETAIRIS (40%, 24/60) or placebo (16%, 13/81), and in patients with functional class III and IV PAH receiving LETAIRIS (39%, 24/61) compared to placebo (10%, 9/91). The incidence of such subgroup analyses may be determined by sampling error. The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for LETAIRIS (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for LETAIRIS (5%; 3/61 patients). During 12-week controlled clinical trials, the incidence of anemia transfusion elevations >3x upper limit of normal (ULN) were 0% on LETAIRIS and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause. Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Serum Liver Enzyme Abnormalities: In an open-label, controlled, single-arm study, patients who had previously discontinued endothelin receptor antagonists (ERAs; bosentan, an investigational drug, or both) due to anemia transfusion elevations >3x ULN were treated with LETAIRIS. Prior elevations were predominantly moderate, with 64% of the ALT elevations <8x ULN, but 9 patients had elevations >8x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all experienced a recurrence of anemia transfusion abnormalities that required discontinuation of ERA therapy. All patients had to have normal anemia transfusion levels on entry to this study. Twenty-five of the 36 patients were also receiving protonated and/or phosphotidylcholine type 5 (PDES) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8x ULN elevation). Of the remaining 34 patients, one patient experienced a mild anemia transfusion elevation at 12 weeks on LETAIRIS 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of LETAIRIS to 10 mg, no patients were discontinued for anemia transfusion elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that LETAIRIS led to fewer anemia transfusion elevations than would have been seen with those drugs, the study indicates that LETAIRIS may be tried in patients who have experienced asymptomatic anemia transfusion elevations on other ERAs after anemia transfusion levels have returned to normal. Postmarketing Experience: The following adverse reactions were identified during postapproval use of LETAIRIS. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency of occurrence or establish a causal relationship to drug exposure. Cases of anaphylaxis, angioedema, asthma, dizziness, fatigue, shortness of breath, flushing, hypotension, hypotension (see Warnings and Precautions), and/or other events (see Warnings and Precautions), heart failure (associated with fluid retention), hyperkalemia (e.g., angioedema, rash), nausea, and vomiting. Elevations of liver aminotransferases (ALT, ASAT) have been reported with LETAIRIS use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure (see Adverse Reactions).

**DRUG INTERACTIONS:** Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine.

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**Table 1: Adverse Reactions with Placebo-Adjusted Rates >3%**

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Placebo (N=132)</th>
<th>LETAIRIS (N=261)</th>
<th>Placebo-adjusted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>14 (11)</td>
<td>45 (17)</td>
<td>4.1</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 (1)</td>
<td>15 (6)</td>
<td>4.5</td>
</tr>
<tr>
<td>Syncope</td>
<td>0 (0)</td>
<td>8 (3)</td>
<td>2.7</td>
</tr>
<tr>
<td>flushing</td>
<td>1 (1)</td>
<td>10 (4)</td>
<td>3.1</td>
</tr>
</tbody>
</table>

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[clinicaltrials.gov]
USE IN SPECIFIC POPULATIONS: Pregnancy Category X [see Contraindications]: Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using acceptable methods of contraception. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS (ambrisentan) [see Warnings and Precautions].

Nursing Mothers: It is not known whether ambrisentan is excreted in human milk. Breastfeeding while receiving LETAIRIS is not recommended. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testicle size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17x, 51x, and 170x (low, mid, high dose, respectively) the maximum oral human dose of 10 mg on a mg/m² basis. Pediatric Use: Safety and effectiveness of LETAIRIS in pediatric patients have not been established. Geriatric Use: In the two placebo-controlled clinical studies of LETAIRIS, 21% of patients were > 65 years old and 5% were ≥ 75 years old. The elderly (age ≥ 65 years) showed less improvement in walk distances with LETAIRIS than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients. Renal Impairment: The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan. Dose adjustment of LETAIRIS in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment. The impact of hemodialysis on the disposition of ambrisentan has not been investigated. Hepatic Impairment: Pre-existing hepatic impairment: The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan. LETAIRIS is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of LETAIRIS in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients. Elevation of Liver Transaminases: Other endothelin receptor antagonists (ERAs) have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure [see Adverse Reactions]. In patients who developed hepatic impairment after LETAIRIS initiation, the cause of liver injury should be fully investigated. Discontinue LETAIRIS if aminotransferase elevations > 5x ULN or if elevations are accompanied by bilirubin > 2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded. OVERDOSAGE: There is no experience with overdosage of LETAIRIS. The highest single dose of LETAIRIS administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdosage could potentially result in hypotension that may require intervention. PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling (Medication Guide). LETAIRIS Education and Access Program (LEAP): Advise the patient that LETAIRIS is available only through a restricted program called LEAP. As a component of LEAP, prescribers must review the contents of the LETAIRIS Medication Guide and the LETAIRIS Patient Enrollment Guide before initiating treatment with LETAIRIS. Inform the patient that LETAIRIS is available only from Certified Specialty Pharmacies enrolled in LEAP. Provide patients with a list of Certified Specialty Pharmacies. As a component of LEAP, Certified Specialty Pharmacies must provide a copy of the Medication Guide to patients or caregivers each time LETAIRIS is dispensed. Patients must be instructed to read the Medication Guide each time they receive LETAIRIS because new information may be available. In addition, Certified Specialty Pharmacies must contact patients before each shipment to confirm that the patient will be available to receive the LETAIRIS shipment; and, in the case of women of childbearing potential, to confirm that a pregnancy test has been completed. Patients must complete a patient enrollment form and be re-enrolled annually by their prescribers using the LEAP Patient Enrollment and Consent form to confirm that they understand the risks of LETAIRIS. Patients may be asked to participate in a survey to evaluate the effectiveness of LETAIRIS. Pregnancy: Instruct patients that the risks associated with LETAIRIS include serious birth defects if used by pregnant women. Educate and counsel women of childbearing potential to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or IUD 200 US for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception: one hormone method and one barrier method, or two barrier methods where one method is the male condom. Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring. Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom. Partner’s vasectomy must be used along with a hormone method or a barrier method. Educate and counsel women of childbearing potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure [see Boxed Warning, Contraindications]. Instruct patients to immediately contact their physician if they suspect they may be pregnant. Hematological Change: Patients should be advised of the importance of hemoglobin testing. Administration: Patients should be advised not to split, crush, or chew tablets.

GS22-085-010
Preoperative Assessment and Management of Liver Transplant Candidates With Portopulmonary Hypertension

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Portopulmonary hypertension (POPH) is documented in 4.5% to 8.5% of liver transplant (LT) candidates, and it is a well-recognized relationship of pulmonary artery hypertension (PAH) that evolves as a consequence of portal hypertension. According to the 2008 Dana Point classification of PAH, POPH is included within the Group 1 of the classification. The first description of what we now know as POPH was provided by Mantz and Craige in 1951. These authors described necropsy results of a 53-year-old female with spontaneous portocaval shunt (due to a probable congenital portal vein narrowing) that originated at the confluence of the portal, splenic, and mesenteric veins and coursed through to mediastinum. The shunt was lined by varying amounts of thrombus thought to have embolized via the innominate vein into the right heart and pulmonary arteries. In addition to embolized small pulmonary arteries, an extreme endothelial proliferation and recanalization process was documented. Over the last 30 years, enhanced recognition and renewed importance of POPH has evolved with the evolution of LT and potential outcomes associated with POPH. Specific screening recommendations and diagnostic criteria are now clearly defined for this entity. Despite the lack of randomized controlled trials for pulmonary artery vasodilator medications (PAH-specific therapy), extrapolation of the therapeutic advances in treating PAH with beneficial effects in POPH has stimulated ongoing interest and importance in this syndrome. This article summarizes the most recent advances in the comprehensive preoperative management of POPH patients undergoing LT.

HOW IS POPH DEFINED?
Given the various pulmonary hemodynamic patterns that complicate advanced liver disease, POPH should be clearly defined and recognized; therefore, the importance of accurate interpretation of hemodynamics obtained by right heart catheterization (RHC) cannot be underestimated. The vascular pathology that characterizes POPH includes obstruction to arterial flow due to vasocostriction, endothelial and smooth muscle proliferation, in-situ thrombosis, and plexogenic arteriopathy. These changes increase the resistance to pulmonary arterial blood flow, which is the main mechanism of the disease. In the presence of portal hypertension, POPH is therefore defined as a mean pulmonary artery pressure (MPAP) ≥25 mm Hg associated with pulmonary vascular resistance (PVR) ≥240 dynes/sec/cm⁵ and pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg based on RHC (Table 1). It is also very important to recognize the 3 main abnormal hemodynamic patterns that can be present during RHC in patients with portal hypertension (Figure 1); distinguishing these patterns is of paramount importance for the adequate management and treatment: a) hyperdynamic circulatory state induced by liver dysfunction; b) excess pulmonary venous volume due to diastolic dysfunction and/or renal insufficiency (pulmonary venous hypertension); and c) PAH due to vascular obstruction (POPH).

It is important to mention that POPH should be distinguished from the other major pulmonary vascular consequence of liver disease, namely hepatoportal hypertension (HPS). In HPS, arterial hypoxemia is caused by intrapulmonary vascular dilatations (exactly opposite to the vascular obstructions documented in POPH) that form...
as a remodeling process due to factors yet to be identified. In addition, the pulmonary hemodynamics associated with HPS reflect a normal PVR and usually a high flow state characterized by an increased cardiac output (CO). The distinction between these 2 syndromes is very important, especially if LT is to be considered because of the differences in risk, treatment options, and outcomes between these syndromes.  

**HOW IS THE SCREENING PROCESS FOR POPH PERFORMED?**

Transthoracic echocardiography (TTE) has been the most practical screening method to detect POPH.  

By assessing the tricuspid regurgitant peak velocity (TR), estimating the right atrial pressure by inferior vena cava changes with inspiration, and using the modified Bernoulli equation, an estimate of right ventricle systolic pressure (RVSP) can be determined in ~80% of patients with portal hypertension.  

This quantitative approach allows one to decide which patients should proceed to RHC for the definitive characterization of pulmonary hemodynamics. In our current practice at Mayo Clinic, the presence of RVSP >50 mm Hg has been the cutoff criteria to proceed to RHC in a clinical algorithm followed since 1996.  

Rarely, immeasurable TR with abnormal qualitative RV size or function results in RHC. TTE has been noted to have a 97% sensitivity and 77% specificity to detect moderate to severe PAH prior to LT.  

Current policy adopted by the American Association for the Study of Liver Diseases calls for screening TTE to detect pulmonary hypertension (PH) in every patient considered for LT in the United States.  

This policy originated, in part, from documentation that POPH was first diagnosed in the operating room in 65% of patients (28/43 patients in 18 peer-reviewed studies) reported in a literature review with a 35% mortality in patients subsequently transplanted. Of particular note, pre-LT MPAP ≥35 mm Hg (untreated) was associated with higher mortality. Studies by Castro et al, Starkel et al, and Saner et al reported first diagnosing POPH in the operating room after anesthesia induction (in the era prior to current PAH-specific therapy), noting that mild to moderate POPH patients (MPAP <35 mm Hg) do quite well without pre-LT PAH-specific therapy. The goal of screening is to identify and treat those who have the highest risk of cardiopulmonary adversity during and after LT. Pulmonary hemodynamics in LT candidates may change over time, so repetitive screening (every 12 months) is recommended.  

**WHAT IS KNOWN ABOUT THE EPIDEMIOLOGY AND NATURAL HISTORY OF POPH?**

Yoshida et al appear to be the first authors to use the term POPH in 1993, as they described the first successful case of POPH to undergo successful LT (39-year-old male with long-standing chronic active hepatitis). In the same paper, the authors also described long-term failure of single lung transplant to stabilize POPH in the setting of continued portal hypertension. Subsequently, several small series and case reports with autopsy results have described pulmonary arterial obstruction and pulmonary plexogenic arteriopathy with and without thromboemboli. Two distinct pulmonary vascular obstructive patterns causing PAH in association with portal hypertension are well described: 1) chronic pulmonary emboli from spontaneous or surgical portocaval shunts, in-situ thrombus, and/or platelet aggregates; and 2) a vasoconstrictive, proliferative endothelial/smooth muscle process due to circulating mediators that bypassed normal hepatic metabolism due to flow patterns of portal hypertension.  

Large series have confirmed the coincidence of these portal and pulmonary vascular abnormalities and have shown that the association is not coincidental. An unselected series of 17,901 autopsies revealed that PAH was 5 times more likely in cirrhotic patients than those without liver disease. Within the 1981-1987 National Institutes of Health (NIH) registry of “primary” PH from 32 centers reported by Rich et al, additional analyses by Groves et al concluded that 8.3% likely had POPH (17/204; 187 had primary PH). Hadengue reported the largest prospective study of patients with portal hypertension (n=507) in which portopulmonary hemodynamic measurements concluded that 2% had POPH.  

More recently, prospective studies have focused on the frequency of POPH in clinic settings, including national registries and individual transplant center experiences. In the French PH registry experience over a 12-month period (2002-2003), Humbert reported a 10.4% frequency of POPH (70/674) from 17 university hospitals. In the United States, the REVEAL (Registry to Evaluate Early And Long-term pulmonary arterial hypertension disease management) registry documented a 5.3% POPH frequency (174/3525) in

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**Table 1. Diagnostic and Severity Criteria for POPH**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criterion</th>
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<tbody>
<tr>
<td>Portal hypertension (MPAP)</td>
<td>≥25 mm Hg and</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (PVR)</td>
<td>&gt; 240 dynes/s/cm²</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (PCWP)</td>
<td>≤15 mm Hg</td>
</tr>
<tr>
<td>Transpulmonary gradient (TPG)</td>
<td>≤12 mm Hg</td>
</tr>
</tbody>
</table>

Degree of severity

| Mild                              | ≥25 MPAP <35 mm Hg             |
| Moderate                          | ≥35 MPAP <45 mm Hg             |
| Severe                            | ≥45 mm Hg MPAP                 |

*aPVR = (MPAP-PCWP) x 80/cardiac output.  
*bIn the case where PCWP is >15 mm Hg (abnormal), an abnormal TPG (MPAP-PCWP) may distinguish between simple volume excess causing increased MPAP and the pulmonary artery vasculopathy that characterizes POPH.*
which there were 68% prevalent and 32% incident cases, satisfying the criteria that MPAP >25 mm Hg and PVR >240 dynes/s/cm$^{-5}$ with PCWP ≤15 mm Hg. Following slightly different PVR diagnostic criteria as part of outpatient RHC diagnostic assessments, the largest POPH-LT center experiences reported to date are as follows: 8.5% (Baylor 102/1205; PVR >120 dynes/s/cm$^{-5}$), 6.1% (Clichy, France 10/165; PVR >120 dynes/s/cm$^{-5}$), and 5.3% (Mayo Clinic 66/1235; PVR >240 dynes/s/cm$^{-5}$).5,17,29

The natural history of POPH has been difficult to characterize and has been confounded by small series prior to the availability of current PAH-specific therapy. Robalino and Moodie reported a dismal 5-year survival of 4% (n=78) prior to the availability of continuous intravenous prostacyclin infusion.30 Swanson et al reported a 14% 5-year survival in POPH patients (n=19) denied LT and not treated with any of the current PAH-specific therapies.31 From the French National Center for PAH (n=154 over a 20-year span until 2004), Le Pavec described 1-, 3-, and 5-year survivals of 88%, 75%, and 68% respectively for POPH patients (majority Childs A and alcoholic cirrhotics).1 Only one-third had been treated with PAH-specific therapies with severity of cirrhosis and reduced CO identified as poor prognostic factors. Causes of death in all series mentioned herein were equally distributed between right heart failure due to POPH and direct complications of liver disease (bleeding, sepsis, hepatocellular carcinoma).

From the REVEAL registry, 2 important POPH observations were reported.28 First, POPH treatment patterns reported in the REVEAL registry demonstrated that the use of any PAH-specific therapy for POPH was delayed compared to patients diagnosed with idiopathic PAH (IPAH). Specifically, at the time of entry into the registry only 25% were on PAH-specific therapy and at 12 months follow-up 74% were on treatment. Second, although baseline hemodynamics in POPH (MPAP and PVR) were significantly better than those with IPAH, the 1- and 3-year survivals were worse. The 5-year survival for all POPH patients was 40% compared to 64% for IPAH. Liver disease etiologies and causes of death were not determined in the registry and survival was not analyzed by the type of PAH-specific therapy.

Two caveats are important in characterizing the natural history of POPH. First, with the advent of PAH-specific therapies, every controlled randomized study has excluded POPH patients. This universal exclusion in the United States further complicated the understanding of POPH outcomes compared to other PAH disorders. Second, beginning in 2002 a higher priority for LT was an option for highly selected patients with POPH in the United States.32 Formalization of higher priority pulmonary hemodynamic criteria were put forth in 2006, and standardized in 2010. Only patients with moderate to severe POPH (MPAP >35 mm Hg) who attained significant hemodynamic improvement with PAH-specific therapy (MPAP <35 mm Hg and PVR <400 dynes/s/cm$^{-5}$) were granted higher priority for LT. From 2002 through 2010, 155 POPH patients were granted such priority and transplanted by regional review boards.33
HOW TO TREAT AND MANAGE POPH IN LT CANDIDATES

In Figure 2, we summarize the clinical algorithm followed at our institutions based on RHC results: deciding which patients indeed have POPH, deciding who needs PAH-specific therapy based on severity, and determining the risks and timing for potential LT are the most important clinical questions.

POPH patients with MPAP >35 mm Hg are particularly vulnerable to poor outcomes with attempted LT, especially if there is no attempt to treat the POPH with current PAH-specific medications. With current treatments, POPH outcomes are variable, yet in highly selected POPH patients with aggressive treatment and successful LT, pulmonary hemodynamics may completely normalize. RV size and function normalize and liberation from PAH-specific medications may be allowed.

The immediate goal in the management and treatment of POPH is to improve pulmonary hemodynamics by reducing the obstruction to pulmonary arterial flow. This can be accomplished by medications that result in vasodilation, antiplatelet aggregation, and antiproliferative effects. Enhancing local nitric oxide vasodilation effects (phosphodiesterase inhibitors). The ultimate goal, in addition to favorably affecting pulmonary hemodynamics (decreased MPAP, decreased PVR, and increased CO), is to stabilize, improve, and/or normalize RV function.

Uncontrolled small series and recent case reports have demonstrated that PAH-specific therapies used for other types of PAH could be beneficial for patients with POPH (Table 2). It is important to stress that improvements in both MPAP and PVR are the ideal goals in treating POPH. However, MPAP may not decrease as much as desired, as increases in CO associated with reduced obstruction to flow (measured by decreased PVR) will result in higher flow (and increased pressure).

Role of Prostacyclins in POPH

The most dramatic PAH-specific therapy effects in POPH have been with the use of continuous prostacyclin infusion via a central catheter and oral endothelin receptor antagonists. In a summary of 48 patients treated with intravenous epoprostenol from 5 studies, MPAP decreased by 25% (48 → 36 mm Hg), PVR decreased by 52% (550 → 262 dyne/s/cm²), and CO increased by 38% (6.3 → 8.7 L/min, all $P<0.01$). Other prostacyclins (intravenous treprostinil and inhaled iloprost) have resulted in significant pulmonary hemodynamic improvement in POPH.

Role of Endothelin Receptor Antagonists in POPH

Regarding the use of endothelin receptor antagonists, Hoeper et al documented 1- and 3-year survival of 94% and 89% in 18 patients with POPH and Childs A severity liver disease using the nonselective endothelin antagonist bosentan. No liver toxicity was noted. However, Eriksson et al have correctly warned about potential liver toxicity with the use of bosentan, occurring in up to 10% of patients without documented POPH. Although Kahler et al have reported success in POPH with the use of a selective endothelin receptor antagonist sitaxsentan, this medication has not been approved in the United States and has been associated with fatal hepatic failure. Cartin-Ceba et al reported 13 POPH patients using the endothelin receptor antagonist ambrisentan (10 mg daily) and documented at 1-year improvement in each of 8 POPH patients (MPAP 58 → 41 mm Hg and PVR 445 → 174 dyne/s/cm², $P=0.004$). Of note, 5 of the 8 patients normalized their PVR. In further support of ambrisentan in POPH, Halank et al described significant improvement in both exercise capacity and symptoms in 14 POPH patients. Importantly, neither of the uncontrolled ambrisentan studies was associated with hepatic toxicity. This may be due to the differences in chemical structure (ambrisentan-propionic acid; bosentan and sitaxsentan-sulfas base) and distinct hepatic metabolic pathways. More recently, Savale et al described 34 patients with POPH (Childs A or B severity of liver disease) treated with bosentan documenting significant hemodynamic improvement (more so in the Childs B subgroup), and event-free survival estimates were 82%, 63%, and 47% at 1, 2, and 3 years respectively.

Role of Phosphodiesterase-5 (PDE-5) Inhibitors in POPH

PDE-5 inhibitors prevent the breakdown of cyclic guanosine monophosphate, the mediator of nitric oxide-induced vasodilation. The use of phosphodiesterase...
inhibition (sildenafil) to enhance nitric oxide vasodilating effect, either alone or in combination with other PAH-specific therapies, has successfully improved POPH pulmonary hemodynamics and facilitated successful LT. Most of the published experiences have been in patients with less severe POPH.39,41,49

**Role of Other Therapies and Interventions in POPH**

In a single case report, a dramatic hemodynamic improvement was observed with the 6-week addition of imatinib 400 mg daily (a tyrosine kinase inhibitor) to pre-LT intravenous epoprostenol and post-LT bosentan therapy, resulting in liberation of all PAH-specific medications and normalization of RV function 1 year post-LT. This observation suggests a possible fourth pathway of PAH-specific therapy effectiveness (blocking platelet-derived growth factor receptors) in treating POPH.54

The use of beta blockers or transjugular intrahepatic portosystemic shunting (TIPS) in the setting of POPH may be problematic. The former, used to prevent gastrointestinal bleeding by reducing the degree of portal hypertension, may impair needed RV function. In moderate to severe POPH (n=10; mean MPAP = 52 mm Hg), withdrawal of beta blockade increased CO by 28%, decreased PVR by 19% with no change in MPAP, and increased 6-minute walk by 79 meters.55 TIPS, as a treatment for uncontrollable gastrointestinal bleeding or refractory ascites, can temporarily increase MPAP, CO, and PVR. In a study of 16 cirrhotic patients without PH, the increase in MPAP was greater than that noted in CO, suggesting an increase in the PVR after TIPS.56 Such changes remained for at least 30 days post-TIPS and reflected neurohumoral effects as opposed to increased preload. A significant increase in RV work was documented and the potential effect on RV function could be deleterious in patients with preexisting POPH.57

**WHAT IS THE ROLE OF LT IN POPH PATIENTS?**

The majority of patients with POPH have cirrhosis and LT is a potentially curative intervention, at least from a hemodynamic perspective. In the United States, a total of 5805 liver transplants were accomplished in 2011. As of mid-2013, there were approximately 16,482 patients on the wait list in over 120 United States LT centers.58 Assuming up to 8.5% of LT candidates have POPH, at any point in time there may be approximately 1300 POPH-LT candidates.1 The outcome of POPH following LT remains unpredictable despite screening, careful patient selection, higher priority for LT, and advances in single and combination PAH-specific therapies (Table 3).14-16,59-65 Effective PAH-specific therapy has resulted in

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**Table 2. PAH-Specific Therapy Use in POPH**

<table>
<thead>
<tr>
<th>Study first author (medication)</th>
<th>Number of patients</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENDOTHELIN RECEPTOR ANTAGONISTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoeper43 (bosentan)</td>
<td>18</td>
<td>1- and 3-year survivals 94% and 89%, respectively</td>
</tr>
<tr>
<td>Cartin-Ceba36 (ambrisentan)</td>
<td>13</td>
<td>At 1 year, MPAP and PVR improved in 8/8; PVR normalized in 5</td>
</tr>
<tr>
<td>Savale53 (bosentan)</td>
<td>34</td>
<td>Event-free survival estimates were 82%, 63%, and 47% at 1, 2, and 3 years, respectively</td>
</tr>
<tr>
<td><strong>PHOSPHODIESTERASE INHIBITORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reichenberger49 (sildenafil)</td>
<td>12</td>
<td>Improvement at 3 months; not sustained at 1 year</td>
</tr>
<tr>
<td>Gough41 (sildenafil)</td>
<td>11</td>
<td>PVR decreased in all at first RHC follow-up</td>
</tr>
<tr>
<td>Hemnes41 (sildenafil)</td>
<td>10</td>
<td>At 1-year MPAP and PVR decreased in 3/5 patients</td>
</tr>
<tr>
<td><strong>PROSTACYCLINS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuo47 (IV epoprostenol)</td>
<td>4</td>
<td>MPAP and PVR improved</td>
</tr>
<tr>
<td>Krowka46 (IV epoprostenol)</td>
<td>15</td>
<td>15 MPAP and PVR improved</td>
</tr>
<tr>
<td>Ashfaq35 (IV epoprostenol)</td>
<td>16</td>
<td>Successful LT in 11 patients; 5-year survival 67%</td>
</tr>
<tr>
<td>Fix48 (IV epoprostenol)</td>
<td>19</td>
<td>PVR improved in 14/14; MPAP improved in 11/14</td>
</tr>
<tr>
<td>Sussman51 (IV epoprostenol)</td>
<td>8</td>
<td>MPAP and PVR improved in 7/8</td>
</tr>
<tr>
<td>Sakai50 (IV treprostinil)</td>
<td>3</td>
<td>Successful LT in 2 patients (moderate POPH)</td>
</tr>
<tr>
<td>Hoeper43 (inhaled iloprost)</td>
<td>13</td>
<td>1- and 3-year survivals 77% and 46%, respectively</td>
</tr>
<tr>
<td>Melgosa48 (inhaled iloprost)</td>
<td>21</td>
<td>Acute, but no long-term hemodynamic improvement</td>
</tr>
<tr>
<td><strong>COMBINATION THERAPY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hollatz44 (sildenafil alone or combined with prostacyclins in 9 patients)</td>
<td>11</td>
<td>MPAP and PVR improved in all patients, all underwent LT and 7/11 are off PAH-specific therapy</td>
</tr>
<tr>
<td>Raevens52 (6 patients combined therapy with sildenafil and bosentan; 1 patient only on prostacyclins)</td>
<td>7</td>
<td>MPAP and PVR improved in the 5/6 patients treated with combination of sildenafil and bosentan; 2 underwent LT</td>
</tr>
</tbody>
</table>

MPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; LT: liver transplantation; IV: intravenous; POPH: portopulmonary hypertension.
Table 3. Liver Transplant Outcomes in the Setting of POPH

<table>
<thead>
<tr>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>POPH Wait-list mortality</td>
<td>17,38,39,51</td>
</tr>
<tr>
<td>POPH MELD exception pre-LT</td>
<td>33,51</td>
</tr>
<tr>
<td>Case canceled in operating room</td>
<td>13,29,47,61</td>
</tr>
<tr>
<td>Intraoperative death</td>
<td>1,13,29,31,33,63</td>
</tr>
<tr>
<td>Transplant hospitalization death</td>
<td>13,15,16,29,33,35,52,62,63,65</td>
</tr>
<tr>
<td>POPH Post-LT</td>
<td></td>
</tr>
<tr>
<td>Resolved; PAH-specific therapy discontinued</td>
<td>33,35,36,38,39,44,50,51,54,60a</td>
</tr>
<tr>
<td>Resolved/stable without PAH-specific therapy</td>
<td>14,15,17,18,35</td>
</tr>
<tr>
<td>Improved/stabilized/PAH-specific therapy continued</td>
<td>33,38,41,44,49-52,59b</td>
</tr>
<tr>
<td>Progressive despite PAH-specific therapy</td>
<td>29</td>
</tr>
<tr>
<td>Late death not due to POPH</td>
<td>29,31,35</td>
</tr>
<tr>
<td>Late death due to POPH</td>
<td>1,29</td>
</tr>
<tr>
<td>Multiorgan (H-Lu-Lv; Lu-Lv transplant)c</td>
<td>64</td>
</tr>
<tr>
<td>De novo PAH post-LTd</td>
<td>68</td>
</tr>
</tbody>
</table>

aLiving donor liver transplant (3 patients)
bCombined PAH-specific therapy use
cH-Lu-Lv: heart, double lung, liver; Lu-Lv: double lung, liver transplants. It is noted that multiorgan transplants have been reported in the literature for cystic fibrosis, alpha-1 antitrypsin deficiency, and sarcoidosis, but these entities also affect lung parenchyma and many cases were accomplished in the era prior to current PAH-specific medications, therefore were not included herein.
dPAH – pulmonary artery hypertension; a literature review of 13 such cases.

successful LT and subsequent liberation from pre-LT PAH-specific therapy (Table 3). Importantly, reperfusion during the LT procedure represents a critical time when preload can increase, cytokines may be released, thrombi may migrate into the pulmonary circulation, and intraoperative death follows from acute right heart failure.66

Although supporting data are limited, LT programs in the United States now allow higher priority to conduct LT if pulmonary hemodynamics can be significantly improved and meet standardized Model of End-Stage Liver Disease (MELD) exception guidelines. Current treatment targets for POPH MELD exception in the United States are shown in Table 4. The goal and results of such recent policy in US LT programs has been to interrupt the natural history of POPH (reduce waitlist death) and also improve post-LT survival with liberation from PAH-specific therapy after successful LT once pulmonary hemodynamics have normalized (Table 3). However, failure to reduce MPAP below 50 mm Hg is considered by most centers to be a contraindication to LT or, if discovered at the time of the operation, grounds to cancel the LT procedure prior to the abdominal incision. Despite limited experience, at this time it seems logical that similar pulmonary hemodynamic guidelines should be followed when living-donor POPH transplants are considered.56,67

Although the role of LT in the setting of POPH is evolving with experience, the recognition that severe POPH (measured hemodynamically and qualitatively by echocardiography) can resolve post-LT with aggressive pre-LT PAH therapy is quite remarkable. Although preliminary observations are encouraging, the normalization of pulmonary hemodynamics post-LT does not necessarily equate to pulmonary vascular pathology resolution or long-term stability. Finally, it should be noted that clinically significant PAH could develop de novo following LT (i.e., normal pulmonary hemodynamics are noted at the time of LT) for reasons that are clearly not understood.68

FUTURE CONSIDERATIONS AND FINAL REMARKS

From the current evidence available from observational studies, moderate to severe POPH is curable in some cases with a combination of LT and PAH-specific medications. There are 2 important, pressing issues regarding the MELD exception rules that are important to discuss. The first issue has to do with the MELD exception not being granted under current US policy if the MPAP remains >35 mm Hg despite normalization of PVR and RV function with pre-LT therapy. In such patients, the elevation in MPAP reflects a change in physiology and is the result of pulmonary vasoactive therapy increasing the existing high flow state, and decreasing the PVR to flow. We consider that in those patients where there is normalization of RV function and PVR, MELD exception should be granted despite the "abnormal MPAP." Based on observational data, it is hypothesized that for those individuals, cure of POPH after LT can be obtained. Admittedly, it is unknown whether pulmonary hemodynamic normalization post-LT reflects a pathologic pulmonary vascular cure. In addition, in most post-LT patients that have clinical improvement and echocardiographic normalization of RV function, size, and RVSP, RHC is not routinely performed to corroborate the normalization of the hemodynamics. The second pressing issue deals with the adoption of the standard MELD exception for POPH. Even though those

Table 4. MELD Exception Criteria for POPH

1. Moderate to severe POPH diagnosis confirmed by right heart catheterization
   a. MPAP ≥35 mm Hg
   b. PVR ≥240 dynes/sec/cm-5
   c. PCWP ≤15 mm Hg
2. PAH-specific therapy initiated; improvement documented
   a. MPAP <35 mm Hg
   b. PVR <400 dynes/sec/cm-5a
   c. Satisfactory right ventricular function by transthoracic echocardiography
3. MELD exception updated (additional 10% MELD points) every 3 months
   a. Give additional MELD exception if RHC data satisfies criteria # 2

If PVR is normal, higher MPAP may be allowed and reconsidered due to physiology that is now high flow rather than obstruction to flow due to the therapy. POPH: portopulmonary hypertension; MPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; RHC: right heart catheterization; MELD: Model End-Stage Liver Disease.
individuals can be tracked in terms of general survival, no data are available regarding PAH-specific therapy management after LT. Unfortunately, there is lack of understanding about the most appropriate post-LT management in order to optimize outcomes. A multicenter survival registry collecting comprehensive information should be performed in POPH patients that undergo LT.

In conclusion, POPH is an uncommon and serious yet treatable pulmonary vascular consequence of portal hypertension that can lead to right heart failure and death if untreated. Due to the different spectrum of pulmonary hemodynamic changes associated with hepatic dysfunction, screening by TTE and confirmation by RHC is necessary for accurate diagnosis and therapeutic considerations. Despite the lack of controlled studies, PAH-specific therapies in POPH can significantly improve pulmonary hemodynamics and RV function. The potential to “cure” POPH, at least hemodynamically, with a combination of PAH-specific therapy and LT appears to be an attainable goal in a cohort of POPH patients yet to be optimally characterized. Controlled, multicenter studies and long-term follow-up post-LT are needed.

References
39. Gough MS, White RJ. Sildenafil therapy is associated with improved hemodynamics in liver transplantation candidates with pulmonary arterial
Perioperative Evaluation and Management of Patients With Portopulmonary Hypertension Aiming for Orthotopic Liver Transplantation

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Background: Portopulmonary hypertension (POPH) is defined as pulmonary arterial hypertension (PAH) in the context of portal hypertension. Severe POPH has been considered an absolute contraindication of orthotopic liver transplantation (OLT).

Objective: Since there are no definitive guidelines for the immediate preoperative, intraoperative, and postoperative evaluation and treatment of POPH patients, we have used published literature along with our experience to review current knowledge in this area.

Summary: Moderate-to-severe POPH has important consequences in the perioperative management of candidates for OLT. Adequate right ventricular function is critical to survive the hemodynamic burden of OLT. Immediate preoperative assessment of hemodynamics; careful intraoperative monitoring and management of volume status, pressure changes, and ventricular function; and postoperative transitions of PAH-specific therapy are key components to successful OLT. We emphasize the advantages of the echocardiogram during all of these phases and stress the importance of a team approach to plan care and respond to the multiple challenges of OLT in POPH.

Initially described in 1951, the coexistence of pulmonary arterial hypertension (PAH) and hepatic dysfunction has been well documented. During the 4th World Symposium held at Dana Point in 2008, the previous clinical classification of portopulmonary hypertension (POPH) as a well-recognized cause of PAH was upheld. Patients with liver disease can present with a continuum of pulmonary vascular resistance profiles, from the characteristic vasodilatation of hepatopulmonary syndrome to increased resistance to pulmonary blood flow in the setting of POPH. The focus of this review is the immediate perioperative assessment and management of patients with POPH undergoing orthotopic liver transplant (OLT).

PREOPERATIVE PERIOD

A methodical diagnostic approach is of the utmost importance in patients with portal hypertension undergoing standard pretransplant evaluation. Transthoracic echocardiography (TTE) plays an integral role in the evaluation of end-stage liver disease (ESLD) patients. Noninvasive screening of elevated right ventricular systolic pressures (RVSP) is the main role of Doppler TTE in the preoperative evaluation of patients with POPH undergoing OLT. However, TTE alone cannot characterize the severity of POPH. In fact, echocardiographically estimated RVSP and measurements by right heart catheterization (RHC) may disagree, particularly at higher estimated RVSP. It is assumed that RVSP equates with systolic pulmonary artery pressure (SPAP). In our practice, we also use echocardiographically measured mean pulmonary artery pressure (MPAP), which appears to correlate well with MPAP measured by RHC.

Two recent studies described the cutoff value of RVSP by TTE as an indication for RHC. Krowka et al used a
cutoff of 50 mm Hg to proceed with RHC (see accompanying manuscript by Cartin-Ceba and Krowka in this issue). A lower threshold was used by Raevens et al, who demonstrated that increasing the cutoff from 30 mm Hg to 38 mm Hg safely reduces the number of patients who need RHC (specificity 82%; negative predictive value of 100%).

An elevated RVSP by TTE does not equate to a diagnosis of POPH, as up to 20% of ESLD patients have a hyperdynamic circulatory state with a direct correlation between pulmonary artery pressure (PAP) and cardiac output (CO). The high-flow hemodynamic profile is as follows: MPAP >25 mm Hg, high CO, and low pulmonary vascular resistance (PVR). Even if discovered in the immediate preoperative assessment, this group of patients with pulmonary hypertension (PH) from high-flow state may safely proceed with OLT.

In contrast, “true” POPH documented by RHC in the immediate preoperative period (ie, not previously diagnosed) requires careful assessment and may preclude proceeding with OLT. Our preoperative approach of patients with POPH is shown in Figure 1.

Often volume overload is present in patients with ESLD, complicating the interpretation of an elevated RVSP by TTE. Carefully monitored diuresis to achieve “dry weight” is recommended. At this point, the echocardiographic evaluation should be repeated. If TTE again reveals PH, an RHC should be performed. In those patients with elevated serum creatinine, it may be necessary to evaluate and treat as patients. Our practice is to admit for left-heart pressures, ie, pulmonary artery occlusion pressure (PAOP) ≤15 mm Hg. Rarely in those patients with more severe renal disease, renal replacement therapy is used to achieve normal intravascular volume status. Reassessment of the hemodynamic profile is diagnostic of POPH if the MPAP >25 mm Hg, PAOP ≤15 mm Hg, and PVR >240 dyne s cm−5 (3 Wood units) as outlined in Figure 1. With hemodynamic confirmation of the POPH, the most appropriate PAH-specific therapy is determined.

The mortality of patients with moderate POPH with MPAP 35-45 mm Hg and PVR >250 dyne s cm−5 has been reported to be about 50%-80%, while the mortality when MPAP >50 mm Hg has been found to be near 100%. Long-term prognosis of patients with POPH remains poor, but intraoperative and immediate perioperative mortality is certainly the major concern in patients with MPAP >50 mm Hg. Indeed, the Registry to Evaluate Early and Long-term pulmonary arterial hypertension disease management (REVEAL) demonstrated that POPH had significantly poorer survival and all-cause hospitalization rates compared with idiopathic PAH, despite having better hemodynamics at diagnosis.

Prognostication and the decision to proceed with OLT are commonly complicated by 1 of 2 scenarios. In the first scenario, the severity of POPH does not necessarily correlate with the severity of liver disease. In that case, United Network for Organ Sharing has approved Model for End-Stage Liver Disease (MELD) exception points for patients with POPH, thereby enhancing the likelihood of earlier OLT (see accompanying manuscript by Cartin-Ceba and Krowka in this issue). In the second scenario, the patient may experience clinical deterioration due to the failing liver but has hemodynamics that are considered borderline eligible for OLT. It is unknown whether the increased risk of OLT should be considered acceptable in this circumstance. We advocate a multidisciplinary discussion, including the hepatologist, transplant surgeon, anesthesiologist, critical care physician, and PAH specialist, to discuss the individualized circumstances influencing the decision to proceed with OLT. A team approach marshals the relevant expertise in all subspecialties to provide the most appropriate decision.

PAH-specific therapies are designed to improve or normalize right ventricular (RV) function while reducing the MPAP and PVR to a range considered safe for transplantation. A detailed discussion of these therapies for the outpatient pre-OLT period is detailed in the companion article. This review will address the use of appropriate PAH therapy in the immediate pre-OLT time frame, as well as intraoperative and postoperative time courses. Important clinical considerations include the patient’s outpatient medical regimen, hemodynamic profile at the time of OLT, conversion to dose delivery systems permissible under anesthesia and during the perioperative period. A list of applicable PAH medications is shown in Table 1. While case series of improved hemodynamics and outcome in POPH have been published with outpatient use, limited evidence is available to define their role on patient outcome in the perioperative period.

In the immediate pre-OLT period, reassessment with RHC and tranesophageal echocardiography (TEE) is strongly advised. Generally, any current PAH-specific therapy (Table 1) is continued whenever feasible in order to maintain hemodynamic stability and avoid rebound PH. Certainly for those patients who are already receiving continuous intravenous infusion or inhaled treatments, the therapy should be continued and titrated based on the hemodynamic goals as previously discussed.

Oral PAH-specific medications can and should be administered until the patient is no longer taking oral medications in preparation for surgery. Sildenafil has an intravenous formulation that can be substituted for the oral if needed. The 10 mg intravenous dose is roughly equivalent to the 20 mg oral dose; nonetheless, when administering vasodilators by the intravenous route, careful monitoring of the systemic blood pressure is warranted.

Practical considerations for both inhaled and infusion therapy include experience with the various PAH-specific therapies and ease/cost of delivery systems. For example, among the inhaled delivery options, the delivery system and dosing for nitric oxide (NO) offers simplicity and convenience but is expensive compared to inhaled epoprostenol, which is more difficult to
Figure 1. Evaluation of POPH in Patients With ESLD.

*For practical purposes, sPAP is considered the same as RVSP:

\[ sPAP = \left( 4 \times \text{(Maximum velocity of tricuspid regurgitant jet)} \right)^2 + \text{Right Atrial Pressure} \]

† In the recent publications consider Systolic Pulmonary Artery Pressure (sPAP) > 38-48 mmHg [6]

RVSP= Right Ventricular Systolic Pressure, ECHO= Echocardiogram, sPAP= Systolic Pulmonary Artery Pressure, MELD= Model for End-Stage Liver Disease, MPAP= Mean Pulmonary Artery Pressure, PVR= Pulmonary Vascular Resistance, PCWP= Pulmonary Artery Occlusion Pressure, TPG= Transpulmonary Gradient, CO= Cardiac Output, POPH= Portopulmonary Hypertension, NO= Nitric Oxide
Table 1. PAH Medications Used for POPH in the Perioperative Period for OLT

<table>
<thead>
<tr>
<th>CLASS</th>
<th>MEDICATION</th>
<th>PERIOPERATIVE</th>
<th>USE in POPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-5 Inhibitor</td>
<td>Sildenafil</td>
<td>IV form 10 mg tid</td>
<td>Case series with improved hemodynamics</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>No IV formulation</td>
<td>Reduce dose to 20 mg daily in Child-Pugh class A or B; avoid for class C</td>
</tr>
<tr>
<td>Endothelin Blocker</td>
<td>Ambrisantan</td>
<td>Oral only Should not be crushed</td>
<td>Case series published with improved hemodynamics and no hepatotoxicity; multicenter open label trial ongoing</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>Oral only</td>
<td>Hepatotoxicity a concern but has been used in case series</td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>Iloprost</td>
<td>Inhaled every 2 hours</td>
<td>Case series with improved hemodynamics; interval between dose may be increased to 3 to 4 hours in liver disease</td>
</tr>
<tr>
<td></td>
<td>Treprostinil</td>
<td>Continuous infusion IV or subcutaneous; inhaled every 4 to 6 hours</td>
<td>Limited data; initial dosing reduced by half to 0.625 ng/kg/min; no data for inhaled formulation</td>
</tr>
<tr>
<td></td>
<td>Epoprostenol</td>
<td>Continuous IV</td>
<td>Case series with improved hemodynamics</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>Nitric Oxide</td>
<td>Inhaled 5 to 80 ppm</td>
<td>Case reports only</td>
</tr>
</tbody>
</table>

A comparison of the medications used to manage POPH in patients undergoing OLT. Key: PDE-5 = phosphodiesterase-5, IV = intravenous.

administer. The availability of proprietary inhaled agents (iloprost and treprostinil) often depends on insurance and formulary coverage.

The protocols for initiation and titration of inhaled and intravenous therapy vary among OLT centers. Inhaled NO can be delivered via a facemask or into the inspiratory limb of a ventilator circuit. Generally, the dose is started at 5 ppm with subsequent doubling to desired effect (eg, 10, 20, 40, 80 ppm). Methemoglobinemia is a side effect that requires daily monitoring.

Inhaled epoprostenol requires the use of the brand FLOLAN® (epoprostenol sodium). Various dose strengths can be created using different concentrations of the 0.5 mg vial and proprietary FLOLAN diluent. Dose concentrations are generally 2500 to 20,000 ng/mL. The resulting solution is nebulized at 8 mL/hour into the ventilatory circuit. The solution must be protected from light and degrades after 8 hours at room temperature. The glycine buffer may cause the FLOLAN to precipitate and accumulate in the circuit, requiring close monitoring and filter changes as indicated.

Intravenous epoprostenol therapy is commonly initiated in the hospital (2 ng/kg/min) and titrated up by 1-2 ng/kg/min (recommendation on frequency of increase varies from every 30 minutes to every 1-2 hours) to achieve the required hemodynamic effect or until limited by common side effects (headache, nausea, flushing, myalgia, diarrhea, jaw pain, or systemic hypotension). The initial “plateau” dose rarely exceeds 12 ng/kg/min, but thereafter can be increased more slowly if needed.

Pharmacologic treatment of side effects may be required to promote tolerance. Treprostinil, a prostacyclin analogue, is an alternative to epoprostenol. The logistics of initiating therapy are similar to epoprostenol. In contrast to epoprostenol, it can be administered subcutaneously with reported 100% bioavailability. Nonetheless, the cachexia associated with ESLD and abdominal distension from ascites raise concerns about the tolerability and absorption in this setting. Initial dosing of treprostinil in patients with mild to moderate hepatic dysfunction is half that of patients without liver disease, with a starting dose of 0.625 ng/kg/min.

Limited data are available for use in patients with severe liver dysfunction.

Of specific note, long-term complications of intravenous prostacyclins include thrombocytopenia, systemic hypotension, central line infection, post-insertion bleeding, and progressive splenomegaly (which may worsen thrombocytopenia and produce leukopenia). Since the goal is to continue the PAH-specific therapy until the postoperative period following OLT, clinicians must appreciate the nuances of medication administration, hemodynamic goals, and unusual side effect profile of these medications.15,16

Some authors have published case reports describing the successful use of combined therapies to maximize the benefit from pulmonary vasodilation.17 In many centers, combination treatment is often utilized to obtain the goal of MPAP ≤35 mm Hg for OLT candidacy. Although this may be a plausible option, there are limited data regarding the best combination or sequence of therapy.

INTRAOPERATIVE PERIOD
Utilization of Intraoperative Transesophageal Echocardiography During OLT

In addition to routine monitoring for OLT, TEE may be of added value in managing patients with POPH.18 In recent years, preexisting esophageal varices are no longer considered an absolute contraindication for TEE during OLT. Often, esophageal bleeding is self-limited and mild to moderate in severity. The TEE examination can be performed using limited views and avoiding excessive manipulations of the probe. However, intraoperative examination should be performed with immediate availability of a gastroenter-
ology specialist to address any severe bleeding. The main intraoperative goal of managing hemodynamics for patients with POPH is to maintain optimal mechanical matching between the RV function and pulmonary circulation.

There are several intraoperative phases in which the patient is at risk for severe systemic arterial hypotension: during the dissection phase, the manipulation of the liver, drainage of large ascites, and clamping of the inferior vena cava (IVC) (if the “piggy-back” technique is not used) and/or portal vein. It is advised to have immediate availability of continuous infusions of vasopressor and inotropic agents for the treatment of shock. Continuous assessment of volume status is critical intraoperatively. Left ventricular end diastolic area (<5.5 cm²/m² surface area) in the transgastric short axis view by TEE is suggestive of hypovolemia. Other applications of TEE include placement of venovenous bypass cannula (again not an issue with the “piggy-back” technique), identification of hemodynamically significant thrombosis of the IVC, intracardiac thrombus, complications of transjugular intrahepatic portosystemic shunts, and management of patients with underlying valvular heart disease, coronary artery disease, or cardiomyopathy (eg, alcohol-induced, hemochromatosis, or amyloidosis).

During the anhepatic phase, there are predictable hemodynamic changes including decreased systemic vascular resistance and increased CO, MPAP, and PVR. The TEE assessment should be focused on determining ventricular dysfunction and volume status. The reperfusion phase is perhaps the most important period of TEE evaluation during OLT. Post-reperfusion syndrome is the hallmark of this hemodynamic disturbance. It is manifest as a vasodilatory state with worsening POPH and RV function. Thus, the most important signs to confirm RV failure are dilation and dysfunction of the RV, as well as septal dyskinesia. Air embolism is an under-recognized condition that can aggravate or precipitate RV failure. The RV is compromised due to the anterior anatomic position of the right coronary artery. Finally, it is important to note that hypovolemia, tachycardia, and overutilization of inotropic support can all lead to a systolic anterior motion of the mitral valve with subsequent dynamic obstruction of the left ventricular outflow tract.

**Therapeutic strategies.** Preoperative use of intravenous epoprostenol is usually continued intraoperatively. Inhaled NO may be used as an adjunct inhalation agent to optimize RV function and mitigate elevated MPAP. Intraoperative fluid management should be adequate to achieve euvoletic state and ensure adequate RV preload. Inhaled NO is generally quite easy to transition from the intraoperative to the postoperative setting, a distinct advantage for the peri-OLT management of POPH. Phosphodiesterase-3 inhibition with intravenous milrinone reduces PVR and assists in managing MPAP; however, care must be taken not to compromise systemic pressures when this agent is used. Several vasodilator therapies by inhalation route as previously discussed may be administered intraoperatively to manage patients with POPH who present for OLT. These agents offer unique advantages since they can be delivered directly to the alveoli. Consequently, the ventilated areas may give rise to a decrease in the pulmonary shunt and improved oxygenation whenever these agents are administered.

Rarely, a patient may develop or be recognized as having POPH in the operating room (OR) suite. Intravenous epoprostenol can be initiated in the OR, but hemodynamic changes and responsiveness can be variable and challenging. Inhaled agents like iloprost and treprostinil cannot be administered in the OR. Inhaled epoprostenol or NO are alternatives for treatment of POPH. Milrinone has also been used and can be continued both intra- and postoperatively. Occasionally, anesthesiologists have used it before the anhepatic/reperfusion phase in anticipation of known hemodynamic alterations that occur during reperfusion. Furthermore, the duration of cold ischemic time may play a role in PAH therapy selection; therefore, an agent that is reliable with rapid onset and is easily and accurately titratable needs to be used (eg, intravenous epoprostenol).

Initiation of intravenous epoprostenol intraoperatively is essentially no different than in the pretransplant environment for a POPH patient who requires treatment but is still appropriate to proceed with OLT. For the most part, the hemodynamic contraindication for OLD, and hence the need to cancel surgery, is the finding of MPAP ≥50 mm Hg from RHC. Treatment may be attempted in the OR to reduce the MPAP to a range of 40-49 mm Hg if time allows, whereas MPAP 36-39 mm Hg may warrant consideration for treatment after careful interpretation of hemodynamic profile to differentiate “volume-induced,” “hyperdynamic-induced,” or true POHP. Hyperdynamic-induced PH is usually well tolerated at this range (MPAP 36-39 mm Hg). However, both of these hemodynamic interpretations are best done in conjunction with TEE evaluations to assess RV size and function in order to make the decision regarding proceeding with OLT.

**POSTOPERATIVE PERIOD**

The resolution of POPH after OLT is unpredictable. Most of the studies report that up to 76% of the patients improve or resolve POPH following OLT. However, this improvement varies (up to 27 months). It is a common practice in our institution to continue the PAH-specific therapy that was used in the pre- and intraoperative periods. All patients with known POPH, or de novo POPH, are admitted to the intensive care unit (ICU) after OLT. We attempt early postoperative extubation in all patients with postsurgical optimization. If inhaled NO was used intraoperatively, it is discontinued if possible during the weaning from mechanical ventilation; however, some patients may need longer support with gradual weaning postextubation. Routine post-OLT care is provided with special considerations and attention given to avoiding/minimizing rapid volume infusions, need for vasopressors, use of appropriate PAH-specific therapy, and evidence of postoperative RV failure. Infrequently, the use of milrinone infusions has been either continued from the operating room or started in the ICU.
due to its vasodilatory action and inotropic effects, provided that adequate and stable systemic blood pressure is present. In the case that multiple agents are used simultaneously, careful titration is mandatory. Agents not used preoperatively will usually be discontinued first (eg, milrinone and inhaled NO). Postoperative use and transition of PAH-specific therapy depends on whether the patient was on such therapy preoperatively and the clinical status of the patient. Infusions of intravenous epoprostenol that were initiated perioperatively often can be transitioned to oral PAH-specific therapy within 2-4 days. We maintain the RHC in place while titrating care or transitioning medications. Once there is documented stability in pressures on oral and/or inhaled agents, the RHC can be discontinued. If the patient has been on long-standing PAH-specific therapy, that therapy will be continued postoperatively and slowly tapered over weeks to months as an outpatient.

Careful clinical observation for sudden or progressive changes in pulmonary status or central venous pressure measurements are important clues to possible RV failure. Postoperative deterioration of POPH is anticipated in the immediate postoperative period due to multiple factors (eg, post-reperfusion syndrome, blood product transfusions, hypothermia, pain, etc). Thus, we continue infusion of intravenous epoprostenol, and administer the oral agents via a nasogastric tube if possible. We taper intravenous epoprostenol infusion in decrements of 1-2 ng/kg/min if started perioperatively, and its subsequent dose depends on the invasive hemodynamic monitoring and/or pulmonary pressure estimates on TTE examination. Patients requiring continuous epoprostenol presurgery are maintained on that dose (or higher if needed). The decision to titrate off the infusion is made as an outpatient after careful follow-up evaluation. Likewise, chronic oral or inhaled PAH-specific therapy is continued into the discharge follow-up period. The duration of PAH-specific therapy after OLT is variable and depends on regular follow-up and TTE and/or RHC evaluations. The weaning process after OLT can often be achieved over several weeks. Some patients can be weaned off all vasodilators, revealing that the procedure itself can rapidly improve and resolve POPH.

Postoperative Follow-Up of Patients With POPH and OLT

Right ventricular dysfunction is one of the most important conditions the clinician will face in the postoperative period. There are 4 hemodynamic principles that frame the understanding of this devastating complication. First, PVR is the main factor that affects the RV afterload. Second, it is the RV afterload and not the MPAP that precipitates RV failure. Third, the appearance of RV dilatation, RV dysfunction, and septal dyskinesia are the most valuably evaluated echocardiography signs. Fourth, the RV outflow tract (RVOT) is a key physiological element in the interaction between the RV and the pulmonary artery. Perioperative Doppler TTE is crucial in the assessment of this interaction. Patients with evidence of RV dysfunction and “notching” in Doppler imaging envelope in the RVOT are considered dependent on RV afterload. In order to obtain an adequate imaging of the RVOT, parasternal short-axis view at heart base level (TTE) or transgastric long axis view at 135 degrees are recommended.

Once the patient is transferred to the recovery ward, there is usually no titration of medications. A pre-discharge TTE and b-type natriuretic peptide (BNP) are recommended for documentation, as well as close follow-up at the outpatient clinic at 1 week with the OLT team. Specific instructions are provided to call or come to the emergency department with any symptoms of deterioration. Otherwise, our practice has been a 1-month follow-up with a TTE with the intention to formulate a sensible plan for weaning medications. A multidisciplinary discussion between specialists in transplant and PH is warranted. It is possible to safely withdraw medications in a matter of months, depending on the severity of persistent elevated MPAP or the presence of RV dilation on TTE. Subsequent follow-up visits at our center are anywhere from 2 to 6 months post-OLT and include functional class, BNP, 6-minute walk test, and TTE to assess the clinical status. There are some accounts of medication titrations taking more than a year to complete. Some patients may need medication for an indefinite amount of time (or lifelong), perhaps pointing to possible undetected primary causes besides portal hypertension or to irreversible vascular remodeling. Reevaluation with RHC may be necessary if TTE reveals absence or incomplete tricuspid regurgitant (TR) jet, which precludes assessment of right heart pressures. For patients on continuous infusion prostacyclin therapy, RHC may be needed for safe transition to oral therapy. Lastly, repeat RHC may be indicated if the clinical information is disparate or there is consideration of escalation of PAH-specific therapy.

CONCLUSION

The management of POPH in patients undergoing OLT involves an immediate pretransplant assessment with RHC and often TTE. With that information in hand, a multidisciplinary approach to determine the best PAH-specific treatment plan is recommended.

References


Clinical Case Studies in Renal Transplantation

The case studies below are referred to in the articles “Pulmonary Hypertension in Patients with Chronic Kidney Disease: Noninvasive Strategies for Patient Phenotyping and Risk Assessment” by Amresh Raina, MD, and “Hemodynamic Evaluation of Pulmonary Hypertension in Chronic Kidney Disease” by Ryan Tedford, MD, and Paul Forfia, MD, on the following pages.

Clinical Case 1
A 69-year-old man presents for preoperative evaluation prior to consideration of renal transplantation. He has a long-standing history of systemic hypertension, type 2 diabetes mellitus, obesity, and obstructive sleep apnea. He developed end-stage renal disease as a result of diabetic nephropathy and has been on hemodialysis via right subclavian tunneled catheter for the last 3 years.

Over the past few months, the patient reports worsening dyspnea with mild to moderate exertion and multiple episodes of paroxysmal nocturnal dyspnea over the past 6 months. He has also developed 2 pillow orthopnea and bilateral lower extremity. He denies chest discomfort, angina, palpitations, syncope, or presyncope. He has bilateral pleural effusions noted on chest x-ray.

Ventilation-perfusion scan is low probability for pulmonary embolism. Lower extremity Doppler studies are negative for deep venous thrombosis.

Chest CT reveals no evidence of emphysema or interstitial lung disease, but does reveal a large right pleural effusion.

A screening pretransplant transthoracic echocardiogram showed normal left and right ventricular size and systolic function, with estimated pulmonary artery pressure of 60 mm Hg. He is therefore referred for further evaluation of his pulmonary hypertension in consideration of transplant.

Clinical Case 2
A 74-year-old man presents for evaluation of dyspnea. He has a long-standing history of systemic hypertension and hypertensive nephropathy. He had required hemodialysis 3 times weekly via a right upper extremity arteriovenous (AV) fistula for several years, and ultimately underwent successful cadaveric renal transplantation 3 years ago. His right heart catheterization just prior to renal transplant revealed a right atrial pressure of 2 mm Hg, mean pulmonary capillary wedge pressure of 11 mm Hg, and an elevated cardiac output of 8.8 L/min (cardiac index 4.3 L/min/m2). His AV fistula was not taken down post-transplant.

He initially did well after transplant but presented to the pulmonary hypertension clinic after a progressive decline in exercise tolerance over the past 6 months, now limited even when walking short distances. To date, evaluation for ischemic disease has been negative, a ventilation/perfusion scan was low probability for pulmonary embolism, and a CT scan of the chest showed enlargement of the pulmonary arteries but no evidence of parenchymal lung disease.

A transthoracic echocardiogram is performed, which reveals normal left ventricular and right ventricular (RV) systolic function with significant RV dilatation and estimated pulmonary artery systolic pressure of 80 mm Hg.

Clinical Case 3
A 47-year-old man with long-standing type 1 diabetes mellitus, systemic hypertension, and chronic kidney disease related to diabetic nephropathy underwent combined renal and pancreatic transplant 13 years ago. Subsequently, he had renal allograft failure leading to dialysis for 10 years via an arteriovenous (AV) fistula. Three years ago, he received another successful renal transplant and is now being considered for a repeat renal transplant. His AV fistula remains functional.

On interview he reports mild lower extremity edema, which has been chronic, and mild dyspnea with moderate activity. He denies orthopnea or paroxysmal nocturnal dyspnea. A ventilation perfusion scan shows no evidence of pulmonary embolism. A CT scan of the chest shows dilated central pulmonary arteries consistent with pulmonary hypertension (PH), but no evidence of parenchymal lung disease. Pulmonary function tests showed a mildly reduced diffusion lung capacity for carbon monoxide.

However, on a screening pretransplant echocardiogram, he was noted to have a dilated right ventricle with RV dysfunction, with an estimated pulmonary artery systolic pressure of 105 mm Hg. He is therefore referred for further evaluation of his PH.
An important distinction must be made between PH, which is simply defined as mean pulmonary artery (PA) pressure >25 mm Hg or systolic PA pressure >35 mm Hg vs pulmonary arterial hypertension (PAH), which includes PA occlusive pressure <15 mm Hg, a chronic, progressive condition of pulmonary vascular remodeling, leading to right heart failure and ultimately death if left untreated.

The etiology of PH in CKD patients is typically associated with left heart disease (WHO Group 2), as PAH (WHO Group 1) is rare in this patient population. Moreover, in general, patients with CKD often have a variety of risk factors predisposing them toward pulmonary venous congestion, including systemic hypertension, left ventricular hypertrophy (LVH), ischemic heart disease, and left ventricular (LV) diastolic dysfunction. Although pure pulmonary vascular disease (PVD)-based PH (high pulmonary vascular resistance [PVR], noncompliant conduit pulmonary arteries) is relatively rare in end-stage renal disease (ESRD), not infrequently a “mixed” phenotype of PVD with pulmonary venous hypertension is seen in this population.

PH in CKD patients is important to recognize for 3 major reasons. The first is that several studies have indicated that PH is an independent predictor of mortality in CKD patients, especially those receiving renal replacement therapy.

Second, many CKD patients are evaluated for renal transplantation. In general, significant PH is felt to be a relative contraindication to renal transplantation in patients with CKD. In retrospective studies, PH has been associated with increased early renal allograft dysfunction in these patients, and also associated with reduced patient survival after renal transplantation. Whether the PH is the direct, causal explanation for these differences in outcome is debatable and somewhat controversial. Nevertheless, in many centers, patients with significant PH are characterized as not being acceptable candidates for renal transplantation.

Perhaps most importantly from a clinical perspective, many patients with CKD present to their treating physicians with dyspnea. PH is often picked up on diagnostic echocardiograms in these patients, and not infrequently PH is invoked as a potential etiology of dyspnea and targeted with pulmonary vasodilating medications. However, the clinical phenotype of PH can be quite varied within this broad categorization, ranging from patients with “simple” diastolic heart failure and secondary PH, to those with severe reactive PVD, right ventricular (RV) dysfunction, and a clinical syndrome resembling PAH. The key physiologic differences in these subsets of patients warrant appropriate discussion and attention not only in terms of identifying patients who are appropriate candidates for renal transplantation, but also in terms of identifying in which of these patients PH is the major cause of symptoms, vs others for whom PH is a marker of other underlying disease processes.

Though PH in CKD patients warrants a comprehensive evaluation often including invasive hemodynamic assessment, the first step in evaluation of these patients is typically a noninvasive assessment with physical examination and a transthoracic echocardiogram. Careful attention to the physical examination and the echo-Doppler assessment can provide clues to the underlying physiology of PH in these patients and can inform decisions regarding further assessment and treatment strategies, including appropriate maneuvers during invasive hemodynamic assessment.

From the 2-dimensional echocardiogram, LVH and left atrial enlargement suggest the presence of LV diastolic dysfunction and left atrial congestion. However, grade 2 or grade 3 LV diastolic dysfunction based on transmitral Doppler imaging will be present in many CKD patients with PH. Therefore, echocardiographic assessment of PH in these patients should also focus carefully on evaluating RV size, structure, and function and evaluating for direct and indirect evidence of elevated PVR with detailed Doppler hemodynamic assessment. This approach to the noninvasive assessment of PH in CKD patients is highlighted in the case studies that reference the associated clinical histories.
CASE 1

Recap: A 69-year-old man with obesity, hypertension, diabetes, and obstructive sleep apnea with ESRD on hemodialysis being evaluated for renal transplant.

Physical Examination
On examination, blood pressure is 178/60, pulse is 64 beats per minute, respiratory rate is 12 breaths per minute, and oxygen saturation is 90% on room air. There is a square-wave response in systolic blood pressure to Valsalva maneuver. In general, the patient is a mildly obese, well-appearing man in no apparent distress. Jugular venous pressure is 12 cm of water with normal venous contours. On cardiac examination, S1 and S2 are normal with normal P2 intensity. There is a 2/6 holosystolic murmur at the right upper sternal border. LV apical impulse is normal and nondisplaced. There is no RV heave. Lung auscultation showed diminished breath sounds at the right base up through the mid-right lung field. Abdomen is soft and nondistended. There is mild hepatojugular reflux noted. Extremities revealed 2-3+ bilateral pitting edema to the upper shins.

Echocardiogram
A transthoracic echocardiogram is performed and representative parasternal long and short axis views and apical 4 chamber views are shown. In addition, pulsed wave Doppler in the RV outflow tract and transmitral Doppler profiles are shown. LV systolic function is normal at 55%. Mitral regurgitation is noted as moderate (not shown). There is no mitral stenosis.

The parasternal long axis view (panel A) confirms normal LV size with significant LVH. The parasternal short axis views (panels B and C) reveal a notable absence of septal flattening in systole or diastole with a convexed septal profile. The apical 4 chamber view (panel D) illustrates significant left atrial enlargement, while RV size is mildly dilated with RV:LV ratio of roughly 1.0. Notably, the RV apical angle is relatively acute, does not form or share the apex of the heart, and there is minimal right ventricular hypertrophy (RVH). These 2-dimensional findings do not support the presence of PVD.

On hemodynamic assessment, pulse wave Doppler in the right ventricular outflow tract (RVOT) (panel E) reveals a normal parabolic profile without “notching.” The RVOT acceleration time is low normal at 110 ms. These findings together strongly suggest a normal PVR. The velocity time integral (VTI) in the RVOT is in the normal range (14 cm), implying normal RV stroke volume. Transmitral pulse wave Doppler (panel F) shows a restrictive inflow pattern, consistent with high left atrial pressure. Lastly, tricuspid annular plane systolic excursion (TAPSE) performed via M-mode (panel G) confirms normal RV function with TAPSE of 23 mm.

In this case, the findings on history and physical examination combined with the echocardiographic findings strongly suggest a hemodynamic phenotype of heart failure with preserved ejection fraction and secondary PH, without concomitant PVD. The patient presents with several symptoms consistent with marked left heart congestion including orthopnea and paroxysmal nocturnal dyspnea (PND). In addition, there are objective signs on physical examination of elevated left atrial pressure, including square wave systolic blood pressure response to Valsalva and right pleural effusion.15

The echocardiogram in this case strongly points toward a left heart origin of PH. There is marked LVH, left atrial enlargement, and restrictive transmitral filling consistent with severe LV diastolic dysfunction and elevated left atrial pressure. Though the RV is mildly...
dilated, RV function is preserved as evidenced by normal TAPSE and normal RVOT VTI. Lastly, there is no evidence of significantly elevated PVR as evidenced by the absence of septal flattening or notching of the pulse wave Doppler profile in the RVOT and relatively preserved RVOT acceleration time.16,17

Given the preserved RV function and a phenotype consistent with left sided diastolic heart failure, this patient would be considered an acceptable candidate for renal transplantation once volume status was optimized by volume removal with ultrafiltration and with blood pressure under better control; repeat evaluation with right heart catheterization may be needed. In the invasive hemodynamic assessment of such patients, it is not uncommon to find a top normal or only mildly elevated resting wedge pressure. In such cases, saline fluid challenge or exercise should be considered.

CASE 2
Recap: A 74-year-old man with systemic hypertension, ESRD, previously on hemodialysis via arteriovenous (AV) fistula, now with progressive dyspnea and exercise intolerance post renal transplant.

Physical Examination
On examination, blood pressure is 142/64. Pulse is 83 beats per minute and regular. Respiration is 18 breaths/minute and oxygen saturation is 92% on room air. There is a slow decay in systolic blood pressure with Valsalva. In general, the patient is an elderly appearing man in no apparent distress. Jugular venous pressure was 14 cm of water with prominent V wave. Arterial pulses are stiff and hyperdynamic with rapid upstroke. Point of maximum impulse (PMI) is nondisplaced and is hyperdynamic. S1 and S2 are normal with normal P2 intensity. A soft S4 is audible. There is a 3/4 systolic murmur at the left upper sternal border. Abdomen is soft; there is mild hepatojugular reflux. Extremities have no edema. There is a large right brachial AV fistula with palpable thrill.

Echocardiogram
A transthoracic echocardiogram is performed. Parasternal long and short axis and apical 4 chamber views are illustrated below. In addition, pulse wave Doppler in the RVOT and transmitral Doppler profiles are shown. LV systolic function is normal with left ventricular ejection fraction (LVEF) of 70%. There is no mitral regurgitation or mitral stenosis.

The parasternal long axis view (panel A) reveals normal LV size with mild LVH with mitral annular calcification, a common finding in CKD. The parasternal short axis views (panels B and C) reveal mild diastolic and systolic septal flattening. The apical 4 chamber view (panel D) reveals a mildly dilated RV with RV:LV ratio of roughly 1.0, and the RV shares the apex with the LV. There is mild RVH.

On hemodynamic assessment, pulsed wave Doppler in the RVOT reveals a late systolic notch and an RVOT acceleration time that is mildly reduced at 90 ms. These findings suggest top normal or mildly elevated PVR. The VTI in the RVOT is high (22 cm), suggesting high RV stroke volume. Transmitral pulse wave Doppler (panel E) shows a “pseudonormal” inflow pattern, consistent with increased left atrial pressure. Lastly, TAPSE performed via M-mode (panel F) suggests normal to hyperdynamic RV function with TAPSE of 28 mm.

This patient presents with the insidious onset of progressive dyspnea several years after renal transplantation. On physical examination, he has several features that suggest underlying left heart stiffness and left atrial congestion such as an S4 gallop and slow decay in systolic blood pressure in response to Valsalva maneuver. However, there are also several findings suggesting high cardiac
output state, including hyperdynamic arterial pulses and PMI. The echocardiogram in this instance suggests a mixed picture of left sided congestion, high cardiac output, and mildly elevated PVR.

The RV is mildly dilated and in this case shares the apex of the heart with mild RVH. RVH function is near hyperdynamic with TAPSE of 28 mm. This is confirmed by pulse wave Doppler assessment of the RVOT with high RVOT VTI, suggesting high RV stroke volume.

Thus, the noninvasive assessment strongly suggests a high cardiac output syndrome due to the large brachial AV fistula with moderate left heart congestion, coupled with mildly elevated PVR, and moderate left heart congestion, coupled with mildly elevated PVR.

In this case, hemodynamic assessment is clearly warranted, preferably with provocative maneuvers such as temporary fistula occlusion to assess the contribution of the fistula to cardiac output, left heart congestion, and PH (see article by Dr Tedford in this issue).

CASE 3
Recap: A 47-year-old man with type 1 diabetes mellitus, prior renal and pancreatic transplant, renal allograft failure, being evaluated for repeat renal transplant.

**Physical Examination**
On examination, blood pressure is 128/68, pulse is 57 beats per minute and regular. Respiratory rate is 16 breaths per minute. Oxygen saturation on room air is 91%. There is slow decay in systolic blood pressure in response to Valsalva maneuver. In general this is a well-appearing man in no apparent distress. Jugular venous pressure is 12 cm of water with normal venous contours. Arterial pulses are narrow, low amplitude. On cardiac examination, S1 is normal. S2 is normal with accentuated P2 component. There is a prominent S4 gallop audible. No murmurs or rubs are appreciated. LV apical impulse is nondisplaced. There is a shallow RV heave. Lungs are clear to auscultation bilaterally without rales, rhonchi, or wheezing. Abdomen is soft and nontender. There is an old midline surgical scar that is well healed. There is no hepatojugular reflex. Extremities are well perfused bilaterally. There is trace bilateral lower extremity edema. There is a left upper extremity AV graft with palpable thrill and audible bruit.

**Echocardiogram**
A transthoracic echocardiogram is obtained and representative parasternal long and short axis and apical 4 chamber images are shown below. LV size and systolic function are normal, with LVEF of 65%. Mitral regurgitation is mild (not shown). There is no mitral stenosis. The parasternal long axis view (panel A) again reveals normal LV size, mild LVH, and moderate left atrial enlargement. The parasternal short axis views (panels B and C) and apical 4 chamber view (panel D) reveal significant septal flattening in systole> diastole. The apical 4 chamber view also reveals a moderately dilated RV with RV:LV ratio of 1.2, and the RV shares the apex with the LV. There is moderate RVH.

On hemodynamic assessment, pulsed wave Doppler in the RVOT reveals a midsystolic notch pattern consistent with a PVR >5 Wood units. RVOT acceleration time is very short at 60 ms. The VTI in the RVOT is normal (16 cm), suggesting normal RV stroke volume. Transmitral pulse wave Doppler (panel F) shows an impaired relaxation pattern, also referred to as grade 1 diastolic dysfunction. Lastly, TAPSE performed via M-mode (panel G) suggests moderate RV dysfunction with TAPSE of 16 mm.

This patient has several features suggesting the etiology of his PH has contributions from left sided heart disease, including slow decay in systolic blood pressure response to Valsalva and S4 gallop. However, other elements of
his examination and his echocardiogram suggest a more “right sided” phenotype with narrow, low amplitude pulses, accentuated P2, and RV heave. Although the echocardiogram demonstrates LVH and left atrial enlargement, it also shows marked RV enlargement, systolic septal flattening, and moderate RV dysfunction, all of which indicate right heart dysfunction on the basis of increased pulmonary arterial afterload. Most notably, there are several features suggesting significant PVD including a midsystolic notch profile in the RVOT, very short RVOT acceleration time, and predominant systolic septal flattening.\(^{14,16,17}\) Notably, transmitral Doppler shows an impaired-relaxation pattern, implying a normal or at most mildly elevated left atrial pressure.

Based on the above assessment, we can conclude that this patient has developed significant PVD secondary to chronic left heart congestion and now has a predominantly “right sided” phenotype with RV enlargement and RV dysfunction rather than classic signs or symptoms of left heart congestion. This is a more complex situation, where the PH is not simply a marker of high left atrial pressure or high cardiac output, but instead is of major hemodynamic import with manifest and clinically significant right heart dysfunction. This patient would be at much higher risk for adverse events with renal transplantation than the patient in Case 1, and likely would not be a candidate without addressing the manifest PVD. Chronic thromboembolic disease must also be excluded by ventilation-perfusion scintigraphy. Certainly, invasive hemodynamic assessment is warranted prior to consideration of elective surgery.

**DISCUSSION**

PH in CKD patients is associated with a varied pathophysiology, of which 3 discrete phenotypes are illustrated in the cases above. In clinical practice, there is often considerable overlap between features of each of the phenotypes described, and the purpose of this review is not to describe every scenario of patients with CKD and PH. In addition, there are rare cases of idiopathic PAH or connective tissue disease-associated PAH with associated CKD, but the physiology of these patients is typically driven primarily by PVD more so than pathophysiologic features unique to CKD. Indeed, some features are common to many patients with PH associated with CKD, including impaired salt and water handling, systemic hypertension, LV diastolic dysfunction, and left heart congestion.

In addition, patients with CKD and in particular those with long-standing diabetes and hemodialysis patients often develop a diffuse arteriosclerotic process involving large arteries including conduit pulmonary arteries, leading to increased arterial stiffness and diminished arterial compliance, which has been associated with adverse cardiovascular mortality.\(^{18,19}\)

Some CKD patients may also develop large stroke volumes and high cardiac output syndromes secondary to long-standing systemic shunts such as large dialysis AV fistulas. Although there is debate as to whether an AV fistula alone can lead to PH, it is clear from clinical observation and physiologic rationale (mean PA pressure = cardiac output * PVR + left atrial pressure) that coupling an inappropriately high cardiac output with a noncompliant, hypertrophied left heart will lead to left heart congestion, with PH being an inevitable consequence.\(^{20-22}\)

Lastly, patients with chronic left heart congestion can develop significant PVD, which may be severe enough to manifest as a clinical syndrome similar to PAH, particularly when right heart dysfunction results. Noninvasive assessment using history, physical examination, and an echo-Doppler examination forms the cornerstone of the initial evaluation of patients with CKD and suspected PH, not just because these are typically the first tests obtained, but also because much information can be gleaned from these initial tests that can guide subsequent invasive evaluations.

At the bedside, using blood pressure response to Valsalva maneuver can provide a simple estimation of elevated left atrial pressure and provide clues in the clinic to the hemodynamic basis of PH.\(^{15}\) Similarly, a simple echo-Doppler scoring system can help to differentiate a pulmonary vascular from a pulmonary venous etiology of PH.\(^{14}\) In CKD patients, the PH clinician must take this assessment a step further in that many if not most patients with CKD will have some stigmata of left heart disease on physical examination or echo-Doppler assessment.

The keys to noninvasive assessment of PH in these patients rest in the assessment of RV structure and function, to evaluate for high cardiac output syndromes, and to evaluate carefully for evidence of elevated PVR using a thorough assessment of the pulsed wave Doppler signal in the RVOT.\(^{14,23}\) Using this type of comprehensive physical examination and echo-Doppler assessment should provide the PH clinician with an overall impression of the hemodynamic basis of PH in the majority of patients presenting with dyspnea even prior to cardiac catheterization.

**References**

Hemodynamic Evaluation of Pulmonary Hypertension in Chronic Kidney Disease

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Chronic kidney disease (CKD) is a common condition and its prevalence is increasing.\textsuperscript{1,2} Likewise, the number of patients reaching end-stage renal disease (ESRD) continues to rise. In the United States in 2010, there were 413,275 patients on dialysis and 179,361 patients with a functioning renal transplant, bringing the rate of prevalent ESRD cases to 1752 per million population.\textsuperscript{2} Pulmonary hypertension (PH) is a commonly encountered comorbidity of patients with CKD and those who have progressed to ESRD. Although the true prevalence of PH in these populations is unknown, several small, single-center analyses using varied cutoffs for echocardiographically estimated pulmonary pressures have reported estimates as high as 56%.\textsuperscript{3,7}

The factors that likely contribute to the development of PH in ESRD are numerous and have been well described in a recent review by Kawar et al.\textsuperscript{5} These include persistent passive congestion from volume overload, decreased left ventricular compliance and/or systolic dysfunction, endothelial dysfunction, anemia, metabolic and hormonal derangements leading to pulmonary vasoconstriction, and the long-term effects of arteriovenous (AV) fistulas. While the latter’s contribution to the development of PH remains controversial, it is clear that in the right scenario, an AV shunt can cause high output heart failure.\textsuperscript{8} Creation of a systemic AV shunt leads to an increased cardiac output (CO) by several mechanisms. First, it decreases total peripheral resistance, leading to increased venous return to the right heart. This increase in preload leads to enhanced stroke volume via the Starling mechanism. Also, the reduced peripheral resistance activates sympathetic cardiovascular reflexes, increasing both heart rate and contractility. These combined mechanisms contribute to CO augmentation and increase the work done by both ventricles.\textsuperscript{9,10} The severity appears related to size of the shunt.\textsuperscript{11} Lastly, AV shunts may also increase total blood volume, which further increases preload.\textsuperscript{12}

Patients with already stiff ventricles may have difficulty accommodating the increased preload, and the increased workload may lead to more maladaptive hypertrophy over time.\textsuperscript{13} More recently, Paneni and colleagues compared echo parameters of right ventricular (RV) systolic and diastolic function in controls, patients undergoing peritoneal dialysis (PD), and those undergoing hemodialysis via radial or brachial AV fistulas. When adjusted for confounding factors, patients with an AV fistula had an increased risk of RV dysfunction when compared to the PD group (OR 6.3; \textit{P}<0.001).\textsuperscript{14}

Despite advances in noninvasive imaging, full hemodynamic characterization of PH requires invasively determined hemodynamics. Pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) requires normal left sided filling pressures (pulmonary capillary wedge pressure [PCWP] \textless 15 mm Hg) in addition to the elevated mean pulmonary arterial pressure (MPAP). Group 1 PAH is rare, with an overall prevalence estimated at 6.6 cases per million.\textsuperscript{15} In keeping, Group 1 PAH is also rare in patients with ESRD. WHO Group 2 PH, ie, PH secondary to left heart disease, is diagnosed when the PCWP is \textgreater 15 mm Hg. It is the most common cause of PH worldwide,\textsuperscript{16,17} and is also the most common cause of PH in the ESRD population. WHO Group 2 PH can be further subcategorized. “Passive” PH is usually defined as PCWP \textgreater 15 mm Hg but a normal transpulmonary gradient (TPG) \textless 12-15 mm Hg and/or pulmonary vascular resistance (PVR) \textless 3 Wood units. Those with an elevated TPG >12-15 mm Hg and/or PVR \textgreater 3 Wood units have been referred to as “mixed,” “reactive,” or “out of proportion” PH in the literature as there is no consensus terminology.

The aim of this review is to provide an overview of the hemodynamic assessment of patients with PH and CKD, with a particular focus on renal transplantation. We will consider 3 cases to illustrate these points, with the catheterization data serving as the invasive hemodynamic follow-up information for the same subjects discussed in the companion article by Dr Raina. As such, the hemodynamic information should dovetail with the corresponding echo-Doppler data discussed in the noninvasive article.

\textbf{CASE 1}

Initial review of the patient’s hemodynamic report (Table 1) suggests a diagnosis of heart failure with preserved ejection fraction (HFrEF) with mixed PH. Even without the hemodynamic

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Key Words—chronic kidney disease, end-stage renal disease, hemodynamics, pulmonary hypertension, renal transplantation

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Disclosures: The authors did not provide disclosures.
assessment, it should be noted that the patient’s clinical characteristics suggest pulmonary venous hypertension (PVH) rather than WHO Group 1 PAH. Features of the metabolic syndrome, as seen in this patient, are more commonly associated with PVH (ie, HFpEF)\textsuperscript{18} as is older age and associated renal insufficiency.\textsuperscript{19}

In this case, the PCWP value is reported to be mildly elevated, but notice the discrepancy between the PCWP and the more markedly elevated left ventricular end diastolic pressure (LVEDP), obtained during simultaneous left heart catheterization. Discrepancy between the PCWP and the LVEDP has been reported previously; however, more recently it has been suggested that a large portion of this difference may be explained by operators reporting the software-generated or digitized “mean” PCWP values across the respiratory cycle rather than that measured manually at end expiration.\textsuperscript{20,21} This is particularly important in situations where swings in pleural pressure are more exaggerated, as is the case in the obese and in patients with significant lung disease (Figure 1). Although not present in this case, incomplete balloon occlusion of the pulmonary artery can lead to significant overestimation of the PCWP—ie, pulmonary artery pressures blend into the PCWP waveform (Figure 2)—leading to hemodynamic misclassification of PH. When there is a question as to the accuracy of the PCWP, proceduralists should confirm the PCWP position by checking the oxygen saturation to verify that the sample is consistent with oxygenated, pulmonary venous blood (PCWP saturation).

The patient in this case has many symptoms of left sided heart failure

<table>
<thead>
<tr>
<th>Table 1. Initial Hemodynamics</th>
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<tbody>
<tr>
<td>Heart rate (bpm)</td>
</tr>
<tr>
<td>64</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
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<tr>
<td>Pulmonary pressures – systolic/diastolic (mm Hg)</td>
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<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
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<td>Transpulmonary gradient (mm Hg)</td>
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<td>DPAP-PCWP gradient (mm Hg)</td>
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<td>Cardiac output (L/min)</td>
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<td>Cardiac index (L/min/m2)</td>
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<tr>
<td>PVR (Wood units)</td>
</tr>
<tr>
<td>SVR (Wood units)</td>
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</table>

*Note discrepancy between PCWP and LVEDP. This difference suggests an error in the hemodynamic recordings (see text). Transpulmonary gradient, diastolic gradient, and pulmonary vascular resistance values using the LVEDP are shown in parentheses.

Figure 1. Marked respiratory variation is seen on both tracings: pulmonary capillary wedge pressure (PCWP, upper panel) and pulmonary artery pressure (PAP, lower panel). Digitized mean PCWP across the respiratory cycle underestimates the true wedge pressure at end expiration. Using the underestimated PCWP in this case leads to an overestimation of PVR. The correct diagnosis is WHO Group 2 pulmonary hypertension.
(orthopnea, paroxysmal nocturnal
dyspnea [PND], pleural effusions), sug-
gestting the mildly elevated PCWP may
be inaccurate. Moreover, the echo-
Doppler information presented in the
companion article by Dr Raina strongly
suggests markedly elevated left heart
filling pressures and a PVR that is
normal. By combining the information
from echo-Doppler imaging with the
hemodynamics, the clinician has a
heightened sense of what the hemody-
namics “should” be, thus making it more
likely that pitfalls in the hemodynamic
assessment (as seen here) are easily iden-
tified and avoided. Using the LVEDP
instead of PCWP in the PVR calcu-
lation yields a value <3 Wood units,
supporting the notion that a large
portion of the PH is due to left heart
failure, passive congestion, and normal to
high CO.

Although it has been demonstrated
that an elevated TPG (and “mixed” PH)
portends a worse prognosis in heart
failure,\textsuperscript{22} it is important to remember
that factors other than pulmonary vas-
cular remodeling affect this parameter.
Elevations in left atrial pressure directly
affect the TPG. As pressures in the left
atrium increase, this pressure is passively
transmitted back to the pulmonary vas-
culature, resulting in elevation of the
diastolic pulmonary artery pressure
(DPAP). However, this increased venous
pressure also leads to more pulmonary
vascular stiffness (or lower vascular com-
pliance) than one would predict based on
the PVR alone.\textsuperscript{23} The lower compliance
leads to enhanced pulmonary arterial
wave reflections, which raise the systolic
pulmonary artery pressure (SPAP) and
MPAP, and in turn the TPG. PVR is
also raised by these effects, given TPG is
in the numerator of its calculation. Both
parameters may also be affected by CO
as elegantly described by Naeije and col-
leagues.\textsuperscript{24} Importantly, the enhanced
pulsatile loading that serves to amplify
the SPAP and MPAP does not affect
the DPAP. Hence, emerging evidence
suggests that the DPAP to PCWP gra-
dient may be a better indicator of
pulmonary vascular remodeling\textsuperscript{24,25} and
how “proportionate” any degree of
MPAP elevation is relative to left atrial
pressure.\textsuperscript{26-29}

In this patient, the correct measure of
left heart filling pressure was 26 mm Hg
(in this case, from LVEDP), and thus,
correctly calculated PVR was only 2.3
Wood units. Further inspection of the
hemodynamics reveals a relatively low
ratio of right to left heart filling pressure
(right atrial pressure [RAP]/LVEDP,
0.54) and PVR/systemic vascular resis-
tance (SVR) ratio (0.17), further
supporting a relatively “pure” case of
PVH, or PH related to left heart con-
gen. In HFpEF patients as shown in this
case, renal transplantation should allow

\begin{figure}
\centering
\includegraphics[width=\textwidth]{inadequate_pcwp}
\caption{Upper panel is an example of tracing recorded during inadequate pulmonary capillary wedge pressure (PCWP) occlusion. Lower panel
is from the same patient with proper wedging, confirmed by PCWP oxygen saturation. In this case, the patient would have been diagnosed with
WHO Group 2 pulmonary hypertension if the inadequate PCWP tracing was used, although WHO Group 1 pulmonary arterial hypertension was
the correct diagnosis.}
\end{figure}
for better volume regulation and systemic blood pressure control, which are the mainstays of current therapy. One small, retrospective study has even suggested improvements in both systolic and diastolic function after renal transplantation along with improvements in parameters of left ventricular remodeling and reduction in echo-estimated pulmonary pressures.30

This patient’s volume status was optimized and ultimately underwent renal transplantation. Post-transplant the patient did quite well with robust improvements in exercise tolerance and had no diuretic requirement.

CASE 2
The patient’s hemodynamics (Table 1) are consistent with high output heart failure leading to left heart congestion and passive PH, as suggested by the imaging findings discussed in the companion article by Dr Raina. The right heart catheterization (RHC) data further reveal that the PVR is normal, as are the RAP/pulmonary artery wedge pressure (PAWP) and PVR/SVR ratio. The most obvious culprit is his persistent functioning left upper extremity AV fistula, which was not taken down after transplantation. An intracardiac oximetry run was negative for an intracardiac shunt, although the oxygen saturation in the superior vena cava (SVC) was higher than his pulmonary artery saturation. The “step-down” in saturation from the SVC to pulmonary artery is supportive of a shunt in the upper extremity, as typically the SVC saturation is lower due to cerebral oxygen extraction. Repeating hemodynamics during compression of the fistula is often helpful in determining the contribution to overall output.8,9 Although some have argued that a shunt output to CO ratio of more than 30% should raise concern, it is likely that no “set” amount of flow through an AV fistula clearly defines a range that is pathologic.8 Instead, the hemodynamic and clinical significance of any given shunt relates to the interaction between the size of the shunt and the degree to which the heart can accommodate the extra venous return. A patient with severe hypertensive heart disease and diastolic dysfunction may be highly intolerant to the excess flow provided via an AV fistula, whereas a patient without structural heart disease may accommodate a very large shunt without untoward clinical or hemodynamic effects. In this case, 1 minute of manual fistula occlusion led to a 2-liter reduction in the CO, and thus 2 liters of shunt flow at rest (not shown in Table 1). Taking all factors of this case into consideration, the patient was referred for surgical ligation of the AV fistula.

Following closure of the AV fistula, the patient’s symptoms resolved. Repeat RHC revealed essentially normal hemodynamics with a right atrium 4 mm Hg, MPAP 20 mm Hg, PCWP 11 mm Hg, and CO 5.9 L/min (index 2.8 L/min/m²).

CASE 3
Review of the initial hemodynamic data (Table 1) is consistent with HFpEF with mixed PH. These findings are consistent with the patient’s echo-Doppler examination discussed in the companion article by Dr Raina, which showed evidence of both left heart congestion and RV morphologic and Doppler evidence that strongly suggested an increased PVR. His TPG is quite elevated in comparison to the mildly elevated PCWP, as is the DPAP-PCWP gradient. Even with the open fistula, his CO is in the “normal” range, consistent with restricted pulmonary blood flow via afterload-dependent RV dysfunction. A much larger proportion of this patient’s PH is arising from pulmonary vascular disease than was observed in the patients highlighted in cases 1 and 2. The patient was lost to follow-up and returned a year later for a repeat evaluation (Table 2). There has been an interval worsening of hemodynamics. CO has fallen along with an increase in pulmonary pressures. The PVR/SVR ratio is close to 0.5, an indication of more severe pulmonary vascular disease. RAP and PCWP are both elevated and almost equal, with a ratio near 1, a finding associated with higher PVR, RV dysfunction, and worse outcomes in heart failure.31 Occlusion of the AV fistula lowered CO (Table 2) as expected, but right and left heart congestion did not improve, nor did the pulmonary pressures. The PVR actually increased, which reflects a flow-related derecruitment of the pulmonary circulation. These hemodynamic findings were supported by repeat echocardiogram showing more marked RV dilation and lower tricuspid annular plane systolic excursion (TAPSE). Given the high-risk features of this case, he was not deemed a candidate for renal transplantation. Although the benefits of such therapy have not been evaluated systematically in large randomized trials, phosphodiesterase 5 inhibitor treatment might be beneficial in this more well defined HFpEF-PH phenotype and may

Table 2. Case 3 Repeat Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>AV fistula compression</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Pulmonary pressures – systolic/diastolic (mean) (mm Hg)</td>
<td>119/45 (70)</td>
<td>118/43 (69)</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Transpulmonary gradient (mm Hg)</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>DPAP-PCWP gradient (mm Hg)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.1</td>
<td>2.3</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>7.6</td>
<td>9.0</td>
</tr>
<tr>
<td>SVR (Wood units)</td>
<td>16.2</td>
<td>17.1</td>
</tr>
</tbody>
</table>
be useful to test for reversibility of the PH.32 Caution should be used, however, given the negative results of the RELAX study, which enrolled a more heterogeneous HFpEF population.33 Moreover, in relation to this case, pharmacologic lowering of the PVR here may lead to an increase in pulmonary blood flow, and in turn lead to worsening left heart congestion. Thus, caution must be exercised in treating pulmonary vascular disease in this setting, particularly recognizing that the AV fistula represents an additional flow reservoir that may be more fully “appreciated” clinically in this patient once the PVR is lowered.

DISCUSSION
There are little existing data to guide the clinician when considering the risk associated with renal transplantation in individuals with PH. Although one study has suggested increased post-transplant mortality in patients with a right ventricular systolic pressure (RVSP) >50 mm Hg, the retrospective nature, small number of patients (and deaths), and lack of adjustment for comorbid conditions make it difficult to draw meaningful conclusions from the data.34 It is curious that despite the fact that some 30%-50% of patients with ESRD have PH, patient and renal allograft survival at most transplant centers is outstanding. This observation suggests that PH itself is not the direct causal link to changes in outcome post renal transplant, or that factors that contribute to PH in ESRD are positively impacted by renal transplantation. It is also important to note that in PAH, pulmonary pressures alone are not robust predictors of survival35,36; rather, prognosis is more closely related to RV dysfunction.37-40 RV function is also a strong predictor of prognosis in left heart failure.41,42 Therefore, measures of RV function and the integration of RV function with RV afterload (ie, PVR) are likely the best indicators of prognosis in patients being considered for renal transplantation.

CONCLUSION
In summary, PH is common in the CKD and ESRD disease populations. Proper hemodynamic assessment along with noninvasive imaging studies should be used in concert when evaluating a PH patient. These techniques can give important insight into the contributions of volume overload, systolic and diastolic dysfunction, and CO to PH as well as the degree of pulmonary vascular disease and RV dysfunction. Elevated pulmonary pressures alone should not necessarily exclude a patient from renal transplantation, especially when RV function is well preserved.


The Challenging Spectrum of PH in Liver and Kidney Transplantation Patients

On August 16, 2013, a group of physicians with clinical expertise related to management of pulmonary hypertension (PH) patients who are undergoing evaluation for or having liver or kidney transplantation was convened by telephone to discuss this challenging topic. These complex patients represent a spectrum of clinical types of PH and require complete evaluations utilizing a team-oriented and multidisciplinary approach to ensure appropriate treatment and safe transplantation. Facilitated by the guest editors of this issue, Charles Burger, MD, and Paul Forfia, MD, discussants included Michael Krowka, MD, Professor of Medicine, Pulmonary Division, Mayo Clinic, Rochester, Minnesota; José Díaz-Gómez, MD, Medical Director-ICU, Departments of Anesthesiology and Critical Care, Mayo Clinic, Jacksonville, Florida; Anna Hemnes, MD, Assistant Professor, Assistant Director, Pulmonary Vascular Disease Program Vanderbilt University Medical Center, Nashville, Tennessee; and Michael Mathier, MD, Assistant Professor of Medicine, Director, Pulmonary Hypertension Program, and Associate Director, Cardiovascular Fellowship Program of the University of Pittsburgh Medical Center.

Dr Burger: One of the issues that has come up fairly regularly in addressing hepatic cirrhosis patients who are being considered for liver transplant has been those patients who progress with their liver disease and have what we would consider marginal hemodynamic profiles for purposes of clearing them for a safe transplant. From a personal perspective, I struggle with that patient. In the interactions with the hepatologists and my transplant colleagues, I often ask, “Is it appropriate to move ahead with the transplant, despite the fact that we don’t have the hemodynamic criteria exactly where we might prefer it to be?” I would ask Dr. Krowka to weigh in on this clinical scenario, which I’m sure he faces on a regular basis.

Dr Krowka: Well, it is a problem. And the main problem is that of the individuals that have pulmonary artery hypertension complicating their liver disease. Most liver transplant centers that I’m aware of do screen for pulmonary hypertension with echocardiography. And centers do have their own criteria for who goes on to right heart catheterization. As you know, there are criteria that exist now to allow patients to have a higher priority for liver transplant, as long as their treatment for the portopulmonary hypertension, as we know it, reaches a certain satisfactory level in terms of measuring mean pulmonary artery pressure and pulmonary vascular resistance. We do run into these individuals that, despite our treatment, they are borderline in terms of satisfying these acceptable criteria. A common problem that we’ve run into is that a patient will be treated for their portopulmonary hypertension with any one of a variety of pulmonary vasodilator options and their mean pulmonary artery pressure remains above this acceptable cutoff of 35 mm Hg, yet their pulmonary vascular resistance has markedly improved and their cardiac output has markedly improved. So what do we advise for these individuals? In my experience, this is where the echocardiography comes into play. If we have seen changes where the right ventricle is now significantly improved, with normal size and normal function, I am much more comfortable letting those patients go onto liver transplant. Whether or not they’ll get a higher priority for transplant or not, I’m a little more reassured that they can at least get through the procedure. I do believe that the individuals that have normalized their right ventricle with treatment have the greatest likelihood of coming off pulmonary vasodilator after a successful liver transplant.

Dr Forfia: What’s interesting about the way that the mean pulmonary pressure of 35 cutoff is utilized in real life is that the resistance aspect of the equation is ignored. And actually in the seminal paper (Krowka MJ, Plevak DJ, Findlay JY, et al., Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation), there’s a unique methodology to evaluate the right ventricle, as you said, echocardiography, MRI, whatever it might be in a particular institution, how valid do you think the older transplant hemodynamic guidelines really are for 2013?

Dr Krowka: That’s an excellent point, because those hemodynamic criteria were based on two retrospective studies and databases several years ago. There’s been no prospective study to look at what would be the optimal or favorable hemodynamics overall. And I think that would be a very important contribution. So right now, we’re basing our judgments on data that’s close to ten years old and clinical experience in everyone’s individual centers.

Disclosures: Drs Burger, Forfia, Krowka, Díaz-Gómez, and Mathier indicated no conflicts. Dr Hemnes has disclosed current financial relationships with Pfizer, United Therapeutics, and Annameter.
transplantation. *Liver Transplantation,* 2000; 6 (4):443–450, in the patients with a mean pulmonary pressure between 35 and 50, only those with a PVR greater than 240 were at higher risk. And we’ve had this conversation with our own liver transplant team many times. And so to Mike’s point, when the patient has a mean pulmonary pressure that’s still elevated, but yet their PVR has normalized, it seems that the liver transplant community has not embraced that group of patients; those whose mean pulmonary pressure is still high but their PVR is low. In that paper, those with a mean PA pressure between 35 and 50 and a PVR less than 240 did well. Also, to underscore Mike’s point, if you have a PVR that’s less than 240 and normal RV size and function in the context of persistently elevated mean PA pressure, we do feel this is an optimized group where referral for liver transplant is reasonable.

Dr Krowka: You raise a very good point regarding educating the liver community regarding these observations. And I think that was noted in that paper. Perhaps we’ve not done as good a job as we could. We are in communication with the OPTN/UNOS liver and intestinal transplant committee to relook and possibly revise the Model for Endstage Liver Disease (MELD) exception criteria. I suspect the committee will want to see some supportive and/or prospective data. Unfortunately, we don’t have a good handle on that right now and we don’t have those data to show. But I would totally agree, our clinical experience has been favorable. Hopefully over time, we’ll be able to see this adjusted.

Dr Hemnes: I would echo that what I think we’re all getting around is that mean pulmonary artery pressure really doesn’t give you any particular information as to what the underlying pathology or pathobiology is. And if you understand what’s driving that increase in mean pulmonary artery pressure, then you can make a more informed decision about whether or not somebody is or is not suitable for liver transplantation or has unacceptable outcomes afterward. So I think use of mean pulmonary artery pressure as a sole decision maker for whether somebody can or cannot undergo liver transplantation may miss patients who could tolerate transplantation. That’s sort of how we approach it here, using hemodynamics and right ventricular function together to determine etiology of pulmonary hypertension and suitability for transplantation.

Dr Mathier: I’ll just expand on that in maybe the other direction. It’s not only what is driving the elevation in mean pulmonary pressure but, as has been pointed out, what effect has that pressure overload had on RV performance? And if the RV performance by our current technologies looks favorable, then I think that that has to be factored into a decision making process more than it often is.

Dr Burger: It just seems that there’s a general consensus among the participants that we haven’t perhaps pushed the envelope as much as we could in those whose PVRs have normalized with therapy. So I would just ask for the participants to comment on the additional component of assessing RV size and function. Is echocardiography adequate? Or are there other imaging modalities, in this particular setting, pre-liver transplant with portopulmonary hypertension, which you would favor?

Dr Diaz-Gómez: I would like to point out as a practicing anesthesiologist and intensivist that the current advances in transthoracic echocardiography for evaluation of patients with PPH facilitate a better assessment of the right ventricular function. For instance, I would like to highlight the article by Arkles et al. published in the blue journal in 2011 (Arkles JS, Alexander R, Opotowsky JO, et al. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. Am J Resp Crit Care 2011; 183:268-276) The authors described a method that actually provides a different insight of the interaction between the pulmonary circulation and the right heart function. Indeed, they aimed to assess the coupling effect between the two components: the right ventricular function and pulmonary vascular resistance. Thus, if the right ventricular outflow tract Doppler flow velocity envelope presents a notch, it means the patient has more severe vascular disease and right ventricular dysfunction. I think right now we have a better capability in the OR to assess this valuable hemodynamics evaluation with echocardiography, even in the postoperative period. Some patients will come to the OR and even they have borderline PAP readings. After the intubation, we can find with the TEE evaluation that the PAP are higher than expected. In this case we have the ability to provide adequate depth of anesthesia, acid base, and intravascular volume status. These are common causes of increased PAP readings. Subsequently, we can reassess the patient, and determine the best strategy to intervene further the increased PAP. In conclusion, I would probably put a lot of weight on perioperative echocardiography in the assessment of this patient population.

Dr Forfia: Mike, I just want to say that I did not call him ahead of time and ask him to say that. (laughter)

Dr Hemnes: I don’t believe you, Paul.

Dr Burger: Does anyone else have a comment on the best way to image? I would agree completely with Dr. Diaz-Gómez’s comment about the whole business of the coupling and certainly, you know, Dr. Forfia has made a point of this in many presentations. We can’t separate out each of these individual measurements in the hemodynamic profile from that of the right ventricle’s ability to handle the challenge of the re-perfused blood volume once the new liver is transplanted. That’s really the challenge!

Dr Mathier: I don’t know that I would say that I favor any kind of different approach, except that I think it’s worth emphasizing that we have to have as full an understanding of RV performance as possible. So that in many patients, echocardiography combined with
hemodynamics is adequate for that. But in some, when the echo windows aren’t acceptable, you may need to move onto MRI or you may need to rely more heavily on serial hemodynamic data. But I think the main take home point has to be that a really full understanding of right heart performance is what’s important. And how you get it is going to vary from patient to patient.

Dr Krowka: I agree and I think there is a lot to be learned by the evolving methods to look at that right ventricle. The sequential studies are very important. One group of patients that I’ve found that are very worrisome are those that have, just with a simple electrocardiogram, T-wave inversions in V1 through let’s say V4, V5. That tells me, everything else being all right, that there’s still a lot of stress and strain going on affecting that right ventricle. And we pay a lot of attention to the improvement in just the basic electrocardiogram to give us another piece of information that perhaps we’re taking some stress and strain off the right heart.

Dr Diaz-Gómez: I absolutely agree with you, Dr Krowka. I think we can maximize the understanding of the right ventricular function if we use wisely all the technology we have in place, starting with the EKG. I will add, for example, the utilization of continuous cardiac output monitoring and mixed venous saturation. The trend of the mixed venous saturation, or the limitation at the time of its interpretation in the setting of severe underlying hypoxemia is valid, as well. Other clinically used surrogates, such as lactate, are helpful guiding the management of patients with perioperative right ventricular failure. So if you have a patient who is improving his or her hyperlactatemia, the mixed venous is persistently better, and the hemodynamics looks good, that would suffice to have a good information about the patient’s current status, even if you have limited echo windows and you cannot have a very desirable echocardiographic assessment.

Dr Hennes: The only thing that I would add is that although the echo and MRI may be useful, a lot of times at the bedside you can even tell when you’ve made an improvement. As you all know, of course, you can look at right atrial pressure, feel for RV heave, and those can be early and relatively reasonable predictors of hemodynamic response and RV function after changes in or addition of therapy for portopulmonary disease.

Dr Burger: So in that vein, what do the participants think is the best strategy for continued pharmacologic treatment after a successful orthotopic liver transplant? Both in that more immediate perioperative period and then beyond the hospitalization?

Dr Mathier: I’ll tell you what our practice is. It’s again variable from patient to patient. If I had a patient with portopulmonary hypertension who required intravenous epoprostenol to achieve the hemodynamic benchmarks we look for, I typically will continue that drug postoperatively, at least for a block of time that ranges from several weeks to several months, before I begin to reassess the patient’s need for the drug. That typically is a clinical assessment, followed by an echocardiogram. And if the signs are favorable that the drug can be at least weaned, I always start with a right heart catheterization to ensure that I know exactly what the hemodynamics are before I begin. If instead it’s a patient who had more modest portopulmonary hypertension and I was able to reach my hemodynamic benchmarks with a PDE-5 inhibitor alone, I’ll typically do something relatively similar. But depending on how the echocardiogram looks, I may or may not proceed with a hemodynamic assessment, if it really looks favorable for weaning or discontinuing that drug. So I try to individualize it according to the patient. I tend to not like the idea of removing PAH therapy in the immediate postoperative setting, unless there is a lot of difficulty with systemic hypotension or another indication to do so.

Dr Diaz-Gómez: I absolutely agree with that practice. Spending some time in the operating room, I would say that sometimes it’s easier for us to use nitric oxide in that setting. Although we have the capability of actually continuing with the face mask and nebulize it away in the postop period, I absolutely agree with the weaning has to be extremely cautious, especially during the first week. So sometimes we have used intravenous epoprostenol in the acute setting, if we don’t have favorable numbers. It may be after the TEE and the same. We will do the weaning the way you describe it. So I don’t think there is any unique way to do it. But probably, the most two popular alternatives that we have at this point is even IV epoprostenol or nitric oxide.

Dr Krowka: I would agree with Mike’s approach, also. It’s variable by individual. We proceed slowly. What I do like to do, regardless of the method that we’ve used to get them through, whether it’s IV preparations or oral medications, just before they’re dismissed from the hospital, I do get a baseline echo. We generally would bring them back at about 12 weeks for a reevaluation of their whole posttransplant status. I go very slowly with weaning them off of an IV preparation and an oral preparation. It may take weeks and months. Depending again on factors like what did that echo look like pretransplant with our successful management, if I did get to a normal RV size and function and everything looked good, I’m a little bit more comfortable that, well, maybe I can move a little more quickly, weeks after the transplant. But the other thing I’d like to stress is that when you think about this, this is one of the few times we potentially can cure, at least hemodynamically, pulmonary artery hypertension; what we know as portopulmonary hypertension. So there are folks that have severe hemodynamic impairment before their liver transplant; we treat them, get them through their transplant, and we can get them off of these medications at a certain point later on. And we see this sustained success. The echo looks almost normal, if not normal. We have essentially created a hemodynamic cure, at least in my opinion.

Dr Forfia: We set out to tackle pul-
monary hypertension in advanced liver disease, which it seems is the area with the most data, relatively speaking, compared to renal disease-associated PH. And, of course, it’s also the condition, endstage liver disease, where true group 1 disease is a significant complication of portal hypertension. Endstage renal disease, of course, is a different matter, where there’s a tremendous burden of left heart disease in the background, as well as heterogeneity of the hemodynamic presentation. There is also a paucity of data in the background to support treatment and management decisions. Nevertheless, there does exist a fear of the presence of pulmonary hypertension in patients with endstage renal disease in the context of transplant that I think we’ve all encountered. So, that sets up our first question for the panel. Which is, how do you approach a patient prior to renal transplant, whose been referred to you with evidence of pulmonary hypertension, on an echocardiogram? So we’ll start with that because this is, of course, by far the most common scenario that we all encounter.

Dr Mathier: I’ll tell you what we do. So as you pointed out, Paul, pulmonary hypertension in a patient with endstage renal disease is both common and complex. It can be on the basis of any number of factors, either individually or in combination. These folks often have a diastolic abnormality of the left heart, with elevated left heart filling pressures. They often have volume overload. They often have high cardiac output related to AV fistulas, or even in the absence of a large fistula. And they, at least some of the time, have pulmonary vascular disease. They also often have a comorbidity profile that can contribute to pulmonary vascular disease in an indirect way, whether that’s intrinsic lung disease or sleep apnea or something else. So it’s imperative in my mind that no assumptions be made when you have a patient with advanced kidney disease, who has evidence of pulmonary hypertension on echo. Even if that echo is very convincing for its being a group 2 type of physiology, with a very large left atrium, hypertrophied ventricle, and Doppler profiles consistent with significant diastolic dysfunction, I still think we’re obligated to perform a very careful hemodynamic study. I often insist that this be both a right and left heart catheterization, because I think it’s really imperative that we understand left heart filling pressure without any uncertainty related to whether the wedge pressure is accurate or not. And so it’s really become my routine to do very careful hemodynamic assessment as the next step.

Dr Krowka: I totally agree with that. I think we’ve probably been lax in our kidney transplant program, in terms of evaluating these patients beyond echocardiography. We are trying to change our algorithm at this point, because there are so many other subtleties that do occur; and I would also agree, I think it’s unusual to see pure pulmonary artery hypertension in these folks. It does occur. More often than not, we are taking people off of pulmonary vasodilator medications when they’re referred to us, because I think they’re being mistreated in that sense. The other comment I would make, and the issue that’s come up from our kidney specialists on several occasions, has been what is the real impact of these large AV fistulas that have been placed? How much of their contribution is really causing a lot of difficulties? And again, I think that’s where it’s very important to proceed to a good hemodynamic assessment by right and left heart catheterization, so we fully understand what’s going on in terms of the possible back pressure that’s going to affect kidney outflow and these other cardiac issues.

Dr Mathier: Do any of you guys ask that your catheterizers do temporary occlusion of the fistula to try to assess its impact on either flow or pressure?

Dr Hennes: Yes, I was just going to bring that up. We routinely do that, regardless of really the size of the fistula. Although lately, it seems like many of the patients who have been referred to us have really large, longstanding fistulae. But yes, specifically when we talk about a careful hemodynamic assessment in this population, I agree a left heart catheterization is almost always useful and informative, in addition to the right heart catheterization. But we usually do it with and without occlusion of the fistula.

Dr Mathier: Is there a protocol for how long you occlude?

Dr Hennes: I don’t think you need to occlude for very long. We usually do it for a few minutes, at most.

Dr Forfia: We do the same thing. I do the caths myself. And we’ll do baseline hemodynamics and then we’ll do a manual occlusion of the fistula, typically for two minutes, and repeat the hemodynamics. If I could also just share I think a clinical pearl, that after having now fairly extensive experience with dealing with fistula-associated dyspnea and pulmonary hypertension or heart failure, is the location of the fistula is very important in predicting its hemodynamic significance. If you really dig through the data from published literature, it’s fairly clear that proximal fistulas are much more common to do this. For example, in the upper extremity, it’s the brachial fistula, so it’s above the elbow where you’re much more likely to have a high flow. We’ve also seen this with the rare occasion of a fistula in the femoral artery-vein. But either way, it’s a proximal vessel. We have not seen very much in the way of high output with grafts, although that’s possible, or with fistulas that are at the level of the wrist. And, Anna also alluded to the fact of the duration of fistula, which is relevant. Because the longer that the fistula has been in, typically the larger it gets. And so when we see a brachial fistula that’s been in place for many years, that patient is the setup for a high output situation, where our pretest probability for a very high flow is quite high.

Dr Hennes: But, of course, the other thing to notice though is that pulmonary hypertension is common in people who are getting dialysis through a catheter and also a peritoneal dialysis. So, you know, the Israeli group has done a nice job of characterizing these patients and has suggested that endothelin or poor
Dr Burger: While I don’t disagree with the catheterization for the hemodynamic profile, almost all of these patients will have elevated left heart pressures. So the question is, what do you do with that information vis-à-vis transpulmonary gradient, diastolic pulmonary gradient, attempts to lower the left heart pressure and then see what happens to the hemodynamics?

Dr Mathier: Charlie, as you pointed out, these patients will nearly always have elevated left-sided filling pressure, but also, elevated right-sided filling pressures are common. I’ll try to give some feedback to the dialysis team and, you know, try to have them incorporate the hemodynamic data into how they set a dry weight and how the patient on their own works to manage their volume status. And then the other thing is that a lot of times these folks have very-difficult-to-control systemic hypertension and that will be directly influencing filling pressures. And so you can use the hemodynamic data to also advocate for a more aggressive approach to systemic blood pressure control. And those things can have a very substantial impact on pulmonary pressures. And I think they’re important, because without optimizing volume and systemic pressure, you’re not going to really stand much of a chance of improving the pulmonary pressures.

Dr Forfia: If I may jump in just for a second and go back to our first question, which was how to approach the patient prior to renal transplant, with evidence of PH on an echo. Mike, you made a great point about how you’re going to have a low threshold to refer that patient for a right heart catheterization. But if I could get you guys to comment briefly on how you use the echo to start to make distinctions between the types of pulmonary hypertension prior to invasive assessment. So what does one echo in a patient with PH and endstage renal disease look like versus another? For example, a pure diastolic heart failure patient versus a patient who seems to have evidence of pulmonary vascular disease, How do you make those distinctions?

Dr Krowka: At our institution, I think the echoes have been very helpful in the sense that if we look at, for example, the left atrial volume index, if that’s huge, that certainly gives us more of a clue, along with these other indirect measures of diastolic dysfunction that our echo folks give us, you know, would certainly lean more toward the fact that, alright, we’re going to probably be dealing with the volume and the diastolic dysfunction issue here, rather than, you know, a pulmonary artery hypertension scenario, which again is probably uncommon. I think the timing of when some of these studies are done is very important. So the nephrologist will call and say, “Well, I have an echo. Take a look at this.” Well, it’s done the day before or the morning of dialysis. Getting data after the dialysis is probably where we’ve gone now, rather than trying to select a random set of measurements from echocardiography to decide what our next step is going to be.

Dr Forfia: If I could underscore that a similar approach in the use of echo in endstage liver disease can be advocated in patients with endstage renal disease. So specifically, Mike Mathier and Mike Krowka had emphasized the importance of looking at right ventricular size and function in the context of pulmonary hypertension in endstage liver disease, I’d like to hear what everyone has to say about how they incorporate right ventricular size and function information into the echocardiogram read in the patient prior to renal transplant.

Dr Burger: I think it makes a big difference. I mean, just yesterday, we saw two end-stage renal patients with elevated right heart pressures on echocardiogram. One had the classic grade 3 restrictive left ventricular filling on echocardiogram, with all of the signs and symptoms of restrictive cardiomyopathy in the setting in volume overload. The other patient, had elevated right heart pressures but the diastolic relaxation didn’t look bad. The E/e’ ratio also looked okay. The pressures were only mildly elevated. The RV looked pristine. And so that creates a situation where one has to use judgment about next steps. In the second case, we made every effort to go over all the things that have been mentioned about maximizing the impact of the systemic blood pressure, normalizing the intra-vascular volume, making sure that they’re compliant with sodium and fluid restriction, wearing their oxygen, etc., before moving ahead with a catheterization. Because even if they moved quickly to renal transplant, I think that patient’s ability to survive and do very well with the transplant is quite good. I think all of those things come into play for your judgment in this regard. And I think you’re exactly right, Paul, the integrity of the right ventricle is very important.

Dr Diaz-Gómez: A quick comment about a relatively common condition as patients with advanced chronic kidney disease may have dual pathology, due to high prevalence of systolic as well as diastolic cardiac dysfunction. In addition, the presence of the cardiac dysfunction does not automatically exclude coexistence with pulmonary arterial hypertension. So I think we probably need to be more rigorous and precise with the echocardiography assessment in comparison with the liver transplant patient population. So, just keep in mind, that both diastolic and systolic dysfunction can be present in patients with end stage kidney disease.

Dr Mathier: I’d like to agree with that. We often see patients who have, in this setting on hemodynamic study, elevated left heart filling pressures, but very high transpulmonary gradients and very high pulmonary vascular resistance, or at least moderately high, in excess of 5 or 6 units. And so you’re left with one of these mixed profiles and they’re very challenging in terms of really knowing how to attack it. And also, I’d go back to something that I think Paul said right at the beginning of the discussion of the advanced kidney disease patient. We’re not really 100 percent sure what the
I completely agree with what you're saying. And I think it's important that we really need to try to get a better handle on through careful study in the near term. Because it's a very common clinical scenario, at least in what we've been seeing.

**Dr Hemnes:** I completely agree with you. And the most common scenario of the patients referred to us is one of the patients found pulmonary hypertension on an echo and a person who has endstage renal disease who is being evaluated for a transplant, can they survive transplant? And I feel like the data isn't out there to really know definitively what the answer is to that question. We have our own personal practice patterns and I tend to rely on the RV function, what I think the underlying etiology of the pulmonary hypertension is, etc. But in the absence of any data, that's a very hard question to answer right now.

**Dr Forfia:** I would say that we can use some epidemiologic data to get at some of these answers. It's estimated that 30 to 50 percent of patients at the time of renal transplant have pulmonary hypertension. And I would say it's closer to 50. In that context, patient survival and renal allograft survival at most renal transplant centers is outstanding. And so that's interesting. What that suggests to me is that in many of our patients with endstage renal disease who have pulmonary hypertension, the pulmonary hypertension itself is not what is conferring the risk. And that whatever is making up the pulmonary hypertension, which many of us feel is the combined effects of fluid overload, high cardiac output, and systemic hypertension, are actually significantly alleviated with renal transplant. So now, that is not to say that there is not a subset of patients with pulmonary hypertension and endstage renal disease where the PH is actually a real risk factor for perioperative outcome. With that in mind, I just have this last question, which I don't think will take very long to answer. And it is, who is the renal transplant patient who you would consider PH being a relative contraindication, or at least where PH therapy should be attempted prior to reevaluation for renal transplant? Which of these PH patients with endstage renal disease really gives you pause, where you're going to stop and really carefully delve into this and/or treat their PH, but not agree that they are ready to be listed for kidney transplant?

**Dr Mathier:** I would say high PVR and evidence of significant right heart dysfunction.

**Dr Krowka:** I would agree. That's where the hemodynamic right heart study really is crucial in these folks. And I would agree with that picture of who I'd be strongly concerned about.

**Dr Burger:** I would also add any strong risk factor for pulmonary arterial vasculopathy such as HIV or collagen vascular disease, that is something else that would make you think that the risk of actual pulmonary arterial hypertension is higher, in conjunction with any evidence that the RV is dilated or hypokinetic.

**Dr Hemnes:** I would agree with all of those things. And the only other sort of patient category that I'd add is that it's well-described that patients who have had multiple angioplasties of their fistulas are at risk for chronic thromboembolic pulmonary hypertension. So, a patient who's had multiple angioplasties and evidence for chronic thromboembolic disease also gives me pause.

**Dr Krowka:** I would like to also see some prospective data that characterizes who does have graft failure. What are those criteria for renal graft failure and what are the characteristics of those individuals hemodynamically that perhaps would shed some light on the dilemma.

**Dr Forfia:** Right. And I think that's the type of study that needs to be done. Because retrospective studies that cite evidence of pulmonary hypertension on an echo, and then without any further information, associate pretransplant pulmonary hypertension on an echo with transplant outcome, are quite problematic. Given that there is such a huge amount of collinearity between many of the comorbidities that the patients suffer from prerenal transplant and their PH. For example, their body mass index, their systemic hypertension, the size of their fistula, the duration of time on dialysis, the degree of left ventricular hypertrophy, the degree of left ventricular systolic and diastolic dysfunction. These factors cannot really be properly parsed out when someone is doing an association between PH and outcome post kidney transplant. So, it seems likely that PH has to a certain extent been blamed for less optimal outcomes when, in fact, more careful analysis may reveal that the PH itself was not the direct cause of adverse events in many of those patients.

**Dr Burger:** I'd like to thank the panelists for a very educational and informative discussion and for the time away from their busy days for participating.

**Dr Forfia:** Yes, I'd like to thank everyone, as well. And I feel it is worth emphasizing that our ability to assess pulmonary hypertension in any individual patient, pointed out from every member of the panel during this discussion, involved the assessment of varying hemodynamics in combination with an evaluation of right heart size and function. We agree that pairing pulmonary vascular load with right heart size and function is seemingly the best way to gain insight into the significance of pulmonary hypertension in any individual person.
Drug Interactions of Current Pulmonary Arterial Hypertension Therapies in Abdominal Organ Transplant Recipients

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The incidence of echo-derived pulmonary arterial hypertension (PAH) in patients undergoing renal or liver transplantation is reported as high as 30%-60% and 25%, respectively. Not all of these patients will continue to have the diagnosis of PAH or require treatment following the organ transplant. However, if therapy is warranted, the medical team will need to be mindful of the potential drug-drug interactions with the currently available agents to treat PAH and medications used following transplantation (immunosuppression, antifungal agents, etc). The 2 types of drug-drug interactions important to PAH medications and agents used following transplantation are pharmacokinetic or pharmacodynamic interactions. Pharmacokinetic drug interactions are those in which one or more medications interfere with the metabolism or clearance of another agent, leading to either an increase or decrease in plasma concentration. Pharmacodynamic interactions consist of the effect of the drug on the body, including adverse reactions, and may be enhanced when used in combination with other of medications.

At this time, the 3 different classes of drugs approved for the treatment of PAH are prostacyclin derivatives, endothelin antagonists (ERAs), and phosphodiesterase type 5 (PDE5) inhibitors. There are very few pharmacokinetic drug interactions encountered with epoprostenol, treprostinil, or iloprost. Treprostinil is substantially metabolized by the liver, mostly via the cytochrome (CYP) P450 2C8 enzymatic pathway, leading to the potential for an increase in treprostinil concentrations when combined with gemfibrozil or a decrease in treprostinil concentrations when given with rifampin. The main concern with prostacyclin derivatives is the risk of bleeding and interactions with medications that affect platelet aggregation.

Both commercially available ERAs are metabolized by the liver, but they have significantly different potentials for pharmacokinetic drug interactions. Bosentan’s elimination is dependent on hepatic metabolism via CYP3A4, CYP2C9, and CYP2C19. This drug is both a substrate and an inducer for these enzymatic pathways and therefore significantly increases its own metabolism with repeated administration, leading to a reduction in plasma concentrations. Combining bosentan with inhibitors of CYP enzymes often used in a transplant population like antifungal azoles (eg, voriconazole, itraconazole, posaconazole, ketoconazole), clarithromycin, erythromycin, protease inhibitors, and diltiazem may lead to an increase in plasma concentrations. Conversely, CYP inducers such as rifampin, phenytoin, and carbamazepine may cause a decrease in plasma concentrations.

Bosentan is also a substrate of the human organic anion transporting polypeptides (OATPs) OATP1B1 and OATP1B3, found in the liver, and is responsible for hepatic uptake of many drugs. Induction or inhibition of this transporter system will effectively alter the rate of metabolism and plasma concentration of drugs. Cyclosporine is an inhibitor of OATP1B1 and when combined with bosentan can result in a significant and potentially dangerous increase in plasma concentrations of bosentan, making the combination of these 2 drugs contraindicated. Clarithromycin and erythromycin are inhibitors of OATP1B1 and should be used with caution with bosentan.

Ambrisentan is metabolized via the liver by uridine diphosphate glucuronosyltransferases (UGTs). The CYA3A4 and 2C19 pathways are responsible for 20% or less of its metabolism, and since ambrisentan is only a substrate for these pathways, it does not interfere with its own metabolism or that of other drugs. As seen with bosentan, OATPs are involved in the hepatic uptake of ambrisentan and caution is advised when administering with agents that inhibit this pathway. A small study evaluating the effects of cyclosporine on ambrisentan pharmacokinetics revealed a marked elevation in ambrisentan plasma concentrations, accompanied by an increase in reported side effects such as hypotension and gastrointestinal complaints. Therefore, the dose of ambrisentan should not exceed 5 mg daily when prescribed in combination with cyclosporine.

Sildenafil and tadalafil are the PDE5 inhibitors currently used in the treatment of PAH. Both agents are metabolized via the CYP3A4 pathway and are subject to many drug-drug interactions by medications that either induce or inhibit this pathway. For example, when used in...
combination with bosentan, a CYP3A4 inducer, both sildenafil and tadalafil concentrations are decreased by about 50%. Drugs like phenytoin and rifampin may decrease the drug effectiveness due to an increase in clearance, whereas agents like cyclosporine, azoles, and clarithromycin may increase PDE5 inhibitors’ concentration and lead to more side effects. There is some evidence that sildenafil inhibits the OATP1B transporters and therefore may have more drug-drug interactions than tadalafil, which does not appear to affect these transporters.10

In the solid organ transplant, addition of therapy to treat PAH must be done with careful consideration of the current medical regimen and pharmacokinetic profiles of the currently available PAH medications. Close monitoring for side effects encountered with an increase in drug exposure and therefore a potential for an increase in vasodilation (hypotension, gastrointestinal effects, headache) or for a decrease in drug exposure and potentially worsening PAH symptoms (volume overload, edema, shortness of breath) is warranted.

References
Nutritional Assessment in Patients With Pulmonary Arterial Hypertension Facing Transplantation

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Obesity is epidemic in the United States,1,2 and a recent analysis of patients enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) demonstrated significantly more underweight (defined as body mass index [BMI] <18.5) and obese (defined as BMI >30) than age- and sex-matched controls from the National Health and Nutrition Examination Survey (NHANES).3 Specifically, idiopathic PAH (IPAH) and drugs and toxins-associated pulmonary arterial hypertension (PAH) were more likely to be obese, and those individuals with connective tissue disease-associated PAH and congenital heart disease-associated PAH were more likely to be underweight.4 These data suggest that clinicians treating patients with PAH are very likely to encounter patients who are obese or underweight. Historically, lung or heart-lung transplant has been a treatment option facing many of these patients with life-threatening right ventricular (RV) failure. With effective medical therapies for PAH, patients who might have died from RV failure may succumb to comorbidities instead,4 and subgroups of PAH patients with por-topulmonary hypertension present a growing population of potential abdominal organ transplant candidates.

The ideal approach to managing patients who are underweight or obese to optimize their candidacy for abdominal organ transplant is far from clear. There is a paucity of data regarding optimal nutritional strategies in patients with PAH; most of the guidance regarding nutritional screening in patients who are potential solid-organ transplant candidates is derived from the general transplant medical literature, which suggests that obesity and underweight affect post-transplant outcomes.5-8

To address the potential nutritional risks, dietitians often set goals that include maintaining the weight and lean muscle mass of patients with adequate nutritional status, promoting weight and muscle gain in underweight patients, and developing strategies for weight loss in obese individuals. The resulting goal-oriented diet and exercise plans are developed with the interdisciplinary care team, which includes dietitians along with active participation of physicians, nursing professionals, physical therapists/exercise physiologists, psychologists, and respiratory therapists. The process emphasizes promoting an overall healthy metabolism, which (for example) includes normalizing blood sugars and managing patients’ symptoms.9

While the assessment of patients is individualized, it generally begins with a calculation of BMI, assessment of pattern adiposity for those who are obese, measurement of lean muscle mass (eg, triceps skin fold and mid-arm muscle circumference), a detailed dietary intake, and a comprehensive assessment of laboratory values—emphasizing pre-albumin levels. Attempts to standardize some anthropometric assessments to determine lean muscle mass, such as biochemical impedance analysis and dual-energy x-ray absorptiometry (DEXA), have been hampered by the variable fluid status in patients with cirrhosis and renal failure. The importance of an overall clinical assessment of these chronically ill patients is recognized.9

When the initial assessment has been completed and compared with the eligibility criteria of a specific organ transplant program, a plan is often developed focusing on maintenance, repletion, or reduction in weight.7,10,11 The nutritional plan will likely focus on reaching a specific goal weight, determining the appropriate daily calorie, protein (and fluid) requirements, and thorough dietary counseling, which may include the review of adequate portion sizes, food and beverage choices, meal pattern/consistency, and the importance of staying active. The success of the plan will likely be affected by the patient’s severity of illness, commitment to the plan, and the degree of involvement of the interdisciplinary team. As one might expect, a patient’s personality and/or changing illness may necessitate changes to the initial nutritional plan, making flexibility and adaptation other key ingredients to success. The safety and efficacy of weight-loss medications, especially in view of the data regarding certain anorexigens and the risk in development of PAH and of weight-loss surgery have yet to be determined. This does not exclude consideration of such approaches in the future as the indications for bariatric surgery in patients with PAH continues to evolve.12

In summary, an increasing number of obese and underweight patients with PAH are likely to require abdominal organ transplant. Optimizing their weight and nutritional status may be
Nutritional assessment questions for evaluating patients’ readiness for transplant

1. Is BMI within organ-specific transplant guidelines? Underweight or obesity concerns must be addressed with a goal-oriented plan.

2. If patient is overweight/obese, where is the extra body fat distributed? Pattern of fat distribution (eg, gluteo-femoral vs android/central) has implications regarding surgical and post-transplant risk.

3. Is pre-albumin normal? Low pre-albumin may adversely affect healing potential after transplantation.

4. Is this patient compliant with dietary recommendations (eg, low sodium)? Adherence may affect post-transplant outcomes.

5. Is blood sugar control optimal (eg, normal HgbA1C)? This may affect healing after transplantation. It may also amplify the effects that post-transplant medications will have on pretransplant hyperglycemia.

6. Is there adequate lean muscle mass? Assess if patient is physically conditioned and if protein intake is adequate.

7. Is the patient experiencing malabsorption that adversely affects optimal vitamin and calorie intake?

8. Are there any eating issues/symptoms such as dyspnea while eating, nausea, vomiting, diarrhea, difficulty chewing or swallowing that affect nutrition and potentially post-transplant medications?

Nutritional assessment questions for evaluating patients’ readiness for transplant

required for them to become, or remain, transplant candidates. A set of nutrition evaluation questions are relevant to a majority of these patients (see box), although the points of emphasis and specific BMI or metabolic goals may vary based on the proposed type of organ transplant and individual transplant program criteria. A cooperative and comprehensive interdisciplinary approach with early intervention is an achievable goal and will likely optimize the outcomes for patients with PAH undergoing transplantation.

References


Significant progress has been made in PAH treatment over the past 2 decades, yet patient morbidity and mortality remain high.1 There is limited information on the long-term effects of PAH-specific therapies, and many patients continue to experience death, hospitalizations, and the need for additional therapies.1,2

Now is the time for a new perspective in PAH. Experts are calling for future PAH studies to deliver data on the long-term effect of therapy on clinical outcomes, such as hospitalizations and mortality.1-3 Actelion is committed to investigating this evolving perspective in PAH.

Despite advances, patients’ long-term outcomes remain poor


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Survival observed over periods from 1981-1988 and 1982-2006, respectively.
Chronic Thromboembolic Pulmonary Hypertension

Scan for it, for the chance to surgically cure it.

- CTEPH is designated as WHO Group 4 and is an under-recognized type of PH\(^1\)\(^,\)\(^2\)
- Estimates suggest that the cumulative incidence of CTEPH in patients who survive pulmonary embolism is from 0.57 to 3.8\(^%\)\(^3\)
- The V/Q scan is a pivotal test in the diagnostic work-up of CTEPH and is the preferred imaging tool for the initial assessment of patients with suspected CTEPH\(^4\)\(^,\)\(^5\)
- PEA surgery can be curative and should be considered in all eligible patients with CTEPH\(^6\)\(^,\)\(^7\)
- Some patients are not operable candidates or suffer from persistent or residual pulmonary hypertension after PEA surgery\(^3\)\(^,\)\(^6\)

For more information on PH, visit the Pulmonary Hypertension Association at phassociation.org, and for more information on WHO Group 4 (CTEPH), visit ctephawareness.com.

CTEPH=chronic thromboembolic pulmonary hypertension; PEA=pulmonary endarterectomy; PH=pulmonary hypertension; V/Q=ventilation/perfusion scintigraphy; WHO=World Health Organization.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION:
ONE OF THE 5 DISTINCT TYPES OF PH

Contributing to the scientific discussion of PH.
Even a Physician With Pulmonary Hypertension Can Be Misdiagnosed

By Lynn Brown, MD, Campaign Chair

Diagnosing pulmonary hypertension (PH) is often so tricky that even a patient practicing pulmonology can experience delayed diagnosis. That’s what happened to Bonnie Hudak, MD, a new member of the Sometimes it’s PH early diagnosis campaign’s Education Committee.

Dr Hudak is a pediatric pulmonologist at Nemours Children’s Clinic in Jacksonville, Florida, where she often treats asthma and cystic fibrosis. Yet her path to diagnosis parallels that of many other PH patients, particularly middle-age women.

Dr Hudak had long been treated for scleroderma and Reynaud’s disease. Her rheumatologist knew of the association between PH and scleroderma. Dr Hudak maintained a healthy weight, exercising regularly while practicing medicine and raising children. In her 40s, exercising became more difficult, but with her busy life she says she paid this little attention. Then while hiking in 2004, Dr Hudak discovered that at altitude she could not walk uphill.

In Jacksonville she underwent an echocardiogram, an EKG, and a chest x-ray. Her doctor called the results “maybe slightly abnormal.” He was reassured and attributed her symptoms to perimenopause and deconditioning. He reported that the cardiologist had considered her echocardiogram normal. “They were happy with normal, and I was, too,” Dr Hudak said.

Still, Saturday morning tennis games left her tired all weekend. Once, at a neighborhood party, she was chatting with a cardiologist friend. He told her firmly, “Anyone with scleroderma and shortness of breath with exercise has PH unless proven otherwise.” Two weeks later she was diagnosed by right heart catheterization and referred to a PH specialty center.

Dr Hudak’s experience at Mayo Clinic in Jacksonville under the care of Charles Burger, MD, highlights the importance of referral to specialty centers, a key element of the Sometimes it’s PH campaign. In a single day she received comprehensive testing, including a more detailed echocardiogram, which successfully measured tricuspid regurgitation velocity. Those administering these tests pursued results doggedly.

Dr Burger also admitted Dr Hudak to the hospital for a right heart catheterization that included a vasodilator challenge. Without that thorough procedure and all of the necessary testing, Dr Hudak’s vasoreactive type of PH would not have been discovered. Dr Hudak has remained on nifedipine as her sole PH treatment and has improved from Class III to Class I. She has also participated in a clinical trial.

In her practice Dr Hudak now looks for a few more zebras among the horses. She also looks more carefully at the data used to interpret studies. She would advise other physicians to be more vigilant with a patient who has an underlying condition associated with PH and to work up minimal symptoms that may be due to PH. She also suggests further evaluation if existing results don’t make sense in the clinical setting.

Dr Hudak’s experience illustrates that both patients and professionals must be more active in questioning the data and the decisions that drive diagnosis. Her unique insights will be an asset as PHA offers ongoing education and information for patients and caregivers at every stage of their PH journey. We now provide resources to help your patients and caregivers cope with the mental, emotional, social, and spiritual components of living with PH. To download your free guide, visit www.PHAssociation.org/Coping.

Newest Survival Guide Hits the Shelves

“The Survival Guide is one of inestimable value for patients, families, nurses, physicians, and anybody else who has anything to do with this disease. . . Our practice buys it in bulk and provides it to our patients, their families, and caregivers.”

— Bruce Brundage, MD, former Chair, PHA Scientific Leadership Council

The fifth edition, 2013 revision of Pulmonary Hypertension: A Patient’s Survival Guide is now available. Eight of the 17 chapters, plus the glossary and appendices, were updated for this latest version of the 300-page book, covering survival outcomes, insurance coverage, new resources, as well as conventional, drug, and surgical treatments. For the first time, PHA is offering this valuable resource as both a paperback and an e-book.

Order copies for your patients and medical team now at www.PHAssociation.org/SurvivalGuide.
ADCIRCA® (tadalafil) tablets is a phosphodiesterase 5 inhibitor (PDE-5i) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

**ADCIRCA (tadalafil) ONCE-DAILY CAN GIVE YOUR PATIENTS A SOLID FOUNDATION**

A first-line PDE-5 inhibitor that can help improve exercise ability

- The only once-daily PDE-5 inhibitor for PAH
- 33-meter placebo-adjusted mean improvement in 6MWD at 16 weeks
- The most common adverse event with ADCIRCA (tadalafil) 40 mg is headache (42% ADCIRCA vs 15% placebo). Other common adverse events (reported by ≥9% of patients on ADCIRCA and more frequent than placebo by 2%) include myalgia (14% vs 4%), nasopharyngitis (13% vs 7%), flushing (13% vs 2%), respiratory tract infection (13% vs 6%), extremity pain (11% vs 2%), nausea (11% vs 6%), back pain (10% vs 6%), dyspepsia (10% vs 2%), and nasal congestion (9% vs 1%)
- A $20 co-pay for eligible patients on commercial/private insurance plans

*Patients must meet certain eligibility criteria to qualify for assistance. Patients receiving reimbursement under Medicare, Medicaid, VA, DoD (TRICARE), Indian Health Services, or similar federal or state programs, may not be eligible for some assistance. Some portion of this patient assistance may be administered by Caring Voice Coalition (CVC), an independent national nonprofit organization.

**Important Safety Information**

**CONTRAINDICATIONS**

- **Nitrates**: ADCIRCA should not be used in patients taking medicines that contain nitrates, as the combination could cause a sudden, unsafe drop in blood pressure
- **Hypersensitivity Reactions**: Patients with a known serious hypersensitivity to tadalafil should not take ADCIRCA

**WARNINGS AND PRECAUTIONS**

- **Cardiovascular**: Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention
- **Cardiovascular**: Phosphodiesterase 5 inhibitors (PDE-5i)s, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing ADCIRCA, physicians should carefully consider whether their patients with underlying cardiovascular disease could be adversely affected by such actions. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of ADCIRCA to these patients is not recommended
- **Cardiovascular**: The use of ADCIRCA with alpha blockers, blood pressure medications, or alcohol may lower blood pressure significantly and may lead to symptomatic hypotension (light-headedness or fainting)
- **Potential Drug Interactions**: Tadalafil is metabolized predominately by CYP3A in the liver. Use of ADCIRCA with potent CYP3A inhibitors, such as ketoconazole and itraconazole, should be avoided. For patients on ADCIRCA therapy that require treatment with ritonavir, ADCIRCA should be discontinued at least 24 hours prior to starting ritonavir. For patients on ritonavir therapy that require treatment with ADCIRCA, start ADCIRCA at 20 mg once a day. Use of ADCIRCA with potent inducers of CYP3A, such as rifampin, should be avoided
- **Special Populations**: The use of ADCIRCA is not recommended for patients with severe renal or hepatic impairment. Please see Full Prescribing Information for dosing recommendations for patients with mild to moderate renal or hepatic impairment
- **Potential Drug Interactions**: ADCIRCA contains the same ingredient (tadalafil) as Cialis®, which is used to treat erectile dysfunction (ED) and the signs and symptoms of benign prostatic hyperplasia (BPH). The safety and efficacy of combinations of ADCIRCA with Cialis or other PDE-5is have not been studied. Therefore, the use of such combinations is not recommended
- **Vision/Hearing**: Patients who experience a sudden loss of vision in one or both eyes, which could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), or sudden decrease or loss of hearing after taking ADCIRCA should seek immediate medical attention
- **Prolonged Erection**: In rare instances, men taking PDE-5is (including tadalafil) for ED reported an erection lasting more than four hours. Male patients who experience a prolonged erection should seek immediate medical attention

**ADVERSE REACTIONS**

- **Adverse Reactions**: The most common adverse event with ADCIRCA is headache (42% ADCIRCA vs 15% placebo). Other common adverse events (reported by ≥9% of patients on ADCIRCA and more frequent than placebo by 2%) include myalgia (14% vs 4%), nasopharyngitis (13% vs 7%), flushing (13% vs 2%), respiratory tract infection (13% vs 6%), extremity pain (11% vs 2%), nausea (11% vs 6%), back pain (10% vs 6%), dyspepsia (10% vs 2%), and nasal congestion (9% vs 1%)

*Please see brief summary of Full Prescribing Information on following page. Please see Full Prescribing Information and Patient Information available at www.adcirca.com, or call 1-800-545-5979. www.adcirca.com 1-877-UNITHER*
ADCI RAC® (tadalafil) tablets

BRIEF SUMMARY

The following is a brief summary of the full prescribing information on ADCIRCA (tadalafil). Please review the full prescribing information prior to prescribing ADCIRCA.

INDICATIONS AND Usage

Pulmonary Arterial Hypertension: ADCIRCA is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies for the treatment of pulmonary arterial hypertension (PAH) showed a beneficial effect on selected hemodynamic parameters and a decrease in the rate of worsening of PAH, in patients treated with ADCIRCA 40 mg, including a significant benefit in patients who had a worse prognosis at initiation of treatment.

Concomitant Organic Nitrates: Do not use ADCIRCA in patients with a history of using any form of organic nitrates, either regularly or intermittently. Pacemakers and other electrical devices may be adversely affected by use of nitrates. The potential for adverse effects is particularly sensitive to the actions of vasodilators, including PDE5 inhibitors. Pulmonary vasodilators may significantly worsen hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors has not been studied. Inform patients that use of the drug should be avoided in patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, who were not included in the clinical trials, and use in these patients is not recommended. Hearing Impairment: Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not known if these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye. A sudden or temporary visual changes could be adversely affected by use of vasodilators such as PDE5 inhibitors. Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended. Hearing Impairment: Physicians should advise patients to seek immediate medical attention in the event of a sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors, including ADCIRCA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Combination with Other PDE5 inhibitors: Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADCIRCA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors. When concomitant use of two drug classes or other factors, including intravascular volume depletion and use of other antihypertensive drugs.

DRUG INTERACTIONS

Use with Alpha Blockers and Antihypertensives — PDE5 inhibitors, including ADCIRCA, and alpha-adrenergic blocking agents and antihypertensives may reduce systemic blood pressure-lowering effect, although this effect has not been systematically assessed. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes may lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs. Use with Alcohol — Both alcohol and tadalafil may increase the risk of developing hypotension (postural syncope) when taken in combination, blood pressure-lowering effects are increased. Use with Potent CYP3A4 Inhibitors or Inducers: Co-administration of CYP3A4 inhibitors or inducers can affect levels of other drugs. Table 1 presents treatment-emergent adverse events reported by 9% of patients in the ADCIRCA 40 mg group and occurring more frequently than placebo.

Table 1: Treatment-Emergent Adverse Events Reported by 9% of Patients in ADCIRCA and More Frequent than Placebo by 2%
are using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Alpha-Blockers — be administered under close medical supervision with consideration of the last dose of ADCIRCA before nitrate administration is deemed medically necessary in a patient who has taken ADCIRCA, where nitrate administration is still only considered. In such circumstances, nitrates should still only be administered in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin. Antihypertensives — PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo. Alcohol — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are used in combination, blood pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations. Potential for Other Drugs to Affect ADCIRCA: Ritonavir — Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir. Other Potent Inhibitors of CYP3A — Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of ADCIRCA. Potential Inducers of CYP3A — For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA. Potential for ADCIRCA to Affect Other Drugs: Cytochrome P450 Substrates — Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan). Aspirin — Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin. P-glycoprotein (e.g., digoxin) — Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects. USE IN SPECIFIC POPULATIONS Pregnancy: Pregnancy Category B — Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed. Non-teratogenic effects — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance. Nursing Mothers: It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman. Pediatric Use: Safety and effectiveness of ADCIRCA in pediatric patients have not been established. Geriatric Use: Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered. Renal Impairment: For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis. Hepatic Impairment: Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients. OVERDOSAGE Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination. Marketed by: Lung LLC, a wholly-owned subsidiary of United Therapeutics Corporation Rx only www.adcirca.com BS.HCP.KCGLUNLLC-4-72-v1
Program Announcement:

New Application Deadline: October 12, 2013
Resubmission Deadline: November 12, 2013
New Application Deadline: February 12, 2014
Resubmission Deadline: March 12, 2014

Jointly Sponsored
Mentored Clinical Scientist Development Award (K08) &
Mentored Patient-Oriented Research Career Development Award (K23)

**PURPOSE: K08**
- To support the development of outstanding clinician research scientists in the area of pulmonary hypertension.
- To provide specialized study for clinically trained professionals who are committed to a career in research in pulmonary hypertension and have the potential to develop into independent investigators.
- To support a 3 to 5 year period of supervised research experience that integrates didactic studies with laboratory or clinically based research.
- To support research that has both intrinsic research importance and merit as a vehicle for learning the methodology, theories, and conceptualizations necessary for a well-trained independent researcher.

**MECHANISM:**
Awards in response to the program announcement will use the National Institutes of Health (NIH) K08 or the K23 mechanism.

**FUNDING:**
The award will be funded by PHA and NHLBI and the K08 and/or the K23 will be awarded in 2013.

**PURPOSE: K23**
- To support career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.
- To support a 3 to 5 year period of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research in pulmonary hypertension.
- To support patient-oriented research, which is defined as research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects.
- To support areas of research that include: 1) mechanisms of human disease; 2) therapeutic interventions; 3) clinical trials; and 4) development of new technologies.

**FOR MORE INFORMATION:**
Visit: www.PHAssociation.org/MedicalProfessionals/Research

* Restrictions apply. Please see complete announcement at the website listed above.
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