Advances in Pulmonary Hypertension

Managing PAH in the Perioperative Setting

Preoperative Considerations in Patients with Pulmonary Hypertension
   Sean M. Studer, MD, MSc

Intraoperative Management of Patients with Pulmonary Hypertension
   Rafael Ortega, MD
   Christopher W Connor, MD, PhD

Post-Operative Care of the Patient with Pulmonary Hypertension
   Rebecca Dezube, MD
   Traci Housten, RN, MS
   Stephen C. Mathai, MD, MHS

Pulmonary Hypertension Roundtable: Bariatric Surgery and the PAH Patient

PHPN: Getting Ready for Surgery: Check List for the Pulmonary Hypertension Patient
   Stephanie J. Harris, RN, MS

Ask the Expert: Perioperative Management of PH Crisis
   Marc A. Simon, MD, MS
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Program Description

The mission of Advances in Pulmonary Hypertension is to serve as the premier forum for state of the art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension. The 2008 Dana Point resolution of the World Health Organization Classification serves as a guide to categories of pulmonary hypertension addressed in Advances in Pulmonary Hypertension. While focusing on WHO Group 1 PAH, the other categories (Group 2, pulmonary venous hypertension; Group 3, associated with chronic lung disease and/or hypoxemia; Group 4, pulmonary embolic hypertension; Group 5, miscellaneous) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

• Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension.

• Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

The Scientific Leadership Council of the Pulmonary Hypertension Association

The mission of the Scientific Leadership Council is to provide medical and scientific guidance and support to the PHA for:

• Developing and disseminating knowledge for diagnosing and treating pulmonary hypertension.

• Advocating for patients with pulmonary hypertension.

• Increasing involvement of basic and clinical researchers and practitioners.

More information on PHA’s Scientific Leadership Council and associated Committees can be found at www.PHAssociation.org/SLC/
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Advance in Pulmonary Hypertension
Official Journal of the Pulmonary Hypertension Association

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General Information
Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned experts with the oversight of the Association’s Scientific Leadership Council. Its mission is to help physicians in their clinical decision making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in the peer-reviewed literature. Each article is reviewed and approved by members of the Editorial Advisory Board.

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.

Manuscript Preparation and Submission Process
Submissions should be sent via e-mail as an attached Word document to the Editor-in-Chief, Myung Park, MD, at mpark@medicine.umaryland.edu. Manuscripts should be double-spaced and follow AMA style. Full-length manuscripts should not exceed 4,000 words including references. References should be limited to 50 entries. No more than 5 figures should accompany the manuscript. Accepted file formats are .gif, .tif, and .jpg. Each figure should be a separate file and figure legends should appear at the end of the manuscript. Each figure should be cited by number in the manuscript. Tables should be self-explanatory and details of the table should not be repeated in the manuscript. Tables should be prepared as part of the Word document. No more than 3 tables should be included with the manuscript. References should conform to AMA style and be numbered consecutively in the text. Reference numbers should be placed in parentheses at the end of the relevant sentence.

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

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Manuscripts are accepted for exclusive publication in Advances in Pulmonary Hypertension and will be copyrighted by the Pulmonary Hypertension Association.

Conflict of Interest Disclosures
A statement of any and all grant, contract, and industrial support or proprietary interests of the author(s) related to the subject matter must be submitted with the manuscript.

Checklist
Authors should be certain to include the following with the manuscript:
1. Title page listing all authors with their academic degree(s) and affiliations.
2. Corresponding author contact information including e-mail and phone number.
3. Copyright release form signed by all authors
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
Surgery in PH Patients: Shedding Some Light in an Unchartered Territory

It is a tremendous honor to take on the role of the Editor-in-Chief of Advances in Pulmonary Hypertension. As the Journal enters its 12th year, it is inspiring to witness its growth over the years. When Advances was created, as the only journal solely dedicated to PH at the time, the founders of the journal envisioned a forum where PH — with all its complexities and uncertainties — would have a home. Indeed, the Roundtable was initiated by the first Editor-in-Chief, Dr. Victor Tapson, as a way for PH clinicians to express their opinions, voice their concerns and questions to each other and the PH community.

The changes the journal has undergone parallel the growth of the field. Under the dedicated leaderships of the editors-in-chief who subsequently took over the helm during the past decade – Drs Vallerie McLaughlin, Ronald Oudiz, Richard Channick, and Erika Berman-Rosenzweig – and the distinguished members of the editorial board, Advances remained true to its mission of bringing the latest development in PH, with a keen focus on clinical relevancy. Indeed, the current organization of the issues with sections dedicated to discussion on clinical research updates as controversies, noteworthy publications related to the field of pulmonary vascular disease, and articles focusing on the important topics related to patient care from allied health groups all reflect the commitment of serving the PH medical community in care of the patients.

Thus to continue fulfilling our goal, with advice and input from the Scientific Leadership Council and the editorial board members, the journal has recently undergone some updates. First, you will see that the journal has a new cover — with the periwinkle color for background to represent PHA — as well as discontinuation of the CME section (in light of CME courses available via “PHA OnLine University”), structured abstract with each article, and changes in reviewing process of manuscripts. So in essence, the “look” of the journal has evolved but the content and intent of the articles remain the same, bringing you quality articles by world’s leading PH experts. In implementing these changes, I would like to thank Rich Channick for his enduring support and encouragement and Erika Berman-Rosenzweig for easing the transition with her helpful advice and planning. I would also like to thank our Managing Editor, Deb McBride, for her tireless effort in transforming all the plans into reality.

We are pleased to bring you this issue titled “Managing PAH in the Perioperative Setting,” which is first of a two-part series in our focus on PH patients and surgery. PH physicians are often faced with the task of providing “surgical clearance” and recommendations for perioperative management when our patients require invasive interventions. Providing a risk assessment and management plan is a daunting task. With no guidelines focused on the topic, clinicians often rely on advice of their colleagues and we wanted to bring you the collective experiences from some of our PH physicians and allied health members. I am grateful to Sean Studer, for serving as the guest editor in taking charge of developing this challenging issue. He has invited outstanding authors to bring their insights in overseeing perioperative management of a PH patient. I hope you find this issue helpful in your clinical practice.

Myung H. Park, MD
Associate Professor of Medicine
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GUEST EDITOR’S MEMO

It is a challenging question for any pulmonary hypertension (PH) clinician to be asked, “Is this patient OK to go to surgery now?” Even if one is able to answer confidently in the affirmative, the follow-up query, “Any specific recommendations for perioperative management?” may result in a longer pause before responding. This topic is a challenge for clinicians to address largely due to the very limited data upon which to make evidence-based recommendations. So, how do we proceed given these uncertainties?

We start with the first of the three articles in this issue that addresses the question of preoperative evaluation and outlines a framework for preparing our patients as well as the entire multidisciplinary care team (including the nurses, pharmacists, cardiologists, pulmonologists, anesthesiologists, and surgeons) for the planned procedure. In the second article, Drs Rafael Ortega and Christopher Connor analyze the approach to optimizing anesthesia and intraoperative management in patients with PH. In the third feature, Dr Rebecca Dezube, Traci Housten, RN, MS, and Dr Stephen Mathai present their approach to an actual patient scenario and focus on the post-operative management.

Considering referral and management in special procedures begins in this issue with a discussion of bariatric surgery and continues with the next issue of Advances, which will review abdominal organ transplantation in patients with PH. Bariatric surgery is becoming increasingly accessible at medical centers and with an increasing body of evidence that metabolic changes associated with obesity may contribute to the pathophysiology of PH, this month’s Roundtable discussion tackles the benefits and risks of bariatric surgery. This edition’s Ask the Expert column, authored by Dr Marc Simon, reviews the treatment of PH crisis in the perioperative period. Finally, the Pulmonary Hypertension Professional Network (PHPN) column of this edition helps conclude the approach to the PH patient requiring surgery with an outstanding checklist that summarizes the practical approach to preoperative assessment and management.

These articles share a common theme regarding the importance of communication among the interdisciplinary team members in the perioperative setting. While frequent and detailed communication is an integral aspect of the medical care of patients with PH, its importance from the preoperative until the postoperative period cannot be overemphasized. We hope that this issue provides readers with valuable insights into the management of PH in the perioperative setting and also that the many unanswered questions are the subject of research in the near future.

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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%)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-5is), 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 ronitavir, ADCIRCA should be discontinued at least 24 hours prior to starting ronitavir. For patients on ronitavir 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

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ADCIROCA® (tadalafil) tablets

BRIEF SUMMARY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension: ADCIROCA is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies result from the combined effects of nitrates and ADCIROCA.

CONTRAINDICATIONS

Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects: Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIROCA. At least 48 hours should elapse after the last dose of ADCIROCA before discontinuing nitroglycerin. If a patient has taken ADCIROCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking nitroglycerin should seek immediate medical attention.

PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCIROCA, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of ADCIROCA to patients with veno-occlusive disease, administration of ADCIROCA to such patients is not recommended. Should signs of pulmonary edema occur when ADCIROCA is administered, the possibility of associated PVOD should be carefully considered. There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic or mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or constrictive cardiomyopathy
- Patients with significant left ventricular dysfunction

Use with Alpha Blockers and Antihypertensives: PDE5 inhibitors, including ADCIROCA, and alpha-adrenergic blocking agents and antihypertensives can lower blood pressure. 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 cause vasodilation and hypotension. When moderate to high doses of alcohol are taken in combination, blood pressure-lowering effects are increased. Use with Potent CYP3A4 Inhibitors or Inducers: Co-administration of a potent CYP3A4 inhibitor such as ritonavir and PDE5 inhibitors has not been studied. Inform patients taking ADCIROCA not to take CIALIS or other PDE5 inhibitors. Prolonged Erection: There have been rare reports of erections lasting more than 4 hours and erections that are painful. If left untreated, prolonged erections greater than 4 hours can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek medical attention promptly. Use of a PDE5 inhibitor, including ADCIROCA, should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as ankyloglossia, caudaverous fibrosis, or Peyronie’s disease). Effects on Bleeding: ADCIROCA is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIROCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration. Although ADCIROCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypotension
- Vision loss
- Hearing loss
- Priapism

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Tadalafil was administered to 398 patients with PAH during clinical trials worldwide. In trials of ADCIROCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIROCA 40 mg and 15% for placebo. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADCIROCA 40 mg were 4% compared to 5% in placebo-treated patients. In the placebo-controlled study, the most common AEs were headache and musculoskeletal pain. Table 1 presents treatment-emergent adverse events reported by ≥9% of patients in the ADCIROCA 40 mg group and occurring more frequently than with placebo.

Table 1: Treatment-Emergent Adverse Events Reported by ≥9% of Patients in ADCIROCA and More Frequent Than Placebo by 2%

<table>
<thead>
<tr>
<th>Event</th>
<th>ADCIROCA 40 mg (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Lower Respiratory Infection</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Priapism</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or if the event appears to be a consequence of the drug exposure. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye. Significant effects in healthy volunteers have been observed with PDE5 inhibitors, including tadalafil. In some of the cases, these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. Cardiovascular and cerebrovascular: Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of the tadalafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these factors, or to other factors. Body as a whole: Hypersensitivity reactions including urticaria, Stevens–Johnson syndrome, and exfoliative dermatitis. Nervous: Migraine, seizure and seizures, ataxia, vertigo, hypnagogic and hypnopompic hallucinations, Visual field defect, retinal vein occlusion, and retinal artery occlusion. Non–arteritic anterior ischecmic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for hearing loss, a combination of these factors, or to other factors. Otolologic: Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have played a role in the etiology of hearing loss. In many cases, medical follow-up information was limited. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Obstructive: Patients with underlying cardiovascular disease, to a combination of these factors, or to other factors. Urogenital: Priapism.

DRUG INTERACTIONS

Potential for Pharmacodynamic Interactions with ADCIROCA: Nitrates — Do not use ADCIROCA in patients who...
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 studies ADCIRCA potentiated the hypotensive effect of nitrates. In 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 were seen during coadministration of tadalafil with diuretics, amlodipine, losartan, and valsartan. Alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies were conducted to assess the effect of tadalafil plasma concentrations. In a patient who has taken ADCIRCA, where nitrate is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by an increase of 5 to 10 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of these studies, tadalafil was given to pregnant rats or mice at doses of up to 500 mg/kg and plasma concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD 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 are 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. 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. OVERDOSE 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

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Scleroderma and PH is not my identity ... If your sickness becomes your identity, then you don’t have a shot. You have to surround yourself with people who do not make you feel sick.”
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**

Survival in PAH, 1988 and 2006*4,5

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

A condition with five distinct types

All types may present similarly.

- The most common presenting symptoms of all types of PH include dyspnea on exertion, fatigue, chest pain, syncope, palpitations, and lower extremity edema

Distinct clinical conditions underlie each of the five types. Correctly classifying PH is critical for selecting appropriate management.

WHO Groups

**WHO Group I**
PAH
Can be IPAH, heritable, induced by drugs or toxins, or associated with other conditions (APAH) such as connective tissue disease, HIV infection, or portal hypertension; PVOD or PCH.

**WHO Group II**
Left heart
Can be due to systolic dysfunction, diastolic dysfunction, or valvular disease.

**WHO Group III**
Lung/hypoxia
Can be due to chronic COPD, ILD, or sleep-disordered breathing.

**WHO Group IV**
CTEPH
Due to obstruction of the pulmonary arteries by thromboemboli, tumors, or foreign bodies.

**WHO Group V**
Other
Due to unclear or multifactorial mechanisms (eg, sarcoidosis or thyroid disorders).

For more information please visit the Pulmonary Hypertension Association at phassociation.org.

COPD=chronic obstructive pulmonary disease; CTEPH=chronic thromboembolic pulmonary hypertension; HIV=human immunodeficiency virus; ILD=interstitial lung disease; IPAH=idiopathic pulmonary arterial hypertension; PAH=pulmonary arterial hypertension; PCH=pulmonary capillary hemangiomatosis; PH=pulmonary hypertension; PVOD=pulmonary veno-occlusive disease; WHO=World Health Organization.

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Upcoming BME events:

4th Annual Pulmonary Hypertension Symposium
Oct. 9, 2013 • Advocate Christ Medical Center • Oak Lawn, Ill.

Midwest PH Symposium*
Oct. 11 - 12, 2013 • University of Kansas Medical Center
Overland Park, Kan.
www.continuinged.ku.edu/kumc/pulmonary-hypertension

5th Annual North Carolina Research Triangle PH Symposium*
Nov. 8, 2013 • Duke University and UNC Chapel Hill
Durham, N.C. • Register at: www.dcri.org

Cleveland Clinic PH Summit*
Nov. 15 - 16, 2013 • Cleveland Clinic • Cleveland, Ohio
Register at: www.ccfcme.org/2013PulHyper

*Offers medical and patient components

To view a full list of educational opportunities for medical professionals, visit: www.PHAOnlineUniv.org/Calendar
How Safe Is Surgery for PAH Patients?

Section Editor
Ioana Preston, MD

SUMMARY

The presence of pulmonary hypertension (PH), whether in its primary form, pulmonary arterial hypertension (PAH), or secondary to heart or lung disorders, is associated with a high risk for complications. The perioperative management of PH patients can be challenging, as it is frequently complicated by the postoperative development of a systemic inflammatory response, profound hypoxemia, worsening of PH, and right heart failure. Two old retrospective studies found a preoperative mortality of 7% and 18%, respectively, but there is a scarcity of data describing the perioperative management of PH patients who undergo surgery.

Most recently, Meyer et al

reported results of the first international, prospective, 3-year questionnaire-based survey among 11 PH centers and collected data from consecutive patients with PAH undergoing noncardiac and nonobstetric major surgery. The definition of major surgery required the need for either general or spinal anesthesia. A total of 114 patients with PAH (70% female, mean age 57 years) were identified. At the time of surgery, 43% were in New York Heart Association functional class III or IV. Eighty-two percent of the interventions were performed under general anesthesia, and the rest were performed using spinal anesthesia. Major complications occurred in 7% and 18%, respectively.

Major complications occurred in 7% and 18%, respectively,

Correspondence: ipreston@tuftsmedicalcenter.org

REFERENCES

Pulmonary hypertension (PH) patients who undergo surgical procedures are at increased risk for complications.\(^1\) Patients need a comprehensive medical team approach involving not only the surgeon, but also the PH specialist, the nurse coordinator, the anesthesiologist, and the medical consult physician.

1. Consider referral to a PH center to provide comprehensive medical care and services, including:
   - PH specialist [Information to provide includes: type of surgery, mode of anesthesia, length of surgery, elective or urgent]
   - Medical consult for surgical risk stratification for all comorbidities\(^2\) [Including coronary artery disease/evaluation for ischemia, diabetes, thyroid disorder, hypertension]
   - Cardiac anesthesiologist [Especially relevant in patients with PAH on advanced treatments, including availability of nitric oxide or inhaled prostacyclins]
   - Postoperative ICU care with physicians, registered nurses, and respiratory therapists with experience in managing
   - Immediate availability of PH medications onsite [Including intravenous prostacyclin (ie, epoprostenol) and oral therapies (ie, sildenafil)]

2. Schedule patient to see a PH specialist for comprehensive evaluation, including consideration of the following:
   - Echocardiogram [Reassess and compare right ventricular size and function, left ventricular function, pericardial effusion, valvular function]
   - Right heart catheterization [More relevant for patients on advanced PH therapies, recent decompensation and/or unstable clinical course]
   - Pulmonary function tests
   - Comprehensive laboratory evaluation including complete blood count, comprehensive metabolic panel, coagulation studies, brain natriuretic peptide
   - 6-minute walk and/or cardiopulmonary exercise test to reassess functional status
   - Optimize medication regimen prior to surgery
   - Careful monitoring and optimization of volume status
   - Provide question and answer discussion and support to the patient and family
   - Confirm code status and health care proxy
   - Discussion of the risk/benefit balance with consideration for the scheduled procedure and patient’s underlying medical conditions

3. Schedule patient to see an anesthesiologist for preoperative evaluation, with special consideration for the following:
   - Anticoagulation—bridging with low molecular weight heparin prior to surgery as appropriate
   - Strongly consider consulting cardiac anesthesiologist for management of PH medications [Use of invasive hemodynamics during surgery as needed, best managed with PH physician/team]\(^3\)
   - Discuss the most appropriate method of anesthesia for the planned surgery [If general anesthesia considered, discuss possibility of alternative methods whenever possible]
   - Clarify “morning of surgery” medication regimen, with recommendation toward continuing all medications for PH as appropriate

With vigilant evaluation and assessment, medical providers can promote positive surgical outcomes for patients with PH.

References
Preoperative Considerations in Patients With Pulmonary Hypertension: Your Patient Needs Surgical Clearance

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New York, NY

Patients with pulmonary arterial hypertension (PAH) are at increased morbidity and mortality risk when facing the need to undergo surgical interventions. The most common complications include those arising from right ventricular (RV) failure and respiratory failure—not surprising given the complex cardiopulmonary pathophysiology of this disease. While data are limited regarding the optimal preoperative approach to these patients, it is imperative to focus on the following key components: ensuring or establishing the patient’s World Health Organization (WHO) classification, pulmonary hypertension (PH) group or subgroup; assessing the status and stability of RV function; optimizing the treatment regimen; and communicating a management plan for intra- and perioperative management to all members of the interdisciplinary clinical team. This article will focus on each of these steps in the preoperative algorithm, highlighting the need for further studies in this area.

Pulmonary arterial hypertension is a condition associated with increased pulmonary vascular resistance, resulting in progressive RV dysfunction.\(^1\)^\(^,\)^\(^2\) Moderate to severe disease is associated with decreased functional capacity and an increased risk for mortality. The risk of surgery is markedly increased in patients with PAH, and for this reason elective surgery should generally be avoided or at least discouraged in this population when possible.\(^3\)^\(^,\)^\(^4\) It is important to recognize that the type of surgery will impact the PAH patient’s risk. Procedures associated with rapid blood loss, venous air embolism, systemic inflammatory response, carbon dioxide insufflation (eg, laparoscopic surgery), fat or cement emboli (eg, orthopedic surgery), and loss of pulmonary vasculature (eg, lung resection) are associated with higher risk.\(^4\) Results of an international prospective registry including 114 patients emphasized the particular risk of emergency surgery with an observed mortality rate of 15% compared to 2% in nonemergent procedures.\(^5\) However, even nonemergency surgery may be unavoidable in many PAH patients, necessitating a specialized preoperative risk assessment and careful preparation for the procedure.

The preoperative assessment in patients with PAH necessarily involves confirming or establishing the patient’s diagnosis according to the WHO classification system,\(^6\) and continues with thorough assessment of current stability with particular focus on measures of right heart function. The preoperative treatment regimen should be optimized to improve or maintain right heart function as well as overall functional capacity. Logistical planning for surgery includes reviewing feasibility of the current medication administration intra- and postoperatively (especially in patients who will not be able to continue oral medications or who may need inhaled nitric oxide [iNO]), communication with the surgeon and anesthesiologist regarding intraoperative fluid management and monitoring, along with a clear delineation of responsibilities for postoperative care. A comprehensive plan also includes establishing a health care proxy for potential postoperative decision making and establishing goals of care should complications occur requiring discussions to address code status.

The value of preoperative medical and anesthesia consultations to address and optimize comorbidities including coronary artery disease, diabetes mellitus, and chronic renal insufficiency, as well as appropriate preoperative testing, is established; there are many other detailed reviews addressing these topics.\(^7\)^\(^,\)^\(^8\) This review for PAH clinicians will primarily address assessing preoperative surgical risks, with focus on PH patients facing “semielective,” noncardiac, nonobstetric surgery.

**IMPACT OF PAH ON SURGICAL OUTCOMES**

Multiple published reports have documented the impact of PAH on morbidity and mortality during pediatric, obstetric, cardiac, and noncardiac surgeries.\(^3\)^\(^,\)^\(^9\^-\)^\(^13\) The threshold for pulmonary artery pressure associated with this increased morbidity and mortality risk has not been strictly established; however, in a study of patients undergoing coronary artery bypass surgery, a mean pulmonary artery pressure (mPAP) measurement of >30 mm Hg was a predictor of increased postoperative mortality.\(^12\) Ramakrishna and colleagues utilized a Doppler echocardiographic estimated right ventricular systolic pressure (RVSP) of ≥35 in their retrospective investigation of 143 patients to evaluate the impact of PH on outcomes in noncardiac surgery.\(^3\) Patients with PH related to left heart disease and those not diagnosed with PH prior to surgery were among those excluded from the analysis of morbidity and mortality within the...
Table 1: Incidence and Type of Early (<30 Days) Morbidity in Patients With Pulmonary Hypertension (n = 145) After Noncardiac Surgery. Reprinted with permission.3

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Patients* (n)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure</td>
<td>41</td>
<td>28</td>
</tr>
<tr>
<td>Cardiac dysrhythm</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Sepsis/hemodynamic instability</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Ischemia/myocardial infarction</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Patients may have had one or more morbid event(s).

first 30 postoperative days. The observed mortality was 7%, with one of the deaths occurring intraoperatively in the setting of RV failure. Table 1 describes the most frequent morbidity events from that study with respiratory failure, dysrhythmias, and congestive heart failure at the top of the list. New York Heart Association functional class (NYHA FC) ≥2 and presence of systemic hypertension were associated with increased morbidity in a univariate analysis, while history of pulmonary embolism and NYHA FC ≥2 were considered predictors of short-term morbidity in the multivariate model. These results were consistent with the findings of Kaw et al, who examined 173 patients who underwent right heart catheterization (RHC) and noncardiac surgery.13 The definition of PH utilized in this study was mPAP >25 mm Hg. Of the 96 patients with PH, 26% suffered a morbidity/mortality event with congestive heart failure, hemodynamic instability, and respiratory failure most commonly observed. Mean pulmonary artery pressure, American Association of Anesthesiology Class, and chronic renal insufficiency were found as independent risk factors. Table 2 contains a summary of patient and operative risk factors based on published data, derived largely from retrospective studies and highlighting the need for prospective investigations in this area. These studies strongly demonstrate the significant negative impact of PH on perioperative outcomes and emphasize the importance of a thorough preoperative characterization and assessment of risk in this patient population.

### Importance of Confirmation and Characterization of PH

Recent registry reports have shown that the delay from onset of symptoms until the diagnosis of PAH may exceed 2 years.16 This suggests that some patients may have their PAH diagnosed at the time of their preoperative assessment. Others may have been given a presumptive diagnosis of PAH based on an echocardiogram finding but have not undergone a thorough evaluation to determine the WHO group.17 Although most of the perioperative management approaches share a similar fundamental basis for different etiologies of PH, establishing and/or confirming the patient’s WHO group diagnosis prospectively by utilizing the recommended diagnostic approach provides guidance regarding the use of PAH vasodilator therapy in the perioperative period.

While pulmonary vasodilators have been proven effective in managing patients with PAH, the results are far less predictable when administered in non-PAH PH patients and may result in deterioration or death.2,18 Of particular concern is the risk of pulmonary edema when PAH vasodilator therapy is utilized in patients with heart failure with preserved ejection fraction (HFpEF; WHO Group 2) or worsening ventilation-perfusion matching resulting in hypoxemia in patients with significant parenchymal lung disease and PH (WHO Group 3). Once PAH diagnosis is confirmed and subgroup classification is established, the preoperative evaluation continues with evaluation of current stability, with a particular focus on right heart function.

### Assessment of PH Stability and Optimizing Therapy

The stability assessment of PH patients typically begins with history and physical examination, where discovery of recent deterioration in functional status, elevated jugular venous pressure, increasing fluid retention, or occurrence of syncope may provide initial indications of failing right heart function. Further information is gathered through blood testing regarding anemia, renal function, and brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) levels. Brain natriuretic peptide levels are sensitive indicators of heart failure and correlate with degree of cardiac stress and dysfunction. While decreasing renal function, increasing age, obesity, and
female gender have all been associated with elevated baseline plasma BNP levels,\(^1\) changes from the patient’s previous baseline may have significant clinical utility. Elevations of plasma BNP from baseline in patients with PAH portend a higher risk of mortality, and decreases in circulating BNP levels have been associated with improved survival, suggesting a role for BNP as a monitoring tool to guide adequacy of vasodilator therapy.\(^{20}\)

For patients at risk for hypoxemia and hypoventilation, relatively simple preoperative maneuvers such as pulse oximetry monitoring, including nocturnal testing during sleep and/or polysomnography, may be of benefit. Improving hypoxemia with supplemental oxygen and adding continuous positive airway pressure (CPAP) in indicated patients may help improve exercise capacity, volume status, and daytime alertness while also establishing the therapeutic regimen that will minimize complications in the postoperative period. Preoperative thoracic computed tomography (CT) scanning and pulmonary function tests (PFTs) are not routinely performed in patients with established PAH; however, they may be useful in some patients for evaluating recent changes in function. In particular, patients with worsening hypoxemia and/or nontypical PAH symptoms such as cough, sputum production, or pleuritic chest pain warrant consideration of thoracic CT scanning. Patients with a history of smoking or interstitial lung disease may benefit from PFTs as significant worsening of FEV1/FVC ratio suggests obstructive lung disease, and diminishing total lung capacity (TLC) may indicate worsening restrictive lung disease. Moderate to severe obstructive or restrictive ventilatory defects discovered during PFTs deserve further evaluation, usually including a pulmonary consult, to determine if the surgery should be canceled or postponed for treatment of the lung disease.

The 6-minute walk test is often pursued in the preoperative assessment. A lower 6-minute walk distance (6MWD) has been correlated with a worse prognosis compared to a higher 6MWD in patients from registry data\(^2\); however, the available data in preoperative risk studies have not supported a specific walk distance predictive of morbidity.\(^3\) Cardiopulmonary exercise testing (CPET) may better define the functional capacity and risk in patients with PAH as it provides a dynamic assessment of cardiac reserve. However, there are no established parameters for exercise level that are clearly predictive of postoperative outcome. Historically, CPET has been utilized in patients with chronic heart failure to make determinations of timing of transplantation, and parameters such as peak oxygen uptake are a recognized part of the general risk stratification of patients with PAH. In vascular surgery patients, the preoperative exercise capacity in metabolic equivalents (METs) has been used to risk stratify patients; those capable of performing less than 1 MET during CPET are recommended for further testing and/or medication therapy while those capable of >1-4 METs are considered functional enough to proceed without further testing.\(^{21,22}\) The most prudent recommendation may be to facilitate ambulation to maintain conditioning in patients prior to surgery without setting a specific functional goal, or routinely delaying a procedure to complete a pulmonary rehabilitation program, since this approach is not supported by the literature.

A transthoracic echocardiogram serves as a core test for preoperative evaluation of patients with PAH as it provides a noninvasive evaluation of right heart function. Patients with normal right atrial and RV sizes and preserved RV function are better risk surgical candidates. Markers of poor prognosis on echocardiogram in PAH include reduced tricuspid annular plane systolic excursion (TAPSE), severe right atrial enlargement, abnormal right ventricular index of myocardial performance (RVIMP or Tei Index), presence of pericardial effusion, and increased left ventricular eccentricity index.\(^{23,24}\) Along with its utility, the limitations of the echocardiogram must be acknowledged. The echocardiogram provides only an estimate of RVSP by extrapolating from the tricuspid regurgitant jet velocity, which may under- or overestimate the actual pulmonary artery pressure when evaluated with RHC.\(^{25}\) Also, while improvement in these echocardiographic parameters is considered a positive sign in patients on treatment, the timing and degree of change that may correlate with an improved postoperative outcome has not been determined. Ramakrishna and colleagues’ study emphasized this point as they observed no association between selected parameters on echocardiogram and postoperative morbidity; however, RV hypertrophy, RVIMP $\geq$0.75, and RVSP to systolic blood pressure ratio of $\geq$0.66 were all significantly associated with increased early mortality.\(^3\)

Right heart catheterization is the only method of obtaining direct assessment regarding cardiac hemodynamics and cardiac output, and for this reason should be considered in patients with PH as part of their preoperative evaluation if other noninvasive tests do not reliably provide status of right heart function. Right heart catheterization can confirm WHO Group diagnosis, and in particular differentiate HfPEF from PAH. The importance of obtaining an accurate pulmonary capillary wedge pressure (PCWP) in this setting deserves emphasis. Utilizing methods that include careful analysis of the pressure tracing, measuring wedged oxygen saturation, and/or deflating the balloon slightly and further advancing the catheter may be necessary to confirm a true and accurate PCWP. Without a true PCWP, the left ventricular end diastolic pressure may be overestimated and the patient misclassified as HfPEF when in fact the correct diagnosis is PAH. If a left heart catheterization is indicated to assess coronary patency or uncertainty regarding the PCWP remains unresolved, confirmation with direct measurement of left ventricular end diastolic pressure will establish the correct diagnosis.

Performing a preoperative RHC will also help guide the use of preoperative diuretics for patients with high right atrial pressures and the postoperative inotropes for patients with a low cardiac index. In selected patients, RHC with vasodilator challenge utilizing iNO may be performed to assess the potential utility of iNO postoperatively to acutely reduce RV afterload. Right heart catheterization will also provide information that helps providers decide that a
potential surgical procedure is too high risk and needs to be avoided.\(^4\)

In patients who are clinically high risk due to NYHA FC IV status and history of syncope, demonstrating high-risk hemodynamic parameters such as low cardiac index and high right atrial pressure\(^2\) leaves PAH clinicians with few options: mainly to cancel surgery or delay until clinical and/or hemodynamic stability might be achieved.

If a delay in surgery is feasible, as in some orthopedic procedures, and therapeutic adjustments are sought, the initiation or addition of phosphodiesterase type-5 inhibitor (PDE-5i) therapy and initiation of or dose increases in parenteral prostacyclin may be considered, although these are not evidence-based recommendations. The potential advantage to PDE-5i therapy, such as sildenafil 20 mg 3 times daily or tadalafil 40 mg once daily, compared to endothelin receptor antagonist therapy as a preoperative choice, is the purported acute vasodilatory and positive RV inotropic effects of the PDE-5i class. Prostacyclin therapy may have similar acute vasodilatory effects as well as positive RV inotropic effects, and increases in dose of a parenteral or inhaled prostacyclin may also be a desirable choice. Any therapeutic changes may result in adverse side effects, including lowering of systemic blood pressure and gastrointestinal symptoms such as nausea and diarrhea, so these should also be considered when medication initiation or dosing changes are made close to the date of any planned surgery. Again, these treatment suggestions are general (and largely hypothetical) recommendations. Further research will hopefully address this area and provide more practical evidence-based algorithms.

**LOGISTICS: IMPORTANCE OF THE HEALTH CARE PROXY, MEDICATION PLANNING, AND THE INTERDISCIPLINARY TEAM APPROACH**

Effective communication preceding surgery between patients and their PH provider team is imperative to help set expectations, discuss potential alternatives to the proposed procedure, determine the ideal hospital for the procedure, and establish the patient’s treatment goals. Given the elevated morbidity and mortality risks, devoting time to establishing a health care proxy to make decisions as the patient’s surrogate when necessary is appropriate. Also, specifically discussing potential circumstances, such as a cerebrovascular accident or severe sepsis, in which the patient may wish to be declared DNR (do not resuscitate) and/or limit certain types of aggressive care is also recommended.

Just as good communication between the PH clinician and the patient is essential to optimizing the treatment regimen, communication among the members of the multidisciplinary team is key to optimizing surgical outcomes. The members of the perioperative care team will typically include PAH clinicians (physician, nurse practitioner, physician assistant, respiratory therapist), surgeon, anesthesiologist, medical consult specialist as well as intensivists, nurses, and allied health care professionals (such as respiratory therapists and pharmacists) responsible for postoperative care. Involvement of a cardiac anesthesiologist is generally recommended for patients with PAH who are considered high risk and for high-risk surgical procedures. The practical issues that need to be addressed among specialists include arranging a preoperative anesthesia consult, preparing for management of comorbidities (eg, obtaining the home CPAP machine for patients with sleep apnea), developing a plan for postoperative medication delivery, and determining which clinicians will be responsible for each aspect of postoperative care. The latter 2 of these issues warrant further discussion.

The perioperative medication plan first needs to ensure that the patients’ current and potential future medication needs are adequately covered in terms of in-hospital availability. Not all hospitals have the range of PAH medications on formulary and/or available, and this may be a factor in determining whether a hospital is suited to perform the necessary procedure. Medication planning also needs to consider feasibility of dosing of oral medications such as PDE-5i and endothelin receptor antago-

nists in patients who may be unable to tolerate oral intake and/or dosing of inhaled prostacyclins in patients who may be ventilator dependent and unable to utilize their usual prostacyclin inhalation delivery system postoperatively. Alternatives to oral and inhaled medications might include temporizing use of iNO, which is not universally available, and inhalation prostacyclin via the mechanical ventilator, with which some centers may not have experience. A more significant risk procedure might also justify initiation of a parenteral prostacyclin as part of preoperative treatment optimization and for perioperative maintenance. Whatever medication treatment plan is developed, establishing lines of responsibility for important aspects of postoperative care is important.

For some institutions with experienced PAH programs, an agreement for postoperative management to be done by the PAH team with the surgical team focusing on the surgical issues has been suggested.\(^4\) This allows the clinicians with the greatest knowledge of the individual patient and with the PAH expertise to make the likely required adjustments to medication dosing, choose appropriate inotropic and/or vasopressor support, and manage mechanical ventilation when required. Not all institutions will necessarily follow that approach, and some larger institutions have intensivists with appropriate experience in their critical care units that is ideally suited to manage the challenges presented in postoperative patients with PAH. In surgical procedures beyond minimal risk, the presence of highly experienced PAH specialists is an important reason to consider scheduling surgery at or transferring to a tertiary care center. While no evidence-based recommendation can be made regarding ideal approach to postoperative care, effective communication pertaining to these issues prior to surgery will serve to minimize conflict and confusion among interdisciplinary team members.

**CONCLUSION**

The risks of postoperative morbidity and mortality are clearly elevated for patients with PAH. While retrospective studies have identified factors such as NYHA
Table 3: Questions to be answered preoperatively for the PH patient

<table>
<thead>
<tr>
<th>1. Is the planned surgery elective and might the morbidity and mortality risks be avoided by choosing a nonsurgical management strategy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Is the type of PH well characterized or is further testing required to confirm WHO group or subgroup diagnosis?</td>
</tr>
<tr>
<td>3. Has the patient been recently evaluated with history, examination, BNP/blood testing, echocardiogram or MRI, and possibly right heart catheterization to assess right ventricular function?</td>
</tr>
<tr>
<td>4. If right ventricular function is not optimized (eg, volume overload/edema/ascites, TAPSE &lt;2 cm, elevated BNP, cardiac index &lt;2), can the surgery be safely delayed while additional treatment options are initiated? Is there time to initiate a pulmonary rehabilitation program?</td>
</tr>
<tr>
<td>5. Has the medical center for the proposed surgery been matched with regard to availability of essential PH medications, anesthesia, and surgical expertise to manage potential intra- and perioperative challenges in patients with PH?</td>
</tr>
<tr>
<td>6. Is there an intra-, peri-, and postoperative plan and lines of responsibility communicated to involve all members of the patient’s PH multidisciplinary care team?</td>
</tr>
<tr>
<td>7. Is there a health care proxy clearly identified and has there been substantial conversation regarding goals of care and complications that might result in changes in DNR status?</td>
</tr>
</tbody>
</table>

FC ≥2, RV hypertrophy, and RVIMP ≥0.075 as preoperative risk factors associated with increased risk, further prospective research is much needed to guide our management of these individuals. A methodical approach to this issue, including a thorough patient assessment and detailed preoperative planning, is imperative to optimize outcome. The best response to the question, “Can I send my patient with PAH for surgery?” may ultimately be, “Have the key preoperative questions been adequately addressed” (Table 3). The process necessitates consideration of nonsurgical alternatives, establishing WHO group, assessing status of right heart function, optimizing the treatment regimen, and communicating potential intraoperative concerns and medication plans to all members of the multidisciplinary care team. Despite the elevated risks facing PAH patients with surgery, careful planning and close collaboration of specialists may provide the best possible outcome.

References

Intraoperative Management of Patients with Pulmonary Hypertension

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Patients with pulmonary hypertension are some of the most challenging for an anesthesiologist to manage. Pulmonary hypertension in patients undergoing surgical procedures is associated with high morbidity and mortality due to right ventricular failure, arrhythmias and ischemia leading to hemodynamic instability, and intra- and postoperative hypoxia. Considering the challenges that these patients pose in the perioperative period, it is critical for anesthesiologists, surgeons, and other physicians who care for these patients to be well versed in managing pulmonary hypertension. The purpose of this article is to review the anesthetic considerations that pertain to patients with pulmonary hypertension in the perioperative period, with particular emphasis on the choice of anesthesia, the relative risks of moderate sedation and general anesthesia, and the most recent intraoperative monitoring recommendations.

Until relatively recently, most patients with idiopathic pulmonary arterial hypertension (IPAH) were not expected to survive more than a few years beyond the initial diagnosis. Pulmonary hypertension was a difficult condition to manage, and a relative contraindication to anesthesia. However, with the advent of innovative treatments, the functional status and life expectancy of patients with this condition has increased significantly. Thus, today, anesthesiologists are more likely to encounter patients with pulmonary hypertension presenting for elective surgical procedures.

The anesthetic management of patients with pulmonary hypertension requires a concerted approach guided by the etiology of the disease and the nature of the surgical procedure. Understanding the cause, type, and severity of pulmonary hypertension allows the clinician to formulate a management plan that balances the risks and benefits of the various anesthetic and surgical alternatives.

**DEFINITION AND CLASSIFICATION OF PULMONARY HYPERTENSION**

Properly defining pulmonary hypertension requires invasive measurement of the pulmonary artery pressures via right heart catheterization. According to the 4th World Symposium, pulmonary hypertension is defined as "a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg at rest, based on a review demonstrating that the normal mPAP is 14.0±3.3 mm Hg."\(^1\)

The disease of pulmonary hypertension arises from several etiologies; the elevations in pulmonary artery pressure may result from increased pulmonary artery resistance, increased pulmonary venous pressures, increased blood flow, or a combination of these factors.\(^2\) The evolution of pulmonary hypertension can be insidious. Many patients present with vague complaints such as fatigue and shortness of breath. Unless there is a high index of suspicion, selecting the appropriate workup to identify the disease can present a diagnostic challenge.

The World Health Organization (WHO) classifies pulmonary hypertension into 5 groups on the basis of the mechanisms causing the disease. These are:

1. Pulmonary arterial hypertension (PAH)
2. Pulmonary hypertension owing to left heart disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension related to disorders affecting the pulmonary vasculature with unclear multifactorial mechanisms

These categories in turn encompass multiple etiologies, such as heritable factors, connective tissues diseases, valvular heart disease, hypoxia, and other yet to be elucidated mechanisms. This classification reveals the extraordinarily varied clinical situations that can lead to this condition.\(^3\) However, the anesthetic management of pulmonary hypertension is so dynamic in nature that the underlying WHO classification, while important for the patient's overall management, does not necessarily dictate the choice of anesthetic technique or monitoring. Rather, these choices are constrained by the overall condition of the patient and the severity of the disease, coupled with the nature of the surgical procedure.

**PREOPERATIVE EVALUATION OF PATIENTS WITH PULMONARY HYPERTENSION**

The signs of pulmonary hypertension (Table 1) include dyspnea, fatigue, angina, and syncope. Syncope is an ominous sign, associated with a poor prognosis.\(^2\) Echocardiography can be used to estimate pulmonary artery pressures, right and left ventricular size and function, valvular abnormalities, and
The practice of anesthesia involves the pharmacological manipulation of patient physiology such that the noxious stimulation of surgery is not perceived by the patient. Two broad strategies exist, and the selection to general anesthesia. Inherent in this is the consideration of pain (usually within a field block around the surgical site) and dynamic titration of sedation. While some degree of hypercapnia is likely to occur due to respiratory depression. Increasing dosages of these or similar agents will lead to a state of general anesthesia, in which the patient may respond only to the most noxious of stimuli and will be unable to maintain suitable ventilation without instrumentation of the airway. Supraglottic airway devices such as the laryngeal mask airway (LMA) are often appropriate for supporting the airway during moderate surgical procedures of the extremities, of less than 3 hours' duration. Placement of these devices is usually well tolerated shortly after the onset of unconsciousness and apnea, and adequate ventilation via the LMA may often be maintained with support once residual spontaneous respiratory activity returns. General anesthesia for major procedures will usually require endotracheal intubation, for which more profound levels of unconsciousness are achieved, accompanied by the induction of paralysis with neuromuscular blockers. Even in the unconscious, paralyzed patient, endotracheal intubation can be a highly stimulating procedure triggering significant sympathetic outflow, tachycardia, and hypertension. Paralyzed patients require controlled ventilation. Ultimately, for major surgeries performed on the heart, lungs, or major proximal blood vessels such as the aorta, cardiopulmonary bypass and even intentional hypothermic cardiac arrest may be indicated.

Within this second strategy, monitored anesthesia care (MAC) is sometimes used to denote the practice of moderate sedation with propofol. However, this nomenclature is incorrect. MAC is the process of continual reassessment of the patient’s clinical state and dynamic titration of sedation. While performing MAC, an anesthesiologist may appropriately provide no sedation at all, or conversely may decide to transition to general anesthesia. Inherent in this is the consideration of pain (usually within a field block around the surgical site) and dynamic titration of sedation. While some degree of hypercapnia is likely to occur due to respiratory depression. Increasing dosages of these or similar agents will lead to a state of general anesthesia, in which the patient may respond only to the most noxious of stimuli and will be unable to maintain suitable ventilation without instrumentation of the airway. Supraglottic airway devices such as the laryngeal mask airway (LMA) are often appropriate for supporting the airway during moderate surgical procedures of the extremities, of less than 3 hours' duration. Placement of these devices is usually well tolerated shortly after the onset of unconsciousness and apnea, and adequate ventilation via the LMA may often be maintained with support once residual spontaneous respiratory activity returns. General anesthesia for major procedures will usually require endotracheal intubation, for which more profound levels of unconsciousness are achieved, accompanied by the induction of paralysis with neuromuscular blockers. Even in the unconscious, paralyzed patient, endotracheal intubation can be a highly stimulating procedure triggering significant sympathetic outflow, tachycardia, and hypertension. Paralyzed patients require controlled ventilation. Ultimately, for major surgeries performed on the heart, lungs, or major proximal blood vessels such as the aorta, cardiopulmonary bypass and even intentional hypothermic cardiac arrest may be indicated.

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### Table 1: Clinical Signs of Advanced Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Dyspnea at rest</td>
</tr>
<tr>
<td>Low cardiac output with metabolic acidosis</td>
</tr>
<tr>
<td>Hypoxemia</td>
</tr>
<tr>
<td>Third and fourth heart sound of right ventricular origin</td>
</tr>
<tr>
<td>Large &quot;a&quot; wave in jugular pulse</td>
</tr>
<tr>
<td>Prominent &quot;v&quot; waves in jugular pulse with holosystolic murmur, indicating tricuspid regurgitation</td>
</tr>
<tr>
<td>Diastolic murmur of pulmonary regurgitation</td>
</tr>
<tr>
<td>Right-heart failure (hepatomegaly, peripheral edema, and ascites)</td>
</tr>
<tr>
<td>Syncope</td>
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</tbody>
</table>

physiological derangements in order to induction of transient but significant of anesthesiology may involve the emergency circumstances. The practice procedure is major and performed under operative period, particularly if the surgical morbidity and mortality in the perioper- tension is associated with increased derangements are generally well tolerated and ultimately reversible without pro- longed adverse consequences. Nevertheless, when administering anesthesia, including induction, maintenance, and emergence, patients may be exposed to physiological insults such as: periods of apnea and hypoventilation, periods of hypoxemia, fluctuations in body temperature, episodes of systemic hypotension, bursts of intense sympathetic stimulation arising from the unconscious experience of somatic pain, rapid fluid shifts and changes in cardiac preload, and mechanical ventilation. The nature of the pathophysiology of pulmonary hypertension is such that any of the abovementioned conditions may be poorly tolerated, leading to rapid and potentially irreversible clinical deteriora- tion. The acuity with which this deterioration can occur makes the intra- operative management of patients with pulmonary hypertension challenging and demands particular attentiveness. The goals of the anesthetic management of pulmonary hypertension therefore include maintaining an adequate balance between the preload and ventricular contractility, and maintaining the cardiac output by exercising control of the pul- monary vascular resistance (PVR) and right ventricular afterload. Hypoxia, hypercarbia, hypothermia, and inade- quately controlled pain must be avoided.

Hemodynamic changes can occur rapidly in these patients, and therefore invasive arterial blood pressure monitoring is almost always indicated as part of the anesthetic plan. In patients with significant pulmonary hypertension, either pulmonary artery catheterization or transesophageal echocardiography can be very helpful in guiding anesthetic management, particularly in high-risk procedures. However, pulmonary artery rupture caused by a pulmonary artery catheter—a disastrous complication—is more likely to occur in patients with pulmonary hypertension and the risks and benefits of this monitoring tool must be carefully weighed. The placement of a pulmonary artery catheter may also result in transient atrial and ventricular arrhythmias that can compromise right ventricular filling. While a small risk of esophageal injury attends to the use of transesophageal echocardiography, this technique provides valuable and direct information on ventricular filling and monitoring of wall motion abnormalities and allows the onset of ventricular ischemia to be detected with high sensi- tivity.

The assessment of perioperative risk depends on the type of surgery, the severity of pulmonary hypertension, and the functional status of the patient. The outcomes of major noncardiac surgeries showed mortality and short-term mor- bidity rates of 7% and 42% respectively. However, for patients with portopul- monary hypertension undergoing liver transplantation presenting with mPAP of greater than 50 mm Hg, mortality was found to be 100%. Thoracic surgery can lead to significant changes in intrathoracic pressures and oxygenation, which in turn can worsen pulmonary hypertension and precipitate right ven- tricular dysfunction. Laparoscopic operations require a carbon dioxide pneumoperitoneum, often resulting in hypercapnea and increased intra-abdominal pressures that are transmitted across the diaphragm to the thorax. These increases in intrathoracic pressures decrease preload and increase afterload that can trigger hemodynamic instability. Therefore, although laparoscopic proce- dures are commonly considered to be more tolerable than the comparable open approach, they may be less well tolerated by patients with pulmonary hyper- tension.

When planning operative man- agement, it is critical to have elucidated the etiology of the disease and to have addressed the underlying causes. For patients receiving warfarin for PAH, it should be discontinued prior to the surgical procedure. The assessment for the need to bridge the patient with heparin must take into consideration the type and length of surgery as well as the patient’s underlying comorbidities and
risks for thromboembolic events and risk of bleeding. For patients being treated for pulmonary hypertension, it is important to minimize any interruption and to continue the therapies before, during, and after the operation. This is especially critical for patients receiving continuous systemic prostanoid infusions (epoprostenol, treprostinil), for any rapid change in dose can potentially lead to hemodynamic worsening and decompensation from right ventricular dysfunction. Systemic hypotension should be managed with vaspressors rather than reducing or stopping the pulmonary vasodilator infusion. Patients receiving chronic inhaled treatments (iloprost, treprostinil) should continue these treatments with the fewest possible interruptions. If patients are unable to perform the inhaled treatments, a short-term bridge with inhaled nitric oxide or a low-dose infusion of epoprostenol should be considered. In the event that the patient does not have a pre-established treatment regimen, and if the surgery is not elective and cannot be delayed to establish one, the treatment of choice is inhaled nitric oxide and/or a phosphodiesterase inhibitor (with close monitoring of systemic blood pressure).

Patients can be provided with light and carefully titrated preoperative sedation in order to induce anxiolysis, and to minimize discomfort from procedures such as arterial line placement. It is prudent to ensure that these patients also receive supplemental oxygen to avoid inadvertent oxygen desaturation. Depending on the nature of the surgery, it may be possible to perform either a peripheral nerve block or a neuraxial block to reduce or even eliminate the pain associated with the procedure. Where possible, the use of these regional anesthetic techniques can help to resolve the dilemma of providing too much parenteral pain relief with opioids, thus inducing respiratory depression and hypcapnea, or providing insufficient analgesia resulting in excessive sympathetic stimulation. The use of spinal anesthesia is considered to be relatively contraindicated due to the rapid fluctuations in systemic blood pressure, and hence afterload and preload changes that this technique will generally cause. However, a similar anesthetic effect may be achievable with epidural anesthesia or with an indwelling subarachnoid catheter, allowing the level of neuraxial anesthesia to be increased incrementally, minimizing the same risk of cardiovascular instability. Care must be taken that any anticoagulation regimen is properly held prior to neuraxial anesthesia in order to reduce the risk of an epidural hematoma. Even when an anesthetic based solely on regional or neuraxial anesthesia is planned, placement of invasive hemodynamic monitors must be considered. Although pregnancy is contraindicated in patients with pulmonary hypertension with known association of high morbidity and morbidity, epidural anesthesia is the preferred modality for analgesia for labor and vaginal delivery, or for caesarian section. Although the mortality and morbidity of pregnant patients with pulmonary hypertension, including those undergoing surgical delivery, seems to have decreased in recent times, it still remains relatively high, having been reported from 30% to 70% depending on the study.

General anesthesia can be induced in the usual manner with either propofol or etomidate. Propofol may decrease systemic vascular resistance (SVR), venous return, and myocardial contractility. Induction with etomidate maintains hemodynamics without affecting the PVR, but may not be as effective in blunting the hypertensive response to laryngoscopy and intubation. Opioids (eg, fentanyl) can be administered to attenuate the sympathetic response to laryngoscopy and intubation, which can otherwise potentially increase mPAP to super-systemic levels and trigger hemodynamic decompensation. The appropriate administration of these drugs depends on the clinical circumstances and the observed patient response. Muscular relaxation can be achieved with depolarizing (ie, succinylcholine) or nondepolarizing (eg, vecuronium, rocuronium) neuromuscular blocking agents. The use of nondepolarizing agents that can trigger histamine release (eg, atracurium, cisatracurium) should be avoided. The induction of general anes-

The anesthetic management during the surgical case involves careful...
Table 2: Suggested Treatment of Pulmonary Hypertension During Surgery

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Inhaled nitric oxide</td>
<td>10-40 ppm</td>
</tr>
<tr>
<td>Milrinone (phosphodiesterase 3 inhibitor)</td>
<td>An infusion of 0.25-0.75 µg/kg/min (initial 50 µg/kg bolus optional, see text)</td>
</tr>
<tr>
<td>Inhaled epoprostenol (continuous)</td>
<td>10-50 ng/kg/min</td>
</tr>
<tr>
<td>Intravenous prostacyclin</td>
<td>4-10 ng/kg/min</td>
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Treatments must be weaned gradually postoperatively.


replacement of fluids and blood products to replace measured and insensible surgical losses in order to maintain euvolemia and right ventricular preload. Table 2 summarizes agents that can be administered to reduce PVR. These agents may also tend to cause systemic hypotension sufficient to require correction. Milrinone can be used with a bolus, as described in Table 2, to assist in separating patients with pulmonary hypertension from cardiopulmonary bypass when undergoing cardiac surgery. Cardiopulmonary bypass provides some protection against the hypotension that may occur with the initial bolus of milrinone.21 In circumstances such as off-pump coronary artery bypass surgery, it may be appropriate to omit the bolus in order to reduce the hypotensive effect.22 In the event of systemic hypotension, inotropic agents should be administered. Dobutamine is the most commonly used agent: a β-agonist that provides chronotrophic and inotropic effects along with systemic and pulmonary vasodilation. If hypotension persists, then a vasoconstrictor should also be added in order to restore coronary artery perfusion. Norepinephrine provides both vasoconstriction and inotropic support through α- and β-adrenergic stimulation and decreases PVR/SVR ratio at lower doses (<0.5 mcg/kg/min). However, its metabolism by the pulmonary endothelium can be inhibited in patients with pulmonary hypertension, causing its serum concentration to increase beyond the intended level with increase in PVR/SVR ratio. Used in lower doses, it can improve right ventricle/pulmonary artery coupling and is considered the best first-line agent in patients with pulmonary hypertension and right heart failure and hypotension. Vasopressin is a V₁ receptor agonist and produces systemic vasoconstriction. Dose-related coronary vasoconstriction has been reported at high doses (>0.4 U/min), though higher doses have been used and can be well tolerated. Vasopressin can be less arrhythmogenic than norepinephrine and is effective for treatment of systemic hypotension refractory to norepinephrine or as a first-line agent.

These perioperative challenges persist into the postoperative period. Any treatments that were instituted intraoperatively should be carefully weaned under close monitoring. Patients with pulmonary hypertension remain at higher risk for complications including sudden death in the days after surgery and should be monitored in an intensive-care setting.

CONCLUSION

Today, anesthesiologists are able to manage pulmonary hypertension more effectively because there is a deeper understanding of the disease, a broader range of therapeutic alternatives, and improved monitoring capabilities. The increasing availability of intraoperative transesophageal echocardiography provides instantaneous information about right and left ventricular dimensions and contractility, which can greatly facilitate the administration of anesthesia. Although the anesthetic management of patients with pulmonary hypertension continues to be a challenge, a thorough assessment of the patient, careful planning, and meticulous attention to detail minimizes the possibility of complications and allows for the best possible outcomes.

References

Severe pulmonary hypertension during pregnancy: mode of delivery and anesthetic management of 15 consecutive cases. *Anesthesiology*. 2005;102(6):1133-1137; discussion 5A–6A.


Postoperative Care of the Patient With Pulmonary Hypertension

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CASE: SH is a 46-year-old woman with idiopathic pulmonary arterial hypertension (IPAH) (World Health Organization [WHO] Group 1), New York Heart Association functional class (NYHA FC) I, treated with bosentan and sildenafil as well as with anticoagulation. She was diagnosed with IPAH 10 years prior and her most recent right heart catheterization (RHC) showed a right atrial pressure of 7 mm Hg, mean pulmonary artery pressure (mPAP) of 48 mm Hg, cardiac output of 5.3 L/min, and pulmonary vascular resistance (PVR) of 7.1 Wood units. She was transferred to our intensive care unit with vaginal bleeding significant enough to cause systemic hypotension associated with a cardiac troponin leak and requiring multiple units of transfusions. Uterine artery embolization was attempted by interventional radiology at our institution, but the patient continued to have significant bleeding postprocedure. The patient ultimately was urgently taken to the operating room and underwent dilation and curettage while receiving general anesthesia. The patient tolerated the procedure well, was extubated, and transferred to the intensive care unit on 100% oxygen delivered by face mask. The surgical team requests consultation regarding postoperative management. What advice would you give?

Summary: Pulmonary hypertension (PH) is a known contributor to increased morbidity and mortality in cardiac and noncardiac surgery. Careful postoperative management is necessary to prevent worsening right ventricular (RV) dysfunction and failure. Attention must be paid to volume status (both hypervolemia and hypovolemia are deleterious), oxygen levels, and acid-base status. Continued administration of pulmonary arterial hypertension (PAH)–specific medications is imperative in the postoperative period; alternative delivery of outpatient medications, adjustment of dosing, or even changes in medication class may be required based on the clinical situation (eg, ability to swallow, dexterity and coordination for inhaled therapy, renal and hepatic functions, etc). Adequate pain control is also important as activation of the sympathetic nervous system can cause worsening PH; however, this must be balanced with the potential for systemic effects of analgesics to negatively affect cardiopulmonary function. While these and other factors likely impact the clinical course and outcomes of patients with PH who undergo surgery, there are scant data in the literature to guide therapy. Taken together, these issues highlight the challenges that exist in the postoperative care of patients with PH. In this manuscript, we present our approach to the postoperative management of PH patients. A general overview of this approach is presented in Figure 1.

LOGISTICS  
Good postoperative care of a PH patient starts in the preoperative period. As discussed in detail elsewhere in this issue of Advances in Pulmonary Hypertension, preoperative assessment is critically important in PH patients. Postoperative complications are likely related to preoperative factors concerning the patient, planned surgery, and anesthesia (see below). One practical aspect of preoperative assessment pertains to postoperative logistics. Before a PH patient is scheduled for surgery, we have found it helpful to determine in which unit(s) the patient will likely reside postoperatively and whether the staff in these units are trained in inhaled, subcutaneous, and intravenous prostacyclin administration. It is imperative to ensure that the patient will be cared for in a unit where nursing staff are experienced in both taking care of PH patients and their medical regimen. If there is a lack of experience with the management of these medications, unit staff should be in-serviced prior to the patient’s scheduled surgery. In our hospital, we often arrange to bypass the postoperative recovery unit for inpatient procedures and return patients to our intensive care unit. Further, we often admit patients overnight for monitoring even for procedures that are generally performed on an outpatient basis.

We ask that our PH faculty and staff...
are notified as soon as our patients are out of the operating room; one member of our team then sees and evaluates the patient as soon as possible, within a maximum of 30 minutes. In addition to reviewing the operative note and anesthesia flow sheets, the PH team member assesses the patient, confirms that PH medications are ordered correctly and immediately postoperatively, and ensures that medications have been given appropriately. Further, he or she reviews management principles (see Figure 1) with the nursing staff and house staff to prevent common therapeutic errors. A member of our PH team sees the patient daily during the admission. We ask our surgical colleagues to defer assessment of medical readiness for discharge and often will assume primary care of the patient when the acute surgical issues have resolved.

SURGICAL AND ANESTHESIA CONSIDERATIONS
The type of surgery and anesthesia used influence the perioperative risk and postoperative management. Multiple factors in each of those realms influence this risk, as shown in Table 1. For example, as one would expect, emergency surgeries are associated with greater mortality than nonemergent procedures. To mitigate this risk in our patient’s case, we recommended a shorter stabilizing procedure (dilation/curettage) for urgent control of bleeding. The hysterectomy, the definitive but more extensive surgery, was deferred to be performed when the patient was more clinically stable. Selection of anesthesia is also important, as detailed elsewhere in this issue. Knowledge of the potential effects of mode, type, and agent used for anesthesia is particularly important in PH patients. Similarly, mechanical ventilation (MV) confers varying degrees of postoperative risk given the complex cardiopulmonary interactions in the PH patient who receives positive pressure ventilation. Our experience suggests patients who are critically ill and require MV have very poor outcomes. Given these considerations, it is our practice to involve cardiac anesthesia specialists for all patients with PH requiring general anesthesia for any procedure. We discuss the operative plan with the surgeon to ensure an understanding of the potential peri- and postoperative risks and of the potential intraoperative complications that would influence postoperative management. Further, we discuss with the surgeon whether it is feasible to avoid MV if at all possible.

PATIENT CONSIDERATIONS
A myriad of patient factors may also influence complications postoperatively. However, there are few studies examining the predictors of peri- and postoperative complications in PH. In a recent prospective study of 114 patients with PAH undergoing noncardiac and nonobstetric surgery, Meyer and colleagues reported a 3.5% perioperative mortality rate, considerably less than the 7%-18% suggested in smaller retrospective studies. The risk factors for major complications (bleeding greater than 1 liter, systemic inflammatory response or sepsis requiring vasopressor therapy, right heart failure [RHF] requiring inotropic support, or death) after surgery were a pre-operative 6-minute walk distance of less than 399 meters and a right atrial pressure of greater than 7 mm Hg. Our patient’s most recent RHC, 2 years prior, showed a right atrial pressure of 7; her 6-minute walk distance was 516 meters.

Ramikrishna et al did not find that 6-minute walk distance affected short-term morbidity after noncardiac surgery, but did find that NYHA FC II
or higher, history of pulmonary embolism, RV hypertrophy, RV systolic pressure to systolic blood pressure ratio >0.6, and RV index of myocardial performance index (Tei index, calculated by dividing the sum of RV isovolumic relaxation and contraction times by the ejection time interval) >0.75 were associated with increased morbidity.

We also consider non-PH–specific patient factors when assessing perioperative risk. Multiple groups have looked at patient factors that influence outcomes in patients admitted for RHF. High respiratory rate, renal dysfunction, hypokalemia, severity of tricuspid regurgitation, systolic blood pressure <100, and the presence of connective tissue disease have each been independently found to be associated with mortality. While some of these factors are immutable and admissions for RHF are certainly different than for surgery, we use these factors as a guideline when considering operative risk preoperatively along with postoperative management and risk assessment.

Based on these studies and our clinical experience, our approach is to assess NYHA FC, 6-minute walk distance, N-terminal brain natriuretic peptide levels (NT-proBNP), renal function, and echocardiography in all PH patients prior to any procedure that requires general anesthesia. If a patient demonstrates significant differences from prior evaluations (typically, we collect these data yearly for clinical purposes), then we augment therapy by increasing diuresis (if clinically indicated) or adding PAH therapy. If a patient requires higher risk surgery (Table 1), we prefer to repeat the RHC to directly assess PH severity and to guide preprocedure interventions (such as increasing diuresis or adding PAH-specific therapy). Occasionally, we will repeat the RHC to determine response to these interventions prior to the planned procedure, particularly if the patient has severe PH. We look for any improvement in pulmonary artery pressures or cardiac output, or decrease in right atrial pressure and PVR. We do not routinely look for a nitric oxide response unless the patient has demonstrated a prior response to nitric oxide and we want to ensure that this response has endured. Due to the urgent nature of the required intervention, we did not perform a RHC prior to our patient’s procedure. However, we did obtain NT-proBNP and an echocardiogram prior to surgery; the NT-proBNP was significantly elevated at 10,500 pg/mL (normal range 0-135 pg/mL), and the echocardiogram demonstrated RV pressure and volume overload with significantly reduced systolic function when compared to the echocardiogram from 1 year earlier. Thus, based upon these data, we recommended a shorter, stabilizing procedure due to our concerns for peri- and postoperative complications.

PULMONARY HYPERTENSION MEDICATIONS

Our patient was on sildenafil and bosentan prior to surgery, both oral medications. Other PH patients may be on continuous intravenous, subcutaneous, or inhaled prostacyclin analogues. Sudden withdrawal of pulmonary vasodilators may result in rebound PH.

Further, perturbations in cardiopulmonary function resulting from the effects of anesthesia, MV, and infusions of fluid can adversely impact RV function. Thus, maintenance of preoperative PAH medications is of paramount importance. We review and potentially change the time schedule of our patients’ PH medications to ensure that daily PH medications are taken on the morning of surgery rather than the night before, and inhaled therapy times are adjusted to allow for a dose to be taken on-call to the operating room. If a patient is on subcutaneous or intravenous prostacyclin therapy, close monitoring and collaboration with the anesthesiology team is required. Additionally, close attention must be paid to the dosing of PH medications if a patient experiences systemic hypotension. Because 1) systemic hypotension may be related to multiple potential etiologies including sepsis, hemorrhage, and acute RHF (among others), and 2) reduction or cessation of pulmonary vasodilators may further exacerbate the systemic hypotension, we ask that any changes to PAH-specific medications be approved by our PH faculty and staff after careful evaluation of the patient. Additionally, issues of potentially increased toxicity or decreased bioavailability related to acute liver, kidney, or gastrointestinal injury must be considered; often we will consult with critical care pharmacists to help with medication dosing in these situations.

Before surgery, a backup plan should be made if a patient is unstable or unable to take oral medications; we often use inhaled nitric oxide (iNO) for pulmonary vasodilation in place of oral agents as a temporizing measure. Availability of this agent varies by hospital and should therefore be confirmed prior to an individual patient’s surgery. Intravenous sildenafil is available commercially, but may not be on formulary at a particular institution. Dosing of intravenous sildenafil is 10 mg 3 times a day, which is equivalent to 20 mg orally 3 times a day. Also due to variations in hospital formularies and availability of medications in general, we ask all patients to bring their PH medications to the hospital, even if the medication is on formulary. We ask

Table 1. Surgical and Anesthetic Risk Factors for Postoperative Complications

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Higher Risk</th>
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<tbody>
<tr>
<td><strong>Surgical</strong></td>
<td>Vascular, Cardiothoracic, Abdominal Emergency</td>
</tr>
<tr>
<td>Type of Surgery</td>
<td>Emergency Greater Than 3 Hours</td>
</tr>
<tr>
<td>Emergency vs Elective</td>
<td>Propofol vs Etomidate</td>
</tr>
<tr>
<td>Duration of Surgery</td>
<td>Nitrous or Halothane</td>
</tr>
<tr>
<td><strong>Anesthesia</strong></td>
<td>Higher vs Lower Tidal Volume</td>
</tr>
<tr>
<td>Type of Induction</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Type of Anesthesia</td>
<td>Hypercapnia</td>
</tr>
<tr>
<td><strong>Mechanical Ventilation</strong></td>
<td></td>
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<tr>
<td>Tidal Volume</td>
<td></td>
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<tr>
<td>Oxygenation</td>
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<tr>
<td>Ventilation</td>
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families to hold the patient’s medications until the patient is admitted to the postoperative unit to minimize risk of misplacement. Our patient was maintained on her oral therapies perioperatively and did not require iNO.

**BLEEDING AND THROMBOSIS**

Many patients with PH are prescribed prostacyclin analogues, which carry a theoretical risk of bleeding. Observational studies have demonstrated a higher prevalence of thrombocytopenia in patients on intravenous prostacyclin. Additionally, patients with PAH have abnormalities in platelet function that may influence bleeding risk. However, studies have not shown any increased risk of postsurgical bleeding in PAH patients in general or in those using prostacyclin analogues.

If a patient develops a postoperative bleed, it is important to assess the severity of the bleed and if a surgical intervention is warranted. Transfusion of packed red blood cells (PRBC) should be used with an appropriate degree of caution, balancing the risks of bleeding with risks of volume overload and subsequent RV dysfunction. Typically, for the patient who develops hypotension in the setting of a bleed, we stabilize the patient with intravenous vasopressors while determining whether the bleeding site can be identified and corrected. We transfuse patients with life-threatening bleeding, but typically follow each unit of PRBC with intravenous diuretic to mitigate the volume effects on the pulmonary vasculature and RV. For patients who are anticoagulated, or have another bleeding diathesis such as thrombocytopenia and develop bleeding, a similar approach is employed. However, we have a very high threshold for correcting such coagulopathies with either fresh frozen plasma (FFP) or platelet transfusions due to concerns about acute worsening of PH. Both of these substances contain thromboxane A2, a potent pulmonary vasoconstrictor, which could theoretically increase RV afterload acutely. While purely anecdotal, we have had several patients experience poor outcomes immediately following transfusion of either FFP or platelets and thus avoid these transfusions if possible. Fortunately, our patient did not have a coagulopathy and did not require these blood products.

The majority of postoperative patients are at increased risk of pulmonary embolism. Patients with right heart dysfunction can decompensate with even a small pulmonary embolism. We therefore recommend immediate non-invasive mechanical deep venous thrombosis (DVT) prophylaxis and pharmaceutical prophylaxis when it is safe to do so. If a patient is anticoagulated for PH, anticoagulation should be restarted when safe from a surgical perspective; such patients do not need to be bridged. (The exception is patients with chronic thromboembolic PH, WHO Group 4 disease, who should be bridged with intravenous or subcutaneous anticoagulation.) Early mobilization strategies should also be employed.

**ARRHYTHMIAS**

Postoperative arrhythmias are common complications after surgery, affecting up to 60% of postcardiac surgery patients and up to 30% of noncardiothoracic surgery patients. In one study of PH patients undergoing noncardiac surgery, 12% developed cardiac dysrhythmia, defined as new onset atrial fibrillation, supraventricular tachycardia, bradycardia with conduction block, or ventricular tachycardia/fibrillation. Atrial arrhythmias, even when rate controlled, are poorly tolerated in patients with PH. The inability to restore sinus rhythm in this population is associated with high 1-year mortality; however, the short-term impact of new onset atrial arrhythmias is unknown. Management of PH patients with atrial arrhythmias postoperatively is challenging. Standard first-line medical therapy for rate control (calcium channel blockers and beta-blockers) is poorly tolerated in patients with significant PH due to potential negative inotropic effects on the RV and should be avoided in the emergent or urgent setting.

If a patient develops a new onset atrial (or other) arrhythmia, management principles do not vary from traditional practice beyond avoidance of beta-blocker and calcium channel blocker therapy. If a patient is hemodynamically unstable with the new onset arrhythmia, then advanced cardiac life support protocols should be employed. If the patient is hemodynamically stable, then identification of potentially reversible causes of new onset atrial arrhythmias should be sought. Commonly, electrolyte imbalances, volume overload, or hypoxia may be the precipitant for these arrhythmias; treatment of these may resolve the problem. Other potential causes, such as pulmonary embolism, should be considered, evaluated, and treated if other etiologies are ruled out or if the clinical picture supports this diagnosis. In any case, our patients with atrial arrhythmias all receive cardiac monitoring. We tend to involve our electrophysiology team early in the process, as elective cardioversion may be indicated given the limited ability of medical therapies to safely return the patient to sinus rhythm. We treat our patients with digoxin and amiodarone (standard loading protocol followed by a maintenance dose of generally not more than 200 mg/day) if digoxin alone is not effective.

**GENERAL POSTOPERATIVE CARE**

As for any patient, good postoperative care in PH patients should focus on prevention of complications. Thus, DVT prophylaxis (as mentioned above) should be maintained. Early mobilization with the assistance of physical therapists if needed is also important. We ask for all of our patients to have daily standing (not in bed) weights and strict collection of intake and output to follow trends. Commonly, patients with PH will experience weight gain 24–48 hours postoperatively that likely reflects mobilization of third-spaced fluid. Augmentation of diuretic dosing is often required and is dictated by symptoms, examination findings of volume overload, and trends in weights and output. Removal of arterial lines and pulmonary arterial catheters should be done as soon as medically appropriate. Pulmonary toilet, with use of incentive spirometer and sometimes flutter—*or a capella*—valves, is useful to promote airway clearance and to reverse or prevent atelectasis. As discussed below, supplemental oxygen should be used to maintain high...
oxygen saturations as hypoxia can worsen PH. We recommend checking ambulatory oxygen saturations as a patient nears discharge to see if he or she may require higher flow rates of supplemental oxygen than baseline or if he or she demonstrates a new oxygen requirement. New or higher flow requirements are often found in our PH patients postoperatively, but the need tends to resolve within a few weeks of discharge with appropriate convalescence. Our patient did develop a new oxygen requirement while in the hospital and was discharged with supplemental oxygen; she was able to discontinue this within 3 weeks of her surgery.

**THE CRITICALLY ILL POSTOPERATIVE PH PATIENT**

**Mechanical Ventilation**

There is a paucity of evidence regarding ventilation strategies for MV in patients with PH. While increasing intrathoracic pressure by positive pressure ventilation may improve left ventricular (LV) function by reducing LV wall stress, attendant increases in alveolar pressure lead to acute increases in mPAP and PVR. In the setting of rapid sequence intubation and subsequent MV, these effects on mPAP and PVR are exacerbated by the systemic effects of anesthetics, analgesics, and sedatives. Subsequent increases in RV afterload lead to decreased pulmonary blood flow and LV preload that will eventually cause systemic hypotension. As hypotension progresses, myocardial perfusion pressure to the RV drops as driving pressure falls and mean ventricular pressure rises; this may lead to RV ischemia, further compromising RV function and exacerbating systemic hypotension. Therefore, minimizing the deleterious effects of MV in PH patients is an important consideration in the management of postoperative complications.

Physiologic studies suggest that PVR is lowest at functional residual capacity (FRC). We therefore recommend a low tidal volume ventilation (around 8 cc/kg ideal body weight) strategy to avoid hyperinflation and decreasing FRC, which increases PVR. While these lower tidal volumes have traditionally been used in the acute respiratory distress syndrome (ARDS), other aspects of ARDS ventilator management should not be routinely employed in patients with right heart dysfunction. High level of positive end expiratory pressure (PEEP) should be avoided, as this can compress alveolar capillaries and cause an increase in PVR. Permissive hypercapnia is not well tolerated in PH patients as carbon dioxide can directly increase PVR; Viitanen et al studied 18 patients with hypercapnia after coronary artery bypass graft surgery and found that hypercapnia increased PVR by 54% and mPAP by 30%. Other studies have shown significant changes in echo-measured maximum tricuspid pressure gradient in response to hypercapnia, even in healthy volunteers. Similarly, hypoxia can increase increased PVR and RV afterload through pulmonary hypoxic vasoconstriction. Thus, whereas oxygen saturations of 90% are well tolerated by the majority of the population, at our center we aim for oxygen saturations of 95% in PH patients. Therefore, we often maintain PH patients on supplemental oxygen during the postoperative period to minimize the risk of hypoxic vasoconstriction. When on MV, we aim for high saturations while balancing the potential for oxygen toxicity.

It is our practice to minimize sedation in our mechanically ventilated patients to quicken liberation from the ventilator. Additionally, many sedatives cause systemic hypotension, which is poorly tolerated in this population. However, inadequate control of pain may lead to sympathetic nervous system activation that increases PVR. Optimal use of sedation and analgesia requires vigilant and careful management.

If a PH patient who was recently liberated from the ventilator develops respiratory distress, we first attempt non-invasive ventilation to prevent the need for invasive ventilation. Similarly, due to the negative effects of invasive positive pressure ventilation on RV function, we will liberate patients from the ventilator who may otherwise be borderline candidates for extubation and immediately place them on noninvasive bilevel support. In our experience, noninvasive support may be better tolerated from a hemodynamic perspective, allowing patients to improve clinically.

**Hypotension and Vasopressors**

Systemic hypotension is a common postoperative occurrence. However, patients with PH may have systemic hypotension at baseline; therefore, it is important to review outpatient records to determine baseline blood pressure. If hypotension is truly new in onset and if there are no overt signs of bleeding as the cause of the hypotension, then one must consider RV volume and/or pressure overload as the etiology of the systemic hypotension. Correction of hypoxia, hypercapnia, arrhythmia, and adequate pain control should be pursued along with other potential causes of hypotension in the ICU such as tension pneumothorax, cardiac tamponade, or sepsis. Unfortunately, frequently the hypotension is refractory to interventions to address these ancillary problems. Aggressive fluid resuscitation in patients with RV dysfunction should be avoided as this can cause right heart dilatation and failure, so we often use vasopressors in our patients with PH and systemic hypotension.

At our center, we recommend the use of dopamine for hypotension. Dopamine use can be limited by the high incidence of arrhythmias associated with its use; however, at low “renal” doses (less than 5 mg/kg/minute infusion), we have found it useful to facilitate diuresis in the setting of RV failure and maintain systemic blood pressure. However, there remain limited randomized controlled data to support the use of dopamine for this purpose. When patients require additional vasopressor support, norepinephrine is often used in this capacity or as initial therapy if there is profound systemic hypotension. Norepinephrine stimulates α and β adrenergic receptors. While this medication does increase both mPAP and PVR, it does so to a lesser degree than other vasopressors while producing similar inotropic effects and supporting myocardial perfusion.

Recent animal studies suggest that dobutamine may offer better inotropic...
support for the RV than dopamine, and some experts recommend this agent as first-line therapy for right heart failure in PH.\textsuperscript{19} We find progressive systemic hypotension limits the utility of dobutamine in many of our patients; therefore, we tend to use it in combination with norepinephrine, particularly if RHF (and not volume depletion) is the major impetus for the hypotension. The majority of dobutamine’s effect is seen at lower doses (5 mcg/kg/min or less). We prefer dobutamine to milrinone, a phosphodiesterase-3 inhibitor, as the latter causes more systemic hypotension and has a longer half-life. However, if dobutamine is not tolerated (ie, arrhythmia), milrinone at lower doses (ie, <0.375 mcg/kg/min) can be considered if the patient has relatively stable blood pressure and preserved renal function (since milrinone is renally excreted). Phenylephrine, a purely α1-adrenergic agent, should be avoided in patients with significant PH. This agent increases mPAP and PVR but decreases cardiac output thereby worsening right heart function.\textsuperscript{20} It may also cause a reflex bradycardia, which can further lower cardiac output. There is a lack of data on the use of epinephrine in patients with PH; at our center we recommend avoiding its use. Vasopressin has historically been avoided because of increased mPAP and PVR with decreased cardiac output in animal models receiving high doses of this medication; however, lower doses may be safe and have been advocated for use by other PH experts as well tolerated and effective in the setting of severe PH, RHF, and hypotension.\textsuperscript{19}

INHALED NITRIC OXIDE

The physical stress of surgery and anesthesia can contribute to RV failure in patients with PH. The keys to treating such failure are optimizing fluid status and reducing RV afterload. We liberally use iNO for the latter. Nitric oxide increases the production of cyclic guanosine monophosphate (cGMP), which reduces intracellular calcium and therefore relaxes smooth muscles. Inhaled nitric oxide acts on the pulmonary vasculature and in theory improves V/Q matching,\textsuperscript{21} as opposed to systemic vasodilators such as nitroprusside, which can worsen V/Q matching and cause systemic hypotension. Nitric oxide has been shown to decrease PVR, increase cardiac output, and increase the PaO\textsubscript{2} to FiO\textsubscript{2} ratio in patients with PH.\textsuperscript{22} The dose of iNO used ranges from 5 to 80 parts per million. If a patient has a pulmonary artery catheter, we titrate iNO dose according to cardiac output and PVR data from the catheter, but we do not require a catheter for its use. We follow daily methemoglobin levels in our patients receiving iNO as iNO can oxidize the heme iron to the ferric state; however, this complication tends to occur in patients who have prolonged exposure at high doses. We also advocate for weaning the iNO once a patient has stabilized. While reductions in dose from 80 ppm to 40 ppm are generally well tolerated, we have found slower weaning once the dose falls below 20 ppm to be a prudent strategy. We recommend reducing the dose by no more than 50% every 3 to 4 hours once the dose is below 20 ppm.

CONCLUSION

In general, good postoperative management of patients with PH depends on 1) a thorough preoperative evaluation as dictated by urgency of surgery) to appropriately risk stratify patients; 2) good communication between the surgeon, anesthesiologist, and PH provider before, during, and after the surgery; 3) prior planning for postoperative care that includes level of care (ICU vs monitored bed), service (medical or surgical), delivery of PAH medications (type, route of administration, and schedule); and 4) institution of usual best practice postoperative care for non-PH patients (DVT prophylaxis, early mobilization, etc). Complications such as development of postoperative arrhythmias and hypotension require thoughtful management as typical interventions, such as intravenous calcium channel blocker therapy for atrial arrhythmia or intravenous phenylephrine infusion for hypotension, may be particularly harmful in the PH patient.

The recommendations proposed in this manuscript are based on experience at our center and are unencumbered by data (ie, there are no guidelines or randomized controlled trial data to which to refer). Additionally, these recommendations pertain to patients with PAH; patients with other forms of PH who require ICU care, for instance, may have specific considerations that would alter management (see Figure 2). For
OUR PATIENT’S OUTCOME
As noted throughout the article, our patient with severe PAH experienced a good outcome despite a significant hemodynamic insult from the massive vaginal bleed. Postoperatively, she did not require reinstitution of invasive MV or institution of noninvasive ventilation. She received her PAH-specific medications orally and did not require iNO. Her postoperative course was otherwise unremarkable and she was discharged home 3 days after the procedure; however, she did require supplemental oxygen for desaturation noted with ambulation. She returned for a total vaginal hysterectomy 3 months later under general anesthesia. She again tolerated this procedure well, was extubated prior to transfer to the intensive care unit, and was discharged home on the second postoperative day.

References
PULMONARY HYPERTENSION ROUNDTABLE

Pulmonary Roundtable – Bariatric Surgery and the PAH Patient

As guest editor of this issue on perioperative issues in PAH patients, Sean Studer, MD, MSc, convened a group of experts to discuss the implications of bariatric surgery for the pulmonary hypertension patient. Given the prevalence of obesity and its sequelae related to PH patients, it’s not an uncommon topic. The approach to patient counseling, minimizing surgical risks, and working with the interdisciplinary team were addressed among the wide range of topics by clinicians on the front lines. Taking part in the conversation were Michael Mathier, MD, Assistant Professor of Medicine, Director, Pulmonary Hypertension Program, and Associate Director, Cardiovascular Fellowship Program of the University of Pittsburgh Medical Center; Dana P. McGlothlin, MD, Medical Director of Combined Heart-Lung Transplantation and Mechanical Circulatory Support, Medical Director of the Cardiac Intensive Care Unit, and Associate Director of the Pulmonary Hypertension Program at the University of California, San Francisco; Ramesh C. Ramanathan, MD, is a surgeon specializing at the University of Pittsburgh Medical Center. Deborah J. Levine, MD, Associate Professor, Pulmonary Disease and Critical Care Medicine, Director, Pulmonary Hypertension Clinic, University of Texas Health Science Center, San Antonio, added comments from the pulmonary perspective to the transcript of the discussion.

Dr Studer: The purpose of today’s roundtable is to gain an interdisciplinary perspective regarding the topic of weight loss surgery in the setting of pulmonary hypertension. Our experts discussants include Dr Michael Mathier (cardiologist), Dr Ramesh Ramanathan (bariatric surgeon), Dr Dana McGlothlin (cardiologist) and Dr Deborah Levine (pulmonologist). Dr Levine’s comments were included following our initial live conversation to include a pulmonary perspective. To begin the discussion, I will ask the participants to comment on the prevalence of obesity in their patient population and their perceptions of its impact on the course of their underlying pulmonary hypertension.

Dr Mathier: I think that obesity is a prevalent issue in pulmonary hypertension (PH) and it’s an increasingly prevalent issue. I think that as we have seen a broader population of patients diagnosed with PH, a subset of whom will be proven to have pulmonary arterial hypertension. We’re seeing more patients who are older, more patients who have the co-morbid conditions that come with age, and obesity is certainly in the mix. While I have not done a formal calculation of this in my own practice, I would estimate that probably a third of the patients that I see have an element of obesity and probably half of those have a degree of obesity that I think significantly impacts their functional status. And you know it may well directly impact the phenotype of their pulmonary vascular disease. Metabolic abnormalities seen in obesity have recently been demonstrated to affect pulmonary vascular structure and function.

Dr McGlothlin: I agree with Mike. I would estimate that about a third of the patients with PAH in my practice have significant obesity as a comorbid condition, similar to what has been shown in the contemporary multicenter, observational, US-based REVEAL registry of PAH patients. And I see obesity in the young patients as well as the old patients, but definitely I would agree that I see it as a more common comorbidity in patients who are older. I also think that it does significantly impact their symptoms of pulmonary hypertension such as functional capacity. I think, Mike, you have some data about the potential impact obesity may have on the pulmonary vascular disease itself. I must admit I know less about that relationship, but perhaps you can share some of what you are learning about obesity and pulmonary vascular disease?

Dr Mathier: It’s very rudimentary at the present time. What we’ve been able to observe is that in a couple of patients who had morbid obesity and clearly diagnosed PAH and were struggling with advanced symptoms despite very aggressive PAH therapy, aggressive weight loss measures markedly improved both functional capacity and to a somewhat lesser extent—but still I think in a meaningful way—their hemodynamics. This was accomplished through bariatric surgery which we’ll discuss as the conversation goes on. I know that the Vanderbilt group has been looking at a more mechanistic understanding of this and there appear to be some very intriguing links between the metabolic changes that are known to occur after dramatic weight loss accomplished through bariatric surgery and subsequent changes to pulmonary hemodynamics. That’s something that I think is going to be more exploration as we go forward so we can really understand the relationship between obesity and PH.

Disclosures: Dr Studer receives research support and has received honoraria from Actelion, Gilead, and United Therapeutics. He has received consulting fees from Bayer, Actelion, and United Therapeutics. Dr McGlothlin has received grant or research support from Actelion and United Therapeutics. Drs Levine, Mathier and Ramanathan report no potential conflicts.
Dr McGlothlin: Yes, I think it’s an interesting relationship and as we’ve seen in the literature on left heart failure, these patients with obesity can have lipotoxicity in the myocardium. I have seen also patients who are obese and have left-sided heart failure with their pulmonary arterial hypertension. And recently at the International Society for Heart and Lung Transplantation, Dr Roham Zamanian presented his data. I know the Stanford group has been interested in insulin resistance and its link to pulmonary arterial hypertension. Interestingly, he found, based on several studies, that it didn’t look like the relationship bore out with regard to its impact directly on the pulmonary vascular disease or the myocardium. But I think the jury is still out. It’s an interesting correlation.

Dr Studer: Do you counsel patients in detail regarding obesity before and at the time of consideration of bariatric surgery? Do you consider weight loss goals pre-op or how we might counsel patients afterward?

Dr Levine: The patient is counseled on their obesity at the time of initial visit and at every visit after that. We have a dietitian at our clinic who not only visits the patients when they are at clinic, but also keeps up with the patient by phone and by email or Facebook to see how their attempt at weight loss is progressing, including both diet and exercise. The dietitian will give our team an update on this at regular intervals. Having this resource has been very beneficial to our patients. Goals of weight, goals of exercise, and ambulation are discussed by the team, including the dietitian, every visit.

Dr Mathier: I think it’s worth pausing here to recognize that the interrelationship between obesity and pulmonary hypertension is a really complex one. And even if we don’t stop to consider the as-of-now somewhat inscrutable mechanistic aspects, we know that obese patients have a physiology that can lend itself to the development of pulmonary hypertension. And that pulmonary hypertension can have any of a number of different kinds of hemodynamic subsets. So we can see in these patients, of course, that they have a diastolic abnormality of the left ventricle with subsequent elevation of left heart pressures and then a secondary form of pulmonary hypertension, what we term WHO Group 2. We know that they can have relatively high cardiac output so that they may end up on hemodynamic assessment having a high transpulmonary gradient but a normal pulmonary vascular resistance. Most of us would not think of that as pulmonary arterial hypertension. We know of course that they can have hypoxemia via either sleep-disordered breathing or the obesity hypoventilation syndrome and that can have an effect on pulmonary pressures where they might be considered a WHO Group 3 patient. And there is a whole host of other things—even short of the kind of well-known metabolic disturbances that occur in obesity—that can play into the development of PH and into the specific phenotype of that PH. So that has to be carefully considered in every patient we see who has the combination of obesity and pulmonary hypertension.

Dr Ramanathan: Both of you said the prevalence of obesity in patients with PH is about one-third. Do you think there are two distinct populations of patients with pulmonary hypertension, with obesity linked to the etiology of PH in one-third and a different mechanism in the other two-thirds?

Dr Mathier: I think that’s too simplistic. I think we honestly don’t know. It is possible for this relationship to exist in either direction. I think there are patients who develop significant PAH and it compromises their functional status so much that they develop obesity over time. In which case the obesity will certainly contribute to their functional limitation, but probably shouldn’t be thought of as potentially causative. But then we also know that people can develop obesity and, through many of these mechanisms that I just spoke about, will develop secondary forms of pulmonary hypertension. Most of us in current PH practice will see the whole spectrum of patients with the combination of obesity and pulmonary hypertension. I think what we have to do is just a very, very careful diagnostic assessment so we can understand as well as possible the relationship between the two.

Metabolic abnormalities seen in obesity have recently been demonstrated to affect pulmonary vascular structure and function.

—Dr Mathier

Dr Studer: Let me ask from that point—as it sounds as if everyone agrees that the problem is increasingly prevalent of obesity in pulmonary arterial hypertension patients and that the relationship between the two is quite complex—when you consider referral to bariatric surgery for these do you look to something like the NIH Guidelines for a body mass index >40 or >35 with comorbidities? Or is it a much more detailed assessment that would lead you to decide who you’re going to ultimately refer for bariatric surgery?

Dr Mathier: Well, I would say the guidelines apply. I don’t think that we should be referring for bariatric surgery patients with more modest obesity simply because they have pulmonary hypertension. We all have to take a breath and realize that if we are going to consider bariatric surgery that there is significant risk in pulmonary hypertension patients. I think an assessment has to be made about whether or not we have truly maximized PAH therapy. That has to be a prerequisite. I think we have to do a careful assessment of that patient’s ability to potentially lose weight through more conservative means. That’s part of the normal bariatric surgery evaluation that Ramesh can expand upon. And then we have to do a really careful risk assessment. We need to make sure that this patient has—while it will undoubtedly be a somewhat elevated risk of a perioperative complication—as low a
risk as possible before we can really consider referring them for surgery. I think.

**Dr Levine:** Patients who we have referred are those morbidly obese patients (usually with a BMI ≥40) suffering from significant comorbidities from their obesity; for example, diabetes, OSA, OHS, atherosclerosis, hypertension; and who have had less severe PAH or those who may have PH Group 2 with stable right heart function. The patients we have referred have had good functional capacity that they are able to at least do some ambulation.

For patients who have other types of PH (WHO Group 3) with other lung disease, we need to look at other considerations, in terms of their other lung disease. We will also need to make sure that all lung diseases are appropriately treated prior to this surgery.

The patients we have referred have, of course, been referred only after all other avenues of weight loss had been exhausted.

**Dr McGlothlin:** I think the question of referring patients for bariatric surgery, particularly in my mind, relates to referring patients with Group 1 pulmonary arterial hypertension for bariatric surgery. While undoubtedly I think losing the weight after bariatric surgery would help the patient’s condition, I think that these PAH patients are at particularly high risk from the surgical standpoint and so I take pause in referring patients who have more advanced pulmonary arterial hypertension, particularly those with right-sided heart failure. I think that the preoperative evaluation is of paramount importance. I just saw a recent study that looked at 185,000 patients who were referred for bariatric surgery and out of all the comorbidities, pulmonary hypertension was the number one risk factor, the greatest risk factor for peri- or postoperative mortality. And so it is an important risk factor. While I think we need to consider bariatric surgery in obese patients based on guidelines, I think that we do need to do our due diligence in assessing the patient’s perioperative risk prior to sending them for surgery.

**Dr Levine:** Additional assessments for patients with other lung diseases include the full preoperative testing (ie, all the pulmonary function tests, etc). All of their medications (PAH and medications for other lung diseases) need to be continued throughout the perioperative period. Patients with OSA need to make sure they are extubated to CPAP after the surgery.

**Dr Mathier:** We have to walk a very fine line here because on the one hand we can never lose sight of the fact that especially the type of PH patients that Dana described—a Group 1 patient with significant disease who is on aggressive therapy maybe with borderline right heart function—those patients are always going to have an elevated surgical risk and we have to be very, very cautious about considering doing any elective or quasi-elective surgery on them. On the other hand, I think we need to recognize that in selected patients who have severe functional limitation that may be largely contributed to by their obesity; they may in fact be acceptable surgical risks. And we have to really try to delineate these two groups so that people are referred when they can be safely operated on and where the surgery is judiciously avoided in those where the risk is simply too high. I’ll echo what Dana said. In my mind, while there is some unpredictability to this, I think that the severity of right heart dysfunction is the key determinant here. In patients with preserved cardiac index and relatively low right-sided filling pressures who have reasonable functional status, you know not fully Class 4; these are folks who I think can be considered. But in folks who have very high right atrial pressures and very poor cardiac index I think this kind of surgery should be avoided because the risk is really excessive.

**Dr Studer:** Ramesh, I’m curious what you think when you get these patients in referral in terms of initial risk. Are there certain additional criteria you would apply beyond what the PH clinician in their office would be concerned about when considering the surgery?

**Dr Ramanathan:** I would definitely have a detailed discussion with the patient and the family regarding perioperative risks including mortality. The 30-day mortality after bariatric surgery has decreased significantly over the last several years and ranges from 0.1% to 0.5%. But patients with PH are extremely high risk. Most of them are female, have a very high BMI, and have multiple comorbidities including obstructive sleep apnea. And when you combine their poor cardiopulmonary functional status, they are probably in the highest risk category of all bariatric surgery patients. I quote a mortality risk of around 5% to 10% for this specific group of people. But by the time they come to my office, they’ve come to the realization that if something is not done, they are going to die soon. Their life expectancy is measured in terms of months or a few years if untreated. So when I say “you could die from this operation”, they all respond “If I don’t do anything, I’m going to die soon anyway.” Fortunately, we’ve been lucky so far in our program. It is largely due to the multidisciplinary approach to these patients with a coordinated care among specialists with expertise in cardiac anesthesiology, cardiology, pulmonology, critical care, and bariatric surgery. So you really want to do this in a tertiary care center that has all the specialties available to monitor and treat them appropriately.

I have a question for the cardiologists. By the time, some of these patients get to see the surgeon to discuss bariatric surgery, they are extremely high risk. They have been managed with medications for years and years and their functional capacity is sometimes being able to walk only a few steps. Is there a way to identify a certain group of
patients with PH who have a better functional status and where we think obesity is specifically contributing to or accelerating their deterioration in functional status? We could possibly intervene earlier with bariatric surgery.

**Dr Mathier:** I think that’s a good point, Ramesh. There is definitely an argument to be made that waiting too long to pursue a surgery like this is going to leave you with a patient who has worsened to the point that their risk becomes certainly higher and potentially prohibitive. I think that we work hard to identify patients who are in the proper window for this type of procedure. If they are “too well,” if you will, and we feel that they can make progress with more conservative efforts at weight loss because they still have very good functional capacity, then certainly you don’t want to send them to surgery prematurely. On the other hand, as you point out, it doesn’t do them any good for us to wait until they can barely move to consider a surgery like this because their risk is likely to be too high. So I think we’re always looking for that window where they’re at a stage where their surgical risk is acceptable and they have clearly shown us that they’re not going to have any success with more conservative measures and that their functional status is not going to be acceptable to them moving forward. That’s the kind of patient in my mind who we can really consider for this kind of surgery.

**Dr Ramanathan:** What criteria do you evaluate before referring a patient for bariatric surgery? I know it’s kind of subjective, but is there any one particular parameter that you look for in the cardiac catheterization that would determine the eligibility or risk status of a patient to undergo an operation.

**Dr Studer:** That’s what I was going to lead into. He mentions the catheterization, but maybe functional status or certain echocardiographic parameters are also factors. For those who are considering referral, are there specific triggers that would either say “this is time” because the severity is met or possibly “this patient is a little too ill and I need to optimize them better”. Dana, would you start with that please?

**Dr McGlothlin:** Sure. I would say a patient with right-sided heart failure, as indicated by elevated right atrial pressure, especially patients with a right atrial pressure above 15 mmHg, and particularly those in whom the cardiac index is low, less than 2.2, are going to be at significant risk of perioperative hemodynamic compromise. In that patient, I really would be hesitant. And you notice I’m not even talking about the pulmonary artery pressure. To me, I think that the key is the status of the right heart as the main marker of how patients might do with this sort of surgery. In terms of indications for the surgery, as Mike already mentioned, if we think that the patient’s obesity is significantly contributing to their symptomatology and disease process, then it may justify a going forward despite a relatively high risk. For instance, if the patient with PH has obesity hypoventilation syndrome contributing to their PH and they have significant symptoms and they do not have significant right heart failure, that would probably be an appropriate patient in whom to move forward with bariatric surgery. But if that patient had severe pulmonary hypertension and right-sided heart failure, we should be very cautious. I think at the minimum we would want to optimize their hemodynamic status by whatever means we could prior to surgery. And, then, if they do actually improve with pulmonary vasodilator therapy, with diuretics, and so forth, then that might be a better situation. You know the surgery itself is—and Ramesh can comment on this in more detail—by and large a laparoscopic surgery which is often considered lower risk compared to open surgeries, but the hemodynamic effects of anesthesia can cause vasodilation, hypotension, and have effects on the myocardium that can worsen right-sided contractility. And mechanical ventilation can increase right ventricular afterload. It has effects on pulmonary vasoconstriction that can lead to decompensation of the right heart during surgery. Also, the laparoscopy requires insufflation of the abdomen with CO₂. That carbon dioxide not only increases intra-abdominal pressure that can compress the vena cava and aorta, but can also increase intrathoracic pressures, making it harder to mechanically ventilate; and this further increases RV afterload. There can also be some subcutaneous emphysema from carbon dioxide that can leak into the bloodstream and worsen pulmonary vasoconstriction and pulmonary hypertension. So there are many ways in which the surgery itself can worsen right heart failure due to its direct effects on the myocardium and the pulmonary vasculature. However, I think it’s worth the risk in the PH patient who has significant symptoms associated with their obesity but who has less advanced disease without significant right heart failure.

**Goals of weight, goals of exercise, and ambulation are discussed by the team, including the dietitian, every visit.** —Dr Levine

**Dr Mathier:** If I could just make one additional point about assessing a patient and assessing their suitability for the surgery. You know one of the things about our field that really is an art form is that we are constantly integrating different markers of risk or prognosis in our assessment of the patient. So it’s not simply about hemodynamics or simply about functional status. We’re really looking at maybe 10 or 12 different markers to give us an integrated sense of where that patient sits in terms of the risks they’re facing or what kind of prognosis they may have. Or whether or not our therapy is adequate or whether we need to be considering intensifying therapy. So it’s very difficult because we haven’t put this integration of all these different markers into any kind of an equation like you see in certain other fields. And instead what we do as individual care providers is with each individual patient we try to integrate these things in our own minds and I very much do that when I’m considering these patients for surgery.
Dr Ramanathan: And we see that variability in how bariatric surgeons’ approach these patients as well. There may be surgeons who would say that a diagnosis of pulmonary hypertension is an absolute contraindication to bariatric surgery.

Dr Studer: Do you think there is any consensus, that a certain procedure is safer or better suited to these patients, since there appears to be a number of options that these patients can go through in terms of type of bariatric surgery?

Dr Ramanathan: I think it’s evolving and I don’t think we have a consensus on the most appropriate bariatric surgical procedure in these very high risk patients. A few years ago we had the option of either the gastric bypass or the laparoscopic adjustable gastric banding. The benefits of the lap band are that it is less invasive with very low perioperative risks. It is also quicker and we can get them off the operating table sooner which would be very desirable in these patients due to the adverse hemodynamic effects of anesthesia and laparoscopy. But the amount of weight loss is lower compared to the gastric bypass and it takes 2 to 3 years to achieve that weight loss. So the question is whether they are going to lose enough weight quickly to benefit their functional status in a meaningful way? On the other hand, the gastric bypass is considered a lot more invasive with a longer operating time and a higher risk of postoperative complications. The advantage is that they could lose a lot of weight (up to 60 to 70% of their excess weight) in the first 6 months to a year and that could have a significant beneficial effect on their functional status. I tended to favor the gastric bypass over the lap band because I thought if you’re going to put them through the risk of an operation you might as well get the best bang for the buck. Now, there is one more option, the laparoscopic sleeve gastrectomy. It is a restrictive type of operation, where the stomach is converted into a long narrow tube along the lesser curve removing more than two-thirds of the stomach, preserving the pylorus and without any intestinal malabsorption. And the weight loss results, at least in the short to medium term, seem much better than the lap band and maybe slightly lower than the gastric bypass. So nowadays, in these high risk patients, I would prefer to do the sleeve gastrectomy rather than the gastric bypass because it’s quicker, has a lower risk of perioperative and long-term complications with an acceptable amount of weight loss.

Dr Mathier: Ramesh mentioned this briefly earlier, but I think it deserves some expansion. I think we try to maximize the outcomes in these patients it’s really critical that a carefully orchestrated multidisciplinary approach is taken. And it’s not simply a matter of having a surgeon and a pulmonary hypertension physician. You need a pulmonologist who can focus on the sleep apnea or hypoventilation aspect of the patient’s disease; typically an endocrinologist who can manage diabetes or other metabolic abnormalities. It’s very important to have either a dietitian or another behavioral modification person involved. Most bariatric programs integrate this so that the patients’ habits can be changed for the better following the surgery. I think it’s critical that especially the surgeon and the pulmonary hypertension specialist speak with the anesthesiologist ahead of time so that we can go over aspects of intraoperative care that may be important including hemodynamic monitoring if necessary, including the possibility of using inhalational therapy through the surgery if necessary. We have as a rule admitted these patients to the cardiac care unit where the nurses I think have much better facility with pulmonary hypertension therapies immediately postoperatively and we’ve gotten good results with that because we can more carefully monitor hemodynamics, monitor fluid shifts, and adjust pulmonary hypertension therapies and other vasoactive medications accordingly. So that kind of a truly integrated multidisciplinary effort I think is mandatory if you’re going to have good outcomes with these patients. They cannot be approached in the same way that you would approach a patient who doesn’t have a severe comorbidity like PH.

Dr McGlothlin: I agree with what Mike just said. I think the perioperative or the multidisciplinary planning is critically important and you know these patients actually don’t usually die in the operating room. They die postoperatively. So that piece is at least as important as what happens in the operating room. Because, just as Mike mentioned the fluid shifts, there are all kinds of conditions postoperatively that lead to changes in pulmonary vascular resistance and the status of the right ventricle. And there’s a risk of infection and bleeding and all of those hemodynamic factors and physiologic factors can lead to a decompensation in the postoperative period. So it’s important to have a good hand off between the anesthesiologist, the surgeon, and the PH specialist and the critical care team after surgery. And then close monitoring, usually at least with central venous pressure monitoring, if not a PA catheter. Definitely not everyone needs a pulmonary artery catheter, but I think we can all agree that central venous monitoring along with arterial hemodynamic monitoring is very important in these patients to really capture changes that are occurring to institute therapies that can prevent a downward spiral postoperatively.

I think that we work hard to identify patients who are in the proper window for this type of procedure.

—Dr Mathier

Dr Mathier: One perhaps obvious point is that you know these patients are going to have an interruption in their ability to take oral medications and so you have to plan ahead for that. Depending on how smooth the postoperative course goes and when they can start taking pills again, that could be a headache or potentially might not be much of an issue. But it should be thought of ahead of time.
Dr McGlothlin: Good point. Do you all frequently use inhaled nitric oxide for these patients intraoperatively and postoperatively?

Dr Mathier: Yes, I would say both. We anticipate that we will use nitric oxide intra- and postoperatively. I think that it’s smart to have it available. It’s smart to make sure that your Pharmacy and Therapeutics committee or your pharmacy is going to sign off on it because, as you know, it’s quite expensive. But it can be really an invaluable sort of bridging agent in a patient like this.

Dr McGlothlin: That’s my experience as well.

Dr Studer: How often do you have these patients that you’re sending over on parenteral therapy? And are there any specific concerns you have in that population?

Dr Mathier: You know we’ve had patients who go on parenteral therapy. As you know by definition this usually identifies a more advanced population and so you might argue that you know it’s a somewhat higher risk population. On the other hand, having them on parenteral therapy means that there is no interruption of the treatment perioperatively and also it gives you a little bit of titrate-ability according to what the hemodynamic needs are. I think it really gets down to how beneficial a hemodynamic effect you have been able to achieve with your therapy, whether it is parenteral or not. And does the patient on their therapy fall into an acceptable risk category as we discussed earlier?

Dr Studer: Ramesh, does it have any specific concerns for you when a patient is receiving parenteral therapy? Is that something you’re likely to feel is managed in a way that creates risk or maybe mitigates it?

Dr Ramanathan: I think, like Mike pointed out, they’ve already reached a more severe form of the disease. The management of the medication postoperatively is easier because you don’t have to deal with oral intake. Some patients after bariatric surgery have a prolonged period of nausea and vomiting with difficulty tolerating oral medications. But clearly you are dealing with a much higher risk patient once they have reached the point where they require parenteral therapy.

Dr Studer: Are there any specific comments about the postoperative period you think we haven’t covered? We talked a bit about monitoring. Are there any other aspects of the postoperative management for those who haven’t had management experience in bariatric surgery patients that you give as things to look for?

Dr Ramanathan: One of the issues is most of these people are on Coumadin or some sort of anticoagulation. Is that right, Mike?

Dr Mathier: Many are, yes. And warfarin would be the typical medicine we would use.

Dr Ramanathan: So we have to transition them over to Lovenox before surgery for a few days after stopping the Coumadin. Then postoperatively the question is how soon to restart anticoagulation? Especially when you’re doing a procedure like sleeve gastrectomy or gastric bypass, there is a lot of mesenteric dissection with staple lines and anastomosis, postoperative bleeding is definitely a concern. The timing of when to restart their anticoagulation can be crucial, because if you end up with bleeding, you may have to take them back to the operating room. But I would like to know from Mike or Dana, how long can you delay the anticoagulation?

Dr Mathier: The good news is that this is not what I would consider a hard indication for warfarin so we have time on our side and we’re generally happy to wait as long as it takes for there to be surgical certainty that it’s acceptable to resume anticoagulation.

Dr Ramanathan: All these patients are transferred postoperatively to the intensive care unit on a ventilator and so the question is when to extubate them and when to do the upper GI study. We usually do an upper GI study the next day after bariatric surgery in other patients to rule out anastomotic or staple line leaks before starting them on oral intake. So transferring these patients to the radiology suite while they’re on a ventilator and have multiple monitoring catheters can be difficult. So we wait for a couple of days to wean them off all of these and then do the upper GI study.

Dr Mathier: Although I would say that the extubation issue more commonly has to do with the patient’s tendency to have obesity hypoventilation than it does with their PH, per se. My approach to patients with pulmonary hypertension who are intubated, especially electively intubated, is that the sooner they’re extubated the better. Just as a kind of guiding principle. But that’s where the pulmonary consultant comes in—whether that’s the actual PH provider or not—where they can help with safe and timely extubation in somebody who you know may have a tendency toward hypoventilation.

Dr Studer: Dana, did you have any other comments based on that postoperative piece that Ramesh and Mike were discussing?

. . .largely due to the multidisciplinary approach to these patients with a coordinated care among specialists with expertise in cardiac anesthesiology, cardiology, pulmonology, critical care, and bariatric surgery. —Dr Ramanathan

Dr McGlothlin: Yes, I agree that in general we like to extubate patients with pulmonary hypertension as soon as possible with the caveat being that these patients might be at greater risk for hypoxic pulmonary vasoconstriction after extubation because of sedation and hypoventilation. I think that does have
from nitric oxide. That may be beyond off quickly. Sildenafil can help wean PH degree of rebound PH in some patients. So we don’t want to just want to wean it rather than faster because there is some We tend to want to do that slower the issue of weaning off the nitric oxide. And you know for those period for patients with PH undergoing surgery. And you know for those situations, particularly in patients with little volume occasionally in appropriate sometimes it is necessary to administer a little volume occasionally in appropriate patients who develop right-sided heart failure. Some patients develop infection reduced systemic vascular resistance either from infection or from the anesthetic agents while they’re on mechanical ventilation and in those patients vaso pressin is a very good pressor agent. It tends to cause some nitric oxide release in the pulmonary vasculature that can lead to some degree of pulmonary vasodilation and decrease in the pulmonary vascular resistance to systemic vascular resistance ratio. Sometimes, although sometimes it is necessary to administer a postoperative management period—especially within the first couple days after surgery—is an important time period for patients with PH undergoing surgery. And you know for those patients who are on nitric oxide, there is the issue of weaning off the nitric oxide. We tend to want to do that slower rather than faster because there is some degree of rebound PH in some patients. So we don’t want to just want to wean it off quickly. Sildenafil can help wean PH from nitric oxide. That may be beyond this discussion but there are those issues postoperatively that require a lot of attention.

Dr Studer: Thank you. I just wanted to sort of wrap up with the question, based on the experience you’ve all had with these patients in bariatric surgery and the concern that the prevalence of obesity as a co-morbid factor is increasing, what do you see as some of the future developments or referral patterns for bariatric surgery? Do you think the role of it is increasing?

Dr Mathier: I think it is increasing in the sense that we’ve come to recognize that when the proper approach is taken, the surgery can be offered to a broader range of patients than we initially thought. Those success rates, as Ramesh indicated, have improved. But at the same time I think we have to recognize that we shouldn’t get complacent and fall into a pattern where we have bariatric surgery as some kind of a safety net and stop trying to energetically encourage patients to lose weight through more conventional means. Or better yet to prevent them from gaining weight to the extent where they become morbidly obese and have such severe limitation in their functional capacity. So one of the educational things I think we can do in pulmonary hypertension patients, especially because there are a large number of them who are young, is to institute very good habits in terms of diet and physical activity emphasizing the importance of avoiding the progression on to obesity.

Dr McGlothlin: Absolutely. And then I would just make another comment about obesity as it relates to candidacy for patients with pulmonary arterial hypertension or who are failing medical therapies and may otherwise need to be considered for lung transplantation. This would be a significant barrier to their being able to have the next step in terms of life-saving treatment for their pulmonary arterial hypertension. It’s a very important issue for these patients, particularly those who are not responding to medical therapy. So I always counsel my obese patients with Group I pulmonary hypertension who have significant disease even at earlier stages of their disease. If they’re significantly overweight, they need to start working on it immediately with diet and as much regular exercise as they can safely tolerate so that that doesn’t become the barrier to lung transplantation should they need it down the line.

Dr Studer: Ramesh, any final thoughts that you have . . . .

Dr Ramanathan: Well, I think educating the patients about the risks and benefits of bariatric surgery is extremely important. Weight regain is a constant battle that we face in follow up. They have to understand that long-term successful weight loss requires significant and permanent changes to their lifestyle along with bariatric surgery. Especially in this patient population, where their physical activity is limited due to their cardiopulmonary status, the changes in their dietary habits have to be really dramatic.

Dr Studer: Those are excellent points. I thank all of you for your thoughtful contributions to this roundtable.
Perioperative Management of Pulmonary Hypertensive Crisis

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Pulmonary hypertensive crisis is characterized by an acute rise in pulmonary pressures, causing pressure overload of the right ventricle (RV) and decreased cardiac output. Reduced cardiac output through the pulmonary circuit leads to hypoxia, further exacerbating the increased pulmonary vascular resistance. Right ventricular dilation shifts the interventricular septum toward the left ventricle (LV), impeding LV filling and further compromising cardiac output. Systemic hypotension, metabolic and respiratory acidosis can ensue. In general, pulmonary hypertension (PH) patients have higher mortality during surgical procedures, ranging from 4%-24%. Pulmonary hypertensive crisis in the perioperative setting is associated with even worse outcomes and mortality may surpass 50%. Survival requires prompt recognition and intervention.

The best way to recognize and/or prevent perioperative pulmonary hypertensive crisis is to be prepared for it ahead of time. Preoperative assessment should include invasive hemodynamics if not recently performed. Recommendations to the surgical team prior to surgery should include local instead of general anesthesia if at all possible, utilization of a cardiac anesthesia team, and preferably one experienced with PH. Local anesthesia with either epidural or peripheral nerve block may avoid the excess morbidity and mortality of general anesthesia. Spinal anesthesia should be avoided in patients with PH due to the potential for systemic hypotension from vasodilation causing hemodynamic collapse. Perioperative invasive hemodynamic monitoring should be performed and will allow for early recognition of pulmonary hypertensive crisis. Continuation of PH medications throughout the perioperative period is also crucial. Postoperatively, patients should be monitored in the intensive care unit. Risk factors for the development of pulmonary hypertensive crisis and poor surgical outcomes in PH patients can be found in Table 1.

Prompt recognition of pulmonary hypertensive crisis is critical. Clinical parameters to identify include systemic hypotension, hypoxia, tachycardia, decreased urine output, and/or frank anuria. Confirmation of pulmonary hypertensive crisis is via invasive hemodynamics, thus the need for perioperative monitoring. Rising pulmonary and right atrial pressures with decreasing cardiac output is the hallmark. Echocardiography may be useful as an adjunctive measure to show worsening RV function and/or RV dilation.

Treatment options for perioperative pulmonary hypertensive crisis include supportive measures, therapies to treat the pulmonary vascular system, including inhaled or parenteral pulmonary vasodilators to lower pulmonary vascular resistance and inotropic support for the RV, and therapies to support the systemic vasculature. Supportive measures include 100% oxygen, hyperventilation to decrease CO2, maintaining lung volumes near or at functional residual capacity (if on mechanical ventilation) to avoid hyperinflation or atelectasis (both of which may raise pulmonary vascular resistance), paralytics to decrease metabolic demand, maintenance of normal core body temperature, and treating acid/base disturbances. Filling pressures should be optimized, which in some cases may require diuretics as severely elevated RV filling pressure may exacerbate renal dysfunction. Acute pulmonary vasodilators can include inhaled nitric oxide or prostacyclins. Prostacyclins can be delivered either via inhalation/nebulization or parenterally. Intravenous use of sildenafil has also been reported and may be of use. Milrinone or dobutamine can be used for inotropic support of the RV. Milrinone has vasodilatory properties as well and so may be preferential to dobutamine. Milrinone has also been reported to be administered by nebulization. Systemic hypotension should be addressed with pressors as needed, with an eye to increase perfusion pressure adequately but avoiding excessive increases in afterload. This can be achieved with low-dose dopamine, norepinephrine (which may also have some positive inotropic effect), or vasopressin. If medical management is unsuccessful, mechanical support with extracorporeal membrane oxygenation (ECMO) can be considered. ECMO may be useful in settings of inability to oxygenate and/or persistent systemic hypotension despite medical support with inotropes and pressors.

In summary, pulmonary hypertensive crisis can be a life threatening perioperative complication. In PH patients requiring surgery, preoperative assessment and planning may by preventive. Successful outcomes require perioperative vigilance and rapid intervention.
Table 1. High-risk parameters for perioperative pulmonary hypertensive crisis.

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Surgical factors</th>
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<tbody>
<tr>
<td><strong>Clinical:</strong></td>
<td><strong>Type of surgery:</strong></td>
</tr>
<tr>
<td>Poor functional class (class III, IV greater risk than I, II)</td>
<td>Intermediate- to high-risk surgery (abdominal, orthopedic, thoracic, vascular,</td>
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<tr>
<td>Low 6-minute walk distance (&lt;330 meters)</td>
<td>transplant)</td>
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<tr>
<td>High BNP (&gt;330)</td>
<td>Emergent surgery at higher risk than planned procedures</td>
</tr>
<tr>
<td>History of a pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td><strong>Echocardiography:</strong></td>
<td><strong>Type of anesthesia:</strong></td>
</tr>
<tr>
<td>Preoperative RV dysfunction (global assessment, RV index of myocardial performance ≥0.75, TAPSE &lt;1.6 cm, more recent measures of tissue Doppler or speckle tracking-derived strain)</td>
<td>Spinal anesthesia high risk and should be avoided; may cause hemodynamic collapse from systemic vasodilation</td>
</tr>
<tr>
<td>RV dilation and/or hypertrophy</td>
<td>General anesthesia higher risk than local anesthesia (epidural or peripheral nerve block)</td>
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<tr>
<td>Flattened, or D-shape, septum with LV diastolic dysfunction</td>
<td></td>
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<tr>
<td>Severe tricuspid regurgitation</td>
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<tr>
<td>Pericardial effusion</td>
<td></td>
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<tr>
<td><strong>Invasive hemodynamics:</strong></td>
<td><strong>Intraoperative events:</strong></td>
</tr>
<tr>
<td>Severe PAH (MPAP &gt;55 mm Hg)</td>
<td>Duration of surgery/anesthesia (&gt;3 hours)</td>
</tr>
<tr>
<td>Evidence of decompensated RV function (RAP &gt;12 mm Hg, cardiac index &lt;2.2 L/min/m²)</td>
<td>Estimated blood loss (hemorrhagic shock leading to catecholamine surge and cardiovascular collapse; need for blood products causing fluid shifts and/or lung injury)</td>
</tr>
</tbody>
</table>

BNP, brain natriuretic peptide; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; LV, left ventricle; PAH, pulmonary arterial hypertension; MPAP, mean pulmonary arterial pressure; RAP, right atrial pressure. See reference 4 for a good review.

References
Recent Reports

Section Editor
Fernando Torres, MD

The Clinical Trials Update highlights new and ongoing research trials that are evaluating therapies for PAH. In this issue, Dr Torres examines a study on the RELAX trial and a study on a revision to the Lung Allocation Score.


Diastolic dysfunction, or heart failure with preserved ejection fraction (HFpEF), is commonly encountered in pulmonary hypertension (PH) programs and carries significant morbidity and mortality. There are no specific medications to treat diastolic dysfunction, and patient management can be challenging, with morbidity and mortality that is as high as that of patients with heart failure with reduced ejection fraction. The study of this disease in the PH community has been difficult, as the definition of this disease continues to evolve. A specific task force from the 2013 World Symposium on Pulmonary Hypertension (WHO) which was held in Nice, France, was assigned to provide a more uniform definition to aid in improving developments of therapies and design clinical trials.

The RELAX trial was initiated to evaluate patients with HFpEF. Enrollment began in October 2008, and finished in February 2012. During this period, 216 stable outpatients with HFpEF were enrolled in a multicenter clinical trial across North America. Twenty-six centers participated. The inclusion criteria consisted of patients with heart failure with ejection fraction ≥50%, elevated NT-proBNP, or elevated invasively measured filling pressures and reduced exercise capacity. The study was designed to capture all types of diastolic dysfunction, not just the patients with pulmonary venous hypertension. The median age in the study was 69 and 48% of participants were female. The median peak oxygen consumption was 11.7 mL/kg/min and mean 6-minute walk distance (6MWD) was 308 meters. The patients were randomized 1:1 to receive either placebo or 20 mg tid of sildenafil for 12 weeks, and then the dose was increased to 60 mg tid for the remaining 12 weeks. At 24 weeks when the patients were reevaluated at the end of the study, the results were disappointing.

The primary endpoint of peak oxygen consumption in patients receiving placebo or sildenafil was not met as there were not significant differences (P=0.90) between the groups. The secondary endpoints of 6MWD and hierarchical composite clinical status score were also not statistically different. Subgroup analysis looking at creatinine, NT-proBNP, endothelin-1, and uric acid levels increased more in patients treated with sildenafil. There were more patients in the sildenafil group who withdrew consent, died, or were too ill to perform the cardiopulmonary exercise test. Furthermore, patients treated with sildenafil had a higher incidence of adverse events and serious adverse events. The investigators also performed multiple subgroup analyses in this population that did not show any trend toward improvement of peak oxygen consumption.

The investigators measured levels of sildenafil in the subjects and were able to show that the serum levels achieved were consistent with other clinical trials that have shown efficacy in other disease states. It is still possible that a higher dose of sildenafil could have a positive effect in this population, though possibly with an increase in adverse events.

This study did not include patients with severe pulmonary arterial hypertension (PAH). This is important, as the Guazzi et al study showed a positive result using sildenafil for the treatment of diastolic dysfunction and included patients with more severe PAH than was noted in the RELAX study. Thus, the potential that sildenafil may only be effective in patients with severe PH remains a possibility. See full results of the RELAX trial.

It is possible that the negative results of this sildenafil study in HFpEF may not be a class effect of all PDE-5 inhibitors. Studies evaluating the efficacy of tadalafil in this population are being developed.


During the ISHLT 2013 conference in Montreal, Dr Gomberg presented data supporting a change of the Lung Allocation Score (LAS) for patients with PAH. Historically, the patients with PAH were placed on the waiting list to undergo lung transplantation as soon as they were diagnosed with the disease. Thus, it was common for PAH patients to be on the waiting list for bilateral lung transplantation for 2 or 3 years. At that time, the donor organs were allocated to recipients solely based on time on the wait list.

In May of 2005, United Network for Organ Sharing (UNOS) introduced the LAS. The new system ranks patients on the waiting list according to the severity of illness and probability of surviving a lung transplant 1 year later. This system significantly benefited the patients with interstitial lung disease (ILD) in time to
transplantation, and over the past 8 years there has been a steady increase in patients with ILD undergoing lung transplantation. Similar changes were noted in patients with cystic fibrosis. Unfortunately, such changes were not seen in the PH population.

While the numbers of transplants has remained stable, the percentage of PH patients undergoing lung transplantation has decreased. Dr Gomberg and colleagues presented data to support changing the score allocated to PH patients on the waiting list for lung transplantation. After the introduction of the LAS system, patients with PH had a worse survival than predicted by the current LAS equation. Gomberg et al created a new equation that will help predict the survival of PH patients on the waiting list. This equation uses 3 variables to predict survival in the waiting list: cardiac output, 6MWD, and oxygen requirement at rest. If this new equation is adopted by UNOS, the way in which organs are allocated should improve for PH patients awaiting lung transplantation.

The Power of PR in Spurring Earlier PH Diagnosis
by Lynn Brown, MD, campaign chair
An online article published April 8, 2013, in JAMA Internal Medicine called for a reevaluation of educational efforts to deepen awareness of pulmonary hypertension (PH) among medical professionals and to improve PH patient care and outcomes. The article, Referral of Patients With Pulmonary Hypertension Diagnoses to Tertiary Pulmonary Hypertension Centers, by Roderick et al raised concerns about late referrals, misdiagnoses, and inappropriately prescribed medications at PH clinics at academic medical centers. (See it online at http://bit.ly/100JZKR.)

PHA’s 5-year Sometimes it’s PH early diagnosis campaign is an important way we are moving toward wider knowledge of PH in medical circles. Direct educational efforts are now being organized through the campaign, and in the meantime a companion PR initiative has already generated several well-placed articles on PH and early diagnosis.

Sometimes it’s PH teaches more professionals in the medical community that PH is a “medical zebra,” or unexpected diagnosis, of common symptoms such as chest pain, shortness of breath, and fainting. The campaign plays off this medical school adage: “When you hear hoofbeats, think horses not zebras.” It reminds practitioners that although sometimes it’s asthma or COPD or sleep apnea, sometimes it’s PH.

In April, the American College of Physicians published an article on diagnosing and treating PH in its monthly membership publication, ACP Internist. The article, available online at www.acpinternist.org, was the cover story of that monthly issue sent to more than 130,000 primary care doctors. The piece covered how to screen for PH, when to refer to a specialist, and how to blend primary and specialty care.

A second article introduced PH awareness to respiratory therapists (RRTs). Appearing in the online news magazine ADVANCE for Respiratory and Sleep Medicine, it explained how RRTs may suspect PH if patients are following their treatment regimens but not feeling better. Author Gerilyn Connors, a respiratory therapist and the Pulmonary Hypertension Professional Network (PHPN) Practice Committee chair, wrote the article, also introducing Sometimes it’s PH and the professional education and growth opportunities available through PHA. The article can be found online at http://owl.li/k9nTS.

Future PR plans also call for publishing review articles and editorials in medical journals, generating coverage in news publications for other allied health professionals, inviting key professional associations to communicate our message to their members, and producing coverage in the mass media.

PHA’s campaign is gaining traction and momentum through careful networking in the health community and by proactively seeking opportunities to bring this rare disease to wider attention. Your ideas and talents to advance early diagnosis are important to the campaign. I welcome the opportunity to hear from you about ways to continue to work toward early and accurate diagnosis of PH. Please send your thoughts to me at Lynn.M.Brown@imail.org. I also encourage you to visit the campaign’s website, www.SometimesItsPH.org, for the latest campaign information.
Medicaid HMOs May Affect PH Patients in 24 States This Year

In 2013, 24 states will move patients who are eligible for both Medicare and Medicaid, or “dual-eligible,” from traditional fee-for-service Medicaid plans to Medicaid Health Maintenance Organizations (HMOs). California began transitioning dual-eligibles to Medicaid HMOs 2 years ago, and while the change was intended to save money and increase efficiency, many Californians living with PH were unable to receive the care they needed under their new HMOs. Some PH patients were forced to see general pulmonologists because their PH specialist was not part of their new HMO’s network. Others experienced medication delays because their new specialty pharmacies were not familiar with PH.

The states planning Medicaid HMOs for dual-eligibles are: AZ, CA, CO, CT, HI, ID, IA, IL, MA, MI, MN, MO, NY, NC, OH, OK, OR, RI, SC, TX, VT, CA, WA, WI. PHA encourages physicians to work with patients who may be affected by helping them understand when the switch will begin in their state, whether they will be able to continue to receive PH expert care after the switch, and what the exemption process and deadlines are for those who wish to stay in a traditional fee-for-service plan.

You can learn more about what’s happening in your state at http://medicaid.gov/Medicaid-CHIP-Program-Information/By-State/By-State.html.

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- Insurance Issues for the PH-Treating Professional

PH Ready – E-Courses for Your Patients

Your patients who have been recently diagnosed with PH probably have a lot of questions and concerns. Or, they may be feeling so overwhelmed by the diagnosis that they aren’t sure what kinds of questions to ask. PHA has created The Newly Diagnosed Self-Study: PH Ready, a series of e-courses that serve as a roadmap for newly diagnosed PH patients. It is full of information about treatments, living with PH, insurance, working with your medical team, and more. Participants will receive a monthly email highlighting relevant resources for newly diagnosed patients.

PH Ready can be started at any time. Register today at: www.PHAssociation.org/PHReadyRegistration.

Global PHCR Membership

In an effort to increase global membership in PH Clinicians and Researchers (PHCR) and foster the sharing of ideas around the world, PHA is offering free first-year membership for non-US physicians, researchers, residents, and fellows interested in PH. Benefits of PHCR membership include case-based learning opportunities by top PH specialists, access to an email group of a growing number of PHCR members, inclusion in PHA’s Find a Doctor Directory, and more. For medical professionals in countries that have a gross national income per capita of less than $5000 USD, PHCR memberships may be renewed at no cost each year. Learn more at www.PHAssociation.org/PHCR.

CALENDAR OF PH ACTIVITIES

To have your event for PH health care providers considered for listing in future issues of Advances in Pulmonary Hypertension, send your announcement to meghanf@PHAssociation.org.

European Respiratory Society Annual Congress 2013
September 7-11, 2013
Barcelona, Spain
www.ersnet.org

European Society of Intensive Care Medicine Annual Congress
October 5-9, 2013
Paris, France
www.esicm.org

CHEST 2013
October 26-31, 2013
Chicago, Illinois
www.chestnet.org

American Heart Association Scientific Sessions 2013
November 16-20, 2013
Dallas, Texas
www.americanheart.org
IMPORTANT SAFETY INFORMATION

ADD MORE: Tyvaso is the only PAH treatment approved as an add-on to oral therapy.

+ PAH may be progressing even if patients seem stable.
+ Many patients plateau on oral therapy (PDE-5 inhibitor or ERA) within 12 weeks.

After 1.7 years (mean) on oral monotherapy, adding Tyvaso for 12 weeks improved median 6MWD by 20 m (P<0.001).

+ 4X daily dosing with short treatment sessions (2-3 minutes) approximately every 4 hours.

Study design: TRIUMPH II was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=273) 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 daily treatment session with a target dose of 0.6 mg (3 sprays) 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, 6-minute walk distance, NYHA functional class, and 6MWD at week 12 (obtained at least 4 hours after study drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.

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 predominantly patients with NYHA 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.

ADD MORE: Tyvaso is the only PAH treatment approved as an add-on to oral therapy.

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

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

Please see brief summary of Full Prescribing Information on following page. For more information, please see Full Prescribing Information, Patient Package Insert, and the Tyvaso Inhalation System Instructions for Use manual. These items are available at www.tyvaso.com.
INDICATIONS AND USAGE

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.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Patients with Pulmonary Disease or Pulmonary Infections—The safety and efficacy of TYVASO have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

Risk of Symptomatic Hypotension—Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with TYVASO may produce symptomatic hypotension.

Patients with Hepatic or Renal Insufficiency.—Titrated slowly in patients receiving anticoagulant therapy.

The following potential adverse reactions are described in Warnings and Precautions:

• Decrease in systemic blood pressure  • Breathing

Adverse Reactions Identified in Clinical Trials—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In a 12-week placebo-controlled study (TRUMPfh II) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions to TYVASO included: cough and throat irritation; headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with TYVASO than with placebo.

Table 1: Adverse Events in ≥4% of PAH Patients Receiving TYVASO and More Frequent* than Placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TYVASO n = 115</th>
<th>Placebo n = 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>62 (54)</td>
<td>35 (29)</td>
</tr>
<tr>
<td>Headache</td>
<td>47 (41)</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Throat Irritation/Pharyngolaryngeal Pain</td>
<td>29 (25)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (19)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Flushing</td>
<td>17 (15)</td>
<td>1(1)</td>
</tr>
<tr>
<td>Syncope</td>
<td>7 (6)</td>
<td>1(1)</td>
</tr>
</tbody>
</table>

*More than 3% greater than placebo

The safety of TYVASO was also studied in a long-term, open-label extension study in which 286 patients were dosed for a mean duration of 23 months. 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, pharyngal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study comprised 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—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulant therapy.

Effect of Other Drugs on Treprostinil—Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both Cmax and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions:

• Decrease in systemic blood pressure  • Breathing

Adverse Reactions Identified in Clinical Trials—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In a 12-week placebo-controlled study (TRUMPfh II) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions to TYVASO included: cough and throat irritation; headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with TYVASO than with placebo.

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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®). Pharmacokinetics—Antihypertensive Agents or Other Vasodilators—Concomitant administration of TYVASO with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension. Anticoagulants—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics—Bosentan—In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

Stilnox—In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed. Effect of Cytochrome P450 Inhibitors and Inducers—In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A. Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diethanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both Cmax and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inhibitor rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8. Effect of Other Drugs on Treprostinil—Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with atorvastatin (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B—There are no adequate and well controlled studies with TYVASO in pregnant women. Animal 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, dosage 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—Plasma clearance 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.

Patients with Renal Insufficiency—No studies have been performed in patients with renal insufficiency. Since treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites and consequently, dose-related adverse outcomes may be more frequent.

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.
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.
ANNOTATIONS:

**LETARIS** (ambisentan) Tablets, for oral use

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

**BOXED WARNING:** CONTRAINDICATIONS IN PREGNANCY

Do not administer LETARIS to a pregnant woman because it may cause fetal harm. Boxed warnings are intended to appear prominently in the labeling and will appear on the Medication Guide provided to the patient. The risk involved in administering the drug to a pregnant woman must be balanced against the risk of the patient remaining untreated. A pregnancy test should be performed before initiating therapy with LETARIS. If pregnancy occurs during therapy with LETARIS, the patient should be informed of the potential risk to the fetus. The risk involved in administering the drug to a pregnant woman must be balanced against the risk of the patient remaining untreated. A pregnancy test should be performed before initiating therapy with LETARIS. If pregnancy occurs during therapy with LETARIS, the patient should be informed of the potential risk to the fetus.

**INDICATIONS AND USAGE:** LETARIS is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness depended predominantly on patients with WHO Functional Class III-IV symptoms and etiologies of diastolic or pulmonic heart failure (WHO Group 3).

**DOSAGE AND ADMINISTRATION:** Healthcare professionals who prescribe LETARIS must enroll in the restricted program called LEAP and must comply with the required monitoring to ensure safe use of LETARIS (see Warnings and Precautions). Because of the risk of birth defects, LETARIS is contraindicated in women who are or may become pregnant. If the 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 the fetus. Pregnancy must be excluded before the initiation of treatment with LETARIS and prevented during treatment and for one month after stopping treatment (see Usage and Administration, Warnings and Precautions). Idiopathic Pulmonary Fibrosis: LETARIS is contraindicated in patients with idiopathic pulmonary fibrosis (IPF) including IPF patients with pulmonary hypertension (WHO Group 3).

**WARNINGS AND PRECAUTIONS:** LETARIS Education and Access Program (LEAP): Because of the risk of birth defects, LETARIS is available only through a restricted program called LEAP. Healthcare professionals who prescribe LETARIS must complete the LEAP Prescriber Enrolment and Agreement Form, enroll in the program, and comply with the REMS requirements. To receive LETARIS, all patients must complete a patient enrollment form and be re-enrolled annually by their prescriber. For women of childbearing potential only, a pregnancy test must be ordered and repeated by the prescriber prior to the initiation of LETARIS 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 LETARIS, and (4) she must agree to be contacted by Glaxo if she becomes pregnant while on LETARIS or within 30 days of treatment discontinuation. Phlebitis or thrombosis following the administration of LETARIS must be enrolled in the program and agree to comply with the REMS requirements. Further information is available at www.letaris.com or 1-866-664-LEAP (5327).

**Fluid Retention:** Peripheral edema is a known class effect of endothelin receptor antagonists. There are no data on the use of LETARIS in pregnant women. LETARIS is contraindicated in women who are or may become pregnant. If the 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 the fetus. Pregnancy must be excluded before the initiation of treatment with LETARIS and prevented during treatment and for one month after stopping treatment (see Usage and Administration, Warnings and Precautions). Idiopathic Pulmonary Fibrosis: LETARIS is contraindicated in patients with idiopathic pulmonary fibrosis (IPF) including IPF patients with pulmonary hypertension (WHO Group 3).

**CONTRAINDICATIONS:** Pregnancy: LETARIS may cause fetal harm when administered to a pregnant woman. Animal data were negative at oral doses of 5 to 25 mg/kg/day in rats and 5 to 25 mg/kg/day in rabbits. It was not studied at doses lower in both. In these studies, there were fatalities with or without treatment, which occurred within 24 hours of treatment. Because the risk involved in administering the drug to a pregnant woman must be balanced against the risk of the patient remaining untreated, a pregnancy test should be performed before initiating therapy with LETARIS. If pregnancy occurs during therapy with LETARIS, the patient should be informed of the potential risk to the fetus. Pregnancy must be excluded before the initiation of treatment with LETARIS and prevented during treatment and for one month after stopping treatment (see Usage and Administration, Warnings and Precautions). Idiopathic Pulmonary Fibrosis: LETARIS is contraindicated in patients with idiopathic pulmonary fibrosis (IPF) including IPF patients with pulmonary hypertension (WHO Group 3).

**ADVERSE REACTIONS:** See Warnings and Precautions for discussion of hematological changes. Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Safety data for LETARIS were obtained from two other LEAP, placebo-controlled studies in patients with pulmonary arterial hypertension (PAH) (ABIES-1 and ABIES-2) and four nonplacebo-controlled studies in 483 patients with PAH who were treated with doses of 1.25, 5, or 10 mg once daily. The exposure to LETARIS in these studies ranged from 1 day to 4 years (N=419 for at least 6 months and N=343 for at least 1 year). In ABIES-1 and ABIES-2, a total of 261 patients received LETARIS at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse reactions that occurred in >3% more patients receiving LETARIS than receiving placebo are shown in Table 1.

| Table 1: Adverse Reactions with Placebo-Adjusted Rates >3% |
|----------------|--------------------|--------------------|
| **Placebo** (N=132) | **LETARIS (N=261)** |
| **Adverse Reaction** | **n (%)** | **n (%)** | **Placebo-adjusted (%)** |
| Peripheral edema | 14 (11) | 45 (17) | 6 |
| Nasal congestion | 2 (2) | 15 (6) | 4 |
| Sinusitis | 0 (0) | 6 (2) | 3 |
| flushing | 1 (1) | 10 (4) | 3 |

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 LETARIS (4%, 26/617) or placebo (7%, 46/637) and in elderly patients (≥65 years) receiving LETARIS (12%, 76/657) and placebo (12%, 75/620). 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 LETARIS (2%; 5/261 patients) and placebo (2%; 3/122 patients). The incidence of serious adverse events after the treatment during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for LETARIS (5%; 13/261 patients). During 12-week controlled clinical trials, the incidence of aminotransferase elevations >3× upper limit of normal (ULN) were 0% on LETARIS 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, nonplacebo-controlled trial in patients who had previously continued endothelin receptor antagonists (ERAs; bosantan, an investigational drug, or both) due to aminotransferase elevations >3× ULN were treated with LETARIS. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5× ULN, but 9 patients had elevations >8× ULN. Eight patients had been re-challenged with bosantan and/or the investigational ERA and all except a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving protonated and/or phosphodiestere type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 5x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on LETARIS 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 LETARIS to 10 mg, no patients were discontinued for aminotransferase 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 LETARIS led to fewer aminotransferase elevations or AA than would have been seen with those drugs. The study indicates that LETARIS may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal. Postmarketing Experience: The following adverse reactions were identified during postapproval use of LETARIS. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency or severity of these reactions and further evaluation is required. Anemia: Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with LETARIS (ambisentan). These decreases were observed within the first few weeks of treatment with LETARIS, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving LETARIS in the 12 week placebo-controlled studies was 0.8 g/dL. Marked decreases in hemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7 of all patients receiving LETARIS (10% and 16% of patients receiving 10 mg; compared to 3 patients of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis. In the long-term open-label extension of the two pivotal clinical studies, mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment. There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion. Measure hemoglobin prior to initiation of LETARIS, at one month, and periodically thereafter. Initiation of LETARIS therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing LETARIS. **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.
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 dose) 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/mm² 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 develop 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 overdose 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 LEAP. 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 Lhg 20IUS 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 patient 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.

GS22-081-010

GILEAD

For detailed information, please see full Prescribing Information. To learn more: call 1-800-GILEAD-5 (Option 2) or visit www.letairis.com.

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2013 PH Professional Network Symposium
The Power of Teamwork:
10 Years of Professional Collaboration in PAH

September 26 – 28, 2013
Crystal Gateway Marriott
Arlington, Va.

An educational and networking event for PH-treating allied health professionals.

2013 SYMPOSIUM HIGHLIGHTS
This Symposium will feature an extraordinary line-up of speakers and topics highlighting the latest advances and research in pulmonary hypertension.

- Nearly 30 educational sessions led by multidisciplinary panels of speakers.
- Networking opportunities with other PH-treating colleagues from across the country.
- Opportunity to advocate for PH patients on Capitol Hill.

SESSION SPOTLIGHT
Surgery and the PH Patient: Oh N-O – it’s a Lot More than N-P-O
Preparing Your PH Patient for Non-Cardiothoracic Surgery
Presenters: Mary Knabe, RN, MSN; Charles D. Burger, MD; Katie M. Muzevich, PharmD, BCPS

It takes a team effort to prepare PH patients for non-cardiothoracic surgery. Join a physician, pharmacist and nurse to learn about the critical steps in preparing patients for a successful experience and full recovery. Discover how one institution has developed a patient-centered surgical team for PH and how you can create one of your own.

PH Professional Network (PHPN) is a recognized network reaching over 1,200 PH-treating healthcare professionals. Members are dedicated to enhancing communication, professional development, research opportunities and education in the medical community.
REGISTRATION NOW OPEN
PHA is offering a reduced fee of $100 for the first 250* PH-treating healthcare professionals who register!

How to Register
- **ONLINE**: Register online at www.PHAssociation.org/PHPN/Symposium
- **BY MAIL**: Download and complete the print registration form from the Symposium website and submit it with payment.
- **BY FAX**: Download and complete the print registration form and fax it to 301-565-3994.

*In order to receive the reduced registration fee, attendee must have an active PH Professional Network membership.

OPPORTUNITY TO EARN CEUs
The programming at Symposium is being planned in compliance with continuing education accreditation policies and procedures. Upon activity approval, this event will provide continuing education credits for the following health professionals:
- Nurses
- Pharmacists
- Physician assistants
- Respiratory therapists
- Social workers

Participants can earn **up to 10.25 hours** of continuing education credit.

For additional information, visit: www.PHAssociation.org/PHPN/Symposium or contact 301-565-3004 x761 or Symposium@PHAssociation.org

Physicians: Encourage the healthcare professionals in your practice to take advantage of this valuable opportunity. Ensure that the latest advances in the care and treatment of PH patients are incorporated into your practice - consider supporting your staff's attendance at this educational program!
Jointly Sponsored

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

**Program Announcement:**

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

**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](http://www.PHAssociation.org/MedicalProfessionals/Research)

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