Evaluation and Management of PH and Right Heart Dysfunction in the ICU

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## The Scientific Leadership Council of the Pulmonary Hypertension Association

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

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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 PHAAssociation.org/SLC/
Submissions should be sent via e-mail as an attached manuscript. manuscripts are reviewed by the editorial board of renowned experts in the field. Acceptance of manuscripts submitted to the journal is independent of the source of the manuscript. The contents of the articles are independently determined by the Editor-in-Chief and the Editorial Advisory Board.

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. Acceptable 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.

Copyright

Authors must confirm they have rights to all material submitted, including a copyright release form with the manuscript. The form can be downloaded from the PHA Web site, wwwPHAonlinetools.org. Authors acknowledge the material has not been previously published nor is being considered for publication elsewhere simultaneously with consideration by Advances in Pulmonary Hypertension.

Any previously published figures, tables, etc. must contain a full credit-line from the copyright owner. Authors are responsible for obtaining permission to reproduce such material and must provide that material in reproducible form.

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.
Managing RV Failure: Seeing a Light at the End of the Tunnel

The appreciation of the right ventricle (RV) can be traced to the work of William Harvey with his landmark publication *Exercitatio Anatomica de Motu Cordis et sanguinis in Animabilis* in 1628, in which based on observations and experiments, Harvey had the incredible insight to differentiate the functions of the two ventricles when he stated: “So it appears that whereas one ventricle, the left, suffices for distributing the blood to the body and drawing it from the vena cava, as is the case in all animals lacking lungs, nature was compelled when she wished to filter blood through the lungs to add the right ventricle. Thus the right ventricle may be said to be made for the sake of transmitting blood through the lungs, not for nourishing them.”

Though Harvey’s keen observations on the human circulatory system have been credited as the beginnings of modern cardiology, the right heart system has been vastly neglected during the last half century of advances in cardiology as most of the attention has been given to the left heart. However, as the recognition of the pivotal role the right heart system plays in determining outcome among patients presenting with cardio-pulmonary disease increases, the pendulum is shifting toward focusing our learning more about the mechanism, pathophysiology, evaluation, and management of right heart dysfunction.

It is my distinct honor to present this issue which highlights key principles in clinical dilemmas in the management of patients with right heart failure in the critical care setting. I am very grateful to our guest editor Deborah Levine, MD, for bringing together a renowned group of experts to collectively share their experiences in the management of this challenging group of patients. Their expertise and insight provide valuable information for clinicians at the bedside as they encounter this unique group of critically ill patients.

On a personal note, I wish to thank the Advances editorial board, PHA leadership and staff, our guest editors and authors, and our managing editor Deb McBride for all the tremendous support I have received during the past 2 years as editor-in-chief. Thanks to everyone’s contributions, we have been able to successfully implement several key changes within Advances including:

- increasing the number of editorial board members
- redesigning Advances as a scholarly journal
- instituting more rigorous peer review in keeping with NLM standards
- providing commentary from the editor-in-chief with each issue’s eTOC
- preparing for the re-launch of research updates
- welcoming a terrific new section, PH Grand Rounds

Through all these efforts, we remain steadfast in our goal to serve the PH clinical community to help in the care and management of patients with pulmonary hypertension. As I welcome the incoming editor-in-chief, Charles Burger, MD, I would like to thank you, our readers, for all the support I have received in serving Advances. It has been a true honor and privilege.

Myung H. Park, MD
Associate Professor of Medicine
Director, Pulmonary Vascular Disease Program
University of Maryland School of Medicine

(Continued on page 214)
ADD MORE to your treatment strategy with Tyvaso, an inhaled prostacyclin analogue*  
+ PAH may be progressing even if patients seem stable**
+ Many patients plateau on oral therapy (PDE-5 inhibitor or ERA) in as few as 12 weeks***

**TYVASO is the only PAH treatment studied solely as an add-on to bosentan (an ERA) or sildenafil (a PDE-5 inhibitor)****

+ Clinically stable patients improved median 6MWD by 20 m (P<0.001) after adding Tyvaso for 12 weeks****
+ 4X daily dosing with short treatment sessions (2-3 minutes) approximately every 4 hours*****

Study design: TRUMP-I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=235) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, Borg dyspnea score, NYHA Functional Classification, trough 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 predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

**IMPORTANT SAFETY INFORMATION**
Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System.

+ The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age.

+ Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect

+ Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants

+ In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension

+ Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn

+ The most common adverse events seen with Tyvaso in 24% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%)

+ Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women

Please see brief summary of Full Prescribing Information 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.

**REFERENCES**


13. PDE-5=phosphodiesterase type 5


15. SCIENCE, INC; 2013.

16. Flolan=Flolan Inhalation Suspension for Use in Pulmonary Hypertension; WHO=World Health Organization.
**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 predominantly 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 less 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—Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.

**Risk of Bleeding**—Since TYVASO 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) 2C enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both Cmax and AUC) to treprostinil. Co-administration of a CYP2C enzyme inducer (e.g., rifampicin) 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
- Bleeding

*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 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, pharyngitis, pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 15 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience. *Adverse Reactions Identified in Post-Marketing Experience*—The following adverse reaction has been identified during the postapproval use of TYVASO. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure: Angioedema

**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 diolamine) and subcutaneously administered treprostinil (Remodulin®).

**Anticoagulants**—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

**Drug Interactions**

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>
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<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>
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<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>11 (9)</td>
</tr>
<tr>
<td>Syncope</td>
<td>7 (6)</td>
<td>1 (1)</td>
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*More than 3% greater than placebo

**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 (i.c.) infusions of treprostinil sodium at infusion rates higher than the recommended human s.c. infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity. Animal reproduction studies are not always predictive of human response; TYVASO should be used during pregnancy only if clearly needed.

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

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

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

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

**Patients with Hepatic Insufficiency**—Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptrile 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.

**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 infusions of treprostinil at an infusion rate of 100 ng/min.**
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 embryo-fetal toxicity.
Letairis® (ambrisentan) 5 mg and 10 mg Tablets, for oral use

BRIEF SUMMARY OF ALL IMPORTANT INFORMATION

Brief summary of all important information. See Full prescribing information. Rx only.

BOXED WARNING: EMBRYO-FETAL TOXICITY

Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant female, as this effect has been seen consistently when it is administered to animals [see Contraindications, Use in Specific Populations].

Exclude pregnancy before the initiation of treatment with Letairis. Females of Reproductive Potential must use accepted methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment [see Use in Specific Populations].

Because of the risk of embryo-fetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS Program [see Warnings and Precautions].

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

DOSE AND ADMINISTRATION: Adult Dosage: Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg once daily if 5 mg is well tolerated. Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in PAH. Pregnancy Testing: Females of Reproductive Potential: Initiate treatment with Letairis in Females of Reproductive Potential only after a negative pregnancy test. Obtain monthly tests during treatment [see Use in Specific Populations].

CONTRAINDICATIONS: Pregnancy: Letairis may cause fetal harm when administered during or after pregnancy. This effect has been demonstrated to occur consistently when it is administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Warnings and Precautions, Use in Specific Populations].

Hematological Changes: Letairis is contraindicated in patients with idiopathic Pulmonary Fibrosis (IPF) including IPF patients with pulmonary hypertension [WHO Group 3] [see Clinical Studies].

WARNINGS AND PRECAUTIONS: Letairis REMS Program: For all females, Letairis is available only through a restricted program called the Letairis REMS Program, because of risk of embryo-fetal toxicity [see Contraindications, Warnings and Precautions, Use in Specific Populations]. Notable requirements of the Letairis REMS Program include that the Prescribers must be certified with the program by enrolling and completing training. All females, regardless of reproductive potential, must enroll in the Letairis REMS Program prior to initiating Letairis. Male patients are not enrolled in the REMS. Females of Reproductive Potential must comply with the pregnancy testing [see Use in Specific Populations].

Pharmacies that dispense Letairis must be certified with the program and must dispense to female patients who are authorized to receive Letairis. Further information is available at www.letairisrems.com or 1-866-664-5327.

Fluid Retention: Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and the possible need for specific treatment or discontinuation of Letairis therapy.

Hypersensitivity: Hypersensitivity reactions including flushing, rash, pruritus, chills, and angioedema were seen in a dose-dependent manner. Angioedema has been reported in patients treated with Letairis. Most events were mild to moderate in severity, and occurred with greater frequency and severity in elderly patients. In all eight clinical trials, 8.5% of patients treated with Letairis experienced at least one angioedema event; 1% experienced at least one anaphylaxis event. Angioedema can occur at any time during treatment with Letairis.

Statin therapy has been associated with increased elevations of serum transaminases [ALT, AST] and hepatic injury. Elevations of ALT or AST at greater than 5:1 upper limit of normal (ULN) without other evidence of hepatic injury, or elevations at greater than 10:1 ULN, should be considered serious hepatic injury, and Letairis should be discontinued. The risk of elevated ALT and AST was increased with concomitant use of erythromycin or amiodarone.

DRUG INTERACTIONS: Aminotransferase elevations were reported in 2.2% of patients treated with Letairis, compared to placebo (0.4%). Elevations were generally mild to moderate, and were not associated with clinical signs or symptoms of liver disease. The majority of patients had elevations that resolved with decreasing the dosage to 2.5 mg, and did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of Letairis to 10 mg, no patients were discontinued for aminotransferase elevations. The uncontrolled study design does not provide information about what would have occurred with a placebo-controlled comparison of previously used ERA and/or other PAH therapies, and that Letairis led to a few more aminotransferase elevations than would have been seen with those drugs, the study indicates that Letairis may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

Peripheral Edema: The incidence of peripheral edema was generally low in the clinical trials. In ARIES-1 and ARIES-2, 5.3% of patients treated with Letairis experienced peripheral edema; 2% of patients treated with placebo experienced peripheral edema. Peripheral edema was more common in the elderly than in younger patients.

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Warnings and Precautions: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for 1 month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning]. Infertility: Males in a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 to 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data (see Nonclinical Toxicology) from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Letairis have an adverse effect on spermogenesis. Counsel patients about the potential effects on fertility [see Warnings and Precautions]. 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 [see Clinical Pharmacology]. 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 [see Clinical Pharmacology]. 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 overdosage could potentially result in hypotension that may require intervention. Patient Counseling Information: See FDA-approved patient labeling (Medication Guide). Embryofetal toxicity: Instruct patients on the risk of fetal harm when Letairis is used in pregnancy [see Warnings and Precautions; Use in Special Populations]. Female patients must enroll in the Letairis REMS Program. Instruct Females of Reproductive Potential to immediately contact their physician if they suspect they may be pregnant. Letairis REMS Program: For female patients, Letairis is only available through a restricted program called the Letairis REMS [see Contraindications, Warnings and Precautions]. Male patients are not enrolled in the Letairis REMS. Inform female patients (and their guardians, if applicable) of the following necessary requirements: All female patients must sign an enrollment form. Advise female patients of reproductive potential that they must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations]. Educate and counsel Females of Reproductive Potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure. Advise prepubertal females to report any changes in their reproductive status immediately to their prescriber. Review the Letairis Medication Guide and REMS educational material with female patients. A limited number of pharmacies are certified to dispense Letairis. Therefore, provide patients with the telephone number and website for information on how to obtain the product. Hepatic Effects: Some members of this pharmacological class are hepatotoxic. Patients should be educated on the symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) and instructed to report any of these symptoms to their physician. Hematological Change: Patients should be advised not to split, crush, or chew tablets.

For detailed information, please see full Prescribing Information. To learn more: call 1-800-GILEAD-5 (Option 2) or visit www.letairis.com. Manufactured and marketed by: Gilead Sciences, Inc., Foster City, CA 94404, USA © 2014 Gilead Sciences, Inc. All rights reserved. LETP0103 January 2014 Letairis is a registered trademark of Gilead Sciences, Inc. Gilead and the Gilead logo are trademarks of Gilead Sciences, Inc. Other brands noted herein are the property of their respective owners.

PHA offers ongoing education and information for patients and caregivers at every stage of their PH journeys. We now provide resources to help your patients and caregivers cope with the mental, emotional and social impacts of living with PH.

Coping with Pulmonary Hypertension Guides are available for:

- Newly Diagnosed Patients
- Long-Term Survivors
- Caregivers
- Teens
- Parents

To download your free guides, visit: www.PHAssociation.org/ForYourPatients
Once-daily OPSUMIT® (macitentan) is the first and only oral PAH therapy indicated to both delay disease progression and reduce hospitalization for PAH.

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.
  - Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
  - Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

IMPORTANT SAFETY INFORMATION

BOXXED WARNING: EMBRYO-FETAL TOXICITY

- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.
- For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS).

CONTRAINDICATIONS

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the OPSUMIT REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 x ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 x ULN were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT.
when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

**Hemoglobin Decrease**
- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

**Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)**
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

**Decreased Sperm Counts**
Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

**ADVERSE REACTIONS**
Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

**DRUG INTERACTIONS**
- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

*Please see Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.*
**Hepatotoxicity**

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 × ULN</td>
<td>3.4%</td>
<td>4.5%</td>
</tr>
<tr>
<td>&gt;8 × ULN</td>
<td>2.1%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.5% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated. Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

**Hemoglobin Decrease**

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated (see Adverse Reactions (Clinical Trial Experience)).

**Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)**

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

**Decreased Sperm Counts**

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility (see Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)).

**ADVERSE REACTIONS**

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity (see Warnings and Precautions (Embryo-fetal Toxicity))
- Hepatotoxicity (see Warnings and Precautions (Hepatotoxicity))
- Decrease in Hemoglobin (see Warnings and Precautions (Hemoglobin Decrease))

**Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 clinical practice. Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

<table>
<thead>
<tr>
<th></th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis/pharyngitis</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Influenza</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9%</td>
<td>6%</td>
</tr>
</tbody>
</table>

**DRUG INTERACTIONS**

**Strong CYP3A4 Inducers**

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided (see Clinical Pharmacology (Pharmacokinetics)).
**Clinical Pharmacology**

**Special Populations**

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

**Renal Impairment**

Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

**Hepatic Impairment**

Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

**Drug Interactions**

**In vitro studies**

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with drugs involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

**In vivo studies**

**Effect of other drugs on macitentan**

The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

**Figure 1**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Macitentan</th>
<th>Active metabolite</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

**Pediatric use**

The safety and efficacy of OPSUMIT in children have not been established.

**Geriatric use**

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

**Females and Males of Reproductive Potential**

**Females**

**Contraception**

Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner’s vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling (see Boxed Warning).

**Males**

**Testicular effects**

Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis (see Warnings and Precautions (Decreased Sperm Counts) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)).

**OVERDOSAGE**

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

- **Strong CYP3A4 Inhibitors**
  - Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors (see Clinical Pharmacology (Pharmacokinetics)). Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment (see Clinical Pharmacology (Pharmacokinetics)).

- **USE IN SPECIFIC POPULATIONS**
  - **Pregnancy**
    - **Pregnancy Category X.**
    - **Risk Summary**
      - OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus (see Contraindications (Pregnancy)).
  - **Animal Data**
    - In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.
  - **Nursing Mothers**
    - It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.
  - **Pediatric use**
    - The safety and efficacy of OPSUMIT in children have not been established.
  - **Geriatric use**
    - Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.
  - **Females and Males of Reproductive Potential**
    - **Females**
      - **Contraception**
        - Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus (see Boxed Warning and Dosage and Administration section 2.2 in full Prescribing Information).
      - **Males**
        - **Testicular effects**
          - Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis (see Warnings and Precautions (Decreased Sperm Counts) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)).

- **Drug Interactions**

  - **Sildenafil**
    - At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

  - **Warfarin**
    - Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

  - **Avoid**
    - Sildenafil: Steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis**

Carcinogenicity studies of 2 years’ duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

**Mutagenesis**

Macitentan was not genotoxic in a standard battery of in vitro and in vivo assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an in vivo micronucleus test in rats.

**Impairment of Fertility**

Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

**Animal Toxicology**

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans. There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

**Manufactured for**

Actelion Pharmaceuticals US, Inc.

5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA

ACT20131018


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I was 24 years old, very active, working full time in Connecticut, and taking some night classes. All of that came to what seemed like a screeching halt. I stopped school and focused my energy into contacting the National Organization for Rare Disorders (NORD) and National Institutes of Health (NIH) for information to give to my doctors, which, at that time, consisted of a transplant team. I attended support groups for transplant patients and waited to learn more about this illness and possible research opportunities. The information and research came many years later. Being a member of the PHA’s Board of Trustees (BOT) and Pulmonary Hypertension Care Centers (PHCC) Oversight Committee is something I dared not dream of back then.

–Diane

A few years earlier, across the country, Rachel was diagnosed with portal hypertension at age 10 following a massive esophageal hemorrhage. After battling back from this scare, my lovely sister began her journey with pulmonary hypertension (PH)—only no one knew she was on this journey. We, along with her medical providers, were unaware that portal hypertension could create another life-threatening condition.

Fast forward another decade or so: Rachel had experienced shortness of breath upon exertion for years, but she was repeatedly told by several physicians that she was out of shape and simply needed to exercise regularly. In August of 1993, a routine physical revealed a heart murmur and a “precautionary” EKG was done. At age 23, my sister was sassy, full of life, and unafraid. Thus, she went to her follow-up appointment alone, where she learned that although further tests were needed, she likely had something she had never heard of (inaudaciously termed PPH) and that she should plan to make the most of the rest of her life—approximately 6 months. The physician who delivered this news had never seen a patient with PH, nor was there a single provider with knowledge of PH in the health system within which she was diagnosed. Rachel lived 18 months with her PH diagnosis before losing her battle in 1995, but clearly she had lived more than a decade with PH-related symptoms. –Laura

At the time that Diane and Rachel were diagnosed, there were no medical treatments for PH. Today, there are 12 FDA-approved treatments, with more on the way. Additionally, there is now a cadre of clinical and research experts who have devoted their careers to understanding PH and caring for those who are living with this complex illness. And, although there is evidence to suggest that many PH patients are living longer with a better quality of life, there are some key aspects of living with PH that have not changed for many patients.

For example, despite advances in understanding the etiology of pulmonary arterial hypertension (PAH), the time from onset of symptoms to recognition of the disease has not improved over the past 2 decades. Data from US adult patients enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) found that 1 in 5 patients (analytic sample n=2494 patients) with PAH experienced a delay of more than 2 years between symptom onset and either receiving a PAH diagnosis or starting PAH-specific therapy. This is particularly relevant given that untreated, PAH results in pathologic changes that are life-threatening and irreversible, and even a 2-year delay in diagnosis can greatly diminish the potential for good clinical outcomes and survival.1

The challenges associated with becoming diagnosed and accessing expert PH medical care are exacerbated for those living great distances from PH centers. These patients are often seen in community and nonspecialist settings for years before locating a PH expert either because they are limited in the ability to travel due to physical or economic constraints, or because their original treating provider is unaware of the complexities of PH and attempts to manage it without the involvement of a PH center. In some cases, patients are simply unaware of who and where the experts are. Additionally, the variability of the pathways leading to the different types of PH and the optimal treatments for

Pulmonary Hypertension Care Centers: Hope for the Future From a Patient’s and Caregiver’s Perspectives

Diane Ramirez
Advocacy Chair, Piedmont North Carolina Support Group
Member, Pulmonary Hypertension Association Board of Trustees

Laura Hoyt D’Anna, DrPH, MPA
Director, Center for Health Equity Research
California State University, Long Beach
Member, Pulmonary Hypertension Association Board of Trustees

In 1987, after three years of being treated aggressively for asthma and then a prolapsed mitral valve, I was finally diagnosed with primary pulmonary hypertension (PPH). I was told I would be lucky if I lived 2 years without having a heart/double lung transplant and that I didn’t have much time to get my affairs in order. There were fewer than 200 patients in the United States at the time. There were no treatment centers, support groups, or even an advocacy group like the Pulmonary Hypertension Association (PHA). I struggled with the loneliness of this diagnosis and the lack of information available.
each of these make PH a highly complex condition to treat and manage successfully. Thus, those who are able to access centers with PH experience may encounter varied diagnostic approaches and treatment compared to similar patients across the country, or even in the next city or town.

For these reasons, the PHA BOT, through the recommendation and guidance of its Scientific Leadership Council, made the commitment to launch the PHCC initiative. This will ensure that a high standard of care is delivered at all PH centers, large or small, by reinforcing standards for practice as agreed upon by the medical experts in the field. This high standard of care is being assured through a PHCC Oversight Committee composed of expert PH clinicians and researchers, PHA BOT members, and patients. Additionally, a detailed center application process, accreditation standards and procedures, site visits conducted by volunteer reviewers with PH clinical and research expertise, and common data points for quality assurance evaluation are other ways in which high quality care will be achieved and monitored through this initiative.

From our unique perspectives, we believe that the PHCC initiative will: 1) promote diagnostic and treatment standards for PH; 2) reduce diagnosis and treatment errors, and improve overall quality of care; 3) increase PH-related knowledge among a broad array of medical professionals; 4) improve communication and linkage between centers; and 5) increase opportunities for additional research funding and activities.

What will this mean for patients and their families?

- Improved awareness of and access to centers with expertise in PH
- Increased information about available treatments
- Increased opportunities to participate in research
- More freedom to travel without the fear of having to see an inexperienced doctor in the case of an emergency
- Increased patient education
- Earlier and accurate diagnosis

In essence, having accredited PH centers across the country should eventually reduce the likelihood of delays in diagnosis, misdiagnosis, and insufficient or inappropriate treatment, and will ideally result in improved quality of life and longevity for many. It is our hope that the PHCC effort will ensure that future patients do not experience what Diane and Rachel did when beginning their journeys with PH.

Reference

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Debuting in Volume 13, No 3 in the Fall of 2014 a new section will appear in Advances in Pulmonary Hypertension dedicated to inspiring new thoughts and providing instruction through case reports and reviews. This section will focus on submissions from trainees and junior faculty interested in pulmonary hypertension (PH). It will emulate Grand Rounds and will highlight clinical cases that describe an interesting or thought-provoking entity, mechanism, presentation, or outcome in patients with PH. The cases will include reviews of topics that provide insights and education for clinicians. Interesting cases with associated teaching points and discussion that the case highlights are encouraged. Mentoring comments from a member of the editorial board will be included with each of the cases.

The Advances editorial board encourages program directors and attendings to promote this opportunity to trainees and junior faculty as an opportunity to share their observations and to obtain valuable comments from leaders in the field. It’s a great way to become involved with other clinicians and researchers.

Potential authors should submit a brief summary for consideration by the editorial board. Selected authors will be notified to prepare the complete case.

**Author Instructions**

Each case study should be submitted double-spaced in Word. Digital files of illustrations are acceptable as long as they reproduce well.

- **Abstract:** 150 words in narrative format
- **Text:** Maximum 1000 words
- **Tables and illustrations:** Total of 3; color allowed
- **References:** Maximum of 8. Do not include any reference management software.

**Format:**

- **Introduction and case presentation**
- **History**
- **Clinical features**
- **Clinical evaluation**
- **Laboratory and study results** (to include imaging if possible, waveforms, etc)
- **Management and therapeutics**
- **Outcomes**
- **Discussion:** Review of the literature
- **Recommendations and comments**
- **Mentoring comments from an editorial board member**

Case reports that have been presented at meetings are acceptable as long as the meeting information is disclosed on the title page.

IRB approval is not required; nevertheless, authors must preserve patient privacy when writing up the case. On acceptance, written patient permission will be requested as a condition of publication.

Cases will be chosen for publication by members of the Advances in Pulmonary Hypertension editorial board.

Submit a brief summary for consideration to: advancesgrandrounds@PHAssociation.org

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San Antonio, Texas
The management of acute right ventricular (RV) failure in acute pulmonary embolism (PE) differs from RV failure in chronic forms of pulmonary hypertension (PH) such as pulmonary arterial hypertension (PAH). In PE, RV failure generally occurs suddenly and there is far less ability to acutely compensate. Parameters that reflect RV function help predict outcome in PE. The mortality in acute PE leading to shock is very high; when cardiopulmonary arrest occurs, it approaches 100%.

Patients with acute PE must be risk stratified, but no perfect algorithm exists. Certain parameters are predictive of a poor prognosis and should be considered. Treatment decisions for the extremes of presentation are relatively straightforward. Patients with small clot burdens, ie, few segmental or solely subsegmental acute PE, particularly with minimal or no residual deep vein thrombosis (DVT) should be treated with anticoagulation alone. Those with massive PE and shock or significant hypotension should receive aggressive measures, including consideration for thrombolysis. Submassive, or “intermediate-risk” PE, ie, without hemodynamic compromise, has been more controversial. Our focus will be the management of RV failure causing hemodynamic compromise.

DEFINITIONS
Massive (“high-risk”) PE is defined by resulting hemodynamic compromise. This is most evident with shock or hypotension requiring pressor therapy. Profound bradycardia may be present. Still, the definition of massive PE includes patients with a systolic blood pressure $\leq 90$ mm Hg for $\geq 15$ minutes or a drop in systolic pressure by at least 40 mm Hg from baseline. Thus, massive PE cases vary in severity, ranging from hypotension responding to fluids, to shock with cardiopulmonary arrest.

Submassive (“intermediate-/moderate-risk”) PE: These patients are normotensive, with evidence of RV dysfunction.

Nonmassive/minor (“low-risk”) PE: The term “nonmassive” is less than ideal, but implies neither massive nor submassive. (None of these definitions incorporates residual DVT.)

RISK STRATIFICATION
A comprehensive review is beyond our scope, but it should be emphasized that it has been repeatedly demonstrated that RV dysfunction is a predictor of mortality in acute PE. The shock index (defined as heart rate divided by systolic blood pressure) of $\geq 1$, has been shown to be an independent predictor of 30-day mortality in acute PE, and may be a better predictor than systolic blood pressure. Mortality is markedly increased when the pulmonary artery obstruction index is greater than 40%. Brain natriuretic peptide (BNP)/NT-pro-BNP, and troponin reflect RV function, and elevations predict a poorer outcome. Not surprisingly, concomitant leg DVT appears to predict higher mortality. Combining these prognostic markers may more reliably predict poor prognosis in acute PE. While controversies regarding aggressive treatment of submassive PE patients beyond anticoagulation alone have persisted for decades, taking an aggressive approach for massive PE is not controversial.

We believe that “submassive” PE patients, however, with profound RV enlargement and significant tachycardia likely have a prognosis that more resembles that of massive PE. Those with “submassive” PE, characterized by only mild RV enlargement/hypokinesis and with no residual leg DVT, likely have a much better prognosis.

RECOGNIZING MASSIVE PE WITH RV FAILURE
Patients with massive PE may merely have hypotension without extreme symptoms. Very extensive PE, eg, saddle emboli, are often associated with severe dyspnea, anxiety, lightheadedness, and syncope. The physical examination can...
reveal hypotension, tachycardia, tachypnea, or cyanosis. Signs of acute RV dysfunction include distended neck veins, a parasternal heave, an accentuated P2, and a tricuspid regurgitation murmur. The EKG will often show sinus tachycardia, an S1Q3T3 pattern, T-wave inversions in V1 to V4, or a pseudoinfarction pattern in lead V1. A firm diagnosis by lung imaging is ideal, but sometimes therapy is predicated on the clinical setting alone when time does not allow for imaging or other ancillary testing. In all patients with acute PE, rapid, weight-based parenteral anticoagulation should be initiated unless contraindicated.

The general approach to RV failure in acute massive PE includes: (1) supportive therapy and (2) directly addressing the embolic burden. These goals are addressed in tandem as dictated by the clinical setting.

**SUPPORTIVE THERAPY**

Supportive therapy consists of fluid and vasopressor management, oxygenation, and when necessary, intubation and mechanical ventilation. Intravenous access should be obtained immediately and oxygen placed and adjusted appropriately. Fluid should be initially administered as a bolus (often 500 to 1000 mL), with the amount determined by perceived hydration status and concomitant cardiovascular disease. Caution is warranted, as excessive fluid administration can worsen RV wall stress and ischemia. Intubation is delayed when possible, as positive pressure can also worsen RV function acutely.

Vasopressor therapy should follow when hypotension persists. No randomized trials have determined the optimal vasopressor for patients with shock due to acute PE. Norepinephrine, dopamine, and epinephrine may be effective. We suggest norepinephrine as the initial agent. Using a combination of dobutamine plus norepinephrine initially may increase myocardial contractility, while minimizing vasodilation and the risk of hypotension. At times, a pure α-adrenergic receptor stimulant such as phenylephrine succeeds in otherwise refractory cases.

**Extracorporeal Membrane Oxygenation**

Pulmonary and circulatory support may be required for severely ill patients with massive PE who remain hypotensive with inadequate oxygenation, or with cardiac arrest. Extracorporeal membrane oxygenation (ECMO) decreases RV volume and allows recovery of ventricular function, optimizing oxygen transport by improving cardiac output and oxygen content. Recent systemic thrombolysis increases the risk of placement of ECMO access cannulas, but is not an absolute contraindication depending on the timing and dose. Patients are supported with ECMO with concomitant heparin administration. Importantly, ECMO can facilitate vortex/suction and surgical embolectomy. The time lag for recovery cannot be predicted and ECMO-related complications may occur. Thrombolysis may hasten hemodynamic improvement and enable more rapid weaning from ECMO. Ideally, a rapid response ECMO team is available.

**REDDUCING THE EMBOLIC BURDEN**

To effectively address severe RV dysfunction, the embolic burden must be acutely reduced. Choices include systemic thrombolysis, catheter-based extraction or clot disruption methods (which can include thrombolyis), and surgical embolectomy. These options depend on the degree of compromise, the rapidity at which deterioration occurs, and the resources available; thus, a case at one institution could be treated differently from an identical case at another facility. However, there are certain scenarios that favor one approach over others.

**Systemic Thrombolysis**

The clearest indication for systemic thrombolysis is massive PE and shock on vasopressors when there are no absolute contraindications and the patient is too unstable to be moved. Absolute contraindications include scenarios in which incited bleeding could be fatal. The most concerning would be brain, spine, or major organ trauma or surgery. Risk/benefit in a critically ill PE patient may favor systemic thrombolysis despite relative contraindications. The most common regimen is tissue-type plasminogen activator (tPA) at 100 mg intravenously over 2 hours. A 50 mg infusion has been studied and may be as effective, with less bleeding. In patients with extreme shock in whom systemic thrombolysis cannot be given, ECMO should be considered (see below).

**Catheter-Based Techniques**

A full discussion is beyond our scope. A number of techniques have been approved for clot extraction in certain specific settings, but not all are approved for acute PE. The EkoSonic Endovascular System (EKOS/BTG) was approved May 2014 for ultrasound-assisted thrombolysis, using a much lower thrombolytic dose than would be administered systemically. It is the most extensively studied technique; a randomized clinical trial of submassive PE patients demonstrated more rapid improvement in RV size than with anticoagulation alone (ULTIMA). Another large nonrandomized study, which included predominantly submassive PE as well as cases of massive PE, also demonstrated that RV function was improved compared with baseline (SEATTLE II). The infusion durations were 12 to 24 hours. In massive PE, the degree of illness and rapidity of deterioration must be weighed to determine whether or not a prolonged infusion should be considered.

The AngioVac catheter (AngioDynamics Inc.) received expanded FDA approval in March 2014 for venous thromboembolic disease. It utilizes vortex aspiration with a large-bore catheter that offers en bloc aspiration of large thromboemboli. The 22 French cannula can be directed to the main pulmonary arteries, although more distal vessels are not easy to access. It is most commonly used for removing clots from the inferior vena cava and the right heart. This is a large-bore catheter technique and usually requires general anesthesia. A perfusionist and access for the bypass-type circuit are required, as enough blood is removed along with thrombus that recirculation is required. The procedure is generally done in the operating room.
Surgical Embolectomy
In patients with massive PE and absolute contraindications to systemic thrombolysis, surgical embolectomy should be considered if the expertise is available. Recent systemic thrombolysis is a contraindication. In certain situations, such as massive PE with right heart clot-in-transit, surgical embolectomy or vortex clot extraction can be undertaken, although systemic thrombolysis may prove effective in this setting as well. Surgical embolectomy has not been compared to catheter embolectomy or systemic thrombolytic therapy.

In summary, there are several options to reduce the clot burden in massive PE and RV failure. These depend on the degree of RV failure and compromise, and the expertise and resources available.

EMPLOYING CLINICAL STRATEGIES: THE PE RESPONSE TEAM
The PE response team (PERT) is a combined team that rapidly responds to selected acute PE cases, similar to how an ST segment elevation myocardial infarction (STEMI) response team reacts to STEMI. Pulmonary critical care specialists, interventional cardiologists and radiologists, vascular medicine specialists, and dedicated cardiothoracic surgeons are often involved. These experts serve to integrate the information collected by the patient and formulate a plan. When the possibility of massive or submassive PE arises, the team is activated. The decisions surrounding reducing clot burden and supportive care can be determined in a multidisciplinary manner and may offer a more rapid, experienced, and effective approach.

References
PHA Online University is the premier online educational and networking resource for medical professionals seeking information about pulmonary hypertension, from diagnosis and treatment to the latest advances in the field.

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Topics include:

- Early Diagnosis & Testing of PH
- Management & Treatment
- PH Due to Left-Heart Failure
- Associated Diseases
- Psychosocial Issues

and more!
Pathophysiologic Principles in the Management of Severe PAH

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In the face of tremendous advances in our understanding of the pathophysiology and new treatment options, for many patients, pulmonary arterial hypertension (PAH) remains a progressive condition. The often-relentless reduction in the cross-sectional area of the pulmonary vasculature leads to progressive increase in right ventricular (RV) afterload. Although the right ventricle can adapt to an increase in afterload, progression of the pulmonary vasculopathy in PAH causes many patients to develop progressive RV failure.1 Alternatively, for those with other forms of pulmonary hypertension, worsening lung disease or cardiac disease may destabilize the RV function. Acute RV decompensation may be triggered by disorders that lead to either an acute increase in cardiac demand (such as sepsis, surgery, or pregnancy), or an increase in ventricular afterload (such as an interruption in medical therapy or pulmonary embolism), or destabilization of a compensated RV (such as arrhythmia or volume overload). The poor reserve of the RV, RV ischemia, and adverse RV influence on left ventricular filling may lead to a global reduction in oxygen delivery and multi-organ failure.2 The goals of this article are to provide an approach to right heart failure in the context of an increase in its afterload. This article will focus on pathophysiologic principles on which to build an approach to medical therapies. Mechanical and surgical strategies will be the focus in the accompanying article by Dr de Perrot.

CAUSES OF WORSENING RIGHT VENTRICULAR FAILURE

The identification of potentially reversible causes should be the first priority in evaluating a patient with right ventricular (RV) failure.3,4 In a French cohort study of 46 patients with pulmonary arterial hypertension (PAH) admitted to a critical care unit for RV failure, 19 (41%) had an identifiable triggering factor.5 These factors included unanticipated withdrawal of PAH-targeted therapy (n=3) or diuretics (n=1), pregnancy (n=1), septicemia (n=7), pneumonia (n=3), and arrhythmia (n=3). The presence of an infection during hospitalization was the strongest predictor of death.

Arrhythmias are often a harbinger of worsening RV function. Patients appear to be more susceptible to atrial as opposed to ventricular arrhythmias. Two retrospective series provide us with some insight into the importance of this complication. In one cohort study, 31 supraventricular tachycardia (SVT) events were identified in 27 patients (of 231 patients followed over 6 years), for a cumulative incidence of 12% and an annual risk of 2.8% per patient.6 Atrial fibrillation (n=13) and flutter (n=15) were more common than atrioventricular (AV) nodal re-entry tachycardia (n=3). Importantly, the failure to restore sinus rhythm was associated with poor outcome. Nine of 11 patients with sustained atrial fibrillation died, compared to only 1 death in patients who had restored sinus rhythm. In a more recent cohort of 239 patients with pulmonary hypertension (PH) (PAH=157, chronic thromboembolic pulmonary hypertension (CTEPH)=82), the cumulative incidence over a 5-year period of observation was 25% (95% CI of 14%, 35%).7 The onset of atrial arrhythmia was associated with death, particularly for those in whom sinus rhythm could not be restored. This may in part relate to the diastolic dysfunction that characterizes the left ventricle (LV) and RV in PAH.8,9 As a result, these patients are particularly susceptible to tachycardia due to an adverse influence of a reduction in ventricular filling time on LV and RV output. Similarly, they are likely adversely affected by the loss of atrial contribution to ventricular filling.

It is unclear whether rate control is sufficient; however, case series seem to support the notion that a return to sinus rhythm is associated with improved outcome. Therefore, it would seem that an attempt to restore normal sinus rhythm should be made. Correction of electrolyte imbalance, careful magnesium administration (rapid bolus may lead to hypotension), antiarrhythmics, and/or electrical cardioversion remain the preferred treatments in patients with acute RV decompensation.3 The use of beta-blocking agents and calcium channel blockers should be cautiously considered, as both classes of agents may directly impair RV contractility. In the case series reported to date, patients were treated with various modalities including antiarrhythmics, electrical cardioversion, and radiofrequency ablation.6,7

The outcome of patients with PAH admitted to hospital with RV failure is poor. In a retrospective review of 119 patients (207 hospital admissions) in a single center, 34 patients either died or...
underwent lung transplantation. Tachypnea (>20 breaths/min), renal dysfunction (GFR <45 mL/min), hypotension (serum sodium <136 mEq/L), and severity of tricuspid regurgitation were associated with a poor outcome. Therefore, the management of these patients requires a committed team with expertise and access to mechanical circulatory support and transplantation.

PATHOPHYSIOLOGY OF RV FAILURE

The RV is highly efficient and well adapted to eject into a high capacitance, low impedance, low resistance circuit that is able to accommodate large increases in blood flow with (relative to the systemic circulation) small changes in pressure. In the face of these differences, the RV and LV are mechanically interrelated by the shared interventricular septum and pericardium. Although the RV is highly efficient, it is ill adapted to sudden increases in afterload. As such, a severe and sudden increase in RV afterload may overwhelm the contractile capability of the RV and lead to hemodynamic collapse. In patients with chronic pulmonary vascular disease manifested by a progressive increase in RV afterload, there is a change in the mechanical characteristics of the RV as it starts to assume a similar pattern of ejection to that of the LV with an increase in RV elastance and a reduction in diastolic compliance. However, in the face of a progressive or sudden worsening in RV afterload, these compensatory mechanisms can be overwhelmed. In addition to rate of progression in RV afterload, the differences in the ability of the RV to compensate for an increase in afterload likely relate further to several factors. These factors include the age of the patient and age at onset of the RV pressure load. Early in life, the fetal RV is well adapted to high afterload, making it well suited to situations where it may assume the role as the systemic ventricle. Indeed, persistence of the fetal phenotype may impart the improved prognosis in patients with post-tricuspid valve septal cardiac defects (eg, ventricular septal defect or patent ductus arteriosis). The cause(s) of the increase in afterload, and in a related manner, the location of the pulmonary arterial occlusion (proximal vs distal) may also affect the ability of the RV to adapt chronically. For example, there may be differences in RV adaptation in the setting of proximal (pulmonary artery banding or pulmonic stenosis) as opposed to more distal pulmonary vascular occlusion (PAH). Finally, the chronically dilated or volume overloaded RV may adapt differently, and may be less capable of compensating for an increase in RV afterload.

Clinically, RV failure is characterized by a reduction in cardiac output, with resultant increase in venous pressure and signs/symptoms of venous congestion such as jugular venous distention, hepatomegaly, peripheral edema, and ascites. A drop in a reduced cardiac output (ie, cardiac index <2.5 L/min/m²) will eventually lead to an impairment of systemic oxygen delivery to metabolically active tissues. The development of systemic hypotension and renal insufficiency portend a worrisome prognosis.

MONITORING RV FUNCTION IN THE ICU

Although there is some rationale for the use of invasive pulmonary hemodynamic monitoring, it is unclear whether an approach guided by changes in pulmonary hemodynamics will lead to an improvement in outcome. In addition to concerns around the development of arrhythmias during insertion, there are both practical and theoretic limitations to the use of pulmonary hemodynamics to guide treatment. In addition, the severity of PH cannot be reliably assessed by the degree of elevation in pulmonary pressures, as a failing ventricle will produce lower pressures. Furthermore, the reliance on pulmonary vascular resistance (PVR) as a measure of disease severity or prognosis may also be problematic. Although a high PVR has been associated with a worse outcome, a recent study emphasized that prognosis is more strongly correlated to RV function, and that changes in PVR are not consistently related to changes in RV ejection fraction (RVEF). These investigators also illustrated that despite medical therapy for PAH, RV dysfunction could progress with a decrease in PVR. Although this was a study in the outpatient setting, there is no reason to believe that these findings would not apply to the acute care setting and illustrates the need to incorporate modalities to directly evaluate RV function. Although there are several echocardiographic measures of RV performance that have correlated with prognosis, it is unclear whether these can be used in the acute setting. Tricuspid annular displacement during RV systole (TAPSE), Tei index, and eccentricity index have all been correlated to RV function and prognosis in the outpatient setting. However, these measurements have not been validated in the critical care setting. Additionally, obtaining accurate images in the ICU setting may be limited. The same limitations in using estimates of pulmonary arterial pressures via direct hemodynamic methods apply to echocardiographic methods to estimate pulmonary artery pressures as a marker of RV function and as a treatment goal in the acute care setting. Although MRI is considered the gold standard of evaluating RV function, it is not practical in unstable patients.

Conventional estimates of the adequacy of tissue oxygenation such as mixed venous or central venous oxygen saturation, arterial lactate, and markers of end-organ function might provide some value in following the effects of various interventions. Although markers of end-organ function may not provide sufficient fidelity to gauge acute effects related to changes in treatment or pharmacological interventions, they likely do signal clinically relevant changes that occur over time. Similarly, levels of brain natriuretic peptide may not provide sufficient reliability or accuracy in a critically ill patient who may also have renal dysfunction.
impairment. Heart rate is an important feature to follow, as tachycardia may reflect worsening RV function and be an undesired side effect of medical therapy.

**GENERAL PRINCIPLES OF MANAGING RV FAILURE**

In addition to the reduction in RV output, an increase in RV wall tension will result in imbalance in myocardial oxygen consumption and delivery. An increase in wall tension and RV size may also worsen RV-LV interdependence and contribute to the spiraling decrease in cardiac function. The main objective of treatment is to restore RV function to the point where either the patient can be stabilized for definitive treatment with traditional oral or parenteral pulmonary vasodilators or undergo lung or heart-lung transplantation. The focus of treatment should be to search for and address reversible causes, reduce RV wall tension, restore RV output, and reduce the adverse influence of a dilated/pressurized RV on LV filling. These goals are obtained through the traditional approach in optimizing cardiac function through manipulating preload, afterload, and contractility without undue side effects from treatment—specifically tachycardia and systemic hypotension.

The general principles of ICU care also apply and include prophylaxis to prevent hospital-acquired infections, venous thromboembolism, and stress ulcers. Although patients presenting with progressive RV failure generally require diuresis, those who present with sepsis or hypovolemia may require judicious fluid administration. The fluid strategy in patients with acute pulmonary embolism is controversial, with conflicting reports regarding the hemodynamic effects of fluid administration. In general, in established PH with demonstrable RV overload, fluid administration may worsen the severity of RV failure.

**REDUCE ADVERSE RV-LV INTERDEPENDENCE: THE IMPORTANCE OF RV PRELOAD**

A reduction in oxygen delivery in PAH is mediated through 2 mechanisms. First, it may result from a decrease in LV filling directly as a result of a reduction in pulmonary blood flow and pulmonary venous return to the LV—a series effect. Second, cardiac output may be reduced via leftward displacement of the intraventricular (and intra-atrial) septum. This septal displacement in turn will lead to a reduction in diastolic compliance and cause a reduction in LV filling. This effect was elegantly demonstrated by Kasner and colleagues, where a temporary reduction in RV preload (by balloon occlusion of the inferior vena cava) in patients with PAH was associated with an improvement in LV end-diastolic volume and a reduction in LV end-diastolic pressure (LVEDP). Importantly, this reduction in RV preload led to an improvement in cardiac output. Their observations are important for several reasons. First, they illustrate the importance of diuresis in improving cardiac function in patients with PAH. Second, their observations illustrate the potential pitfalls in volume loading these patients. Specifically, these patients may paradoxically have a reduction in LV filling with fluid administration. Finally, their study also illustrated the concerns about the effect of tachycardia, as the adverse LV filling was compounded during rapid atrial pacing.

This adverse ventricular interaction may be further enhanced through prolongation of RV contraction. Indeed, an increase in RV wall tension is associated with a longer duration of RV ejection. This prolongation causes RV contraction to continue beyond LV contraction, with resultant RV systolic encroachment upon LV filling. This prolongation of RV ejection has stimulated interest in RV pacing. In theory, if the RV is paced to facilitate ejection earlier, it may allow for better mechanical coupling between the RV and LV and allow for improved LV filling. Recently dual-chamber (RA-RV) sequential pacing led to an improvement in LV function in 14 CTEPH patients. Whether RV pacing will play a role in chronic or decompensated RV failure in patients with PAH remains to be determined.

At present, the mainstay of reducing adverse RV-LV diastolic influence has been on optimizing RV afterload and preload; a reduction in either or both will result in a reduction in wall tension. RV preload may be reduced by diuresis or, in the setting of renal insufficiency, ultrafiltration. The use of venodilators is generally not recommended due to potential adverse effects on systemic blood pressure. Although in selected patients, atrial septostomy has been shown to improve cardiac function and symptoms of RV failure, survival, and has been used as a bridge to transplantation, the procedure is dangerous in unstable or hypoxemic patients.

**REDUCING RV AFTERLOAD**

The failing RV is likely benefited by even minor changes in RV afterload. Reduction in RV afterload may lead to an improvement in cardiac function through a variety of mechanisms, including: 1) a reduction in RV wall tension, 2) reduced myocardial oxygen consumption, 3) improved coronary macrovascular and microvascular perfusion, 4) an increase in RV stroke volume, and 5) improved LV filling through a reduction in RV septal shift. One of the most important interventions to reverse RV failure is to reduce RV afterload using pulmonary vasodilators or PAH-targeted therapies. An ideal pulmonary vasodilator would have selectivity for pulmonary circulation, avoid systemic hypotension, and not worsen intrapulmonary shunt. In general, this profile is afforded by inhaled medications such as nitric oxide (NO), prostanooids, or phosphodiesterase (PDE) type 5 or PDE3 inhibitors. The limitations of systemic vasodilators include systemic hypotension and potentially worsening of intrapulmonary shunt. Currently no agent has demonstrated clinical superiority over another. Most of the trials relate to comparing the relative hemodynamic effects of one agent over another, often in postsurgical cardiac patients, PH secondary to LV failure or pulmonary embolism. The use of PDE5 inhibitors in combination with NO is particularly attractive, but the additive effects are not consistently seen in a given patient. Once the patient is stabilized, the choice of definitive PAH-targeted therapies depends to some extent on previous treatment. However, in general, parenteral intravenous prosta-
With PH and RV failure, but it has not yet been thoroughly investigated in these patients.

**RESTORING CONTRACTILITY**

Contractility may be improved through direct (inotropes) and indirect (maintaining systemic blood pressure and coronary perfusion) strategies. Indeed, a reduction in RV preload as discussed may lead to a reduction in wall tension with an attendant increase in regional myocardial perfusion and reduction in myocardial oxygen consumption. Both effects, in theory, should lead to an increase in contractility.

To directly increase contractility, inotropic agents may be used. These include β agonists, PDE inhibitors, and calcium channel sensitizers; however, as nicely summarized by Price et al, no study of any agent has evaluated more relevant outcomes or conclusively demonstrated superiority of one agent over another. The β1-agonist dobutamine augments myocardial contractility and reduces PVR, making it an attractive agent in RV failure. However, it may also lead to a reduction in systemic vascular resistance (SVR) and require the concomitant use of a systemic vasoconstrictor. The use of dobutamine is also limited by the development of tachycardia. Agents that have less of an effect on heart rate such as PDE5 inhibitors may be preferable in some patients. PDE3 inhibitors may have direct inotropic effects by increasing levels of endogenous cAMP and indirectly augment cardiac function by reducing afterload. More recently, PDE5 inhibitors have been evaluated in the treatment of RV failure. In addition to their role as pulmonary vasodilators, these agents may have a direct inotropic effect on the failing RV. However, due to systemic effects, PDE inhibitors may also require concomitant administration of a systemic vasoconstrictor. Levosimendan, a calcium-sensitizing agent with positive inotropic and vasodilatory effects, holds promise for patients with PH and RV failure, but it has not yet been thoroughly investigated in these patients.

**OXYGEN AND MECHANICAL VENTILATORY SUPPORT**

Adequate oxygenation should be maintained, though patients with chronic pulmonary to systemic shunts may tolerate severe arterial hypoxemia. Anemia should be treated as it may contribute to an increase in cardiac demand. Furthermore, relative anemia in patients with chronic pulmonary to systemic shunts and hypoxemia may need to be treated to ensure adequate oxygen delivery to the systemic circulation. For patients with refractory hypoxemia, continuous positive airway pressure or noninvasive ventilation should be considered before intubation. If intubation and mechanical ventilation are deemed necessary, hypotension and loss of RV contractility must be prevented and the administration of catecholamines prior to anesthesia should

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**Table 1: Principles of Managing Patients with PH and Acute RV Failure** (Granton J, Mercier O, De Perrot M. Management of severe pulmonary arterial hypertension. *Semin Respir Crit Care Med.* 2013;34:700-713. © Georg Thieme Verlag KG, reproduced with permission.)

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<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Goal/effect</th>
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<tr>
<td>Identify reversible causes for acute RV decompensation</td>
<td>Depends on cause (eg, atrial arrhythmia, infection, pulmonary embolism)</td>
<td>Reduce RV demand</td>
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<tr>
<td>Reduce RV afterload</td>
<td>Pulmonary vasodilators (NO, prostanoids, PDE inhibitors)</td>
<td>Reduce RV wall tension</td>
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<td>Control PaCO₂</td>
<td>Improve RV output</td>
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<td>Reduce alveolar hypoxemia/atelectasis</td>
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<td>Extracorporeal support</td>
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<td>Lung transplantation</td>
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<td>Reduce RV preload</td>
<td>Diuretics, Ultrafiltration, Atrial septostomy</td>
<td>Reduce RV wall tension</td>
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<td>Reduce RV-LV influence</td>
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<tr>
<td>Improve RV contractility</td>
<td>Inotropic agents (PDE inhibition, β-1 agonists, levosimendan)</td>
<td>Improve RV output</td>
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<tr>
<td>Avoid tachycardia</td>
<td>Caution re use of β agonists</td>
<td>Preserve LV and RV diastolic filling</td>
</tr>
<tr>
<td>Maintain systemic blood pressure</td>
<td>Alpha receptor agonists, Vasopressin</td>
<td>Maintain coronary perfusion</td>
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<td></td>
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<td>Reduce RV-LV influence</td>
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</table>
be considered. Despite the lack of controlled clinical trials, etomidate and ketamine are the preferred drugs for induction of general anesthesia given their relatively beneficial hemodynamic profiles, pulmonary vasodilation, and minimal negative inotropic effects.\textsuperscript{37,38} The potential adverse effects of positive end-expiratory pressure (PEEP) on RV afterload are well described. However, equally, atelectasis may have adverse effects on RV function. In a rat model of acute lung injury, the development of atelectasis was associated with echocardiographic evidence of severe RV dilation.\textsuperscript{39} Treatment of atelectasis through alveolar recruitment led to an improvement in RV function. Whether the development of atelectasis in PAH patients will have the same deleterious effect on the decompensated RV needs to be established. It is clear that high levels of PEEP can have adverse effects on RV function. To the extent that alveolar recruitment occurs and hypoxic pulmonary vasoconstriction is reduced, the cautious application of PEEP may be associated with an improvement in RV function. In general, however, airway pressures should be kept to a minimum, while at the same time hypercapnia avoided because of its deleterious effects on pulmonary hemodynamics.

**CONCLUSION**

The approach outlined in Table 1 is limited by the absence of properly conducted clinical trials and is admittedly based on physiological principles, often derived from experimental observations in animal models or small case series in humans. In treating unstable patients, it is imperative to recognize the need to identify potentially reversible causes of RV failure and ensure that the systemic blood pressure is preserved. Thereafter, efforts can focus on optimizing RV preload and afterload. There should be consideration regarding the importance of RV-LV interactions and the influence that modifications in RV preload and afterload have on RV performance, LV filling, and end-organ function. Equally, it is incumbent on teams to recognize when medical treatments are not achieving their goals and consider extracorporeal support for those who are eligible for destination therapy such as lung or heart-lung transplantation. Sadly, in patients with advanced PAH where a treat-to-recovery goal is not a realistic endpoint and transplantation is not an option, palliative intent of treatments should be the focus of discussions with the patient and family.

**References**


Right Ventricular Metabolism: A Brief Review

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The primary function of the right ventricle (RV) is to receive systemic venous return and pump it into the normally low-pressure, highly distensible pulmonary arterial system. Compared to the left ventricle (LV), the RV is thinner with less mass, has 2 layers of muscles rather than 3, and has a bellow shape rather than an ellipsoid shape. Due to its typically low afterload, the metabolic demand for the RV is lower. The normal RV stroke work index is at 25% of the LV. Animal studies have shown that the right coronary artery flow is lower, the oxygen extraction is lower in the RV compared to the LV, and the mean RV myocardial oxygen consumption is less than half that of the LV. The study of myocardial metabolism has been dominated by studies of the LV metabolism until recently, with increasing recognition that RV performance affects patients’ morbidity and mortality in patients with pulmonary hypertension and even in patients with left-sided heart failure.

**MYOCARDIAL METABOLISM**

Contraction of the heart muscle requires conversion of the chemical energy received from the substrates to mechanical energy in the form of adenosine triphosphate (ATP). In the adult heart, fatty acid metabolism is the major contributor to ATP production, whereas during early embryogenesis, anaerobic glycolysis is the major energy-producing metabolic pathway. The transition to fatty acid oxidation (FAO) as the primary source of energy for the heart begins right after birth, with increased expression of the genes encoding for the enzymes in the FAO pathway. In fact, in its basal metabolic state, the adult heart utilizes 60% to 90% of the fatty acids as the energy source and 10% to 40% of the carbohydrates, with minimal contributions from ketones and lactate. In the adult heart under stress or exercise, the efficiency of glucose as substrate, especially glycolysis, may lead to energy starvation and heart failure.

Randle et al proposed the glucose-fatty acid cycle (Figure 1), where the fuel selection and uptake are controlled by the competition between the substrates. In this reciprocal inhibitory mechanism, fatty acids inhibit glucose oxidation at the level of pyruvate dehydrogenase complex, and the inhibition of FAO by glucose is through the inhibition of the enzyme carnitine-palmitoyl transferase I by malonyl-CoA.

With comorbidities (hypertension, diabetes, heart failure), various studies have shown a shift in the predominant metabolic pathway in the heart with decreased reliance on the fatty acid oxidation pathway. The factors commonly attributed to this alteration include changes in the mitochondrial lipid content, increased cellular oxidative stress, the decrease in the myocardial enzyme activity, or changes in the myocardial nuclear receptor peroxisome proliferator activated-receptor leading to downregulation of genes controlling the FAO pathway. The long-term dependency on glucose as the primary substrate, especially glycolysis, may lead to energy starvation and heart failure.

The overview of myocardial metabolism in normal and diseased states is presented in Table 1.

**RV METABOLISM IN DISEASE**

Pulmonary arterial hypertension (PAH) is associated with increased pulmonary vascular resistance (PVR), which leads to higher afterload for the right ventricle (RV). The thin-walled RV hypertrophies initially followed by dilation and eventually failure. Metabolic imaging in humans and mammals allowed interrogation of metabolic alterations that accompany RV hypertrophy (RVH) and RV failure.

The relationship of RV fatty acid metabolism and functioning was first studied using single-photon emission computerized tomography (SPECT) and a branched chain analog of iodophenyl pentadecanoic acid (BMIPP) in 21 patients with pulmonary hypertension. Patients with normal myocardial fatty acid uptake had higher RV ejection fraction, and patients with impaired fatty acid metabolism had higher death rates when compared to patients with normal fatty acid metabolism. In another study of 27 subjects, the existence of impaired fatty acid metabolism in patients is correlated with severe RV hypertrophy.

$^{18}$F-FDG, a glucose tracer analog used in positron emission tomography (PET), is taken up by viable myocytes in a similar manner to glucose, but cannot be metabolized further after being converted to $^{18}$F-FDG 6-phosphate and thus trapped in myocytes. The uptake of $^{18}$F-FDG in the heart depends on the glucose concentration in the plasma, the rate of glucose delivery to the heart, and its use. Oikawa et al studied the impact of PH on RV FDG uptake in 24 patients. Increased RV free wall FDG uptake correlated with the underlying RV pressure overload. In 10

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Key Words—cardiac metabolism, fatty acid pathway, glucose utilization, myocardial metabolism, right ventricular failure

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patients (NYHA Class II/IV) who received epoprostenol therapy for a period of 3 months and a follow-up PET showed decreased RV FDG accumulation, which correlated with improved RV function (Figure 2). Bokhari et al.19 evaluated myocardial blood flow (MBF) using 13N-NH3 for perfusion and 18F-FDG for glucose metabolism in 16 patients with idiopathic PAH. MBF was normal in all patients, but RV/LV glucose uptake ratio was correlated with pulmonary arterial pressures (PAP).19

Alteration in RV metabolism can also be seen in disease where pulmonary pressures might not be significantly elevated or secondary to elevated pulmonary diastolic pressure. Choi et al reported an increase in FDG uptake in the RV myocardium in patients with chronic obstructive lung disease, which is correlated with the severity of lung obstruction and pack-year of smoking.20 Meilniczuk et al.21 studied 68 patients with a history of congestive heart failure (NYHA Class II-III) with moderate PH. As the RV function worsened, the ratio of RV/LV glucose uptake increased.

18F-FDG studies are limited as the information gathered only pertains to the glucose uptake in the disease state. Further probing of oxidative component of the metabolism was performed by Yoshinaga et al.22 using 11C-acetate as a marker in 36 subjects (27 PH patients and 9 healthy controls). PET imaging showed higher RV kmono (indicative of higher oxidative metabolism) than controls that correlated significantly with mean PAP, PVR, and brain-natriuretic peptide values. However, no correlation was noted between RV kmono and RV end-diastolic volume index, RV mass index, or 6-minute walk test. LV Kmono was not elevated compared to controls. These data indicate that increased RV oxidative metabolism might exist as a compensatory mechanism before RV failure ensues.

The cause of increased RV FDG in RV metabolic derangement was further investigated by Paio et al, who hypothesized that RV dysfunction in RVH is in part caused by activation of pyruvate dehydrogenase kinase (PDK)-induced glycolytic shift from glucose oxidation (GO) to glycolysis in the RV.23 Two different rat models were compared: one RVH with PAH (induced using monocrotaline) and the other RVH without PAH (induced using pulmonary artery banding). In RVH with PAH, glucose transporter-1 expression and pyruvate dehydrogenase (PDH) phosphorylation were increased, along with reduced RV oxygen consumption and increased glycolysis. A PDK inhibitor, dichloroacetate, increased glucose oxidation and reversed the effects of monocrotaline on RV function. In the RVH without PAH model, the glycolytic shift and the benefit with dichloroacetate inhibition were also seen, albeit less compared to RVH with PAH.

Studies aimed at targeting the reversal of this metabolic shift by using partial inhibitors of FAO and exploiting the reciprocal relationship between FAO and GO (Randle’s cycle) showed that both trimetazidine and ranolazine decreased FAO and restored PDH activity and GO in a rat pulmonary banding model.24 Potential beneficial effect has been seen in patients with PAH associated with heart failure with preserved ejection fraction.25 An ongoing trial of ranolazine in patients with PAH is enrolling and cardiac magnetic resonance imaging, 18F-FDG, and 11C-acetate PET are used as readouts for the effect of ranolazine on the metabolic shift (NCT01839110).

**CONCLUSION**

Cardiac metabolism in general and specifically RV metabolism changes in response to the oxygen and substrate availability. The RV is dependent on the fatty acid oxidation pathway for energy production and its performance under rest and normal conditions. Under conditions of increased metabolic demand, there is an initial increased oxidative metabolism associated with increased glucose utilization. Accompanying this process, a metabolic switch is also observed, which leads to inhibition of the fatty acid pathway and activation of the glycolytic pathway. Key molecular pathways that are involved in compensated metabolic remodeling in RV

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### Table 1: Overview of Myocardial Metabolism in Physiological and Pathological Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Glucose Metabolism</th>
<th>Fatty Acid Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female)</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Aging</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td>Increased</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Heart Failure/Hypertension</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
hypertrophy vs. the eventual RV failure still need to be better elucidated. Minimal data are currently available to support metabolic interventions for the management of impaired RV function and the failing heart.

References
Sepsis and Pulmonary Arterial Hypertension in the ICU

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The management of sepsis in the patient with pulmonary arterial hypertension (PAH) is dependent on 2 primary principles: 1) optimizing right ventricular (RV) function, and 2) reducing pulmonary vascular resistance. In this review, we will discuss the major challenges that health care providers face in trying to achieve these goals. We will start with an overview of normal RV function and modulators of pulmonary vascular tone. A general approach to managing RV failure and hemodynamic instability will be provided, along with a discussion of how modern therapies for the treatment of PAH can best be used in the setting of sepsis.

The inflammatory response to sepsis results in increased vascular permeability and vasodilation, leading to decreased intravascular volume and a fall in systemic vascular resistance (SVR) that must be compensated for by an increase in cardiac output (CO). Unfortunately for patients who suffer from pulmonary arterial hypertension (PAH), the ability to acutely increase CO may be severely limited, and significant pulmonary hypertension (PH) in the setting of acute illness can lead to rapid deterioration of right ventricular (RV) function, hemodynamic instability, and death. As a result, the management of critically ill PAH patients can be extremely challenging. As a group, these patients have a poor prognosis, with intensive care unit (ICU) mortality rates between 30% and 41%.1-3 Whereas a considerable number of studies have examined left ventricular (LV) and systemic circulatory responses to sepsis,4-6 relatively little attention has been directed at the RV and pulmonary circulation.

Whereas a considerable number of studies have examined left ventricular (LV) and systemic circulatory responses to sepsis,4-6 relatively little attention has been directed at the RV and pulmonary circulation. This is unfortunate because the pulmonary and systemic circulations are connected in series, and despite its smaller size, nearly the entire circulation must pass through the right heart and pulmonary vasculature before it reaches the systemic circulation.

Normally, vascular resistance in the lungs is low and the pulmonary circulation is able to accommodate large increases in CO by recruiting unused or underperfused vessels. As a result, impairment of pulmonary blood flow or RV function rarely limits CO and oxygen delivery (DO₂) to peripheral tissues. However, when pulmonary vascular resistance (PVR) is high, as occurs in patients with PAH, pulmonary blood flow and RV function may become the primary determinants of adequate circulation.

The Normal Pulmonary Circulation and RV

Although the CO generated by the RV and LV is essentially the same, the vascular bed they pump it through is considerably different. In the healthy adult, PVR is remarkably low, considering the drop in pressure across the pulmonary circulation [mPAP (15 mm Hg) – PCWP (8 mm Hg) = 7 mm Hg, where mPAP = mean pulmonary artery pressure and PCWP = pulmonary capillary wedge pressure] is less than a tenth of that across the systemic circulation [MAP (90 mm Hg) – CVP (5 mm Hg) = 85 mm Hg, where MAP = mean systemic arterial pressure and CVP = central venous pressure]. Despite a rise in CO during heavy exertion that may be 4-fold above baseline, PAP increases minimally and PVR falls. In the systemic circulation, increased CO during exercise is associated with an increase in MAP. The difference between the 2 circulations is the relatively low degree of vascular motor tone in the proximal pulmonary vascular bed, and the ability of the lung to recruit partially collapsed or unused vessels as CO increases. In the systemic circulation, muscularized resistor vessels allow for marked alterations in SVR via sympathetic stimulation or the release of endogenous catecholamines or vasodilators such as nitric oxide (NO) and prostaglandins. A variety of vasoactive drugs can also be used to sharply increase or decrease systemic vascular tone. In contrast, the pulmonary circulation has relatively low vascular tone, making it difficult to acutely increase or decrease PVR.

During fetal life, PVR is higher in the uninfated lung than it is in adult life, and the elevated pressure helps direct right-sided blood flow across the foramen ovale and into the left atrium. After birth, lung inflation reduces PVR considerably, and blood from the RV is redirected to the low resistance of the
pulmonary circulation. During normal development, the ventricles take on distinct structural characteristics designed to compensate for the marked differences in afterload they work against. The unique structural and functional characteristics of the RV and LV result in different responses to afterload and preload.

The LV has a thick muscular wall and global shape. High systolic pressures are achieved by circumferential contraction, resulting in the lateral free wall and interventricular septum (IVS) moving toward each other. In contrast, the RV is a crescent-shaped chamber formed by a thin, triangular-shaped piece of myocardial tissue wrapped around the IVS (Figure 1). At end diastole, the normal RV free wall is only 2 to 3 mm in thickness, compared to 8 to 11 mm in the LV. The CO from the RV is achieved by longitudinal contraction of the apex up toward the lateral leaflet of the tricuspid valve in a peristaltic pattern. Dilatation of the outflow region causes an initial expansion of the pulmonary artery (PA), thereby increasing its compliance and priming it to receive the RV stroke volume. The high compliance of the proximal PA facilitates RV output.

In fact, blood has been observed to flow from the RV into the proximal PA even during diastole.8 Its high compliance allows the RV to accommodate large increases in venous return, with only a small increase in RV end-diastolic pressure (RVEDP) or stroke work (Figure 2A).9-11 RV output is well preserved over a range of volumes until dilatation of the ventricle is limited by the IVS septum and pericardium.12 At that point, further increases in RV filling pressure outdistend myocardial fibers, increasing RV stroke work and decreasing CO.13,14 The structural properties of the RV that allow it to accommodate large increases in preload make it highly sensitive to increases in afterload. Its smaller muscle mass and peristaltic contraction is poorly suited to increasing pressure when PVR is acutely increased. In healthy animals, RV stroke volume and output decline dramatically as resistance is increased by constricting the main PA (Figure 2B). In contrast, the LV tolerates increased afterload fairly well, but is sensitive to increases in preload (Figures 2A-2B).

The RV is also more affected by changes in intrathoracic pressure than the LV. Deep inhalation increases RV transmural filling pressure because intrathoracic pressure falls while systemic venous pressure is unaffected. Conversely, even a small rise in intrathoracic pressure can substantially reduce RV filling pressure. Normally, the fall in RV filling caused by increased intrathoracic pressure is compensated for by increasing systemic venous tone and elevating CVP, but this can be difficult to achieve in patients with sepsis because of decreases in vascular tone and intravascular volume and because of the use of sedatives and analgesics.

The RV and LV share a common septum, and changes in pressures of one ventricle can be transmitted across the septum and affect the compliance of the other ventricle. Normally, LV end-

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Figure 1: Structure and shape of the adult right and left ventricles. (Reprinted from Chan CM, Klinger JR. The right ventricle in sepsis. Clin Chest Med. 2008;29(4):661-676, with permission from Elsevier.)

Figure 2: Differences between right and left ventricular response to increasing afterload (left panel) and increasing preload (right panel). Right ventricular stroke volume falls sharply as mean vascular pressure is increased from 20 to 30 mm Hg in the pulmonary artery, but left ventricular stroke volume remains fairly constant as mean aortic pressure is increased from 100 to 140 mm Hg. In contrast, left ventricular stroke work increases rapidly as left atrial pressure is raised from 10 to 20 cm H2O, while the increase in RV stroke work in response to the same elevation or right atrial pressure is much more modest. (Reprinted with permission from Braunwald E. Pathophysiology of heart failure. In: Braunwald E, ed. Heart disease. A textbook of cardiovascular medicine. Philadelphia, PA: Saunders, 1980;453-471.)
Diastolic pressure (LVEDP) is greater than RVEDP, allowing the IVS to move toward the RV during diastole. This motion allows for maximal chamber enlargement in the concentric LV. However, as RVEDP exceeds LVEDP, the IVS can move paradoxically toward the LV lumen during diastole. This is best seen on 2-dimensional echocardiography as a flattening of the normal concave shape of the septum or a bowing of the septum toward the LV (Figure 3). As the IVS shifts toward the LV, compliance decreases and LVEDP rises resulting in decreasing LV output. The ability of RV filling pressures to affect LV filling pressure via the IVS is referred to as ventricular interdependence, and represents one of the greatest challenges to fluid management in septic patients with PAH. The lungs normally contain only about a tenth of the total intravascular volume, or approximately 500 mL in an average-sized adult, and LV filling is largely dependent on blood flow through the lungs determined by RV output. Intravascular volume expansion must improve RV output enough to increase transpulmonary blood flow and increase blood return to the LV. If not, the increase in RVEDP transmitted through the IVS will decrease LV transmural filling pressure and can impede CO.

APPROACH TO MANAGEMENT OF THE PAH PATIENT WITH SEPSIS
The key to managing sepsis is to maintain adequate tissue perfusion until its cause can be eradicated. This is normally achieved by expanding intravascular volume and maintaining the increase in CO that sepsis demands. As mentioned earlier, for the patient with PAH, achieving these goals centers on maximizing RV function while reducing PVR. These 2 goals are closely interrelated. Maximizing RV function requires optimizing RV preload, improving RV contractility, and reducing RV afterload. The latter, of course, is achieved primarily by reducing PVR. In general, the pulmonary vascular disease of PAH is relatively fixed, and acute reduction in PVR is difficult. Management, therefore, is usually directed at optimizing RV function and making sure that PVR does not increase in response to metabolic derangements caused by sepsis or vasoactive medications administered during resuscitation.

RV Preload
Proper fluid management is critical for successful management of the septic patient with PAH. In the early phase of sepsis, CVP is reduced due to a fall in intravascular volume from increased vascular permeability and a decrease in venous vascular tone. Adequate right-sided filling pressure is essential in maintaining CO in patients with acute RV failure. Therefore, volume resuscitation should be initiated if low intravascular volume is suspected. However, RV preload requirements differ substantially based on whether RV afterload is normal or increased. When RV failure occurs in the setting of normal PVR, RVEDP often needs to be increased above normal levels to maintain CO. However, when RV failure occurs in the setting of increased RV afterload, as occurs in the septic patient with PAH, volume loading can result in displacement of the IVS toward the LV and impair LV diastolic filling. In this setting, intravascular volume may need to be decreased.

Initial attempts at volume reduction may have little effect, because the RV has a relatively flat pressure volume curve, meaning there is less of a change in RV contractility over a wide range of filling pressures. Hence, a considerable amount of volume unloading may be necessary before any improvement in RV function is seen. At the same time, care must be exercised not to allow RV preload to become too low, because RV
output is particularly dependent on adequate RV filling when RV afterload is high. In general, RV filling pressures should be kept moderately elevated in the 8 to 12 mm Hg range. The use of positive-pressure ventilation should be avoided if at all possible as it has a marked effect on reducing right-sided filling pressures.

Measurement of RV filling pressure can be challenging in the critically ill patient with PAH. A central venous line can measure CVP and provides access to superior vena cava oxygen saturation (SvO₂) that can help assess oxygen delivery. Normal SvO₂ is 70% to 80%, and lower values in the setting of normal arterial oxygenation can be suggestive of reduced CO. If RV preload is too high, reductions in CVP via diuresis or dialysis should be accompanied by improvement in CO as assessed by SvO₂ or systemic organ perfusion. Echocardiography may also be helpful. Evidence of RV dilation and impingement on LV filling suggest that further reduction in preload may be necessary. Ultrasound assessment of inferior vena caval filling can also be used to assess RV preload. If these assessments of RV function are inadequate, placement of a PA catheter may be necessary. Although the routine use of a PA catheter has not been found to improve outcome in the management of severe sepsis and has not been well studied in the management of acute RV failure, there are times when measurement of pulmonary hemodynamics may be helpful in guiding clinical decision making. In our practice, we do not typically place Swan-Ganz–style catheters for continuous monitoring of RVEDP, CO, or PAP in septic patients with PAH, but do not hesitate to catheterize patients when we are uncertain of their filling pressures or afterload.

**RV Contractility**

RV function becomes critically important to the maintenance of adequate CO in the patient with PAH and sepsis. RV failure can occur because of insufficient or excess preload or an increase in afterload from worsening PH. But even when these factors have been corrected, RV function can be reduced from baseline due to a fall in myocardial contractility. Reduced RV contractility occurs due to 3 interrelated factors: 1) derangements in cellular metabolism leading to decreased myocardial contractile forces, 2) insufficient oxygen delivery due to decreased coronary arterial perfusion, and 3) overstretching of the RV free wall placing the myocytes at a mechanical disadvantage.

A variety of metabolic derangements including acid/base disturbances, generation of reactive oxygen species, and inflammatory cytokines impair oxygen utilization and contribute to decreased RV contractility. These derangements should be minimized whenever possible, but are often difficult to correct in patients with sepsis.

Insufficient coronary artery perfusion is often the most important contributor to decreased RV function. Increases in RV preload and/or afterload increase RV free wall tension and oxygen demand while impeding LV filling. This results in reduced LV output that in turn can decrease coronary artery pressure. Perfusion of the RV free wall is determined by the difference in RV free wall tension and coronary artery pressure. Normally, coronary artery pressure is greater than RV pressure throughout the cardiac cycle, and the RV receives blood from the coronary arteries during systole and diastole. As RV systolic pressure approaches systemic levels in advanced cases of PAH, coronary perfusion of the RV decreases during systole (Figure 4).

The lack of RV perfusion in patients with PAH is only made worse in the setting of systemic hypotension that may occur during sepsis. In this situation, it becomes critical to keep systemic arterial pressure at least as high as RV systolic pressure. Excessive fluid resuscitation can increase RV size and free wall tension without improving systemic arterial pressure and can actually decrease RV perfusion. Drugs that increase myocardial contractility should be held until this first goal is achieved, because they increase RV oxygen demand and can worsen RV ischemia if systemic arterial pressure is not increased.

**Vasopressors**

Several vasoactive drugs have been used to manage PAH patients with sepsis (Table 1). The ideal agent should increase systemic arterial pressure and RV contractility without raising PVR. In
responsiveness to catecholamines and NO, but at higher doses it increases vasodilation via stimulation of endothelial receptors on vascular smooth muscle.

In a small study of septic patients with right heart failure, norepinephrine use was associated with improved RV myocardial oxygen delivery due to an increase in SVR, but PVR increased and no change was seen in RV ejection fraction. Phenylephrine is a pure α1 receptor agonist that augments right coronary artery perfusion, but also increases PVR and does not improve RV contractility. Reflex bradycardia can also result in decreased CO. Epinephrine is a mixed α/β receptor agonist that can induce vasoconstriction and increase inotropy. In one animal study, it improved CO without increasing PVR, and in a small study of patients with septic shock was found to increase RV contractility.

Vasopressin is a mixed α/β receptor agonist that can induce vasoconstriction and increase inotropy. In one animal study, it improved CO without increasing PVR, and in a small study of patients with septic shock was found to increase RV contractility.

Dobutamine is another inotrope that acts via β1 receptor stimulation, but may also cause vasodilatation due to β2 effects. At low doses (5 to 10 μg kg⁻¹ min⁻¹), dobutamine improves PA/RV coupling in animal studies and improves myocardial contractility and PVR in patients with left heart failure. Dobutamine has been shown to improve hemodynamics in patients with PH at liver transplantation and after RV infarction.

Table 1: Vasoactive Drugs for Management of Pulmonary Hypertension in Sepsis and their Mechanism of Action

<table>
<thead>
<tr>
<th>Agent</th>
<th>Receptor Binding</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Norepinephrine</td>
<td>+ + +</td>
<td>Improves PA/RV coupling in animals</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>+ + +</td>
<td>Increases PVR; may induce reflex bradycardia</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++ ++ +</td>
<td>Dose-dependent pulmonary vasodilatation (0.01–0.03 U/min) and vasoconstriction</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>++ +</td>
<td>Risk of arrhythmias</td>
</tr>
<tr>
<td>Dopamine</td>
<td>+ + +</td>
<td>β2-mediated drop in SVR; risk of arrhythmias</td>
</tr>
<tr>
<td>Low (&lt;5 μg/kg/min)</td>
<td>+ + +</td>
<td>Phosphodiesterase-3 inhibitor; inotropy and pulmonary vasodilatation; drop in LVEDP and SVR; risk of arrhythmias</td>
</tr>
<tr>
<td>Medium (&gt;10 μg/kg/min)</td>
<td>+ + +</td>
<td></td>
</tr>
<tr>
<td>High (&gt;10 μg/kg/min)</td>
<td>+ + +</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>++ +</td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>+ + +</td>
<td></td>
</tr>
</tbody>
</table>

D= dopaminergic receptor; V1= vasopressin receptor 1; PA= pulmonary artery; RV= right ventricle; PVR= pulmonary vascular resistance; SVR= systemic vascular resistance; LVEDP= left ventricular end-diastolic pressure.

Vascular disease because it can improve inotropy and pulmonary vasodilatation. Milrinone is frequently the agent of choice in patients with PH from biventricular failure, and in those recovering postventricular assist or following cardiac transplantation. Several small studies have also examined the use of inhaled milrinone in patients with pulmonary vascular disease to avoid systemic hypotension. The use of inotropes to improve RV contractility increases the risk of tachyarrhythmias, and their use in sepsis has been controversial. At the same time, it is important to avoid increasing CO above normal levels because this can increase PAP and thereby increase RV workload. In general, they should not be used in PAH patients with sepsis unless there is evidence of inadequate oxygen delivery despite the correction of abnormalities in RV preload, afterload, and ischemia. Calcium sensitizers such as levosimendan enhance myocardial contractility without increasing cytosolic calcium and thereby have less effect on increasing oxygen demand. Clinical trials have shown improvement in RV systolic and diastolic function in patients with left heart failure, and recent reports describe improved RV function in RV failure associated with chronic thromboembolic PH and heart transplantation.
ventilating with FiO2. Response was defined as the difference between baseline pulmonary artery pressure when vasoconstrictive response is greater when tension (PAO2) or decreased oxygen in response to decreases in alveolar oxygen. Pulmonary vasoconstriction can occur in increased PVR during sepsis. Hypoxic pulmonary vasodilator therapy. Attempting to administer maximal pulmonary tone while at the same time factors that can increase pulmonary vasconstriction is not a reliable indicator of pulmonary arterial oxygenation. Adequate systemic arterial oxygen saturation (SaO2) routinely monitored by pulse oximetry in the ICU effectively excludes alveolar hypoxia, but is not a reliable indicator of pulmonary arterial oxygenation.

Lung volume also affects PVR. Overdistention of alveolar vessels at high lung volume increases PVR, as does the collapse of extra-alveolar pulmonary vessels at low lung volume. PVR is lowest at functional residual capacity (FRC), and this should be kept in mind in septic patients with PAH who require mechanical ventilation. Although, as mentioned earlier, the use of positive-pressure ventilation should be avoided if possible.

Several vasoactive factors that have been implicated in the pathogenesis of PAH such as endothelin and thromboxane are elevated during sepsis and have been shown to correlate inversely with CO. Other mediators of PH such as serotonin and interleukin-6 are also upregulated in sepsis and the acute respiratory distress syndrome (ARDS). Endotoxin can suppress NO synthesis and has been shown to increase PVR in sepsis. Finally, just as disseminated intravascular coagulation can impede perfusion in the systemic circulation, sepsis can cause thrombosis in situ in the pulmonary circulation and raise PVR. Prior to the use of pulmonary vasodilators, every attempt should be made to lower PVR by reversing any of the above factors that are known to increase pulmonary vascular tone. Alveolar hypoxia and hypoxemia should be corrected as much as possible, and hypercapnea and acidemia reversed. Ideally, SaO2 should be raised to 92% or greater and pCO2 and pH should be kept as close to normal as possible.

Several classes of drugs that target cellular pathways that are abnormally regulated in PAH have been developed over the last 2 decades (Table 2). These drugs have been shown to improve functional capacity and reduce PVR in patients with PAH, but their ability to improve pulmonary hemodynamics in PAH patients with sepsis has not been studied. Despite the lack of clinical evidence showing efficacy in this situation, it is reasonable to use these drugs in PAH patients with sepsis in an attempt to lower PVR and improve CO. It should be remembered, however, that in addition to their pulmonary vasorelaxant properties, most of these drugs have significant effects on the systemic circulation and are capable of causing hypotension. Furthermore, pulmonary vasodilators can worsen gas exchange by blunting hypoxic pulmonary vasoconstriction and impairing ventilation perfusion (V/Q) matching.

By virtue of their route of administration, inhaled agents have the most selective effect on the pulmonary circulation. Inhaled NO (iNO) is a potent pulmonary vasodilator with a rapid onset of action and an extremely short half-life, making it an ideal agent for unloading the RV in the septic patient.

**Figure 5** Effect of oxygen tension and acidemia on pulmonary vasoconstriction. (A) Pulmonary vasoconstriction increases as alveolar O2 tension (Pao2) falls while keeping mixed venous oxygenation constant (mixed venous PO2 indicated for each solid line from 60 to 10 Torr, panel A). The combined effect of allowing Pao2 and mixed venous PO2 to fall is shown by the dashed line, where Pao2 and mixed venous oxygen saturation O2 are the same. (B) Pulmonary vasoconstriction in newborn calves as a function of inspired O2 under conditions of different levels of arterial blood pH. Hypoxic pulmonary vasoconstriction is increased and occurs at a higher level of inspired O2 as arterial pH is decreased. Maximal pulmonary vasoconstrictor response was defined as the difference between baseline pulmonary artery pressure when ventilating with FiO2 = 0.21 and perfusate FO2 = 0.06, and the pulmonary artery pressure when both the inspired and the perfusate FO2 were 0. The pressure response at all other combinations of inspired and perfusate FO2 were expressed as a percent of this maximum (%Rmax). Adapted from Marshall BE, Marshall C. Anesthesia and the pulmonary circulation. In: Covino BG, Fozzard HA, Rehder K, Strichartz G, eds. Effects of anesthesia. Bethesda, MD: American Physiological Society, 1983.
Furthermore, its greater effect in well-ventilated lungs prevents the increase in A-a gradient that can occur with pulmonary vasodilators administered via oral or intravenous routes. Also, in some patients, iNO can improve oxygenation by reducing intrapulmonary shunt. Although the use of iNO in PAH patients with sepsis has not been studied, it has been shown to improve RV ejection fraction and end-diastolic volume in patients with ARDS and improve pulmonary hemodynamics in patients with acute RV failure.

Three prostacyclin derivatives are currently available for treatment of PAH in the United States, and all can be administered by inhalation, making them reasonable alternatives when iNO is not available. Like iNO, these drugs have rapid onset of action with short half-lives and have potent vasodilator properties on the pulmonary circulation. Inhaled epoprostenol has been used successfully to manage patients with RV failure after cardiac surgery and to improve gastric mucosal pH in septic patients with PH.

Phosphodiesterase type 5 (PDE5) inhibitors are effective pulmonary vasodilators that reduce pulmonary vascular tone by inhibiting the metabolism of cGMP. Interesting studies in animal models of PH suggest that they can also improve contractility in the setting of RV hypertrophy, but little is known about their use in critical illness. The PDE5 inhibitors should be used cautiously in septic patients with PAH and any patient who is hemodynamically unstable because of their systemic hypotensive effects and extended half-life.

The considerably shorter half-life of sildenafil, compared to tadalafil, makes it the drug of choice if PDE5 inhibitors are considered. An intravenous form of sildenafil is also available if the enteral route cannot be used.
MECHANICAL SUPPORT

When medical therapy for acute RV failure in the ICU is ineffective, mechanical support may be considered. Extracorporeal life support, specifically veno-venous and veno-arterial extracorporeal membrane oxygenation have been used in PAH patients as a bridge to endarterectomy or lung transplantation, and recent reports have described their use to support patients with PAH through critical illness. The use of extracorporeal life support in the critically ill patient with PAH is described in a later section of this issue of Advances in Pulmonary Hypertension.

CONCLUSION

The management of sepsis in patients with PAH is challenging. The limited ability of the RV to augment cardiac output in the PAH patient makes it difficult to compensate for vasodilatory shock. There must be careful assessment of intravascular volume and vasoactive drugs should be used judiciously. One must weigh the risk:benefit ratio of initiating a pulmonary vasodilator to augment the RV and reduce PVR with its potential effects on systemic hemodynamics. Lastly, mechanical ventilation should be avoided as much as possible given how small shifts in intrathoracic pressure can dramatically affect PVR and CO.

References


Table 2: Currently Available Pulmonary Vasodilator Medications

<table>
<thead>
<tr>
<th>Name</th>
<th>Drug Class</th>
<th>Action</th>
<th>Route of Administration</th>
<th>Terminal Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan</td>
<td>Endothelin receptor antagonist</td>
<td>Blocks endothelin receptor –A</td>
<td>Oral or intravenous</td>
<td>15 hours</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Endothelin receptor antagonist</td>
<td>Blocks endothelin receptor –A and –B</td>
<td>Oral</td>
<td>5.4 hours</td>
</tr>
<tr>
<td>Macitentan</td>
<td>Endothelin receptor antagonist</td>
<td>Blocks endothelin receptor –A and –B</td>
<td>Oral</td>
<td>14-18</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Phosphodiesterase type-5 inhibitor</td>
<td>Slows metabolism of intracellular cGMP</td>
<td>Oral or intravenous</td>
<td>4 hours orally</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Phosphodiesterase type-5 inhibitor</td>
<td>Slows metabolism of intracellular cGMP</td>
<td>Oral</td>
<td>17.5 hours</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Prostacyclin</td>
<td>Increases intracellular cAMP</td>
<td>Intravenous or Inhaled*</td>
<td>&lt;6 minutes</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>Prostacyclin derivative</td>
<td>Increases intracellular cAMP</td>
<td>Intravenous, subcutaneous, or inhaled</td>
<td>4 hours</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Prostacyclin derivative</td>
<td>Increases intracellular cAMP</td>
<td>Inhaled</td>
<td>20-30 minutes</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>Soluble guanylate cyclase stimulator</td>
<td>Increases intracellular cGMP</td>
<td>Inhaled</td>
<td>Seconds</td>
</tr>
<tr>
<td>Riociguat</td>
<td>Soluble guanylate cyclase stimulator</td>
<td>Increases intracellular cGMP</td>
<td>Oral</td>
<td>7-12 hours</td>
</tr>
</tbody>
</table>

*Not FDA-approved for this route of administration.

cAMP=cyclic adenosine monophosphate; cGMP=cyclic guanosine monophosphate.

recently approved soluble guanylate cyclase stimulator riociguat, should probably be avoided in the septic patient with PAH unless the patient was taking these medications prior to becoming septic. Endothelin receptor antagonists have less acute pulmonary hemodynamic effects and greater potential to affect liver function and the metabolism of other drugs. Riociguat is a soluble guanylate cyclase stimulator and may have significant systemic vasodilator effects, especially under conditions such as sepsis where endogenous NO production may be increased. Calcium channel blockers should also be avoided because they have negative inotropic effects and have been shown to increase RV stroke work index.88
Patients with pulmonary hypertension that progress to acute decompensation present high mortality rates. The main mechanism of death in this population is right ventricular failure. Once this scenario becomes refractory to optimized medical therapies, mechanical support is increasingly considered as either a bridge to recovery or, most often, as a bridge to definitive surgical treatment (such as lung transplantation, surgical embolectomy, or pulmonary endarterectomy). This review will focus on the existing evidence on mechanical support for the failing right ventricle, all in the context of precapillary pulmonary hypertension.

MECHANICAL SUPPORT FOR THE FAILING RIGHT VENTRICLE

Mechanical support for the right ventricle (RV) can address key mechanisms of right heart failure in the setting of pulmonary hypertension (PH), including: 1) reduction of RV preload, 2) reduction of RV afterload, and 3) provision of pump function. Moreover, lesser mechanisms contributing to ventricular failure can also be improved theoretically by mechanical support such as less tricuspid regurgitation secondary to ventricular dilatation and improved left ventricular (LV) filling and function due to minor septal bowing.

One important concept to consider in the management of RV failure is that, although the RV is less adaptable to situations of pressure overload, it carries a substantial potential for recovery once its afterload is normalized. This particular scenario is well illustrated by RV recovery post-lung transplantation for PH.²

Although it is difficult to establish ideal timing for initiation of mechanical support for the failing RV, refractoriness to pharmacological therapies should prompt the evaluation by a multidisciplinary team composed of an intensivist, respiratory/cardiologist, and cardiothoracic surgeon. It is crucial to consider the patient’s bridging potential to avoid the futile initiation of extracorporeal life support (ECLS) at all costs. For patients with either acute massive pulmonary embolism (PE) or chronic thromboembolic pulmonary hypertension (CTEPH), the possibility of stabilization on ECLS for interventional embolectomy or pulmonary endarterectomy (PEA), respectively, should be considered. In patients with idiopathic pulmonary arterial hypertension (iPAH), candidacy for lung transplantation should have been assessed previously, although emergent evaluation may be considered on an individual basis. Another potential (but less likely) scenario is the use of ECLS as a bridge to recovery in iPAH patients that are either treatment-naive or that are still not optimized on PH-targeted therapies.

Contraindications for mechanical support include: 1) irreversible neurological or end-organ damage; 2) intracranial bleeding or other major contraindication for anticoagulation; 3) inaccessible vessels for cannulation; 4) patients with irreversible cardiopulmonary failure not candidates for transplantation; and 5) septic shock.³-⁶

ECLS modes typically include a pump, an oxygenator, and the circuit tubing. Technological improvements have decreased the heating and thrombosis issues with earlier centrifugal pumps, leading to less hemolysis.³ Modern oxygenators can now be used for prolonged periods and have significantly lower resistance compared to the older-generation ones.³ Moreover, heparin-coated tubing circuits are now widely available and require less systemic heparinization.³

MODES OF SUPPORT FOR RV FAILURE SECONDARY TO PH

Venovenous Extracorporeal Membrane Oxygenation

Venovenous extracorporeal membrane oxygenation (VV-ECMO) for mechanical support for RV failure was successfully reported by the group from the University of Maryland in a 35-year-old female patient presenting with a pulmonary hypertensive crisis. Hemodynamic instability was observed at attempts to initiate milrinone and intravenous epoprostenol.⁷ Taking advantage of a large patent foramen ovale (PFO), they described the use of a dual-lumen single cannula with the outflow jet directed toward the left atrium through the PFO. This strategy allowed for PH-targeted medication titration, and the patient was successfully weaned from ECLS after 10 days. Except in particular circumstances in which patients have a large PFO or atrial septal defect (ASD), VV-ECMO is not considered an appropriate mode of support for RV failure due to the lack of hemodynamic support.

Another exceptional role for VV-ECMO support in patients with
PH is in the context of respiratory failure following PEA for CTEPH. Ischemia-reperfusion injury and the pulmonary artery “steal” phenomenon can lead to severe respiratory failure secondary to ventilation/perfusion mismatch. The experience from the University of California, San Diego illustrates this application well, with 20 patients (from 1790 cases) requiring VV-ECMO after PEA. Six patients survived to hospital discharge and all of them were cannulated within 120 hours after PEA.

**Venoarterial ECMO**

One of the most frequently utilized modes of support for patients with PH and RV failure is venoarterial (VA) ECMO. Vascular access is typically obtained peripherally, either percutaneously or through cut-down dissection of the femoral vessels. A multifenestrated inflow cannula in the femoral vein is advanced to the right atrium (RA) and the outflow cannula is inserted in the femoral artery. It has the advantage of implantation under local anesthesia for unstable patients too high risk for general anesthesia induction. Nevertheless, since the cannulae are positioned in the groin, patients cannot ambulate. Another disadvantage is that despite the possible insertion of a distal limb perfusion catheter, femoral VA-ECMO is prone to limb malperfusion and arterial complications. Moreover, since the arterial flow is retrograde with this configuration, patients are at risk for upper-body malperfusion, increased LV afterload, and poor oxygenation, especially if concomitant respiratory failure is present.

Additional cannulation sites include upper limb and central. Upper-limb cannulation is performed with access through dissection of the axillary vessels. This mode can be initiated under local anesthesia, but since a graft needs to be sewn end to side with the axillary artery (to prevent distal upper-limb malperfusion), it usually requires more time than femoral vessel cannulation. On the other hand, important advantages include ambulatory capability (there are no cannulae in the groin) and adequate perfusion/oxygenation to the upper body in the event of respiratory dysfunction. Lastly, central cannulation is performed with the inflow cannula inside the RA and the outflow cannula in the ascending aorta. It requires general anesthesia and a sternotomy, but since the outflow is antegrade through the ascending aorta, there is optimal upper body and coronary artery perfusion/oxygenation.

**Pulmonary Artery to Left Atrium ECLS**

This mode of support consists of a membrane oxygenator (Novalung Interventional Lung Assist Device, Novalung, Germany) connected in parallel with the pulmonary circulation (pulmonary artery to left atrium). Due to its low oxygenator resistance, it can facilitate the bypass of approximately 50% of the cardiac output from the pulmonary circulation. A pump is not required since the blood flow is driven by the patient’s own RV. By creating a low-resistance circuit in parallel with the right heart, hemodynamic improvement by decreasing RV afterload is obtained. This mode of ECLS also provides carbon dioxide removal and oxygenation, although the inability to achieve higher flows due to the absence of a pump limits oxygenation capacity. Another advantage is that since the cannulation is central, patients can remain ambulatory for rehabilitation.

The drawback of pulmonary artery to left atrium (PA–LA) ECLS resides in the requirement of general anesthesia and a median sternotomy. Since patients tend to be hemodynamically unstable, peripheral cannulation for VA-ECMO initiation is usually performed under local anesthesia before induction of general anesthesia for a median sternotomy and central cannulation for the PA-LA ECLS. It is important to highlight that in cases of combined intrinsic LV failure this pumpless mode will not provide adequate systemic hemodynamic support.

**MECHANICAL SUPPORT AS A BRIDGE TO RECOVERY IN IPAH**

Even though mechanical support as a bridge to recovery for iPAH patients with RV failure seems unrealistic for most cases, there have been some recent reports of successful outcomes in very well selected cases. In one by the group from Columbia University, a 48-year-old female still on submaximal PH-targeted therapy was supported with VA-ECMO when presenting with RV failure. Medications were optimized and she was decannulated after 6 days, surviving to hospital discharge. Another report describes 2 additional patients with iPAH who were supported with VA-ECMO. The first patient received an iPAH diagnosis at the moment of acute decompensation with RV failure, was then started on targeted therapy, and successfully weaned from the circuit after 16 days. The second patient already had known iPAH and presented with cardiogenic shock with no clear stressor. Dysfunction of multiple organs and systems followed and support was withdrawn after 13 days. This report emphasizes the role of patient selection and the higher potential of a favorable outcome with ECLS in patients with iPAH who are still not optimally treated.

As described above, VV-ECMO with a dual-lumen single cannula was used in the context of a PFO to support a treatment-naïve patient presenting with decompensated RV failure. ECLS was discontinued after 10 days and the patient successfully transitioned to targeted therapy. Again, the reversibility of this scenario by initiation of PH-targeted therapy is closely linked to the favorable outcome achieved.

In our experience, one additional situation where VA-ECMO has been integral to recovery was the development of severe pulmonary edema related to undiagnosed pulmonary venous obstructive disease after the introduction of pulmonary vasodilative therapy.

**MECHANICAL SUPPORT AS A BRIDGE TO LUNG TRANSPLANTATION FOR IPAH**

Although management of PH has improved substantially, it is still not possible to predict treatment response and, more importantly, how fast a patient will deteriorate once he or she becomes refractory. Given that expert panel recommendations for lung transplant referral include patients with New York Heart Association class III or IV during
escalating therapy; rapidly progressive disease; and use of parenteral targeted therapy, lung transplant programs are often left with a narrow window of opportunity that should encompass patient assessment, enlistment, and a wait for a suitable donor to become available. This clinical scenario, along with the fact that iPAH patients are often young and experience excellent outcomes conditional to 1-year survival after lung transplantation, makes it logical to consider advanced bridging strategies to support this population when they present with RV failure.

The PA-LA ECLS constitutes an adequate mode for bridging iPAH patients to lung transplantation because of several key features: 1) enables active rehabilitation while on the wait-list; 2) can be utilized for prolonged time, such as cases described with 175 and 69 days; and 3) has been used successfully in the pediatric population. According to early reports, this mode of support began being used clinically as a bridge to lung transplant by 2005. Schmid et al reported a 38-year-old female with RV failure secondary to iPAH who was initially supported with central VA-ECMO. With progressive deterioration and inability to wean, authors got approval to use the PA-LA ECLS. The patient improved, was weaned from the ventilator, and became ambulatory while waiting for lung transplantation. After 62 days on the device, she received a successful double-lung transplant.

Subsequently, 4 PH patients were bridged to either double-lung or heart-lung transplant in the combined experience of the Toronto and the Hannover lung transplant programs. The PA-LA ECLS was used from 8 to 30 days until the patients received a transplant with favorable early outcomes. These authors also reported that although the circuit may become dysfunctional due to fibrin deposition, it could be easily exchanged. Moreover, another important lesson involved the benefit of preparation for peripheral VA-ECMO cannulation under local anesthesia for patients at high risk of cardiocirculatory collapse at induction. Once stabilized on VA-ECMO, the team can safely proceed with general anesthesia, median sternotomy, and PA-LA ECLS cannulation. The VA-ECMO can then be weaned at the end of the procedure.

Subsequent contributions by the group from Hannover focused on the concept of awake ECLS as a bridge to transplant. Most recently, they reported 26 such patients, including 7 iPAH patients supported with femoral VA-ECMO initiated under local anesthesia. Most of these patients remained extubated until transplantation or death on ECLS. In an intention-to-treat analysis, authors reported 62% survival at 6 months. Of note, the outcomes were significantly better in the awake bridge population than in the intubated and mechanically ventilated one. Likewise, this was also true in the comparison between those patients remaining awake versus those initially on awake ECMO but eventually requiring intubation.

The impact of ECLS as a bridge to transplant in patients with iPAH is highlighted by the study from de Perrot and coworkers from the University of Toronto. When comparing an early 1997-2005 listed cohort with a more recent 2006-2010 listed cohort (the second one aggressively managed with availability of ECLS as bridge to transplant), the wait-list mortality significantly decreased from 22% to 0%. Importantly, this higher risk profile in the recipient population has not compromised outcomes: the 30-day mortality went from 16.5% to 9.5%. The authors note, however, that this strategy may be associated with a longer post-transplant ICU stay.

Recently, 2 large series reinforced the positive outcomes observed previously. The combined report from the University of Kentucky/University of California, San Francisco included 31 patients bridged to lung transplant with ECLS, with 13 of them presenting with RV failure and requiring VA-ECMO or PA-LA ECLS. Outcomes were excellent, with 1-year survival of 93%. The second study describes the experience from the University of Pittsburgh. Out of 31 patients, 9 were bridged with VA-ECMO for RV failure. With a 1-year survival of 74%, this series pointed to a high incidence of primary graft dysfunction in bridged patients: 13 of the 24 patients actually transplanted required postoperative ECLS due to primary graft dysfunction. Recently, one interesting algorithm for managing unstable candidates for lung transplantation reinforced the interchangeable nature of the support modes, always targeting the least invasive one able to provide ambulatory status while patients await donor lungs.

Since peripheral groin cannulation prevents patients from being ambulatory and able to pursue a more aggressive rehabilitation while on the wait-list, the use of upper-extremity cannulation may be advantageous and deserves further consideration.

As described above, another support mode that assists the ambulatory status is the VV-ECMO with a dual-lumen single cannula in patients with large ASD. Ideal positioning includes the direction of the outflow jet toward the defect, providing oxygenated blood to the left heart through the right atrium. This mode of support has been tested in animal models and translated to clinical use. Since the use of balloon septostomy has been successfully described as a palliative measure for PH patients presenting with RV failure, whether this strategy coupled with the benefits of dual-lumen single-cannula VV-ECMO providing not only optimal RV unloading but also adding oxygenated blood through the newly created right-to-left shunt could be superior than the VA-ECMO or PA-LA ECLS modes remains to be studied.

Lastly, another potential application for VA-ECMO is as bridge to recovery for patients with ventricular dysfunction following lung transplantation. Some programs indeed have described its routine use in the early post-transplant period for patients with iPAH.

ADDITIONAL ECLS APPLICATIONS IN RV FAILURE SECONDARY TO PH

Besides the growing use of ECLS for patients with iPAH, there have been interesting reports focusing on its use for patients with CTEPH and patients with acute massive PE. VA-ECMO can be...
considered in very well selected patients with CTEPH and RV failure as a bridge to PEA, as reported by Mydin et al.\textsuperscript{31} Another application is as a bridge to recovery post-PEA, when VA-ECMO can be lifesaving for patients with persistent PH and/or airway hemorrhage. This clinical scenario is well illustrated in the study of Berman et al, describing the Papworth Hospital experience with 7 patients (from a total of 127) requiring VA-ECMO for cardiopulmonary support post-PEA.\textsuperscript{32} All patients presented with persistent PH and RV failure post-PEA, with 5 being successfully cannulated and 4 achieving hospital discharge.

For patients with RV failure secondary to massive PE, ECLS has been utilized as either a bridge to recovery or bridge to embolectomy. Since massive PE is a reversible condition and a previously healthy RV will likely fail once submitted to overwhelming increases in afterload, the use of VA-ECMO for temporary cardiopulmonary support seems adequate. The group from the University of Michigan has reported a total of 43 patients initially referred for ECLS consideration due to massive PE.\textsuperscript{33} Ultimately, 19 were placed on VA-ECMO and 2 on VV-ECMO, with the remainder not meeting criteria due to the following reasons: too stable (n=7); prolonged cardiopulmonary resuscitation with irreversible damage (5); age >70 years (4); weight above the air transportation limit (3); prolonged mechanical ventilation (3). Of the 13 patients surviving to hospital discharge (62%), 4 of them were treated with embolectomy, while the remaining were treated with anticoagulation/thrombolytics.

Similar to other previously described situations, the RV has a remarkable potential to recover in post-cardiovascular surgery scenarios (post-cardiotomy, post-heart transplant, post-LVAD insertion). In this setting, Cheung et al have reported a 78% successful RVAD explantation rate.\textsuperscript{34} Nevertheless, while these devices can be considered as rescue therapy in RV failure post-cardiotomy, post-heart transplant, and post-LVAD implantation, they should not be considered appropriate therapy in cases of unresolved severe PH since they do not address the main pathophysiological mechanism of RV failure (pressure overload).\textsuperscript{35}

**CONCLUSION**

ECLS strategies can be lifesaving for patients with precapillary PH presenting with RV failure refractory to medical therapies. It is crucial that the multidisciplinary team establishes each patient’s true bridging potential (to recovery or to surgical therapy) and avoids futile ECLS initiation. For lung transplant candidates, recent literature favors the use of ambulatory modes that enable active rehabilitation and spontaneous breathing during the waiting period.

**References**


Pulmonary Hypertension and Right Heart Failure in the ICU: Tackling Difficult Issues

A group of thought leaders in management of pulmonary hypertension gathered by phone on January 27, 2015 to discuss their approach to difficult issues encountered when PAH and RV-failure patients are in the ICU. Read on to learn their perspective as guest editor Deborah Levine, MD, medical director of the PH Center at University of Texas Health Science Center in San Antonio moderates a discussion among Jeffrey Sager, MD, director of the Cottage Pulmonary Hypertension Center in Santa Barbara, California; Stephen Mathai, MD, MHS, assistant professor of medicine at Johns Hopkins University and member of the pulmonary hypertension program; and Todd Bull, MD, director of the Pulmonary Vascular Disease Program at the University of Colorado and member of the pulmonary and critical care and cardiology sections.

Dr Levine: Thank you for taking the time to join our discussion today. This issue of Advances is dedicated to the challenges we face while taking care of our patients with PAH and those with RV dysfunction/failure in the ICU setting. Our roundtable today will focus on our experience and challenges with issues that are not covered in the rest of the journal.

Dr Levine: Much of what we discussed in the articles in this issue focuses on patients with PAH (sepsis, RV dysfunction relating to the PAH patient, etc.). But one topic that we do not discuss, which is a major problem for intensivists, is patients with Group 3 PH—patients who are admitted to the ICU with chronic lung disease, who may have some PH and/or RV dysfunction, related or as a complication of their lung disease, who are acutely decompensating in the ICU. How do we go about evaluating and treating these patients? Do these patients undergo RHC? Do we initiate PAH medications? How do we treat them differently from our Group 1 PH patients? Todd?

Dr Bull: I think what you’re asking is how we manage patients with an underlying parenchymal lung disease who also have some associated right ventricular dysfunction. That’s kind of a tricky group to start out with, in that I think many of us recognize that pulmonary hypertension is associated with this patient population. This is one of the lung parenchymal categories of pulmonary hypertension or WHO Group 3 PH. It’s unclear, though, how specifically to deal with the pulmonary hypertension in that group, other than correcting the underlying lung disease or hypoxia. Now, that being said, there are those patients who have certainly more significant RV dysfunction, which in the past has been termed “pulmonary hypertension out of proportion” to their lung disease. And I think many of us in the field think that at least that’s a group that may merit consideration of treatment, though it’s certainly an area of debate right now.

Now, how to deal with them in the ICU setting: my personal thought on this topic in general is that patients go as their RV goes. The RV in a way is a window to the soul, if you will. So, if their RV is severely dysfunctional, based on their underlying lung disease or another problem, then that can really determine or impact their outcomes in the intensive care unit—or at least can play a big role in that. If their RV function is relatively good, then I think their underlying process, whether that be parenchymal disease, may more accurately determine how they do. Launching into treatment, again, I really pay more attention to what the RV size, RV function, what their hemodynamics are in that scenario, as to whether I would consider thinking about other PH specific therapies. But I think you have to be really careful of adding any of our medications to that patient group, because you can certainly induce V/Q mismatch.

Dr Sager: I completely agree with Todd. One aspect is that these patients with pre-existing parenchymal disease or cor pulmonale have very little reserves. Usually an acute event such as infection or pulmonary embolism leads to rapid decompensation. They may have chronic right ventricular compensation for many years until this acute event occurs. When this happens, the right ventricle that is in a chronically compromised situation leads to a spiral of death. The focus of ICU management is to try to reverse the acute reason for decompensation and support the right ventricle. I am extremely cautious about using PAH-specific therapies. Before considering these PAH-specific therapies, I try to maximize right ventricular afterload reduction. For example, focus on improving patient’s oxygenation, optimize fluid balance, and deal with arrhythmias. There is the risk of using PAH-specific therapies in patients with parenchymal lung disease due to potential worsening oxygenation and V/Q mismatch. I will use, for example, in the intensive care unit, inhaled epoprostenol as salvage therapy for refractory acute hypoxemic respiratory failure not responding to more conventional therapies. Presently, we do not have enough data to be using PAH-specific therapies upfront in patients with WHO Group 3 disease who had decompensated in the ICU.

Dr Mathai: I also agree with everything that’s been said. Some specific things that I might do a little bit differently for patients who have pulmonary hypertension in the setting of parenchymal
lung disease in the ICU compared to other patients is maybe set my goals for oxygenation a little bit higher. Not be satisfied with a saturation of 90% or a PaO2 of 60, looking for actually reducing some of the vasoconstriction that may be induced by the hypoxia. I agree with the sentiment that we should be aggressive about diuresis. Then also think supporting right ventricular contractility with specific ionotropic agents might be another potential intervention that could be helpful in these patients. Obviously, the impact of mechanical ventilation on cardiopulmonary interactions, either with intubation or even positive pressure ventilation, should be considered strongly in the evaluation and management of these patients, recognizing that the hemodynamic impacts of these interventions may further worsen an already impaired RV.

Dr Levine: Thanks Steve, I completely agree. Often we have patients with lung disease in our ICU or transferred from other facilities to the PH center who are so hypoxic that the question becomes, if you initiate PAH therapy, will you be able to improve their significant hypoxemia? What has been your experience and what are your thoughts using these agents in these very sick hypoxic patients (many of whom are ventilated)?

Dr Mathai: One thing that I would like to raise is the possibility of increasing right-sided pressures leading to a PFO and a right-to-left shunt, which could be contributing to the general hypoxemia that’s being observed in these patients. I think that’s something that should be checked whenever a patient seems to have hypoxia that is markedly worse than prior. Then the management strategies that we proposed regarding supporting the right ventricle and diuresis would be potentially very effective and helpful in reducing shunt and perhaps improving hypoxia. I’ll let Jeff and Todd talk about the particular vasodilator agents.

Dr Sager: I would add that physiologically it seems reasonable to use inhaled therapies in patients who have ARDS or acute hypoxemic respiratory failure. It makes sense that you would be getting a drug to an area that is ventilated and reduce problems related to V/Q mismatch. It would make sense to try and use vasodilators in areas that are being perfused and ventilated. Additionally, there is less systemic hypoten sive effect. Although it sounds good, it doesn’t always bear out in the literature. For example, inhaled nitric oxide in ARDS has been studied and although it improves oxygenation in the first 24–48 hours, hospital mortality and long-term outcome data were no different. I believe that although the long-term outcome data may not be significant, being able to buy the patient improved oxygenation for 24–48 hours allows you time to improve oxygenation and hopefully get the patient to turn the corner. Many times we struggle to get patients through the first 24–48 hours of the acute hypoxemic respiratory failure. If you can get them over the hump with using agents like this, they may actually survive. So although the primary outcome of that particular study didn’t show mortality benefit with using inhaled nitric oxide, I believe there is potential benefit for these agents. The other potential benefit of inhaled agents is the ability to use PEEP levels that keep the lung in a low stretch protective strategy. In my practice, I don’t use inhaled agents up front but rather as salvage modality. I hope that this can be further studied to help guide clinical practice.

Dr Bull: Yes, my take on that is similar. I think, as I mentioned at the beginning of this discussion, how I decide whether I’m going to go after an agent to treat the pulmonary hypertension or pulmonary vascular disease in my mind really relates to what the RV looks like. What is it doing? How is it functioning? All the better if I have invasive hemodynamics, if that’s what I think might be going on. But I think the echo in these scenarios can be useful. And really, I think where people get led astray is just looking strictly at the pressure. In my mind, the pressure is always the least interesting variable; it is how the right heart is responding to the pressure that is important. We know that parenchymal lung disease is one of the things that can make an accurate read on right ventricular systolic pressure by echo inaccurate. Also, if the patient is on the ventilator, then estimating right atrial pressure becomes difficult as you cannot rely on IVC dilation as an indicator of RA pressure in that setting. Now, I guess the topic we brought up here is inhaled therapy, which in theory could improve V/Q matching by improving perfusion to areas of good ventilation, which is the beauty behind nitric oxide. And it is pretty clear that inhaled nitric oxide initially works to improve oxygenation acutely, as Jeff mentioned, as salvage therapy in severe ARDS; but as he stated, it has never been shown to improve long-term outcomes. There’s a strange tachyphylaxis that occurs once it’s applied that, after 24–48 hours it quits working, which I’ve always found kind of fascinating. Whoever can figure out why that is and figure out how to keep that from happening is going to be really onto something, because then it would become potentially a lot more useful. We’ve also been looking at inhaled prostanoids in this scenario, and in particular, inhaled epoprostenol just because of the expense of inhaled nitric oxide. I know other centers have used that, as well. But to me, again, it really comes back to is the problem the right ventricle? And is there really an RV function problem or are you just reading off a pressure? I always caution our house staff: don’t just read the pressure on the echo report without looking at RV size and function—ideally, look at the echo yourself. But at least read the report on the RV size and RV function, because that will give you a better idea of what’s happening.

Dr Levine: Thank you Jeff. Moving on to evaluation in the ICU. Many of these patients may have echocardiograms, but many do not have previous RHC. Is your experience to place PA catheters in these patients? Have you found it assists you in initiating or choosing the correct therapeutic options?

Dr Bull: That’s always kind of tricky. A lot of what we’re going to end up discussing in this scenario is from the
ARDS literature, because that's where most of our trials in critical care literature reside because of the ARDSNet. The FACTT trial (Fluid and Catheter Treatment Trial), which wasn't addressing pulmonary hypertension, showed no benefit to a PA catheter as opposed to a central line in terms of patients' outcomes with ARDS. So, in this particular patient population, we no longer grab a PA catheter. Because there were 1,000 patients in that study and 500 of them had PA catheters, we looked at that study and said, “Oh, what a great opportunity to look at what the incidence of pulmonary hypertension is in patients with ARDS.” We reported that 70% of the patients had pulmonary vascular dysfunction defined as an elevated transpulmonary gradient and these patients had an increased mortality. There was a dose effect with the worse the pulmonary vascular dysfunction, the higher the mortality. To go back to your question, I would consider a PA catheter in certain scenarios, but usually we find it not necessary in this group. I would do it when I really think the RV is involved and I’m trying to decide if I need to add PH treatment. I’d be curious to hear what Steve and Jeffrey think on the use of PA catheters in this situation.

Dr Mathai: So I rarely use a PA cath in the ICU. I agree with Todd that there may be cases in which it could be helpful. My concern is that if these patients have multi-organ involvement, are on the ventilator, and have underlying RV dysfunction, while serial data such as serial measurements of right atrial pressure and looking for changes in right ventricular function, etc., might be useful, I think most of the time we can manage these patients based on an echocardiogram and what we’re seeing with systemic hemodynamics along with oxygenation and ventilation. However, there definitely are cases in which you’re kind of confused by the clinical picture and data gathered from the Swan can be helpful.

Dr Bull: Yeah. Now, specifically we’re talking – or I think we’re sort of leaning back to ARDS or other parenchymal lung diseases in the ICU, because that’s how we started off this conversation. And I definitely agree with Steve, it’s pretty unusual that we’d need to put a PA catheter in those patients. And again, FACTT shows us that it didn’t really help. Though there were problems with FACTT, I would argue. But I think now if you expand our discussion to patients with PAH, severe pulmonary arterial hypertension, and we’re trying to add pressors and/or inotropes, etc., I have to say I find PA catheters useful in that situation. So I don’t know if we’re going to break this talk away from the parenchymal lung disease or sort of stay there for the moment. But I do think there are indications where the PAH patient comes in and is quite sick that I like a PA catheter to help me decide what to do with inotropes and pressors volume.

Dr Sager: Todd, we know that ARDS can cause pulmonary hypertension and, in fact, it can be one of the reasons for significant RV failure in these very sick patients. I agree with you, in those situations we do not routinely place pulmonary artery catheters because we are able to look at the echo and other parameters to help guide therapy. I think the most difficult areas are with patients who have chronic right ventricular dysfunction, for whatever reason, who get into trouble. These patients can be a challenge to figure out the fluid status and filling pressures and often will need a pulmonary artery catheter to help guide therapy. There are significant limitations with using a pulmonary artery catheter in patients in the ICU on ventilators and interpretation needs to be done cautiously with experience. There are hemodynamic changes from the ventilator itself.

Dr Levine: Thanks everyone for your thoughtful comments on this challenging issue. Unless anyone had anything else to add on this subject, let’s move on to surgical issues in the ICU in patients with chronic PAH. This has become a more frequent ICU scenario, especially in PH centers, as we often have these patients transferred to us. There is a lot of planning and discussion among anesthesiologists, surgery, PH physician, and the intensivist which should occur prior to surgery, peri-operatively and post-operatively. Jeff, what is important when looking into these situations? Besides getting a multi-disciplinary team together, what other issues are important?

Dr Sager: This is a timely question as I gave an update to the anesthesia department this week on peri-operative pulmonary hypertension issues. The key to successful operation in patients with pulmonary hypertension results from a multi-disciplinary approach and clear, concise pre-operative, peri-operative, and post-operative plans. A frank discussion is needed among the surgeon, anesthesiologist, and PH specialist. The best type of anesthesia is no anesthesia! One needs to decide on type of surgery and if surgery could be avoided by other therapies. If surgery is needed, a pre-operative assessment of the right ventricle to ensure its stability is paramount. We know from a registry looking at risk factors for mortality in patients with pulmonary hypertension that emergent surgery was one of the highest risks for death in these patients. So if emergent surgery can be avoided in these patients, clearly that’s the way to go. Having a surgical plan for both intra-operative and post-operative management of pulmonary hypertension will likely provide the best outcomes for these patients. You need to anticipate post-operative hemodynamic changes.

Dr Mathai: Yeah, I agree. I think other factors to include are the location of the surgery, above the diaphragm, below the diaphragm. Is it vascular? Also, the duration in addition to the type of anesthesia that’s planned. I completely agree with Jeff, that while no anesthesia is the best strategy, if there’s a way to do a local anesthesia for any elective procedure, that is also preferred over systemic.

Dr Levine: Agree completely, and really the main reason to meet and develop a plan is so that all know what back up plans are available.
Dr Bull: I would add to Jeff's point regarding elective versus emergent. Jeff, you had mentioned Dr. Meyer's publication in the ERJ in 2010. We contributed patients to that registry. An important point of that study was that the mortality was not actually near as high for PAH as had been put forward in a previous case series, where mortalities were listed as high as 50%. The overall mortality was only about 3.5 percent. But if the case was emergent, which was only a small subgroup of about 4 patients, the mortality was 15%. So it went up dramatically when the case became emergent.

The other key point, I think, to that study was that these were all centers expert in the management of patients with pulmonary arterial hypertension. These were centers where you had expertise in pulmonary hypertension; you likely had expertise in cardiac anesthesia, and surgical and critical care expertise. I do agree that the team is a key aspect. One of the things we always stress is that we need cardiac anesthesia involved, because they are most familiar with the potential hemodynamic changes that can occur during induction, during intubation, following intubation—which in my mind are the most dangerous times.

Dr Mathai: So to echo that and just to give one example, we have a cardiac anesthesiologist here who is quite interested in the peri-operative management of patients with pulmonary hypertension. He has agreed to see all of our patients in pre-operative evaluation. He contacts us after he evaluates them. We go over the most recent hemodynamic data, echo data, functional data, and then come up with a plan jointly, prior to surgery. Importantly, we decide whether or not cardiac anesthesia is absolutely required for the surgery or procedure. I think it gives some structure to a program where we all have people who are living longer and develop other complications from general medical conditions that require surgical intervention. I've recently cared for a patient with long-standing iPAH who developed lung cancer that needed resection. That's obviously a complex scenario to undertake. But at the same time, with these kinds of approaches that Jeff and Todd have mentioned, I think we can be successful in managing these patients through these surgeries.

Dr Levine: Agreed, these conversations between each team and the patient are exactly what needs to happen for these cases to be successful. This includes, as Steve noted, to discuss if the benefit of the surgery is greater then the risk. Patient involvement in these conversations is imperative.

Dr Sager: Debbie, just one point to add is about patients who need semi-elective surgeries who appear stable and are often referred to outpatient surgery centers. An example would be a simple cholecystectomy in a PAH patient who is “looking good” should always have this surgery done in a facility where complete management of post-operative pulmonary hypertension can be performed. I do not believe these patients are good candidates for outpatient surgery centers. It's this cohort of patients that are not recognized as being potentially catastrophic cases for whom there's no preparation when you do these cases at an outpatient surgery center.

Dr Bull: I think that's a great point. Again, we have cardiac anesthesia involved when the PA, PAH is severe. And then we mandate, really, that even “simple” (if there is such a thing) operations are placed in the ICU afterward and are managed by our pulmonary hypertension team, because our understanding of the hemodynamic shifts that can occur peri-operatively is important. Because this is what we do for a living, we know what to watch for. Also frequently they're on therapies like prostanoids that can't be interrupted. You had asked earlier, what do we do with their therapies around pulmonary hypertension? Of course, that's part of our education is that we've got to keep the PH medications going, if that means moving to IV PDE-5's, for example, that's what needs to happen, or making sure the prostanoids aren't stopped.

Dr Levine: Very important point. These surgeries/procedures should all take place at a center that is recognized in being able to handle the situations that may occur.

Dr Bull: Yeah, and I suspect that's, you know, from that Mayer ERJ paper that we were mentioning from 2010. The mortality is so much lower than what we've seen in previous case series and this may relate to the fact that all the enrolling centers in this registry were major PH centers and were taking these precautions.

Dr Sager: Yeah, I agree.

Dr Mathai: Can we talk about management of arrhythmias?

Dr Levine: Absolutely, this is one important area, that both affects the patients while in the ICU and brings the patient to the ICU.

Dr Mathai: One of the questions that commonly come up I think from others who are managing patients with pulmonary hypertension in the ICU is the development of arrhythmias. I think it's a particularly challenging scenario in a patient with pulmonary arterial hypertension, due to the impact on outcomes and the potential for adverse outcomes related to the standard therapy for arrhythmias. If we look back at the literature and look at arrhythmias that occur at cardiopulmonary arrest in PAH, what you see mostly is bradycardia. This is from a paper by Marius Hoeper back in 2002, describing arrhythmia at the time of a cardiopulmonary arrest in patients with PAH. But if you look into the ICU realm in patients with PAH—and we went back and looked at this in our cohort of patients who ended up in the ICU with PAH—a significant proportion of those patients, nearly 40% of those patients, ended up in the ICU because of new onset atrial fibrillation or flutter. So atrial arrhythmias were the precipitant for ICU admission due to hemodynamic instability or frank right ventricular failure. And I think that's supported if we look though the literature again at the cumulative incident of SVTs in PAH, which is about 25%. So I think it's a significant issue. I'm curious about how the other panelists approach
the evaluation and management of these patients when they present to the ICU.

Dr Bull: I definitely agree that of the things that bring our patients to the intensive care unit, arrhythmias—in particular atrial arrhythmias—is very high on the list. In fact, I’ve been over the last couple weeks dealing with this over and over again in a number of different patients with PAH with very severe RV dysfunction. And it’s the sort of thing that as soon as we see it, we’re moving them over to the intensive care unit because it can be such a dramatic occurrence. As you lose your atrial kick, you drop an already depressed cardiac output even further, and then when you’re in a rapid ventricular rate scenario you don’t have filling time. Hemodynamically, they can really unravel. And so our approach is the use of amiodarone up front, assuming again that we’re not in an ACLS type scenario where we have profound hypotension. In that case, ACLS trumps all and electrical cardioversion becomes necessary. But when we can, we like to use amio. I’ve had a fair amount of success with that agent. We strictly avoid beta blockers and calcium channel blockers because of their effect on already depressed RV function. And again, I’ve had luck with amio boluses and amio loading. Digoxin can be thrown in there, but really do we do not find it very useful for the acute scenarios. So that’s our approach. I’d be curious to hear what you do in the face of a fast A-fib or A-flutter.

Dr Sager: This is a great question. It’s something that we see very frequently in our PH patients. It is often a dramatic finding with significant worsening in the symptoms when it occurs. When the patient’s go into an acute arrhythmia, particularly supraventricular arrhythmias, they often decompensate pretty rapidly. I agree with everyone on the panel that we move them to the ICU. We are very reluctant to use calcium channel blockers and beta blockade and often will start with amiodarone. I’m fortunate here in Santa Barbara, where we have very well-trained EP cardiologists who are willing to perform high risk cardiac ablations under direct intracardiac echocardiogram. I have seen several patients turn around quite dramatically as soon as we can get the supraventricular arrhythmia ablated.

Dr Bull: I’ve become very aggressive about seeking A-flutter ablation. We’re not doing this in the acute scenario either. We either have controlled with amio or, if we can’t control, then we’ll look at electrical cardioversion. But following that, we have some great electrophysiologists here as well who are getting a lot of experience with this because I’ve been calling them more and more about ablation, in particular for A-flutter. We have not been as aggressive about A-fib. But in typical flutter, our success rate is good.

Dr Mathai: And I agree with all that’s been said. You know, I think one of the things that really dictate our management and how aggressive we are is the fact that we believe, although there’s little data to support this, that rate control is insufficient. So it’s not just getting the heart rate below 100 beats per minute, but actually restoring sinus rhythm, which is the key to improving RV function overall. This is based on some observational data looking at studies of right ventricular function in the setting of atrial fibrillation. In the normal right ventricle, you can expect 20–30% of RV function to be dependent upon normal atrial contraction. If you get to someone who’s got pulmonary hypertension, about 40–50% of RV function is dependent on normal atrial contraction. You can see this clinically if you look at the impact on outcomes. Two studies looking at this recently within the past 3 years have shown a 2- to 5-fold increased risk of death for those PH patients who remain in atrial arrhythmia, compared to those who have no atrial arrhythmia. Another study by Marius Hoeper’s group showed significant improvement in functional capacity, assessed both by WHO functional classification and six-minute walk distance with restoration of sinus rhythm. So I think for us, it really is an aggressive push, not only to get rate control but to get rhythm control. I think ablation is usually necessary in patients who have flutter, as Todd mentioned.

Dr Bull: Yeah, that was great. And, you know, your comments on outcomes jive well with the 2010 ERJ paper by Humbert showing that, arrhythmias, in particular atrial arrhythmias, was one of the markers of bad outcomes in PAH patients in the ICU. It was not a huge study but it was one of the factors that fell out.

Dr Mathai: I think one other thing that we run into sometimes when we were consultants on a case and not primary attendings, we get into the issue of amiodarone toxicity. Many physicians are concerned with the possibility of amiodarone toxicity. Many physicians are concerned with the possibility of amiodarone toxicity, but I think this is a bit overblown. I’ve recently gone back and looked at the literature to try to get a better understanding of what kind of proportion of patients actually have adverse side effects directly related to amiodarone and it’s pretty low. I mean, aside from corneal deposits which will develop in the vast majority, most of the side effects occur in less than 5% and less than 1% in many cases of the things we typically think of, like interstitial lung disease. Specifically, the incidence of that is on the order of 1–2%, if someone’s on less than 400 mg a day, which I think is the upper limit of the dose that we would all advocate for long-term management of these types of patients. So I don’t know what your thoughts are, if you’ve run into that situation also in your management of these patients.

Dr Sager: One thing that Steve mentioned, worth emphasizing, many cardiology colleagues will be very happy with rate control of these patients, yet they remain significantly dyspneic. It’s not just about rate control but rhythm control in patients with underlying right ventricular dysfunction and pulmonary arterial hypertension. These patients are volume dependent and rely on the filling pressures of the atria more so than patients with no pulmonary hypertension.

Dr Levine: Are any of you using cardioversion to restore rhythm?
Dr Bull: We do it when we need to. I mean, again, if you’re moving toward a hypotensive scenario or you have a perfusion problem or we’re not getting on top of them or the amio is not working—though again, it’s my experience.

Dr Levine: Our time is up and I would like to again thank all of you so much for participating in this discussion. I look forward to continuing the conversation on all of these topics.

References
Meeting the Challenge of Hospitalized PAH Patients Receiving IV Prostacyclins

Section Editor
Mary Bartlett, MS, RN, CS, FNP

In this PHPN column, we invited members from around the country to share their experiences and tips on several aspects of dealing with PAH patients in the hospital setting, particularly related to infusion pumps. Former section editor Martha Kingman, DNP, FNP-C, University of Texas Southwestern Medical Center at Dallas, provides valuable insight as an introduction to the topic.

Pulmonary arterial hypertension (PAH) patients receiving intravenous (IV) prostacyclin therapies pose significant challenges for nurses in the hospital setting. Even at large pulmonary hypertension (PH)-treating hospitals, the number of PAH patients receiving IV prostacyclin in the hospital at any given time will be small. Therefore, many nurses, and some doctors, may have limited or no knowledge of the complex dosing and safety profile of these medications. Intravenous prostacyclins are dosed in nanograms per kilogram per minute, and have a very patient-specific and narrow therapeutic range. Sudden increases or decreases in dose can lead to significant adverse events, including death. Further complicating the safety of this therapy in the hospital setting involves the infusion pumps. There are safety concerns when nurses are not familiar with ambulatory pump operation, and maintaining competence can be challenging. There are also concerns when patients are transitioned to hospital pumps, which require a change in pump rate or medication concentration, thus introducing opportunity for errors.

Regardless of hospital policies on the use of home infusion pumps or hospital pumps, extensive ongoing education is required for nurses caring for hospitalized PAH patients. At a minimum, nurses should understand the disease process and be able to identify the difference between prostacyclin side effects and PH symptoms. If patients are sustained on their home infusion pumps in the hospital, nurses must be proficient in pump operation. This instruction can be accomplished in a collaborative way between the PH staff and the specialty pharmacy nurses. Additional educational topics should include direction on how to prime the central lines and avoid common errors such as flushing the central line. In our survey of 97 PH programs, flushing the line was the most common error mentioned. Other common errors reported by 20 or more respondents include: wrong dose due to miscalculation (N=29), use of a prostacyclin cassette or bag intended for another patient (N=25), incorrect rate programmed into the infusion pump (N=24), and pump inadvertently turned off for a period of time (N=24).1

In this issue, our distinguished panel of nurses and nurse practitioners with extensive hospital experience caring for PAH patients discuss how best to address some of these important topics. Additional information regarding prostacyclin safety practices can be found within Online University on the Pulmonary Hypertension Association’s Web site.

What are the most common errors you are aware of related to hospitalized infusion patients, and what are some tools you use in an attempt to prevent these errors?

Jacqueline Brewer, BSN, RN
Beaumont Health System

We have instituted numerous effective policies and practices at our institution to prevent the occurrence of errors with prostacyclin medications—including but not limited to incorrect dose, weight, patient, and drug. Upon entering the institution, a mandatory PH alert page is activated to notify all parties involved that a patient on IV/subcutaneous (SC) prostacyclin therapy has arrived. Patients and caregivers are interviewed immediately with questions regarding drug, pump rate, next cassette change, and specialty pharmacy. Promptly following a mandatory physical check of the pump and verification of backup pump, supplies, and medication by a PH-certified rapid response team nurse and pharmacist, the pharmacy team places a call to the patient’s specialty pharmacy to confirm proper dose, concentration, and dosing weight. All patients on epoprostenol are admitted to the PH-dedicated unit (CICU) despite need for critical care services. If on treprostinil, patients may be admitted to a dedicated telemetry unit if not warranting critical care.

Once admitted, an absolute double-check is performed in the pharmacy as well as at the bedside for all cassette or syringe changes. Barcode scanning is also utilized as an additional verification for all medications, and patients and caregivers are strongly encouraged to participate in the entire authentication process. All treprostini and epoprostenol cassettes and syringes have brightly color-coded, drug-specific labeling. These labels and coordinating signage are applied to IV tubing, lines, pumps, etc, and storage is located within both the CICU and main pharmacy. Treprostinil is not stored on the unit but is requested one hour prior to cassette or syringe changes, whereas epoprostenol is kept refrigerated on the unit in properly marked bins.

Line errors also occur (including but not limited to) with improperly primed lines, flushing, and coinfusion of other medications. All lines are dedicated for prostacyclin-only administration and are clearly identified with brightly color-
Patients on prostacyclins are only admitted to specific nursing units in our cardiovascular center. These nurses are all prostacyclin-competent. University of California, San Diego (UCSD) provides many training sessions throughout the year. We also have quarterly “roaming in-services” featuring hands-on pump demonstrations. The nurses at UCSD are very comfortable with inpatients, as more than 50 infusion patients are admitted each year. Many of these patients endure lengthy stays in the hospital, so it is very likely that there is an infusion patient present at all times.

**What is your opinion on keeping infusion patients on home infusion pumps vs transitioning to hospital pumps? If you do transition to a hospital pump, please describe your protocol for priming the Hickman line.**

Michelle Calderbank, RN, BSN, CPN
Beth A. Coleman, RN, MSN, CPNP
Children’s Hospital Colorado

Our experience has been that fewer dosing errors, microboluses, and infusion interruptions occur when the patient can be maintained on the home/micro-infusion pump (CADD Legacy and Crono5). As a large referral center, many of our patients are admitted to out-of-state institutions where prostacyclin is not on formulary, staff are unfamiliar with the drug, and maintenance on the home pump is safest.

If young patients hospitalized to our center are stable and able to manage their pump (or have a parent present who is competent in pump management), our policy is to maintain the prostacyclin patient on their home infusion pump. If a parent cannot be present or the patient becomes unstable, requiring escalation of care or transfer to the ICU setting, our procedure dictates that the patient be converted from the home infusion pump to the hospital syringe pump to allow for titration and management of the prostacyclin infusion by the health care team.

Each patient’s central line internal volume is assessed at the time of line insertion and documented on the current prostacyclin dosing flow sheet. Many pediatric patients use miniaturized IV infusion pumps running at lower flow rates (0.3–0.5 mL/hr), and will require a concentration decrease to transfer to the hospital syringe pump to achieve a hospital minimum flow rate (1 mL/hr). This necessitates the more concentrated home prostacyclin be aspirated from the line to avoid bolusing, and the patient is then connected to the new infusion via the hospital syringe pump and prime via the syringe pump’s prime function.

**PROS for maintaining home pumps:**
- Patient feels stable infusion rate
- Empowers the patient/family
- Less risk of error because the syringe or cassette is changed every 24 hours instead of every 8 hours

**CONS to maintaining home pumps:**
- Nursing staff less familiar with pump devices
- Not ideal for frequent dose changes

If an infusion patient has an interruption of infusion therapy—for instance, the Hickman line is clotted or cracked, or the SC catheter has fallen out—what is the best next course of action?

Joanna Wapner, ACNP-NP
Pennsylvania Hospital

First, remain calm. Assess the patient’s vital signs. If warranted, place the patient on supplemental oxygen. If an inpatient is on an IV formation, he/she should ideally have an alternative access to ensure minimal interruption of therapy. If there is an issue with the Hickman, medication should be switched immediately to the peripheral access. For SC administration, nurses should check the site every 4 hours (half-life of the medication) to ensure timely identification of site loss. If a nurse notices that the site is lost, under ideal circumstances, a new site should be established and medication restarted. If the tools are not available to place a new site, the patient should be transitioned to IV remodulin through peripheral access until either a new SC site can be placed or, if circumstances warrant, central access is established.

**Reference**

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

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.
Cardiovascular Effects: Discuss with patients the appropriate action to take in the event that they experience anginal chest pain while taking ADCIRCA following intake of ADCIRCA. At least 48 hours should elapse after the last dose of ADCIRCA before taking nitrites. If a patient has taken ADCIRCA within 48 hours, administer nitrites under close medical supervision with appropriate cardiovascular monitoring. Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention. PDE5 inhibitors, including tadalfil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCIRCA, 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 be used as an alternative to or in combination with cardiovascular disease (WHO Group II) symptoms and etiologies of idiopathic or heritable PAH (61%). Use with Alpha Blockers and Antihypertensives — PDE5 is found in platelets. When tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of ASCIRCA. Potent Inducers of CYP3A — For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ASCIRCA. Use in Renal Impairment: In patients with mild or moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment — Avoid use of ASCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis. Use in Hepatic Impairment: In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) — Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once daily. ASCIRCA in patients with severe hepatic cirrhosis has not been studied. Avoid use of ASCIRCA. Visual Loss: Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such loss of vision may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION). Prolonged Erection: There have been rare reports of prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, 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 emergency medical attention. ASCIRCA 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 an angulation or Peyronie’s disease). Effects on Bleeding: ASCIRCA is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ASCIRCA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ASCIRCA 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
- Visual loss
- Hearing loss
- Priapism

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of tadalfil. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ASCIRCA. They are not necessarily the result of a direct relationship to the use of PDE5 inhibitors or other factors. Adverse reactions are reported voluntarily from a population of uncertain size. It is not possible to 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 death, stroke, chest pain, palpitations, and tachycardia, have been reported in temporal association to the intake of PDE5 inhibitors. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because 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.

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 396 patients with PAH during clinical trials worldwide. In trials of ASCIRCA, 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 plasbo-controlled trial were 4% for ASCIRCA 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 ASCIRCA 40 mg was 4% compared to 5% in placebo-treated patients. In the placebo-controlled study, the incidence of AEs was generally transient and mild to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥2% of patients in the ASCIRCA 40 mg group and occurring more frequently than with placebo.

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combination of these factors, or to other factors.

**Ototologic:** — 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 also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events were related directly to the use of tadalafil, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or to other factors.

**Urological:** —Priapism.

### DRUG INTERACTIONS

Potential for Pharmacodynamic Interactions with 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** — PDE5 inhibitors, including ADCIRCA, and 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 have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin.

**Antihypertensives** — PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure–lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide/thiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo.

**Alcohol** — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure–lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

**Potential for Other Drugs to Affect ADCIRCA:**

**Ritonavir** — Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.

**Other Potent Inhibitors of CYP3A** — Tadalafil is metabolized predominantly by CYP3A4 in the liver. In patients taking potent inhibitors of CYP3A4 such as ketoconazole, anditraconazole, and use of ADCIRCA.

**Potent Inducers of CYP3A** — For patients chronically taking potent inducers of CYP3A4, such as rifampin, avoid use of ADCIRCA.

**Potential for ADCIRCA to Affect Other Drugs:**

Cytochrome P450 Substrates — Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan).

**Aspren** — Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin.

**P-lycoprotein** (e.g., digoxin) — Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

### USE IN SPECIFIC POPULATIONS

**Pregnancy:** Pregnancy Category B — Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.

**Non-teratogenic effects** — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

**Nursing Mothers:** It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness of ADCIRCA in pediatric patients have not been established.

**Geriatric Use:** Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.

**Renal Impairment:** For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC). limited clinical experience, and the lack of ability to influence clearance by dialysis.

**Hepatic Impairment:** Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients.

### OVERDOSAGE

Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination.

**Marketing by:** Lung Biotechnology Inc., a wholly-owned subsidiary of United Therapeutics Corporation

Rx only

www.adcirca.com


BS.HCP.KCGLUNGLLC-4-72.v2
**PHA Resources Notepad, a Tom Lantos Community Service Project**

These notepads were made so it is easier for you to tell patients about the resources the Pulmonary Hypertension Association has to offer. Intended to be used as part of a discharge packet, circle the parts of PHA’s website you are “prescribing” for your patient. Created by the Generation Hope Advisory Board and funded by the Tom Lantos Innovation in Community Service Award. To order, go to www.phassociation.org/Store/FreeMaterials.

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**GUEST EDITOR’S MEMO**

(continued from page 162)

Elsewhere in the issue, Victor Tapson, MD and Danny Ramzy, MD, PhD provide expert response to the question of management of right ventricular failure in the setting of pulmonary embolism. Our round table discussion among Drs Steven Mathai, Todd Bull, and Jeffrey Sager addressed additional controversial and difficult issues we often encounter with PAH patients in the ICU. Further, this issue’s PHPN section offers a “virtual roundtable” among expert members regarding pump issues as well as education regarding PAH needed by ICU nurses and staff. The patient perspective regarding Pulmonary Hypertension Care Centers is provided by Diana Ramirez and Laura Hoyt D’Anna, DPh.

Again, we would like to thank all of the authors and participants that worked so hard to make this issue successful. We would like to thank Myung Park for all of her work and commitment to this and all issues over the last two years. We also thank Deb McBride for her daily editorial management of the publication.

We hope you will find this issue of *Advances* to be a guide for all ICU clinicians on the evaluation and management of PAH/RV dysfunction in the ICU.

**Deborah J. Levine, MD**
Associate Professor
Lung Transplant Pulmonologist
Director of Pulmonary Hypertension Center
University of Texas Health Science Center at San Antonio
Indication

Orenitram is a prostacyclin vasodilator indicated for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%).

When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this. Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

Important Safety Information for Orenitram

CONTRAINDICATIONS

- Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C)

WARNINGS AND PRECAUTIONS

- Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms
- Orenitram inhibits platelet aggregation and increases the risk of bleeding
- Orenitram should not be taken with alcohol as release of treprostinil from the tablet may occur at a faster rate than intended
- The Orenitram tablet shell does not dissolve. In patients with diverticulosis (blind-end pouches), Orenitram tablets can lodge in a diverticulum

ADVERSE REACTIONS

- In the 12-week placebo-controlled monotherapy study, adverse reactions with rates at least 5% higher on Orenitram than on placebo included headache, diarrhea, nausea, flushing, pain in jaw, pain in extremity, hypokalemia, and abdominal discomfort

Please see brief summary of Full Prescribing Information on following page. For additional information about Orenitram, visit www.orenitram.com or call 1-877-UNITHER (1-877-864-8437).

INDICATIONS AND USAGE
Orenitram is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (73%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the effect seen in patients who received sildenafil. Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

CONTRAINDICATIONS
Severe hepatic impairment (Child Pugh Class C).

WARNINGS AND PRECAUTIONS
worsening PAH symptoms upon abrupt withdrawal
Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms.

Risk of Bleeding—Orenitram inhibits platelet aggregation and increases the risk of bleeding.

Increased exposure with Alcohol—Do not take Orenitram with alcohol as release of treprostinil from the tablet may occur at a faster rate than intended.

Use in Patients with Blind-end Pouches—The tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum.

ADVERSE REACTIONS
Clinical Trial 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 clinical practice. In a 12-week placebo-controlled study (Study 1; WHO Group 1; functional class II-III), the most commonly reported adverse reactions that occurred in patients receiving Orenitram included headache, nausea, and diarrhea. Table 1 lists the adverse reactions that occurred at a rate on Orenitram at least 5% higher than on placebo. Orenitram patients in Table 1 for Study 1 (N = 151) had access to 0.25 mg tablets at randomization. Approximately 91% of such patients experienced an adverse reaction, but only 4% discontinued therapy for an adverse reaction (compared to 3% receiving placebo). The overall discontinuation rate for any reason was 17% for active and 14% for placebo.

Orenitram was studied in a long-term, open-label extension study in which 824 patients were dosed for a mean duration of approximately 2 years. About 70% of patients continued treatment with Orenitram for at least 1 year. The mean dose was 4.2 mg BID at one year. The adverse reactions were similar to those observed in the placebo-controlled trials.

TABLE 1. Adverse Reactions with Rates at Least 5% Higher on Orenitram Monotherapy than on Placebo

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Orenitram (N=151)</th>
<th>Placebo (N=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>63%</td>
<td>19%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30%</td>
<td>16%</td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
<td>18%</td>
</tr>
<tr>
<td>Flushing</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>Pain in jaw</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 1. Adverse Reactions with Rates at Least 5% Higher on Orenitram Monotherapy than on Placebo

No treprostinil treatment related effects on labor and delivery were seen in animal studies.

Nursing Mothers—It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

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

Patients with Hepatic Impairment—Plasma clearance of treprostinil is reduced in patients with hepatic insufficiency. Patients with hepatic insufficiency may therefore be at increased risk of dose-dependent adverse reactions because of an increase in systemic exposure. Titrate slowly in patients with hepatic insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic function. In patients with mild hepatic impairment (Child Pugh Class A) start at 0.125 mg BID with 0.125 mg BID dose increments every 3 to 4 days. Avoid use of Orenitram in patients with moderate hepatic impairment (Child Pugh Class B). Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C).

Patients with Renal Impairment—No dose adjustments are required in patients with renal impairment. Orenitram is not removed by dialysis.

OVERDOSAGE
Signs and symptoms of overdose with Orenitram during clinical trials reflect its dose-limiting pharmacologic effects and include severe headache, nausea, vomiting, diarrhea, and hypotension. Treat supportively.

United Therapeutics Corporation, Research Triangle Park, NC 27709
Rx only
October 2014
www.orenitram.com
Stimulating

**Soluble Guanylate Cyclase**

What could Adempas mean to your patients?

**INDICATIONS**
- Adempas (riociguat) tablets are indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

*Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

**IMPORTANT SAFETY INFORMATION**

**WARNING: EMBRYO-FETAL TOXICITY**
Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.
Adempas could mean moving from the couch to the kitchen

Patients walked farther with Adempas at Week 12: results from Week 2 onward

36m improvement (mean) in 6-minute walk distance (6MWD) over placebo at Week 12 (95% Confidence Interval (CI): 20m-52m; p<0.0001) for PAH (WHO Group 1) patients.

WHO FUNCTIONAL CLASS

50% more PAH patients improved WHO Functional Class vs placebo (p=0.0033; Adempas: n=53/254 [21%], placebo: n=18/125 [14%]) at Week 12.

PATIENT: 443 PAH patients were studied. (Adempas 2.5 mg n=254, 1.5 mg n=63, placebo n=126)
Baseline characteristics:
- PAH defined as: pulmonary vascular resistance (PVR) > 300 dyn·sec·cm⁻¹, mean pulmonary arterial pressure (mPAP) > 25 mm Hg
- Mean age: 51 years (approximately 80% female)
- PAH etiologies: idiopathic (61%), familial (2%), associated with connective tissue disease (25%), congenital heart disease (8%), portal hypertension (3%), or anorexigen or amphetamine use (1%)
- Mean 6MWD was 363m
- Concomitant medications: Oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed

CONTRAINDICATIONS

Adempas is contraindicated in:
- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite)
- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.
Patients walked farther with Adempas at Week 16: results from Week 2 onward

46m improvement (mean) in 6MWD over placebo at Week 16
(95% CI: 25m-67m; p<0.0001) for CTEPH* (WHO Group 4) patients.

WHO FUNCTIONAL CLASS

<table>
<thead>
<tr>
<th>Status</th>
<th>Patients with Adempas</th>
<th>Patients with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability</td>
<td>52% (n=89/173)</td>
<td>74% (n=66/89)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>4% (n=6/173)</td>
<td>2% (n=2/89)</td>
</tr>
</tbody>
</table>

Patient population was: 72% inoperable by pulmonary endarterectomy (PEA) (pulmonary vascular resistance [PVR] >300 dyn·sec·cm⁻² and mean pulmonary arterial pressure >25 mm Hg measured at least 90 days after the start of full anticoagulation); 28% recurrent or persisting pulmonary hypertension (PH) following PEA (PVR >300 dyn·sec·cm⁻² measured at least 180 days following PEA). The majority of patients were WHO Functional Class II (31%) or III (64%) at baseline. Patients with systolic blood pressure <95 mm Hg were excluded.

WARNINGS AND PRECAUTIONS

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas REMS program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.
More than 90% of Adempas patients survived at 2 years*

*Data from CHEST-2 and PATENT-2 open-label extension studies. Without a control group, these data must be interpreted cautiously.

WARNINGS AND PRECAUTIONS

**Hypotension.** Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

**Bleeding.** In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemeses, and intra-abdominal hemorrhage.

**Pulmonary Veno-Occlusive Disease.** Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and if confirmed, discontinue treatment with Adempas.

MOST COMMON ADVERSE REACTIONS

- The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).

- Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For important risk and use information, please see the Brief Summary of the full Prescribing Information, including Boxed Warning, on the next page.

Visit Adempas-US.com for more information

FOR PAH, FOR CTEPH.
ADEMPAS (riociguat) tablets, for oral use

Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)
- Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 2.5, 5.2, 8.6)
- For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2)

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class [see Clinical Studies (14.1)].

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class II–IV, and to delay clinical worsening. Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies established effectiveness included predominately patients with WHO functional class II–IV, and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) [see Clinical Studies (14.2)].

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant following:

- Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 2.5, 5.2, 8.6)
- For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2)

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program [see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)].

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program [see Warnings and Precautions (5.1)]. Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- For all patients of reproductive potential, must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one patient with an fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:
- Embryo-Fetal Toxicity [see Warnings and Precautions (5.1)]
- Hypotension [see Warnings and Precautions (5.3)]
- Bleeding [see Warnings and Precautions (5.4)]

6.1 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.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naïve or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years [See Clinical Studies (14.1, 14.2)].

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naïve or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Adempas % (n=490)</th>
<th>Placebo % (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Dyspepsia and Gastritis</td>
<td>21 8</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Anemia (including laboratory parameters)</td>
<td>5 2</td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension [see Contraindications (4.2) and Clinical Pharmacology (12.2)].

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension [see Contraindications (4.3) and Clinical Pharmacology (12.2)]. Clinical experience with co-administration of Adempas and
other phosphodiesterase inhibitors (for example, milrinone, cilostazol, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Adempas concentrations in smokers are reduced by 50%-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antifungals (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) may increase riociguat exposure and result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat [see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John’s Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered [see Clinical Pharmacology (12.3)].

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and there are no adequate and well-controlled studies in humans. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [see Boxed Warning and Contraindications (4.1)].

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established [see Nonclinical Toxicology (13.2)].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over [see Clinical Studies (14)]. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas [see Clinical Pharmacology (12.3)].

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, and may during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after discontinuation of treatment with Adempas. Patients may choose one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner’s vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning].

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis [see Clinical Pharmacology (12.3)].

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]. Instruct females of reproductive potential to use effective contraception and to contact their physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program [see Warnings and Precautions (5.2)]. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

• All female patients must sign an enrollment form.
• Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
• Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
• Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

• Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
• Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
• Instruct patients on the dosing, titration, and maintenance of Adempas.
• Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
• Advise patients that antacids should not be taken within 1 hour of taking Adempas.
• Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines [see Adverse Reactions (6.1)]. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.
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- Share your expertise or benefit from someone else’s through the PHPN Mentor Program.
- Stay informed with free copies of:
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  - *Pulmonary Hypertension: A Patient’s Survival Guide*, a soup-to-nuts guide answering many of the questions patients and their loved ones have about living with pulmonary hypertension;
  - *PH Roundup*, PHA’s monthly e-newsletter highlighting the current PH opportunities and findings in the field.
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Building Medical Education in PH
A Partnership Initiative to Advance Medical Understanding of Pulmonary Hypertension

Building Medical Education in PH (BME) events are designed to foster partnerships between PHA, PH Centers and medical professionals. The program promotes continued education in the field of PH through CEU/CME educational events.

Participating in PHA’s BME program can benefit your event by providing you with:

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- Advertising support through PHA’s publications and online communities
- Complimentary print and multimedia educational materials for distribution to attendees
- PHA staff to exhibit and/or speak at event (pending invitation and availability)

To partner with PHA in Building Medical Education in PH for your upcoming CME event, please contact 301-565-3004 x776 or BME@PHAssociation.org.

To learn more about this partnership, visit www.PHAssociation.org/ BME

To view a full list of education opportunities for medical professionals, visit: www.PHAOnlineUniv.org/ Calendar

Healthcare Professionals Needed to Advocate for Improved Patient Care

On Thursday, Sept. 17, PHA’s PH Professional Network Symposium will kick-off with PHPN Advocacy Day on Capitol Hill. This is a rare, critical opportunity for healthcare professionals to represent the needs of PH patients before congress.

PHPN Advocacy Day to Focus on Access to Treatment

This year, Advocacy Day participants will focus on ensuring that PHers have access to the treatment their physician thinks is best for them. Advocates will talk with legislators about the burden created by fail-first policies, high co-insurance and other treatment barriers.

Encourage Your Team to Join PHA for this Free Event, Thursday, Sept. 17

PHA PHPN Advocacy Day is free and open to all. No previous advocacy experience is needed. Signing up is as simple as checking the Advocacy Day box on the PHPN Symposium registration form.

For more information, visit www.PHAssociation.org/Symposium/AdvocacyDay.
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For more information on support groups or to request PHA materials for your office, contact Debbie Drell at DebbieD@PHAssociation.org or 301-565-3004 x755.
Program Announcement:

New Application Deadline: June 12, 2015
New Application Deadline: October 12, 2015
Resubmission Deadline: July 12, 2015
Resubmission Deadline: November 12, 2015

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

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

**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.

**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.

Learn about all of PHA’s research opportunities at www.PHAssociation.org/MedicalProfessionals/PHAResearchProgram

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