The Role of Exercise in PH
The Scientific Leadership Council of the Pulmonary Hypertension Association

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**Program Description**

The mission of Advances in Pulmonary Hypertension is to serve as the premiere forum for state of the art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension. The 2008 Dana Point revision of the World Health Organization Classification serves as a guide to categories of pulmonary hypertension addressed in Advances in Pulmonary Hypertension. While focusing on WHO Group I PAH, the other categories (Group II, pulmonary venous hypertension; Group III, associated with chronic lung disease and/or hypoxemia; Group IV, pulmonary embolic hypertension; Group V, miscellaneous) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions. In addition, a special section in selected issues entitled “Profiles in Pulmonary Hypertension” recognizes major contributors to the field and serves as an inspiration to the PH community to cure pulmonary hypertension.

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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 www.PHAAssociation.org/SLC/
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Advances in Pulmonary Hypertension: Author Guidelines

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
- Articles with original data
- Case reports
- Reviews of current topics

Full-length manuscripts should not exceed 4,000 words including references. Each figure should be accompanied by a figure legend. Figures 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. Figure legends should be placed in parenthetical context at the end of the relevant sentence. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with AHA style.

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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. Disclosure forms can be downloaded from the PHA Web site, www.PHAssociation.org.

Checklist

Authors should be certain to include the following with the manuscript:

1. Title page listing all authors with their academic degrees 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
Exercising Our Resources About PH

The topic of exercise as it relates to pulmonary vascular disease is a critical one. As we all know, most of the symptoms of pulmonary hypertension occur not at rest, but during exertion. Yet, most of what we know about the pathophysiology of pulmonary hypertension is based on resting hemodynamics.

I would like to now provide a shameless plug. In the Pulmonary and Critical Care Unit at Massachusetts General Hospital (MGH), my professional home for the past 9 months, we have a cardiopulmonary exercise laboratory that is, in my humble opinion, without equal. We have the ability to completely describe the cardiovascular and pulmonary pathophysiology of exercise intolerance. Through integrated measurements of hemodynamics, ventilatory equivalents, and cardiac function, the cause of unexplained dyspnea can almost always be determined.

So, when we decided to devote an issue of Advances to exercise and PH, I immediately approached my colleagues, Drs. David Systrom and Greg Lewis, Director and Associate Director of the Exercise Physiology Lab at MGH. David and Dr. Will Oldham, a Pulmonary and Critical Care Fellow in the combined Harvard program, have written a useful description of the technical aspects of performing exercise physiology studies and provided some case studies in which cardiopulmonary exercise testing was diagnostic.

Greg has contributed a comprehensive review of the topic of exercise induced pulmonary hypertension. Although an elevated pulmonary arterial pressure during exercise has been removed from the definition of pulmonary hypertension, I think you will agree it is still an important finding that deserves further study. Greg’s article truly is a state-of-the-art review of the topic.

Two of my good colleagues, Drs. Charles Burger of Mayo Clinic Jacksonville and Sonja Bartolome of UT Southwestern, have rounded out this issue by addressing 2 additional important topics. Charles has written a review of the 6-minute hall walk test. This simple measure of exercise capacity, although not as “cool” as the Level 3 exercise studies described by my MGH colleagues, turns out to be powerful in its own right as an easy to perform and prognostically robust tool.

Finally, Sonja has reviewed the therapeutic effects of exercise and pulmonary rehabilitation in patients with pulmonary hypertension, an area in which our thinking has evolved considerably. We no longer view exercise as “contraindicated” in our patients and, in fact, data are emerging to suggest great benefits to pulmonary rehab in PAH patients.

It was a pleasure editing this issue and I look forward to any feedback you have regarding this or any other topic related to Advances.

Richard Channick, MD
Editor-in-Chief

Watch for Upcoming Issues of Advances in Pulmonary Hypertension

Autumn 2010: Inflammation and Growth Factors in PAH: PHA’s 9th International Pulmonary Hypertension Scientific Sessions, guest edited by Karen A. Fagan, MD

Winter 2011: Ethical Considerations in Pulmonary Hypertension, guest edited by Harrison Farber, MD

Spring 2011: WHO Group 2: Pulmonary Hypertension Owing to Left Heart Disease, guest edited by Myung Park, MD
Our Commitment to Patients Continues
INDICATION: LETAIRIS is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

Clinical worsening is defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape.¹

Early escape criteria were two or more of the following after a minimum treatment period of 4 weeks: ≥20% decrease in 6-minute walk distance; worsening WHO functional class; worsening right ventricular failure; rapidly progressing cardiac, hepatic, or renal failure; and refractory systolic hypotension <85 mm Hg.¹,²

IMPORTANT SAFETY INFORMATION

WARNINGS: POTENTIAL LIVER INJURY AND CONTRAINDICATION IN PREGNANCY

See full prescribing information for complete boxed WARNINGS

- Elevations of liver aminotransferases (ALT, AST) have been reported with LETAIRIS and serious liver injury has been reported with related drugs
- Monitor liver aminotransferases monthly and discontinue LETAIRIS if >5× ULN or if elevations are accompanied by bilirubin >2× ULN or by signs or symptoms of liver dysfunction
- May cause fetal harm if taken during pregnancy
- Must exclude pregnancy before the start of treatment
- Prevent pregnancy during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is needed

Important safety information regarding hepatotoxicity

LETAIRIS is not recommended in patients with elevated aminotransferases (>3× ULN) at baseline because monitoring liver injury may be more difficult. If aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, itching, or jaundice) or increases in bilirubin >2× ULN, LETAIRIS treatment should be stopped. There is no experience with the reintroduction of LETAIRIS in these circumstances.

In the postmarketing period, at least one patient receiving another ERA developed pronounced elevations in aminotransferases and bilirubin levels with long-term use (>20 months), reinforcing the importance of monthly liver monitoring for the duration of treatment.¹

Contraindication

- Do not administer LETAIRIS to a pregnant woman because it can cause fetal harm
LET AIRIS offers

Simple dosing

LET AIRIS is the only ERA administered as one pill, once a day1

Two therapeutically effective doses—5 mg and 10 mg tablets1

• Tablets should not be split, crushed, or chewed
• Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg if 5 mg is tolerated
• Treat women of childbearing potential only after a negative pregnancy test, and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests
• Liver function testing is required prior to treatment and at least every month thereafter; not recommended in patients with moderate or severe hepatic impairment

Reliable improvements

Up to +59 m placebo-adjusted mean change from baseline in 6MWD at 12 weeks with LET AIRIS*1

• LET AIRIS was studied in two 12-week, randomized, double-blind, placebo-controlled, multicenter studies (ARIES-1, N=201, and ARIES-2, N=192); 6MWD was the primary endpoint. Baseline mean 6MWD was 341 ± 76 m in ARIES-1 and 348 ± 84 m in ARIES-2.2
  —ARIES-1: +51 m (10 mg, p<0.001) and +31 m (5 mg, p=0.008)
  —ARIES-2: +59 m (5 mg, p<0.001)
• In both studies, LET AIRIS or placebo was added to current therapy, which could have included a combination of anticoagulants, diuretics, calcium channel blockers, or digoxin, but not epoprostenol, treprostinil, iloprost, bosentan, or sildenafil

Manageable program for liver function monitoring

Because of the risk of liver aminotransferase (ALT/AST) elevations to at least 3× ULN, liver function testing is required prior to initiation of treatment and at least every month thereafter. LET AIRIS treatment was associated with aminotransferase elevations >3× ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations >3× ULN has been accompanied by bilirubin elevations ≥2× ULN.

• Only LEAP offers LabSync—a program that helps coordinate monthly testing for healthcare professionals and patients enrolled in LEAP

because every day matters
LETAIRIS® (ambrisentan) 5 mg and 10 mg Tablets

Brief summary of full prescribing information. See full prescribing information. Rx only.

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to >10× upper limit of normal (ULN) and bilirubin to >2× ULN in patients with pulmonary arterial hypertension (PAH). Liver function tests should be measured prior to initiation of treatment with LETAIRIS and periodically during the course of treatment. In patients treated with LETAIRIS for up to 1 year, decreases in the aminotransferase levels were observed in clinical studies with LETAIRIS. These decreases were most often accompanied by elevated bilirubin levels.

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INDICATIONS AND USAGE: LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (PAH) Group 1, in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

DOSAGE 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 be swallowed whole. The dose should be increased at intervals of no less than 2 weeks, up to a maximum daily dose of 10 mg once daily, and can be titrated up to 60 mg daily in other patients with pulmonary arterial hypertension (PAH).

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WARNINGS AND PRECAUTIONS: Potential Liver Injury (see BOXED WARNING): Treatment with endothelin receptor antagonists has been associated with liver injury. Liver function tests should be measured at baseline and periodically during the course of treatment. LETAIRIS is contraindicated in patients with a history of liver disease or who have had a previous episode of liver injury.

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CONTRAINDICATIONS: PREGNANCY

TERATOGENICITY is a class effect of endothelin receptor antagonists. Women of Childbearing Potential: If this drug is used during pregnancy, or if the patient becomes pregnant while receiving LETAIRIS, it is advisable to consider discontinuing LETAIRIS. In women of childbearing potential, LETAIRIS can cause elevation of liver aminotransferases (ALT and AST) and total bilirubin >2× ULN in at least 6% of patients receiving LETAIRIS. These decreases were most often accompanied by elevated bilirubin levels.

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DRUG INTERACTIONS: Drug interactions with LETAIRIS were evaluated in clinical studies with LETAIRIS. Ambrisentan is predominantly metabolized by the CYP3A4 isoenzyme, with minor contributions from the CYP2C9 isoenzyme. Ambrisentan is a substrate of the organic anion-transporting polypeptide 1B1 (OATP1B1) and is not a substrate of the organic cation transporter 2 (OCT2). Ambrisentan does not inhibit CYP3A, CYP2C9, or CYP2C19.

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ADVERSE REACTIONS: Clinical Trials Experience: Safety data for LETAIRIS were obtained from two 12-week, double-blind, placebo-controlled studies (ARIES-1 and ARIES-2) and four open-label, long-term extension studies: ARIES-1 (N=483 patients with PAH who were treated with doses of 1.25, 2.5, or 10 mg once daily. The exposure to LETAIRIS in these studies ranged from 1 day to 4 years (N=81 for at least 6 months and N=343 for at least 1 year). In ARIES-1 and ARIES-2, a total of 261 patients received LETAIRIS at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse events that occurred in >3% of the patients receiving LETAIRIS and were more frequent on LETAIRIS than placebo are shown in Table 1.

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IN PULMONARY ARTERIAL HYPERTENSION (PAH) NYHA CLASS III OR IV

SECOND WIND®

IN PAH

The only inhaled PAH therapy to demonstrate a spectrum of PAH efficacy

- Significant clinical improvement ($p=0.0033$)$^{1,2}$
- Significant functional class improvement ($p=0.03$)$^{1,2}$
- Significant hemodynamic improvement (PVR, CO, and mPAP; $p<0.001$)$^{1,2}$
- Significant 6MWD improvement ($p<0.01$)$^{1,2}$

Ventavis 20 mcg/mL: Higher concentration to give appropriate patients shorter treatment times*†

*The 20 mcg/mL concentration is intended for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times which could result in incomplete dosing. Ventavis 10 mcg/mL ampules are still available. Ventavis should be taken 6 to 9 times daily, at least 2 hours apart.†

†Data based on an in vitro study with a manually generated 28.3-L/min, 15-sec inhalation cycle breathing pattern.

AIR PIVOTAL TRIAL Randomized, double-blind, multicenter, placebo-controlled trial to evaluate the efficacy and safety of Ventavis monotherapy in the treatment of PAH (WHO Group I) NYHA Class III or IV (n=146). Clinical improvement is a combined endpoint defined as ≥10% increase in 6MWD, improvement in NYHA functional class, and lack of clinical deterioration or death.$^{1,2}$

IMPORTANT SAFETY INFORMATION: In clinical studies, common adverse reactions due to Ventavis included vasodilation (flushing), cough, headache, trismus, and insomnia. Serious adverse events reported at a rate of less than 3% included congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure. Vital signs should be monitored while initiating Ventavis. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mmHg. Stop Ventavis immediately if signs of pulmonary edema occur; this may be a sign of pulmonary venous hypertension.

Please see brief summary of full prescribing information on adjacent page.
**INDICATIONS AND USAGE**

Ventavis is indicated for the treatment of pulmonary arterial hypertension (WHO Group II) in patients with NYHA Class III or IV symptoms. In controlled trials, it improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration (see CLINICAL PHARMACOLOGY, Clinical Trials section of Full Prescribing Information).

**CONTRAINDICATIONS**

There are no known contraindications.

**WARNINGS**

Ventavis is intended for inhalation administration only via either of two pulmonary drug delivery devices: the I-neb® AAD® System or the Prodose® AAD® System (see DOSAGE AND ADMINISTRATION section of Full Prescribing Information). It has not been studied with any other nebulizers.

**VITAL SIGNS**

Vital signs should be monitored while initiating Ventavis. In patients with low systemic blood pressure, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mmHg. Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of syncope. Syncope can also occur in association with pulmonary arterial hypertension, particularly in association with physical exertion. The occurrence of exertional syncope may reflect a therapeutic gap or insufficient efficacy, and the need to adjust dose or change therapy should be considered.

**SIDE EFFECTS**

Should signs of pulmonary edema occur when inhaled iloprost is administered in patients with pulmonary hypertension, the treatment should be stopped immediately. This may be a sign of pulmonary venous hypertension.

**PRECAUTIONS**

**General**

Ventavis solution should not be allowed to come into contact with the skin or eyes; oral ingestion of Ventavis solution should be avoided. Direct mixing of Ventavis with other medications in the I-neb® AAD® System or the Prodose® AAD® System has not been evaluated.

Ventavis inhalation can induce bronchospasm, especially in susceptible patients with hyperreactive airways. Ventavis has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections. Such patients should be carefully monitored during therapy with Ventavis.

**Information for Patients**

Patients receiving Ventavis should be advised to use the drug only as prescribed with either of two pulmonary drug delivery devices: the I-neb® AAD® System, following the manufacturer’s instructions (see DOSAGE AND ADMINISTRATION section of Full Prescribing Information). Patients should be trained in proper administration techniques including dosing frequency, ampule dispensing, I-neb® AAD® System operation, and equipment cleaning.

Patients should be advised that they may have a fall in blood pressure with Ventavis, so they may become dizzy or even faint. They should stand up slowly when they get out of a chair or bed. If fainting gets worse, patients should consult their physicians about dose adjustment.

Patients should be advised that Ventavis should be inhaled at intervals of not less than 2 hours and that the acute benefits of therapy are typically noted within 15 minutes. They should stand up slowly when they get out of a chair or bed. If fainting gets worse, patients should consult their physicians about dose adjustment.

**Drug Interactions**

In studies in normal volunteers, there was no pharmacodynamic interaction between inhaled iloprost and either nifedipine, dilazep, or captopril. However, iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. Since iloprost inhibits platelet function, there is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants. During clinical trials, iloprost was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory agents, corticosteroids, and other medications. Intravenous infusion of iloprost had no effect on the pharmacokinetics of digoxin. Acetylsalicylic acid did not alter the clearance (pharmacokinetics) of iloprost. Although clinical studies have not been conducted, in vitro studies of iloprost indicate that no relevant inhibition of cytochrome P450 drug metabolism would be expected.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Iloprost was not mutagenic in bacterial and mammalian cells in the presence or absence of extrinsic metabolic activation. Iloprost did not cause chromosomal aberrations in vivo in human lymphocytes and was not clastogenic in vivo in NMR/SSP mice. There was no evidence of a tumorigenic effect of iloprost at therapeutic (13% iloprost by weight) in Sprague-Dawley rats dosed orally for up to 8 months at doses of up to 125 mg/kg/day (Cmax of 45 ng/mL serum), followed by 16 months at 100 mg/kg/day, or in CD-1® (ICR) albino mice dosed orally for up to 24 months at doses of up to 125 mg/kg/day (Cmax of 156 ng/mL serum). The recommended clinical dosage regimen for iloprost (5 mcg) affords a serum Cmax of 0.16 ng/mL. Fertility of males or females was not impaired in Han-Wistar rats at in vivo rates of up to 1 mcg/kg/day.

**Pregnancy**

**Pregnancy Category C** In developmental toxicity studies in pregnant Han-Wistar rats, continuous intravenous administration of iloprost at a dosage of 0.01 mg/kg/day (serum levels not available) led to shortened gestation of the thalamic and ependymal tissues and pup size in comparable studies in pregnant Sprague-Dawley rats which received iloprost clathrate (13% iloprost by weight) orally at dosages of up to 50 mg/kg/day (Cmax of 88 ng/mL), in pregnant rabbits at intravenous dosages of up to 0.5 mg/kg/day (Cmax of 88 ng/mL), and in pregnant monkeys at dosages of up to 0.14 mg/kg/day (serum 1 ng/mL), to such digital anomalies or other gross structural abnormalities were observed in the fetuses/pups. However, in gravid Sprague-Dawley rats, iloprost-clathrate (13% iloprost) significantly increased the number of non-viable fetuses at a maternally toxic oral dosage of 250 mg/kg/day and in Han-Wistar rats was found to be embryotoxic at 15 of 44 litters at an intravenous dosage of 1 mg/kg/day. There are no adequate and well-controlled studies in pregnant women. Ventavis should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

It is not known whether Ventavis is excreted in human milk. In studies with Han-Wistar rats, higher mortality was observed in pups of lactating dams receiving iloprost intravenously at 1 mg/kg/day. In Sprague-Dawley rats, higher mortality was also observed in nursing pups at a maternally toxic oral dosage of 250 mg/kg/day and in Han-Wistar rats was found to be embryotoxic. Iloprost at a dosage of 0.01 mg/kg/day (serum 1 ng/mL) is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Ventavis, a decision to discontinue nursing should be made, taking into account the importance of the drug to the mother.**

**Pediatric Use**

Safety and efficacy in pediatric patients have not been established.

**Geriatric Use**

Clinical studies of Ventavis did not include sufficient numbers of subjects age 65 and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

**Hepatic or Renal Impairment**

Ventavis has not been studied in patients with pulmonary hypertension and hepatic or renal impairment, both of which increase the mean AUC in otherwise normal subjects (see CLINICAL PHARMACOLOGY, Special Populations section of Full Prescribing Information).

**ADVERSE REACTIONS**

**Pre-marketing experiences**

Pre-marketing safety data on Ventavis were obtained from 215 patients with pulmonary arterial hypertension receiving iloprost in 2-week clinical trials at two long-term (1 year) extensions. Patients received inhaled Ventavis for periods of from 1 day to more than 3 years. The median number of weeks of exposure was 15 weeks. Forty patients completed 12 months of open-label treatment with iloprost. Table 1 shows adverse events reported by at least 4 iloprost patients and reported at least 3% more frequently for iloprost patients than placebo patients in the 12-week placebo-controlled study.

**Overdose**

Ventavis is intended for inhalation administration only via either of two pulmonary drug delivery devices: the I-neb® AAD® System or the Prodose® AAD® System (see DOSAGE AND ADMINISTRATION section of Full Prescribing Information). It has not been studied with any other nebulizers.

**ADVERSE REACTIONS**

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Table 1 shows adverse events reported by at least 4 iloprost patients and reported at least 3% more frequently for iloprost patients than placebo patients in the 12-week placebo-controlled study.

Pre-marketing serious adverse events reported with the use of inhaled iloprost and not shown in Table 2 include congestive heart failure, chest pain, supraventricular tachycardia, dyspepsia, peripheral edema, and kidney failure.

In a small clinical trial (the STEP trial, see CLINICAL TRIALS section of Full Prescribing Information), the frequency of new cases of cardiac conduction disturbances receiving concomitant bosentan and iloprost was consistent with those observed in the larger experience of the Phase 3 study in patients receiving only iloprost.

**Adverse events with higher doses**

In a study in healthy volunteers (n=160), inhaled doses of iloprost solution were given every 2 hours, beginning with 5 mcg and increasing up to 20 mcg for a total of 6 dose inhalations (total cumulative dose of 70 mcg) or up to the highest dose tolerated in a subgroup of 40 volunteers. There were 13 subjects (32%) who failed to reach the highest scheduled dose (20 mcg). Five were unable to increase the dose because of [id] to moderate] transient chest pain/discomfort, tightness, usually accompanied by headache, nausea, and diaphoresis. The remaining 8 subjects discontinued for other reasons.

**POSTMARKETING EXPERIENCE**

The following adverse reactions have been identified during the postapproval use of Ventavis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cases of bronchospasm and wheezing have been reported, particularly in susceptible patients with hyperreactive airways, such as patients with comorbid diseases affecting the airways (see PRECAUTIONS). Cases of epistaxis and gingival bleeding have been reported within one month of starting iloprost treatment. Cases of dizziness and diaphoresis have also been reported with the use of Ventavis.

**OVERDOSAGE**

In clinical trials of Ventavis, no case of overdose was reported. Signs and symptoms to be anticipated are extensions of the dose-limiting pharmacological effects, including hypotension, headache, flushing, nausea, vomiting, and diarrhea. A specific antidote is not known.

Interruption of the inhalation session, monitoring, and symptomatic measures are recommended.

**Distributed by:**

5000 Shoreline Court, Ste. 200, South San Francisco, CA 94080
August 2009

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Indication
REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

Important Safety Information
Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α-blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

Patients with the following characteristics did not participate in the preapproval clinical trial: patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months, unstable angina, hypertension (BP >170/110), retinitis pigmentosa, or patients on bosentan. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

Did you know REVATIO samples are just a phone call away?

Order REVATIO Starter Samples by phone
Contact the REVATIO Sample Fulfillment Program by calling 1-866-833-9559

Please see Brief Summary of Prescribing Information on the following pages.
www.REVATIO.com
REVATIO® (SILDENAFIL)  
Brief Summary of Prescribing Information  
INDICATIONS AND USAGE: REVATIO® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. The decision in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Limitation of Use  
The efficacy of REVATIO has not been adequately evaluated in patients taking bosantan concurrently.

DOSE AND ADMINISTRATION  
Pulmonary Arterial Hypertension (PAH)  
REVATIO Tablets  
The recommended dose of REVATIO is 20 mg three times a day (TID). REVATIO tablets should be taken approximately 4-6 hours apart, with or without food. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended. Dosages lower than 20 mg TID were not tested. Whether dosages lower than 20 mg TID are effective is not known.

REVATIO Injection  
REVATIO injection is for the continued treatment of patients with pulmonary arterial hypertension (PAH) who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication.

The recommended dose is 10 mg (corresponding to 12.5 mL) administered as an intravenous bolus injection three times a day. The dose of REVATIO injection does not need to be adjusted for body weight. A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of sildenafil and its N-des-methyl metabolite equivalent to that of a 20 mg oral dose.

CONTRAINDICATIONS  
Use with Organic Nitrates  
Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Hypersensitivity Reactions  
REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any component of the tablet.

Rare cases of hypersensitivity have been reported in association with the use of sildenafil including anaphylactic reaction/shock events and anaphylactoid reaction. The majority of reported events were non-serious hypersensitivity reactions.

WARNINGS AND PRECAUTIONS  
Cardiovascular Effects  
REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients with resting hypotension [BP < 90/50], fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction).

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

As there are no controlled clinical data on the safety or efficacy of REVATIO in the following groups, prescribe with caution for:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with coronary artery disease causing unstable angina;
- Patients with hypertension (BP > 170/110);
- Patients currently on bosantan therapy.

Use with Alpha-blockers  
PDE5 inhibitors, including sildenafil, 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. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported (see Drug Interactions). No cases of syncope or fainting were reported during these interaction studies. The safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

Effects on Bleeding  
In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans. The incidence of epistaxis was 13% in patients taking sildenafil with PAH secondary to connective tissue disease (CTD). This effect was not seen in primary pulmonary hypertension (PPH) (sildenafil 1%, placebo 2%) patients. The incidence of epistaxis was also higher in sildenafil-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Use with Ritonavir and Other Potent CYP3A Inhibitors  
The concomitant administration of the proton pump inhibitor omeprazole (a highly potent CYP3A inhibitor) substantially increases serum concentrations of sildenafil. Therefore, co-administration of omeprazole or other potent CYP3A inhibitors with REVATIO is not recommended.

Effects on the Eye  
Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE5 inhibitors, including REVATIO. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported postmarketing in temporal association with the use of all PDE5 inhibitors, including sildenafil, when used in the treatment of erectile dysfunction. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

The majority of adverse events associated with the use of PDE5 inhibitors, including sildenafil,regardless of whether the vision change was unilateral or bilateral, have been transient or non-sight-threatening.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Impairment  
Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

Combination with other PDE5 inhibitors  
Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

Prolonged Erection  
Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukaemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

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

- Hypotension [see Warnings and Precautions]
- Vision loss [see Warnings and Precautions]
- Hearing loss [see Warnings and Precautions]
- Priapism [see Warnings and Precautions]

Clinical Trials Experience  
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data were obtained from the 12-week, placebo-controlled clinical study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg TID were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg TID was 3% and was the same for the placebo group. In the placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg TID) and were more frequent in REVATIO patients than placebo patients, are shown in Table 1. Adverse events were generally transient and mild to moderate in nature.

Table 1. REVATIO All Causality Adverse Events in ≥ 3% of Patients and More Frequent (> 1%) than Placebo

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n=70)</th>
<th>REVATIO 20 mg TID (n=69)</th>
<th>Placebo-Subtracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Flushing</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea exacerbated</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Rhinitis nos</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea nos</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Gastritis nos</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Table note:

- Not otherwise specified

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinting to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage in the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.
In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg TD and increased to 40 mg TD and then 80 mg TD), as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (>6% difference) are shown in Table 2.

Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (> 6%) than Placebo

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
<th>Placebo Epoprostenol (n = 131)</th>
<th>Revatio Epoprostenol (n = 134)</th>
<th>Placebo-Subtracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34</td>
<td>57</td>
<td>23</td>
</tr>
<tr>
<td>Edema</td>
<td>13</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

*includes peripheral edema

REVATIO injection

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting plasma concentrations between 10 and 500 ng/mL (up to 8 times the exposure of the recommended dose). Adverse events in PH patients were similar to those seen with oral tablets.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sildenafil (marketed for both HIV and erectile dysfunction), and in other studies of sildenafil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

Decreases in and Loss of Vision

When used to treat erectile dysfunction, non-arteriolar anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors [see Warnings and Precautions].

Loss of Hearing

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including REVATIO. In some of these 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 are related directly to the use of REVATIO, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or to other factors [see Warnings and Precautions].

Other Events

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Seizure, seizure recurrence

DRUG INTERACTIONS

Nitrates

Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

Ritonavir and other Potent CYP3A Inhibitors

Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended [see Warnings and Precautions].

Alpha-blockers

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects [see Warnings and Precautions].

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine

When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg TD. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis). There are, however, no adequate and well-controlled studies of sildenafil in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The safety and efficacy of REVATIO during labor and delivery has not been studied.

Nursing Mothers

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

Geriatric Use

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Renal Impairment

No dose adjustment is required (including severe impairment Clcr < 30 mL/min).

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased. In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for up to 24 months at doses that produced a systemic exposure (AUC) to unbound sildenafil of its major metabolite 33 and 37 times, for male and female rats respectively, the human exposure at the RHD of 20 mg TD. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m^2 basis. Sildenafil was negative in in vitro bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and in vitro human lymphocytes and in vivo mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 30 times for males and females, respectively, the human exposure at the RHD of 20 mg TD.

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction.
- Advise patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.
- Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of a sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

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S.P. Pharmaceuticals
Pulmonary Rehabilitation’s Role in Pulmonary Hypertension

Pulmonary rehabilitation (PR) should be considered an adjunct therapy for the pulmonary hypertension (PH) patient. The definition of PR published by the American Thoracic Society (ATS)/European Respiratory Society (ERS) in 2006 states: “Pulmonary rehabilitation is evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory disease who are symptomatic and often have decreased daily activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease.” This definition applies to the PH patient with the ultimate goal of optimizing his or her quality of life through assessment, education, and therapeutic exercise. The PH patient’s success in PR starts with a strong partnership between the referring PH clinic and the local PR program.

Pulmonary rehabilitation is not just exercise or education but must have the essential components including respiratory and nutritional assessment, education, therapeutic exercise, psychosocial intervention, and long-term adherence. In fact, the typical PR program may meet 3 times a week, over an 8-12 week period of time, include approximately 10 to 15 hours of education and 30 hours of therapeutic exercise. The commitment by the PH patient is great but so are the benefits. The success of the PR program is also measured by the strength of the PR’s medical director who guides the multidisciplinary team in evidence-based practice.

The PR goals for the PH patient are not that different from the goals of PH medical management: improve cardiovascular endurance, increase exercise performance, enhance ability to perform activities of daily living (ADL), improve quality of life, reduce hospitalizations, and decrease symptoms—especially dyspnea through breathing retraining and ensuring adequate oxygenation at rest and with activity.

The table lists the components of standard PR that should be addressed with the PH patient plus additional areas of concern for PH-specific PR. The initial assessment allows the PR program to develop an individualized treatment plan for the 40+ hours of PR treatment.

Pulmonary rehabilitation can play a critical role in optimizing the treatment and quality of life for the PH patient. Pulmonary rehabilitation should become a standard of medical care for the PH patient through collaboration with PH clinics.


References


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### Table: Comparison of PR and PH-Specific PR Components

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary Rehab</th>
<th>PH-Specific Pulmonary Rehab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessment</strong></td>
<td>H&amp;P</td>
<td>Evaluate symptoms (syncope, dizziness, palpitations, fatigue, chest pain, peripheral edema, blood pressure)</td>
</tr>
<tr>
<td></td>
<td>Diagnostic test review</td>
<td>Right heart catheterization hemodynamics</td>
</tr>
<tr>
<td></td>
<td>ADL critique</td>
<td>WHO Group diagnostic class</td>
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<td></td>
<td>Psychosocial evaluation</td>
<td>WHO Functional class</td>
</tr>
<tr>
<td></td>
<td>6-minute walk test</td>
<td>Sleep study and/or overnight oximetry</td>
</tr>
<tr>
<td></td>
<td>Goal development</td>
<td>Current PH drug treatment, delivery method, dose, expected side effects, back-up pumps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anticoagulation and INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung transplant candidacy status</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>Lung anatomy and physiology</td>
<td>Identify and self-monitor PH symptoms</td>
</tr>
<tr>
<td></td>
<td>Chronic lung diseases</td>
<td>Recognize symptom-limited exercise</td>
</tr>
<tr>
<td></td>
<td>Description and interpretation of diagnostic tests</td>
<td>Know signs of right heart failure</td>
</tr>
<tr>
<td></td>
<td>Breathing retraining</td>
<td>Avoid falls if on anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Bronchial hygiene</td>
<td>INR test results and frequency</td>
</tr>
<tr>
<td></td>
<td>Pulmonary medication use and side effects</td>
<td>Expected reaction to PH medications</td>
</tr>
<tr>
<td></td>
<td>Importance and benefits of supplemental oxygen therapy</td>
<td>Emergency procedures (pumps and lines)</td>
</tr>
<tr>
<td></td>
<td>Exercise principles</td>
<td>Heart catheterizations</td>
</tr>
<tr>
<td></td>
<td>Energy conservation and ADLs</td>
<td>Pregnancy risks</td>
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<tr>
<td></td>
<td>Nutrition</td>
<td>Lung transplantation</td>
</tr>
<tr>
<td></td>
<td>Coping</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Advance directives</td>
<td></td>
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<tr>
<td></td>
<td>Self assessment and symptom management to prevent exacerbations</td>
<td></td>
</tr>
<tr>
<td><strong>Psychosocial</strong></td>
<td>Coping strategies</td>
<td>Quality of life testing (eg, CAMPHOR)</td>
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<tr>
<td><strong>Interventions</strong></td>
<td>Depression management</td>
<td>Loss of job or income due to disability</td>
</tr>
<tr>
<td></td>
<td>Control of panic and anxiety</td>
<td>Family dynamics</td>
</tr>
<tr>
<td></td>
<td>Stress reduction</td>
<td>Pregnancy issues</td>
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<tr>
<td></td>
<td>Relaxation techniques</td>
<td>Impact of severe lung disease at relatively young age</td>
</tr>
<tr>
<td></td>
<td>Anger control</td>
<td>Genetic testing</td>
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<tr>
<td></td>
<td>Support systems, including caregiver/spouse issues</td>
<td>Lack of visible signs of illness</td>
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<td></td>
<td>Sexuality</td>
<td>Possible lung transplant evaluation</td>
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<tr>
<td></td>
<td>Modifying addictive behaviors</td>
<td></td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td>Quantify exercise capacity including functional status</td>
<td>PH PR exercise documentation form to include PH symptoms</td>
</tr>
<tr>
<td></td>
<td>Prescription for exercise training</td>
<td>Collaborative partnership with PH clinic and PR required to communicate concerns, issues, symptoms</td>
</tr>
<tr>
<td></td>
<td>Detect exercise-induced hypoxemia</td>
<td>How to exercise safely and overcome fear of exertion</td>
</tr>
<tr>
<td></td>
<td>Determine need for supplemental oxygen therapy, assessing type of portable system, delivery device (pulsed vs continuous) and liter flow rate, especially when high liter flows are required</td>
<td>Know the safety measures for lines/pumps with exercise equipment</td>
</tr>
<tr>
<td></td>
<td>Determine best home oxygen system to deliver adequate flow for safe home activity</td>
<td>Avoid exercises that increase intrathoracic pressure or valsalva maneuvers</td>
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<tr>
<td></td>
<td>Understand nonpulmonary limitations to exercise; ie, orthopedic, balance, fall risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetic patients must bring glucometer, diabetic medications, and snacks</td>
<td></td>
</tr>
<tr>
<td><strong>Long-term</strong></td>
<td>Disease management including a maintenance exercise program</td>
<td>PH medications will be needed for life</td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
<td>Schedule and keep pulmonary MD follow-up appointments</td>
<td>Attend PH support groups</td>
</tr>
<tr>
<td></td>
<td>Keep primary MD informed and updated on medical status</td>
<td>Treatment goals to prolong life, increase functional capacity and quality of life</td>
</tr>
<tr>
<td></td>
<td>Attend support and educational groups</td>
<td>Exercise with a partner or in a supervised setting, never alone</td>
</tr>
<tr>
<td></td>
<td>Be connected with the national association for your specific disease process</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbidites treated</td>
<td></td>
</tr>
</tbody>
</table>
You can help your patients be within that 30 percent.

**Quick Tip:**
Make notes in your patients’ medical records about their limitations in addition to the progress they’ve made. The Social Security Administration needs to see medical evidence that the applicant has limitations and what those limitations are.

Find more tips and resources for you and your patients at [www.PHAssociation.org/Patients/Insurance/Disability](http://www.PHAssociation.org/Patients/Insurance/Disability), including:
- A patient starter-kit with successful PH-based SSD applications to reference.
- An inside look at how the SSA views PH, including an educational video.
- A detailed outline of the disability process.

This study reports the observed survival of patients with idiopathic, familial (heritable), and anorexigen-associated pulmonary arterial hypertension (PAH) from the French Network on Pulmonary Hypertension. This registry draws from 17 pulmonary vascular centers in France. A total of 354 consecutive patients (56 incident, 298 prevalent) were enrolled from October 2002 to October 2003, and followed prospectively. Of the prevalent cases, only those with diagnosis less than 36 months from the time of enrollment were included in the survival analysis. The final cohort of 190 patients was followed for 3 years.

The baseline characteristics of the 190 patients revealed a mean age of 52.5; 63% were female. The majority of patients were in NYHA functional class III (68.4%). Only 17.4% were in either functional class I/II. PAH treatment was administered with the following distribution: epoprostenol 14.7%, bosentan 35.3%, sildenafil 21.2%, iloprost 21.2%, beraprost 2.6%, treprostinil 0.5%, combination 12.6%. PAH targeted therapy was observed in 76.8% of the cases. Conventional therapy, consisting of calcium channel blockade (13.8%) or patients unable to receive a PAH targeted agent, was observed in 29.5% of the cohort. Background therapy included: warfarin 90.5%, diuretics 69.5%, and oxygen 30.3%.

For the 190-patient cohort, survival at 1, 2, and 3 years was 82.9%, 67.1%, and 58.2%. These rates were roughly 10% higher than those estimated based on the NIH registry formula. Cox analysis found the following variables associated with improved survival: female gender, greater 6-minute walk distance (6MWD), lower right atrial pressure, and higher cardiac output. Although NYHA functional class I/II had a hazard ratio of 0.402, the 95% CI was 0.158-1.019 with a P value of 0.06. Specific cutoff or change in 6MWD or cardiac output was not reported, which correlated with improved outcome.

The authors concluded that this represented a “real-world” observational study on PAH survival (as opposed to formulary predictions) in the era of modern therapies. Although survival is better than predicted, incident cases of idiopathic, heritable, or anorexigen-associated PAH remains a progressive and often fatal disease. This observation, however, does not expand or elaborate on the seemingly low rate or timing of intravenous prostanoïd therapy. Also, with 21.4% of incident cases and 13.8% of combined cases receiving calcium channel blockade therapy, argument can be made that this cohort was a transition group over-represented with conventional therapy.


This report utilized data generated from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) to discern predictors of survival in pulmonary arterial hypertension (PAH). The currently available prognostic tool based on the original 1980s NIH Registry of Primary Pulmonary Hypertension has limitations when applied to other PAH subtypes and in the current era of multiple PAH targeted therapies.

This study analyzed data from 2716 registered patients from US treatment centers. These represent both prevalent (86.5%) and incident (13.5%) cases. The primary goal was to come up with predictors of 1-year survival. Based on the predictors, a formula was derived and presented for clinical application. Table 1 details the baseline characteristics of the 2716 patients at the time of enrollment into the registry. Mean age was 50. More female and Caucasian patients were represented—79% and 73% respectively. Nearly half of the patients were functional class III (48.2%) at the time of enrollment. Only 5.5% were functional class IV. Idiopathic PAH represented nearly half of all patients (46.5%). Connective tissue disease associated PAH was the second largest cohort, representing 23.9%. The distribution of PAH targeted therapies was relatively even across the 3 classes: prostacyclin analogs 41.6%, endothelin receptor antagonists 46.9%, and phosphodiesterase-5 inhibitors 49.6%. Combination therapy was being used in 40%; intravenous prostacyclin therapy was observed in 26.2%. Calcium channel
blockade therapy was observed in 9.2% as monotherapy, or 15.8% as combination therapy.

The observed 1-year survival was 91.0% (95% CI 89.9-92.1). Multivariable analysis identified several independent risk factors. Greater than 2-fold increase in mortality was associated with PAH associated with portal hypertension (HR 3.6, 95% CI 2.4-5.4), family history of PAH (HR 2.2, 95% CI 1.2-4.0), men >age 60 (HR 2.2, 95% CI 1.6-3.0), NYHA functional class III, resting systemic systolic blood pressure <110 mm Hg, resting heart rate >92 bpm, 6M WD <165 m, BNP >180 pg/mL, presence of pericardial effusion, predicted DLCO <32%, and mean right atrial pressure >20 mm Hg. Four variables associated with improved 1-year survival were: NYHA functional class I, 6M WD ≥440 m, BNP <50 pg/mL, and percent predicted DLCO ≥80%. The report discusses numerous other parameters that were not found to be independent risk factors by the current analysis.

The authors concluded that this study identified key predictors of survival leading to a contemporary prognostic equation for PAH. The authors acknowledged the potential survival bias by analyzing mostly prevalent cases (86.5%). They recommended ongoing reassessment and external validation of the observed predictors and the proposed equation. Whether the foreknowledge of these risk factors will alter outcome is unknown.
Program Overview
Pulmonary arterial hypertension (PAH), an incurable disease, is characterized by medial hypertrophy, intimal fibrosis, and in situ thrombi in small muscular pulmonary arteries. PAH was considered a rapidly fatal illness with a median survival of 2.8 years in the 1980s when no evidence-based therapies were available. Since then the treatment of this disease has made tremendous advances, and in the last 10 years the discovery of new medications have positively influenced the prognosis and survival of patients with PAH.

This self-study activity is based on 4 articles that review exercise and movement in pulmonary hypertension (PH). This activity is jointly sponsored by the University of Michigan Medical School and the Pulmonary Hypertension Association.

Target Audience
This self-study activity is appropriate for cardiologists, pulmonologists, rheumatologists, and other physicians who treat patients with PH.

Learning Objectives
Upon completion of this activity, participants will be able to:
1. Understand the diagnostic workup and clinical significance of exercise-induced PH
2. Discuss the performance and interpretation of a cardiopulmonary exercise test and its use in workup of the patient with suspected PH
3. Understand the use of 6-minute walk testing in evaluation and monitoring of patients with PAH
4. Describe the safety and efficacy of exercise training in patients with PAH

Self-Assessment Examination
See pages 116-117 for self-assessment questions, answer key, and evaluation form.

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Agenda
Pulmonary Vascular Response Patterns to Exercise
Gregory D. Lewis, MD
Cardiopulmonary Exercise Testing in the Evaluation of Unexplained Dyspnea
William M. Oldham, MD, PhD, and David M. Systrom, MD
6-Minute Walk Test Primer and Role in Pulmonary Arterial Hypertension
Charles D. Burger, MD, and Tonya Zeiger, RRT
Exercise Training and Pulmonary Rehabilitation in the Pulmonary Hypertension Patient
Sonja D. Bartolome, MD

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Michigan Medical School and the Pulmonary Hypertension Association. The University of Michigan is accredited by the ACCME to provide continuing medical education to physicians.

Credit Designation
The University of Michigan Medical School designates this activity for a maximum of 2.0 AMA PRA Category 1 Credits™. Physicians should claim credit commensurate with the extent of their participation in the activity.

Instructions for Earning Credit
This activity is a self-study program; a self-assessment examination is included on page 116 to help physicians review important points. A form is also included on page 117 for physicians to evaluate the CME activity. Completion of this activity involves reading the journal and completing the self-assessment examination and evaluation form, which may take up to 2 hours. Credits for this self-study program are available from August 31, 2010 through September 1, 2011. There is no fee for this program. Please note that this self-study program may also be viewed online at http://www.cme.med.umich.edu/

University of Michigan Privacy Statement
http://www.cme.med.umich.edu/privacy.asp

Oversight and Accreditation
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Disclosures
The Accreditation Council for Continuing Medical Education and the Association of American Colleges have standards and guidelines to ensure that individuals participating in CME activities are aware of relationships between authors and commercial companies that could potentially affect the information presented. To be disclosed to participants are all personal financial relationships with a commercial interest whose products are relevant to the content of this CME activity. The University of Michigan Medical School follows these national policies to ensure balance, independence, objectivity, and scientific rigor in all its CME activities. Each author was asked to complete a disclosure information form for this activity. Disclosures are reported below:

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Kevin Chan, MD, has received grant/research support from Alnylam Pharmaceuticals and Gilead.
Pulmonary Vascular Response Patterns to Exercise: Is There a Role for Pulmonary Arterial Pressure Assessment During Exercise in the Post-Dana Point Era?

Pulmonary hypertension (PH) is often diagnosed late in its course when it purports a particularly poor prognosis. Exercise effectively unmasks early forms of several cardiopulmonary diseases but the role of performing pulmonary arterial pressure measurements during exercise in the evaluation of PH remains unclear. Whether pulmonary arterial pressure-flow relationships during exercise may provide a window into earlier diagnosis of functionally significant pulmonary arterial hypertension and left ventricular dysfunction or add incrementally to our armamentarium of diagnostic tests and prognostic indicators in PH is the topic of active ongoing investigation. Evidence is emerging that abnormal pulmonary arterial pressure response patterns to exercise, when properly indexed to increased blood flow, may help to identify early forms of heart failure and pulmonary arterial hypertension. This article will discuss approaches to performing hemodynamic measurements during exercise as well as the potential clinical utility of identifying normal and abnormal pulmonary vascular response patterns to exercise.

Methods for Measurement of Pulmonary Hemodynamics During Exercise

Invasive Hemodynamic Measurements During Exercise

Right heart catheterization (RHC) with invasive hemodynamic monitoring is the gold standard for evaluating the pulmonary vasculature during exercise, as it is at rest. Exercise testing with invasive hemodynamic monitoring has been successfully performed using upright and supine cycle ergometry, leg presses, and treadmill protocols. A detailed description of methods utilized in our laboratory at Massachusetts General Hospital, where ~150 cardiopulmonary exercise studies with invasive hemodynamic measurements are performed annually, is described by Drs Oldham and Systrom in this issue of Advances in Pulmonary Hypertension (101–106).

Upright cycle ergometry offers the advantage of simulating upright posture employed in activities of daily living, while allowing precise continuous ramp incremental work and eliciting near maximum exercise capacity without excessive upper body movement during hemodynamic measurements. Multisite oxygen saturation measurements should be performed upon insertion of the right heart catheter if left-to-right shunting is suspected, particularly when measuring Fick cardiac outputs (CO) during exercise. High fidelity micromanometer-tipped catheters, which can be advanced via fluid filled catheters inserted for routine RHC, are preferred when available to maximize accuracy of pressure measurements. Pulmonary capillary wedge pressure (PCWP) should be verified based on characteristic waveforms, systemic oxygen saturation, and/or appearance on fluoroscopy. The critical extravascular closure pressure imposed by the lung parenchyma that contains the pulmonary vasculature is typically below that of the PCWP during exercise, and therefore PCWP can be used as the downstream pressure in order to determine transpulmonary pressure gradients (TPG = mPAP - PCWP) and pulmonary arterial pressure measurements during exercise in the evaluation of PH.

Key Words—cardiac output, exercise pulmonary artery pressure, heart failure with preserved ejection fraction, pulmonary capillary wedge pressure, pulmonary hemodynamics

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vascular resistance (PVR = TPG/CO). Care should be taken to maintain consistent upright posture relative to the leveled transducers throughout exercise. Serial measurements of mPAP, PCWP, and CO should be performed at regular intervals (ie, every minute) during incremental exercise to characterize pressure-flow relationships. In light of increased thoracic pressure changes with exercise, particularly in overweight or deconditioned patients, it is important to uniformly measure pressures at end-expiration, when intrathoracic pressure most closely approximates atmospheric pressure, in order to ensure consistency in data interpretation.

Assessment of exercise-induced increases in mPAP should be interpreted relative to increases in blood flow (ie, ΔPAP/ΔCO) and specific work rates rather than relying on a single absolute PAP threshold (ie, 30 mm Hg) or a peak exercise mPAP. Indexing changes in mPAP to work rate or changes in CO accounts for interindividual variability in peak exercise intensity levels achieved. Determination of relative contributions to exercise mPAP from increases in left sided hydrostatic pressure (ie, PCWP or LV end-diastolic pressure [LVEDP]) and precapillary PAP (ie, the transpulmonary gradient, [TPG]) is also critical in order to discern the etiology of exercise limitation.

Noninvasive Measurements During Exercise

Doppler echocardiography is increasingly utilized as a screening procedure for pulmonary arterial hypertension (PAH) and may be performed to estimate right ventricular systolic pressure (RVSP), which approximates systolic PAP (PASP) in the absence of pulmonary valve stenosis or RV outflow tract stenosis. One report found an excellent correlation between catheter-based and echocardiographic measurements obtained simultaneously during exercise (R = 0.98). Recently echocardiographic estimates of cardiac output and mPAP have been combined with reasonable approximation of normal exercise PAP-flow relationships in healthy individuals (Table 1).

However, tricuspid regurgitant velocity to estimate PASP is technically challenging to ascertain during exercise and both overestimation and underestimation of PASP have been reported to occur. In addition, exercise echocardiography has limited capacity to measure LV filling pressures during exercise in order to exclude the common condition of impaired LV filling mediating pulmonary venous hypertension during exercise. Exercise echocardiographic indices of RV structure and function play a very important role in characterizing PH, and emerging echo-based measurements such as strain-rate imaging, eccentricity, TDI indices, and TAPSE offer valuable information. Echocardiographic indices of RV function have not been widely validated during exercise. Therefore, further investigation is needed to determine if exercise echocardiography should be utilized in the evaluation of PH.

PULMONARY VASCULAR RESPONSES TO EXERCISE IN HEALTHY SUBJECTS

The relationship between PAP and blood flow during exercise in normal individuals and in patients with cardiopulmonary diseases was first reported by Drs. Hickam and Cargill in 1948, and was among the first observations in human cardiac catheterization. In 8 healthy subjects (age 23 ± 7 years) undergoing low-level supine leg press exercise (~20 watts) they observed a modest increase in mPAP (2 ± 2 mm Hg) in the context of a 3.5 ± 2.8 L increase in CO. Subsequent studies in healthy individuals have employed various exercise modalities, postures, and protocols resulting in widely variable absolute mPAP values achieved during exercise.

A recent meta-analysis was conducted that consisted of 47 studies describing 72 populations of healthy volunteers who underwent submaximal exercise with invasive measurement of PAP at rest and during exercise. Importantly, data were stratified by sex, age, type of exercise (ie, cycle ergometry, treadmill exercise), body position (upright vs supine), and exercise levels (slight, submaximal, and maximal). Normal resting mPAP was 14 ± 3 mm Hg. The upper limit of normal (ULN) was 21 mm Hg. During slight exercise, the mean and ULN for mPAP was 21 ± 7 and 33 (supine) and 20 ± 4 and 29 mm Hg (upright). During maximal exercise, the ULN was 37 (supine) and 35 mm Hg (upright).

The size of this study permitted several important observations regarding relationships between exercise PAP and potential covariates. Age ≥50 years was associated with slightly higher mPAP at rest (15 ± 4 mm Hg vs 13 ± 3 mm Hg in subjects <50 years old), and markedly higher mPAP during slight exercise (29 ± 8 vs 20 ± 5 mm Hg, P < 0.0001). Gender did not significantly influence resting or exercise mPAP and upright position was associated with a modest reduction in exercise mPAP and cardiac output along with increased heart rate. One limitation of this study was the lack of information about the influence of body mass index (BMI) on exercise PAP, due to the paucity of overweight and obese subjects studied. Population-based studies have indicated higher PASP in individuals with higher BMI, suggesting that exercise PAP relative to CO is likely to be greater in obese individuals.

In comparing studies of exercise pulmonary hemodynamics derived from heterogeneous exercise protocols and intensity levels, it is helpful to index exercise-induced increases in PAP to increases in blood flow (ie, ΔPAP/ΔCO, Table 1). Linear pressure-flow relationships have been observed across a wide range of flows in isolated lung preparations, intact animal models, and in the majority of humans who underwent serial PAP and CO measurements during exercise (Figure 1). Accordingly, an average PAP increment of ~1 mm Hg per liter of CO in young, healthy controls was evident in high intensity exercise protocols (240-276 W) and in protocols with lower intensity exercise (~20 W).

Early studies of pulmonary hemodynamics during exercise often did not measure exercise PCWP to permit assessment of postcapillary, LV hydrostatic pressure contributions to increases in exercise PAP. Studies in which serial measurements of mPAP and PCWP were performed during upright exercise in normal young individuals indicate a greater contribution of ΔPCWP compared to ΔTPG to ΔmPAP with a ratio of approximately 2:1 (ie, ΔPCWP = 0.67 mm Hg/L CO and...
TABLE 1: Pulmonary Arterial Pressure Responses to Exercise

<table>
<thead>
<tr>
<th>Condition</th>
<th>Author</th>
<th>N</th>
<th>Age</th>
<th>Exercise Protocol</th>
<th>Work Rate (Watts)</th>
<th>CO at Rest (L/min)</th>
<th>CO With Ex (L/min)</th>
<th>mPAP at Rest (mm Hg)</th>
<th>mPAP With Ex (mm Hg)</th>
<th>ΔPAP/ΔCO</th>
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<tbody>
<tr>
<td>NORMAL</td>
<td>Hickam</td>
<td>8</td>
<td>23±7</td>
<td>Supine leg press</td>
<td>20±7</td>
<td>7.1±1.8</td>
<td>10.4±3.5</td>
<td>11±3</td>
<td>13±1</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Lonsdorfer</td>
<td>7</td>
<td>31±8</td>
<td>Upright cycle</td>
<td>276±50</td>
<td>5.4±1.5</td>
<td>20.0±3.3</td>
<td>14±2</td>
<td>27±6</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Degre</td>
<td>11</td>
<td>41±5</td>
<td>Upright cycle</td>
<td>NA</td>
<td>5.0±0.9</td>
<td>13.3±1.7</td>
<td>11±4</td>
<td>23±5</td>
<td>1.4</td>
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<tr>
<td></td>
<td>Slonim</td>
<td>5</td>
<td>22±2</td>
<td>Supine leg press</td>
<td>20±2</td>
<td>4.9±0.6</td>
<td>7.2±0.8</td>
<td>15±2</td>
<td>19±2</td>
<td>1.6</td>
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<td></td>
<td>Wagner</td>
<td>8</td>
<td>30±6</td>
<td>Upright cycle</td>
<td>180</td>
<td>6.9±2.0</td>
<td>20.5±2.5</td>
<td>13±3</td>
<td>30±6</td>
<td>1.2</td>
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<td></td>
<td>Damato</td>
<td>24</td>
<td>31±6</td>
<td>Upright treadmill</td>
<td>160±23</td>
<td>5.1±0.8</td>
<td>17.5±2.0</td>
<td>15±5</td>
<td>29±8</td>
<td>1.1</td>
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<tr>
<td></td>
<td>Reeves</td>
<td>9</td>
<td></td>
<td>Upright cycle</td>
<td>240</td>
<td>6.7±1.2</td>
<td>24.7±3</td>
<td>15±2</td>
<td>29±8</td>
<td>0.8</td>
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<tr>
<td></td>
<td>Tolle</td>
<td>16</td>
<td>46±15</td>
<td>Upright cycle</td>
<td>156±43</td>
<td>5.8±1.0</td>
<td>15.5±3.2</td>
<td>14±3</td>
<td>27±4</td>
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<td>45° cycle</td>
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CO indicates cardiac output; mPAP indicates mean pulmonary arterial pressure; ΔPAP/ΔCO indicates the slope of the pulmonary arterial pressure-flow relationship during exercise; COPD indicates chronic obstructive pulmonary disease; HFrEF indicates heart failure with reduced ejection fraction; HFrEF indicates heart failure with preserved ejection fraction.

ΔTPG = 0.33 mm Hg/L CO. Older individuals have greater augmentation in mPAP relative to blood flow during exercise but similar relative contributions of changes in TPG and PCWP to changes in mPAP during exercise. The modest increment in TPG relative to CO during exercise results in a reduction in PVR to less than 1 Wood unit. The reduction in PVR with exercise is attributable to passive recruitment and distention of a compliant pulmonary circulation and active flow-mediated vasodilatation.

From investigations to date in normal individuals, it can be concluded that the compliant pulmonary vasculature can accommodate large increases in blood flow during exercise with a proportionate modest increment in mPAP and a fall in PVR. When assessing mPAP, it is critical to account for CO augmentation; therefore, determination of ΔmPAP/ΔCO or PVR is preferable to mPAP alone.

EXERCISE HEMODYNAMIC MEASUREMENTS TO UNMASK EARLY FORMS OF PAH AND LV DYSFUNCTION

When advanced, heart failure with preserved ejection fraction (HFrEF) and PAH are readily apparent through routine clinical evaluation and diagnostic testing performed at rest. However, the diagnosis of earlier stages of HFrEF and PAH may be challenging, as exertional dyspnea is not specific for either condition, and biomarkers and hemodynamic indicators in “early stages” of these conditions may be unremarkable at rest. Therefore, individuals who experience dyspnea on exertion despite normal resting hemodynamics (ie, PCWP or LVEDP <15 mm Hg and mPAP <25 mm Hg) may benefit from confrontational testing with exercise with particular attention to relative increases in PCWP and TPG components of PAP.

Exercise-induced Heart Failure With Preserved Left Ventricular Ejection Fraction

HFrEF constitutes approximately 40% of the HF population and is associated with a similar prognosis to HF with reduced LV ejection fraction (LVEF). Current
guideline-based diagnostic criteria for HFpEF include objective evidence of elevated cardiac filling pressures based on cardiac catheterization, echocardiography, or natriuretic-peptide assays.42 The potential for over-diagnosis of HFpEF based on these criteria has garnered significant attention43-45 but less is known about the potential under-diagnosis of HFpEF in symptomatic patients without overt hypervolemia.

Borlaug et al reported hemodynamic responses to exercise in 55 euvolemic subjects with exertional dyspnea, normal natriuretic peptide levels, and normal resting hemodynamic measurements.26 Supine exercise with cycle ergometry (N=42) or arm weights (N=13) was performed, with an exercise PCWP threshold of ≥25 mm Hg for the diagnosis of HFpEF. This PCWP value was chosen based on previous studies in normal controls showing that peak PCWP and LVEDP during supine exercise are <20-23 mm Hg46,47 and <25 mm Hg,48 respectively. HFpEF subjects experienced significantly greater exercise-induced increases in mPAP (ie, from 19±4 to 43±7 mm Hg) compared to subjects with noncardiac dyspnea (ie, from 15±4 to 23±5 mm Hg, Figure 2A) despite achieving lower peak COs. Exaggerated increases in mPAP in HFpEF were related exclusively to elevations in exercise PCWP as evidenced by similar increments in TPG and reductions in PVR from rest to exercise in HFpEF and noncardiac dyspnea patients. Exercise-induced changes in PCWP and PAP in patients with HFpEF remained significantly higher than those in patients with noncardiac dyspnea following adjustment for age, BMI, CO, and work rate.

Borlaug and colleagues further examined the discriminatory capacity of exercise PAP for the diagnosis of HFpEF. They focused on exercise PASP because it was closely related to exercise PCWP (R=0.76, \( P<0.0001 \)) and is amenable to noninvasive estimation by echo Doppler. PASP >45 mm Hg identified HFpEF with 96% sensitivity and 95% specificity (Figure 2B). Strict exclusion of patients with pulmonary vascular disease (ie, mPAP >25 mm Hg at rest or >30 mm Hg during exercise with a PCWP <15 mm Hg) likely inflated the specificity of exercise PASP for the diagnosis of HFpEF, compared to an unselected population of patients with exertional dyspnea, but exercise PASP outperformed resting PASP, natriuretic peptide levels, and echocardiographic indicators for diagnosing HFpEF.

Kitzman et al similarly found that compensated outpatients with HFpEF had normal resting PCWP but marked increases in exercise PCWP, suggesting that HFpEF may initially manifest with only intermittent elevations in cardiac filling pressures.49 Both studies indicate the incremental value of exercise hemodynamics in the diagnosis of HFpEF and may pro-

Figure 1: Pulmonary arterial pressure (PAP)-flow relationships based on serial measurements of mean PAP and cardiac output during incremental exercise. Normal subjects (□), patients with scleroderma with PAP in the lower normal range (○) and upper normal range (●), and patients with resting PAH (●) demonstrate approximately linear pressure-flow responses during exercise. Higher \( \Delta \)PAP/\( \Delta \)CO than normal may be indicative of early pulmonary vasculopathy in the scleroderma groups. Data from (□) Reeves,35 Kovacs (○,●),54 and (●)Janicki.13

Figure 2: (Panel A) Mean PAP increased to a greater extent during exercise in patients with HFpEF compared to patients with noncardiac dyspnea. (Panel B) Clinical measures (B-type natriuretic peptide levels and echocardiographic E/e’ and the European Society of Cardiology (ESC) diagnostic algorithm42 did not robustly distinguish HFpEF from noncardiac dyspnea. In contrast, PCWP with leg raise and exercise PASP showed excellent discrimination between HFpEF and noncardiac dyspnea. Reprinted with permission from Wolters Kluwer Health: Borlaug BA, et al. Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure with Preserved Ejection Fraction. Circ Heart Fail. 2010 Jun 11. [Epub ahead of print]
clude a primary contribution of elevated exercise-induced elevations in mPAP provides a window into earlier diagnosis of the condition. However, prior to labeling elevations in exercise hemodynamics as "early forms" of PH-pEF, more information is needed on the natural history of patients with exercise elevations in PAP and PCWP to determine the rate at which they go on to develop overt HF.

Exercise-induced PAH
Aalogous to HFP EF, PAH is often diagnosed late in its course when it purports a particularly poor prognosis. Whether exercise-induced elevations in mPAP provide a window into the diagnosis of early, potentially more treatable forms of PAH remains controversial.6,50,51 Definitions of exercise-induced PAH (EIPAH) and the rigor with which pulmonary venous hypertension has been excluded in studies performed to date varies.1,52,53 Furthermore, follow up to determine natural history of EIPAH is lacking. However, there is emerging evidence that EIPAH, if properly defined, may represent an important intermediate PAH phenotype.1,54 Tolle and colleagues conducted a comprehensive study of 406 sequential patients undergoing incremental cardiopulmonary exercise testing with invasive hemodynamic monitoring to evaluate dyspnea on exertion and thereby compiled the largest EIPAH experience reported to date. "Exercise-induced PAH" was defined as resting mPAP <25 mm Hg coupled with exercise PCWP <20 mm Hg, mPAP >30 mm Hg, and PVR >80 dyne-cm⁻². Patients with EIPAH (N = 78) were compared to patients with normal exercise capacity and hemodynamics (N = 16) and patients with resting PAH (mPAP >25 mm Hg, PCWP <15 mm Hg, N = 15). The inclusion of an exercise PVR minimum in the definition of EIPAH was particularly important in light of the subsequently published meta-analysis by Kovacs indicating that mPAP = 30 mm Hg is often surpassed during exercise in normals performing maximum exercise, particularly when high workloads are achieved.33,35 In addition, a PCWP <20 mm Hg during maximum exercise represents a relatively strict threshold to exclude a primary contribution of elevated left sided hydrostatic pressures to PH during exercise and further helps to validate the findings from this study.

Tolle and colleagues found that the percent predicted peak VO₂ (on the basis of age, sex, and height) was lowest in resting PAH (55.8% ± 20.3%), intermediate in EIPAH (66.5% ± 16.3%), and highest in normals (91.7% ± 13.7%), whereas mPAP (48±11 vs 37±6 vs 27±4 mm Hg) and PVR (294±158 vs 161±60 vs 62±20 dyne-cm⁻², respectively; all P <0.05) followed an opposite pattern. These data suggest that EIPAH is an intermediate phenotype between normal subjects and those with resting PAH. Of note, the ULN mPAP in the upright position is likely closer to 20 mm Hg instead of 25 mm Hg, but Tolle et al noted that resting mPAP 21-25 mm Hg in this study did not predict EIPAH. The important findings of this study characterizing EIPAH merit further exploration of the natural history of EIPAH to determine its prognostic implications and responsiveness to therapy.

Subsequent studies have provided further evidence of the functional significance of exercise-induced elevations in PAP. Kovacs and colleagues studied 29 patients with systemic sclerosis, an "at-risk population" for PAH, in whom resting mPAP was <25 mm Hg. Stratification by median mPAP at rest (mPAP = 17 mm Hg) and during exercise at 25 and 50 watts (median PAP = 23 mm Hg and 28 mm Hg, respectively), indicated that higher resting PAP within the normal range, and particularly higher exercise PAP was associated with reduced 6-minute walk distance and reduced peak workload.34 Notably, the PVR failed to fall in the above-median PAP, EIPAH group (rest: 168±47 dyne-cm⁻², 25W: 161±36 dyne-cm⁻², 50W: 166±41 dyne-cm⁻²). These values are strikingly similar to the PVR values reported by Tolle et al in EIPAH (161±60 dyne-cm⁻²). A second recent publication in patients with systemic sclerosis demonstrated the utility of exercise hemodynamics in identifying the primary mediator of potentially multifactorial exercise limitation.56

EIPH and LV Dysfunction
The studies described above compartmentalize patients as having either HFP EF or PAH unmasked by exercise. However, in some patients exercise will elicit exaggerated increases in both TPG and PCWP. The entity of "PH out of proportion to LV dysfunction," alternatively named "PH-LVD" or "mixed PH," as identified by abnormal resting hemodynamics, is being increasingly recognized in patients with both HFP EF and HF with reduced LV EF (HFrEF).58 For example, Lam et al recently described a wide spectrum of PASPs in patients with HFP EF, with higher PASP potently predicting worse outcomes.57,59 The identification of exercise-induced mixed PH, with partitioning of relative contributions of PCWP and TPG, may help to further phenotype patients with dyspnea and eventually inform targeted interventions directed at either the left ventricle or the pulmonary vasculature.

Based on studies to date in normal individuals and in dyspneic patients in the studies described above, a suggested algorithm is proposed in Figure 3 whereby patients can be further classified on the basis of exercise hemodynamic values. The initial branch point is based on marked differences in pressure-flow relationships in the pulmonary vasculature in normals relative to individuals with HF or PAH (Table 1).
Heart Failure With Reduced LVEF

Resting PH is present in the majority of patients with LV systolic dysfunction (LVSD) and is associated with RV dysfunction, reduced exercise tolerance, and poor prognosis.\(^6\,6^2\,6^3\) There is a strong inverse relationship between resting PH and RV dysfunction in LVSD, less is known about the PAP response patterns during exercise in subjects with LVSD, and their relationship to exercise capacity and outcomes.

In our laboratory we studied 2 cohorts of subjects with LVSD who underwent cardiopulmonary exercise testing (CPET) with measurements of PAP, PCWP, and Fick CO.\(^1^5\,6^5\) We observed an exaggerated increase in PAP relative to CO during exercise of 4.9 mm Hg/L and 5.0 mm Hg/L in 2 separate studies. Despite uniform increases in PCWP, PVR failed to fall normally with exercise, remaining in excess of 3 Wood units on average during exercise in both studies. Exercise PVR was strongly associated with 3 established prognostic indicators in HF: peak VO\(_2\), RV ejection fraction (RVEF), and V\(_{\text{EO2}}\)/VCO\(_2\) slope.\(^6^6\,6^7\) Janicki et al similarly observed an increment in PAP relative to CO of 5.9 mm Hg/L.\(^1^3\) in 42 subjects with HF. Notably, patients with resting mPAP <19 mm Hg, indicating well compensated HF, had an average increment in PAP of 4.1 mm Hg/L whereas those with resting mPAP >19 mm Hg had an increment in mPAP of 6.8 mm Hg/L. Unlike our group, Janicki observed a modest decrement in PVR in both subgroups during exercise, but the average PVR remained above 2 Wood units during exercise.

Two studies have examined whether invasive hemodynamic measurements during exercise,\(^6^8\,6^9\) including mPAP, provide incremental prognostic information in HF. Mancini et al examined rest and exercise hemodynamics and gas exchange variables in 65 patients who underwent cardiac transplantation evaluation and stratified them into 2 groups: those who died or required urgent transplant (N = 16), and those who survived (N = 49) over an average follow-up of 8±4 months. Nonsurvivors did not differ from survivors in resting hemodynamics, including mPAP and CO. However, during exercise nonsurvivors had higher mPAP (55±8 mm Hg) than survivors (46±12 mm Hg, P = 0.01, Table 1) and higher increment in mPAP per liter of CO (8.0 vs 4.9 mm Hg/L). In a similar study, Metra et al evaluated 219 patients (181 survivors and 38 nonsurvivors) and found that both rest and exercise PAP were higher in nonsurvivors than in survivors, despite lower workloads achieved in nonsurvivors.\(^6^8\) Furthermore, exercise PVR, but not resting PVR, distinguished survivors from nonsurvivors. Both studies indicate superior prognostic value of measuring exercise pulmonary hemodynamics compared to resting measurements alone.

Peak exercise mPAP, however, was not retained in multivariate analyses of predictors of survival in either study. Whether this finding was attributable to limited incremental prognostic value of exercise mPAP, failure to account for lower workloads in nonsurvivors, or to inclusion of interrelated exercise hemodynamic variables into the multivariate models (ie, stroke work index) requires further investigation.

Several mechanisms may account for the heightened mPAP/CO relationship observed in HF. Increased hydrostatic pressures during exercise due to LV dysfunction are to be expected, but persistent elevations in PVR reflect exaggerated increases in TPG during exercise as well. This may be due to maximally recruited pulmonary vasculature at rest on account of elevated resting hydrostatic pressures, thus limiting passive recruitment and distension during exercise observed in normals. Alternatively, subnormal mixed venous oxygen saturation in HF during exercise may contribute modestly to hypoxic-vasoconstriction.\(^7^0\) Finally, in one echocardiographic study, PH in HFREF was closely related to the severity of functional mitral regurgitation and diastolic dysfunction, both at rest and during exercise.\(^7^1\,7^2\) Trials are currently underway to evaluate the role of pulmonary vasodilator therapy in LV dysfunction with disproportionate PH (ie, LEPHT—LEf ventricular systolic dysfunction associated with Pulmonary Hypertension Ricciogi et Trial).\(^7^3\) Further defining the extent of disproportionate PH (ie, ΔPVR) vs LV dysfunction (ie, ΔPCWP) during exercise may offer improved patient phenotyping to inform targeted interventions.
**Chronic Obstructive Pulmonary Disease**

Pulmonary hypertension is a well-known complication of chronic obstructive pulmonary disease (COPD). Descriptions of mPAP response patterns to exercise in COPD are limited by the heterogeneity in the small cohorts studied. In Hickam’s original series, despite normal average resting mPAP (18 ± 4 mm Hg), the average increment in mPAP relative to CO was steeper in patients with emphysema (4.0 ± 1.7) relative to normals (0.9 ± 1.4). Blanco et al found an even steeper increment in mPAP relative to CO (7.0 mm Hg/L) in patients with COPD selected on the basis of resting mPAP >20 mm Hg.24

In a third study of 10 subjects undergoing lung volume reduction surgery with mild PH (resting mPAP = 26 ± 6 mm Hg), mPAP at rest and during exercise were examined relative to the degree of thickening of excised small (100-200 μm diameter) muscular pulmonary arteries (ie, intima + media as a percentage of vessel diameter) as an indicator of pulmonary arterial remodeling. Interestingly, there was no relationship between resting mPAP and arterial wall thickness, but exercise PA and change in PA with standardized exercise (25W) were strongly related to wall thickness (R = 0.72 and R = 0.90, respectively, both P < 0.05). The authors acknowledge the multiple potential mechanisms mediating PH in emphysema beyond vascular remodeling. However, based on these findings exercise PH may be indicative of reduced recuitability and distensibility of pulmonary vessels and the degree of remodeling cannot be estimated by resting mPAP.

**Mitral Valve Disease**

The development of PH in the presence of mitral stenosis (MS) and mitral regurgitation (MR) has been well described for over 40 years.75,76 Yet mechanisms mediating heterogeneity in pulmonary vascular responses to left atrial hypertension among patients with mitral valve disease at rest and during exercise remain incompletely understood.77,78 Schwammtenthal et al showed that elevated PAP at rest and during exercise in MS is closely related to net atrioventricular compliance, to a greater extent than mitral valve area.79 Reduced compliance (< 4 ml/mm Hg) predicted the need for mitral valve replacement (MVR) or commissurotomy and defines an MS cohort in which PH is closely linked to functional capacity.80

**PHARMACOTHERAPIES FOR TREATMENT OF PAH ALTER EXERCISE PAP**

The observed improvements in exercise capacity with short-term aerosolized iloprost exposure, despite minimal changes in resting hemodynamics,81 led Blumberg and colleagues to hypothesize that iloprost would elicit more favorable effects on pulmonary hemodynamics during exercise than at rest. Indeed, one-time dose of iloprost was associated with a 6 ± 8% reduction in resting PAP and an 18 ± 11% fall in exercise PAP at a standardized sub-maximum workload (25W or 50W, P < 0.05) in a cohort consisting of primarily Group 1 PH.60 One limitation of this study was the short duration between exercise studies that raised the possibility of reduced PA responses on the post-intervention study on account of repeated testing. A second small study (n = 5) of PAH patients with implantable hemodynamic monitors (ChronicR IHM, Model 9520, Medtronic, Minneapolis, MN) also showed reduction in PAP with iloprost during submaximal exercise.65

Calcium channel antagonists have been shown to reduce absolute values of exercise mPAP and PVR and to blunt the increment in mPAP during exercise in PAH82 and PH due to COPD83 despite patients achieving a greater workload. In contrast, hydralazine did not reduce exercise PAP in a similar small study, but did reduce PVR because CO increased.85 This study is an example of why mPAP alone is insufficient, as greater CO with hydralazine resulted in equal mPAP at peak exercise but lower PVR. Further work is needed to ascertain whether there are treatment-specific approaches that differentially modulate pulmonary hemodynamics during exercise.

The influence of PDE5 inhibitors on exercise pulmonary hemodynamics has been studied in secondary forms of PH. Our group demonstrated that sildenafil, administered over 12 weeks in a random-

**FUTURE DIRECTIONS**

**RV-Pulmonary Vascular Interactions**

Characterization of pulmonary vascular response patterns to exercise to date have largely focused on changes in PAP and PVR, which is simply a measure of position to the mean component of flow. However, the pulmonary vasculature is a low resistance, high compliance system, making the pulsatile component of hydraulic load and wave reflection important to consider as well.88 Impedence is the measure of opposition to pulsatile components of flow and provides a more complete indicator of RV afterload.89 Several studies have described changes in resting impedance arising from large-artery stiffening and remodeling in PH.90 This abnormal pulsatile load may have detrimental effects on ventricular–vascular coupling, unfavorably loading the still-ejecting RV. Measurements of impedance in the frequency domain, and pressure-wave forms in the time-domain during exercise are needed to more completely characterize RV-pulmonary artery interactions during exercise. Whether RV responses to increased pulsatile flow during exercise predict future development of RV dysfunction or response to specific PH therapies merits further investigation as well.

Further development and validation of multimodality noninvasive methods to characterize RV-pulmonary artery structure and function during exercise hold promise in advancing our understanding of pulmonary vascular responses to exer-
vasive. Finally, future studies are needed to define the natural history of "early" forms of PH unmasked by exercise (ie, EIPH and HFpEF) and the extent to which these conditions may be amenable to treatment.

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Unexplained exertional dyspnea or fatigue can pose a significant diagnostic challenge to physicians as these symptoms are often relatively mild, poorly characterized, or insidious. Routine cardiac and pulmonary evaluations may be unrevealing. Invasive cardiopulmonary exercise testing (CPET) with pulmonary and radial arterial catheters is uniquely suited to evaluate these symptoms as it provides a general assessment of exercise capacity and defines the specific contributions of any cardiac, pulmonary mechanical, pulmonary vascular, hematologic, muscular, or neurologic limitations. In other words, the test can determine the presence or absence of disease, and if present, the nature of the limitation(s).

Since invasive CPET allows accurate measurement of pulmonary arterial and cardiac filling pressures during exercise, it can be most helpful in characterizing an abnormal response of the circulatory system to exertion. Indeed, exercise-induced pulmonary arterial hypertension (ePAH) has been shown by CPET to be an early, mild, and symptomatic phase of the PAH spectrum. In this review, we describe the protocol for invasive CPET at Massachusetts General Hospital and provide 3 case studies where this testing aided the diagnosis of pulmonary vascular disease.

**INVASIVE CPET AT MGH**

The MGH Cardiopulmonary Exercise Laboratory performs approximately 150 clinically indicated invasive CPETs per year. The majority of tests are performed for the evaluation of dyspnea or fatigue of unclear etiology, with the balance performed as part of an evaluation for cardiac or pulmonary transplantation. Upon arrival, the patient receives a pulmonary artery catheter through the internal jugular vein in the cardiac catheterization laboratory, where initial, supine, resting pulmonary pressures and cardiac output are measured. Subsequently, a radial artery catheter is placed in the exercise laboratory. If the patient has a pulmonary capillary wedge pressure (PCWP) <5 mm Hg at rest, intravenous normal saline is provided in 0.5 L boluses up to 1.5 L to increase the PCWP above 5 mm Hg. This is standard practice to overcome the effects of volume depletion secondary to the patient’s nil per os status prior to the test. The patient then performs a single bout of incremental cycling exercise to exhaustion (Medgraphics CPE 2000, Medical Graphics Corp., St. Paul, MN). The test begins with 2 minutes of rest, followed by 3 minutes of unloaded pedaling. Work is then continuously increased by 6.25 to 25 W/min depending on the patient’s subjective exertional tolerance. The test ends when the patient can no longer continue to exercise, usually due to dyspnea, leg fatigue, or both.

Throughout the test, breath-by-breath pulmonary gas exchange and minute ventilation are measured by a metabolic cart (Medgraphics CPX/D, Medical Graphics Corp., St. Paul, MN). Mean systemic arterial pressure, end-expiratory right atrial pressure, and mean pulmonary arterial pressures (mPAP) are measured continuously (CALYSTO Series IV, Witt Biomedical Corp., Melbourne, FL). Heart rate and rhythm are also monitored by continuous 12-lead recording. End-expiratory PCWP is measured at 50% of the a-wave descent at rest and during each minute of exercise. At peak exercise, the patient is instructed to pause or slow the respiratory rate with the glottis open in an effort to accurately measure central pressures by minimizing the effect of pleural pressure changes. Blood samples are obtained from the pulmonary and radial artery catheters at rest and during each minute of exercise for measurement of PO2, PCO2, pH, lactate, hemoglobin concentration ([Hb]), and oxygen saturation. Finally, right and left ventricular ejection fractions (RVEF, LVEF) and left ventricular end diastolic volume (LVEDV) are measured at rest.

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**Key Words**— cardiopulmonary exercise testing, pulmonary hypertension, heart failure with preserved ejection fraction, preload failure

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Case 1
Patient 1 is a 27-year-old woman who was referred to the pulmonary clinic at MGH for evaluation of exertional dyspnea in April 2009. Two years before her presentation, the patient was in excellent health. She routinely ran 6 miles daily without difficulty, participated in road races, and was a competitive swimmer in high school and college. In the summer of 2007, she began to experience nausea, muscle aches, dizziness, headache, and breathlessness when she ran. She had no other significant past medical, family, or social history. Her physical exam was notable for a BMI of 20, with a slightly elevated VE/VCO₂ of 38 and low end-tidal PCO₂ (PetCO₂). After this CPET, she ran a 15 km race where she developed left leg pain, palpitations, breathlessness, chest pain, nausea, and lightheadedness. She was evaluated on December 15, 2008, for these symptoms, which were attributed to anxiety, and referral to a sports psychiatrist was made.

On December 18, 2008, she developed acutely worse symptoms now with presyncope and was seen by her primary care physician whose evaluation was notable for a D-dimer elevated at 2236, and so she was referred to the emergency department of another hospital for evaluation. Pulmonary CT angiography demonstrated multiple bilateral pulmonary emboli, 2 wedge infarctions, and multiple bilateral deep vein thromboses. An echocardiogram showed RV strain. She did not receive thrombolytics given her hemodynamic stability and the risk of bleeding into the infarcted lung. She was anticoagulated with low molecular weight heparin as a bridge to warfarin. At the time of her presentation, she was taking oral contraceptive pills, which were discontinued at discharge, and she denied recent travel, smoking, cancer, and any family or personal history of clotting. A hypercoagulability evaluation was notable for the Factor V Leiden mutation.

Despite therapeutic anticoagulation, the patient presented to the pulmonary clinic at this hospital 4 months later with persistent exertional dyspnea, nausea, palpitations, and lightheadedness, which occurred 5 minutes after running at a slow pace. Her symptoms quickly resolved with rest. She had no other significant past medical, family, or social history. Her physical exam was notable for a BMI of 23, pulse of 52 bpm, blood pressure of 110/70 mm Hg, and respiratory rate of 16 breaths per minute. The jugular venous pressure was 5 cm H₂O with sustained hepatoujugal reflex. The lung exam was normal. The heart exam was notable for a loud P2 without murmur or gallop rhythm. An EKG showed sinus bradycardia with an incomplete right bundle
branch block. An echocardiogram was notable for mild tricuspid insufficiency, right atrial dilation, dilated inferior vena cava with limited respirophasic variation, an estimated RV systolic pressure (RVSP) of 35 mm Hg, with a mildly, diffusely hypokinetic RV. Repeat CT pulmonary angiography showed multiple bilateral webs related to organized, chronic pulmonary emboli. Given concern for chronic thromboembolic pulmonary hypertension, the patient was referred for invasive CPET. Notably, the patient had normal pulmonary pressures when measured in the catheterization laboratory (Table 1); however, the invasive CPET was diagnostic of ePAH (Tables 1 and 2) based on decreased VO₂max, early VT, elevated VE/VCO₂ at the VT, high dead space fraction (VD/VT), increased A-a gradient, decreased RVEF, decreased PetCO₂, and increased mPAP and PVR with exercise. The etiology was presumably chronic thromboembolic pulmonary hypertension given chronic deep vein thrombosis (DVT) and pulmonary emboli. Results of the CT angiography were consistent with distal disease, which was not thought to be amenable to surgical pulmonary arterial endarterectomy; however, the patient did undergo percutaneous balloon angioplasty of the distal pulmonary arteries in September 2009, and started tadalafil 40 mg daily. At her most recent follow-up in May 2010, the patient had returned to running 4 miles daily without exertional symptoms.

Case 2
Patient 2 is a 55-year-old woman who was referred to the pulmonary clinic at MGH for evaluation of exertional dyspnea in November 2009. In 1994, she underwent a renal transplant due to complications of lupus. Since the winter of 1995, she has noted progressively worsening shortness of breath with exertion. At the time of her presentation, she was having difficulties climbing stairs or vacuuming. Her symptoms were associated with wheezes and chest discomfort with no cough. An extensive evaluation had already been completed by the time she arrived to this hospital. Exercise treadmill tests were negative for coronary ischemia. In 2006, coronary angiography was normal and resting right heart catheterization showed

<table>
<thead>
<tr>
<th>Table 1: Hemodynamic measurements upon pulmonary arterial catheterization, at rest, and at peak exercise</th>
</tr>
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<tbody>
<tr>
<td>Qt</td>
</tr>
<tr>
<td>Case 1 Cath</td>
</tr>
<tr>
<td>ePAH Rest</td>
</tr>
<tr>
<td>Peak</td>
</tr>
<tr>
<td>Case 2 Cath</td>
</tr>
<tr>
<td>eHFpEF Rest</td>
</tr>
<tr>
<td>Peak</td>
</tr>
<tr>
<td>Case 3 Cath</td>
</tr>
<tr>
<td>PLF Rest</td>
</tr>
<tr>
<td>Peak</td>
</tr>
</tbody>
</table>

*Qt in the catheterization laboratory is measured by thermodilution.
normal pressures (RAP 7, mPAP 12, PCWP 8 mm Hg). In 2009, a dobutamine stress echocardiogram showed a normal ejection fraction, mild aortic stenosis (mean gradient 15 mm Hg), mild mitral and mild-moderate tricuspid regurgitation, an RVSP of 41 mm Hg, and no evidence of ischemia. A chest CT showed a few scattered areas of scarring. Exercise oximetry was normal and pulmonary function testing revealed a mildly reduced DLCO.

Her other medical history was notable for hypertension, hyperlipidemia, and gastroesophageal reflux disease. She quit smoking in 1989 after 14 pack-years. She was taking cyclosporine, mycophenolate mofetil, prednisone, atenolol, digoxin, lisinopril, furosemide, aspirin, atorvastatin, albuterol, famotidine, estradiol, medroxyprogesterone, and allopurinol. Her family histories were unremarkable. The physical exam showed a BMI of 19, pulse of 76 bpm, blood pressure of 102/62 mm Hg with no change upon standing, and respiratory rate of 16 breaths per minute. Cardiovascular and pulmonary examinations were normal. The patient was referred for cardiac MRI, which confirmed a structurally normal heart with normal ventricular size, morphology, and function. She was referred for noninvasive CPET, where she had a VO\textsubscript{2}max 56% predicted with early VT and increased VE/VCO\textsubscript{2} at the VT, consistent with a central cardiovascular limit to exercise. Throughout exercise, a progressive decline in PetCO\textsubscript{2} was noted, which could be consistent with pulmonary arterial hypertension or hyperventilation. An invasive CPET was recommended to identify the etiology of the cardiovascular limit.

Given the relatively low filling pressures initially noted upon placement of the pulmonary artery catheter (Table 1), the patient received 1.5 L of intravenous normal saline before the start of the test. Despite this, her ventricular filling pressures remained low throughout exercise, consistent with the low LVEDV determined by FPRVS (Table 2) and low Qtmax (77% predicted). The patient was anemic, with a [Hb] of 11.5 g/dL, which also limited VO\textsubscript{2}max. Interestingly, the Ca-VO\textsubscript{2} was 8.4 mL/100 mL blood, suggesting an additional impairment of systemic oxygen extraction, as this should approximately equal the [Hb]. Given low resting filling pressures that failed to augment with exercise despite volume repletion, this patient was diagnosed with preload failure.

Table 2: Gas exchange and first pass radionuclide scanning variables

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO\textsubscript{2}max, % predicted</td>
<td>72</td>
<td>58</td>
<td>46</td>
</tr>
<tr>
<td>VT, % VO\textsubscript{2}max predicted</td>
<td>27</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>VE/VCO\textsubscript{2} (VT)</td>
<td>41</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>VT/VT (rest), %</td>
<td>21</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>VT/VT (peak), %</td>
<td>30</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>PetCO\textsubscript{2} (rest)</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>PetCO\textsubscript{2} (peak)</td>
<td>24</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>RVEF (rest), %</td>
<td>41</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>RVEF (peak), %</td>
<td>30</td>
<td>49</td>
<td>62</td>
</tr>
<tr>
<td>LVEF (rest), %</td>
<td>65</td>
<td>69</td>
<td>71</td>
</tr>
<tr>
<td>LVEF (peak), %</td>
<td>66</td>
<td>59</td>
<td>68</td>
</tr>
<tr>
<td>LVEDV (rest), mL</td>
<td>116</td>
<td>102</td>
<td>105</td>
</tr>
<tr>
<td>LVEDV (peak), mL</td>
<td>122</td>
<td>151</td>
<td>99</td>
</tr>
</tbody>
</table>
The patient was referred for tilt table testing that was diagnostic of postural orthostatic tachycardia syndrome (POTS). After 10 minutes, her pulse increased to 142 bpm and blood pressure decreased to 77/42 mm Hg. Given this result, the patient was prescribed midodrine, increased salt intake, and compression stockings. With these interventions, her symptoms resolved and she was able to exercise without limitation. She underwent extensive endocrine and neurologic evaluations for adrenal and autonomic insufficiency that were normal.

DISCUSSION

Each of the 3 cases above describes a patient with long-standing, unexplained exertional dyspnea who had undergone an extensive evaluation prior to her presentation to MGH. These cases illustrate how elusive these diagnoses may be, primarily due to the absence of symptoms at rest. Unfortunately, this may lead to a premature diagnosis of a psychiatric limitation to exercise, as in Case 1, where anxiety was diagnosed and a referral to a sports psychiatrist was made. The first benefit of CPET is in determining the presence or absence of disease based on VO2max, CPET is in determining the presence or treatment could improve outcomes. However, there are limited data regarding the natural history of eIPAH and the decision to treat remains controversial.7 Our practice is to initiate treatment, and anecdotal reports suggest clinical improvement in symptoms.

Similarly, eHFpEF, defined by an elevation of PCWP =25 mm Hg with normal resting pressures and normal ejection fraction, may also represent an early form of disease.8 A gain, the natural history of eHFpEF is unknown, but these patients may likely benefit from the initiation of targeted medical therapy to alleviate exertional symptoms and prevent further cardiac and vascular remodeling.

While eIPAH and eHFpEF comprise the majority of diagnoses of unexplained dyspnea in our exercise laboratory, we have identified a cohort of patients, mostly young women, who have a cardiovascular limit to exercise characterized by lower cardiac output due to low cardiac filling pressures, as described in Case 3. For these patients, the limitation appears primarily due to failure to augment preload during exercise, noted by low RAP and PCWP. As per our protocol, all patients are resuscitated with up to 1.5 L of intravenous normal saline, so it is unlikely that volume depletion accounts for this phenomenon. Several of these patients have had positive tilt table testing, and experience some improvement in symptoms with β-receptor antagonists, mineralocorticoids, or midodrine. Interestingly, many of these patients also have evidence of defects in peripheral oxygen extraction, which may suggest a common underlying etiology of PLF at the microcirculatory level. We propose that PLF should be added to the differential diagnosis of unexplained exertional dyspnea or fatigue. This approach may assume a more important role as the clinical significance of exercise-induced pulmonary vascular disease is better understood.

CONCLUSION

The use of CPET with invasive hemodynamic monitoring is a powerful tool in the diagnosis of unexplained exertional dyspnea or fatigue. This approach may assume a more important role as the clinical significance of exercise-induced pulmonary vascular disease is better understood. If these entities represent an early stage of disease, where treatment will improve outcomes, invasive CPET will be essential in the management of these patients for diagnosis and monitoring response to therapy. Despite the significant resources involved in administering these tests, they are, for now, the best way of obtaining data on central hemodynamics during exercise.

References
The 6-minute walk test (6MWT) is an easy to perform and practical test that has been used in the assessment of patients with a variety of cardiopulmonary diseases including pulmonary arterial hypertension (PAH). It simply measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Nonetheless, the result reflects the integrated exercise response of complex physiology involving the pulmonary and cardiovascular systems, systemic and pulmonary circulations, and neuromuscular function. The metabolic rate stabilizes at a level representative of maximal oxygen consumption; therefore, the test is a good measure of aerobic exercise capacity.

The correlation with maximal cardiac output renders the test an indirect measure of right ventricular function in patients with significant PAH. An understanding of the test logistics is important to the clinician utilizing this test to evaluate patients with pulmonary arterial hypertension.

TECHNICAL ASPECTS

Though the instructions for both the administrator of the test and the patient are straightforward, there are several technical aspects of the 6MWT that require attention. The American Thoracic Society has published guidelines for a detailed understanding of the test logistics. In addition, a document titled “Pulmonary Rehabilitation Toolkit,” is available on the following Web site: www.pulmonaryrehab.com.au/index.asp?page=19. Instructions to the patient are specific. The patient should be advised to dress comfortably with appropriate footwear and use his or her usual walking aids (eg, cane, walker). A light pre-test meal is recommended. The patient should not engage in strenuous exercise for 2 hours prior to testing. In addition, the patient should rest for 10 minutes prior to the walk test, after which time baseline vital signs including oxygen saturation are assessed. As mentioned previously, the test is performed at an unencouraged intensity. In addition, the patient is allowed to stop and rest during the test. The patient should evaluate the degree of dyspnea both at baseline and at the end of the test with a validated scoring system such as the Borg dyspnea score. It is important that the patient not engage in “practice” walks. Indeed, if the walk test needs to be repeated for clinical purposes, the patient should rest for an hour and the longest distance recorded.

The equipment required includes a pulse oximeter, timer (stopwatch), and blood pressure cuff. Effort should be devoted to producing conditions that create an environment representative of the patient’s normal functional status. For example, appropriate support should be available for the patient to transport their oxygen if they typically use oxygen with activity. If the patient is oxygen dependent, then an appropriate delivery device should be provided. The technician performing the test should not push or carry the oxygen delivery device for the patient. Some patients may require a mobile chair to push or pull while walking. Fortunately, advanced exercise equipment is not required. A hallway marked for distance with lap counter and/or pedometer can be used to measure distance in feet or meters. It is also reasonable to have an automatic defibrillator (AED) available in the vicinity.

CLINICAL INDICATIONS AND CONTRAINDICATIONS

There are a variety of conditions in which the 6MWT has been shown to be indicative of disease state. Those conditions...

are listed in Table 1. In addition, there are both absolute and relative contraindications to 6MWT as displayed in Table 2.1

VARIABILITY

Certain factors determine 6-minute walk distance variability between patients including age, sex, anthropometrics, and comorbidities (impaired cognition, cardiopulmonary disease, anemia, musculoskeletal limitations).1,7 Variability may also be seen in an individual patient (ie, with serial tests). It should be appreciated that prior testing increases the distance walked (“learning effect”). Comparative tests ideally should be performed at similar times during the day. Reproducibility is possible for both “encouraged” and “unencouraged” walks but the process must be standardized to eliminate variability. It may be best to avoid the phrase “walk as fast as you can” to avoid premature fatigue or other limiting symptoms. Use the same oxygen flow rate if possible. If the clinical situation demands an increase in flow rate, this should be appropriately documented.

Other technical issues that may introduce variability should be noted. For example, the interaction between the patient and the person performing the test may result in the patient “tracking” the tester’s pace.8 To avoid this confounding factor, the technician should not walk with or in front of the patient. If it is necessary for the technician to accompany the patient for data monitoring or patient safety, it is recommended that the technician walk behind the patient so he or she sets the walking pace. Variations in oxygen delivery devices (portable concentrator, liquid oxygen, or gas tank), interface (nasal cannula, transtracheal oxygen, or mask), and flow delivery (continuous or pulse) must be noted. If the oxygen flow requires adjustment during the walk test, then the reason needs to be documented. Medications (type, doses, and administration times) may also potentially affect the test results and should be carefully documented.

Reference (normative) equations exist for predicting normal 6-minute walk distance based on several variables.7 Even using such equations, 60% of the variance in 6-minute walk distance remains. In addition, although the percent predicted value may help in the interpretation of the test, its prognostic value is not superior to the absolute distance measured.9-10 The normative equations were developed in subjects older than 40 years7 so caution should be observed in the application to patients younger than that.

INTERPRETATION

The change in the distance walked in the 6-minute walk can be used to evaluate the efficacy of an exercise-training program or to trace the natural history of change in exercise capacity over time. The 6MWT is most commonly used as a baseline and follow-up assessment after a specific intervention or in monitoring disease progression. Unfortunately, the ideal representation of this comparison has not been determined. The available options include: absolute difference in distance walked, percentage change, or change as compared to predicted normal.

The minimally important clinical difference has not been determined for pulmonary vascular disease. There are available criteria for both chronic obstructive and interstitial lung disease. The minimum important difference (ie, improvement) in the distance walked in the 6-minute walk has traditionally been estimated as 54 meters (with 95% confidence limits of 37 to 71 meters).11 The value may be less for patients with chronic obstructive pulmonary or interstitial lung disease.12-13 Percentage change in the distance walked may also be used for comparison to prior testing.

SPECIFIC ISSUES OF 6-MINUTE WALK TESTING IN PAH

The 6MWT is commonly used in the diagnosis and evaluation of patients with PAH.14-23 The test estimates aerobic capacity and correlates with cardiac output thereby rendering the result and indirect measure of right ventricular function.3 The 6-minute walk distance had an independent correlation with survival in the cardinal study of intravenous epoprostenol for idiopathic PAH.14 Since that time, treatment-associated improvements in the 6-minute walk distance for PAH patients have been used as primary end points in most of the efficacy studies of currently FDA-approved pulmonary arterial vasodilator therapy.15-16,24

Despite the extensive deployment in the pulmonary vasodilator studies, the test

### Table 1: Indications for the 6MWT

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Functional Status</th>
<th>Outcome Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>Pulmonary hypertension</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>COPD</td>
<td>COPD</td>
<td>COPD</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Heart failure</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>Cystic fibrosis</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Lung resection</td>
<td>Peripheral vascular disease</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>Fibromyalgia</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Lung volume reduction surgery</td>
<td>Older patient</td>
<td>Older patient</td>
</tr>
</tbody>
</table>


### Table 2: Contraindications to the Use of the 6-Minute Walk

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>Resting tachycardia (120)</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>Poorly controlled systemic hypertension (MAP ≥135)</td>
</tr>
<tr>
<td>Unable to ambulate</td>
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</table>

has not been standardized in patients with PAH. It is our sense from conversations with staff from other pulmonary hypertension (PH) centers that 6-minute walk methodologies vary between institutions. While most centers make every effort to be in compliance with the American Thoracic Society recommendations, certain differences are dictated by the architectural design of the facilities in which the test is performed. One such example is the utilization of a single hallway vs a continuous track. Recommendations for the performance of the 6MWT have been provided in the protocol in many of the pulmonary vasodilator studies; however, the level of specificity within a trial and consistency across trials varies. In the absence of widespread standardization, there remain significant gaps in the understanding and interpretation of the 6MWT for patients with pulmonary vascular disease. Nonetheless, the combination of the simplicity of the testing and its consistent use in efficacy studies has resulted in widespread employment in the clinical evaluation of patients. Serial measurements have been recommended by the currently available clinically based guidelines. The 6MWT may be used to evaluate both disease progression and clinical response to therapy. In addition, the distance walked has been demonstrated to correlate with WHO functional class and hemodynamic assessment of PAH.

The 6-minute walk distance has also been incorporated into treatment guidelines for risk stratification. It has been suggested that lower risk patients, such as those who walk at least 400 meters, may respond to oral monotherapy. Conversely, higher risk patients who walk less than 300 meters may require more complex prostanycin or combination therapy. Although such stratification is based on both rational considerations and experiential evidence, it has not been rigorously studied. In addition, the utility of the 6MWT in PH patients who walk more than 450 meters may be more limited.

PROGNOSIS

Early literature demonstrated a relationship to 3-year survival using a breakpoint of 332 meters. Only 20% of patients lived 3 years if the distance walked was less than 332 meters compared to 92% if greater. The 6MWT was reviewed in the American College of Chest Physicians evidence-based clinical guidelines. The quality of evidence for use of exercise tolerance to monitor patients was determined to be "good" with a net "substantial" benefit. Overall, the strength of recommendation for its use in PAH was an "A."

A longer distance of 380 meters was employed in a goal-oriented approach to treatment of PAH. The correlation with outcome and emphasis on objective treatment goals has resulted in risk stratification recommendations involving the distance walked. Such recommendations are predicated upon the poor outcome of a low distance walked and imply that more "aggressive" therapies such as infusion prostacyclin be employed. While perhaps reasonable, such an approach to treatment selection has not been proven.

More recently, an analysis of 664 patients with idiopathic PAH from the REVEAL registry determined that the 380-meter cutoff point had a sensitivity of 79% with a specificity of 55%. The use of a breakpoint distance that equated to 65% predicted was also examined. The latter had a sensitivity of 65% with a specificity of 69% indicating less sensitivity but more specificity than the absolute distance cutoff. A 70% predicted cutoff had similar sensitivity and specificity to the absolute distance of 380 meters. In addition, 1-year survival for those patients with 6-minute walk distance in excess of 380 meters was 98% compared to 89% with lower walk distances.

MISCELLANEOUS

Comorbidities

Approximately 50% of group 1 PAH patients are classified as associated PAH due to coexisting morbidities, many of which may adversely affect the 6-minute walk distance. A bout half of the associated PAH patients have scleroderma. It should be noted that the distance walked is generally decreased in patients with scleroderma without lung disease. The distance walked is further reduced by both pulmonary vascular and parenchymal lung disease.

Clinical Trials

As previously mentioned, improvement in the 6-minute walk distance was first shown to correlate with a favorable response to treatment with epoprostenol. It has since been either a primary or secondary end point in most of the studies of FDA-approved vasodilator therapy. In general, the walk distance improved by approximately 40 meters (range 16 to 59) compared to placebo in short-term studies (3 to 4 months).

While the 6-minute walk distance has been used as a primary end point in most of the clinical trials in PAH, its role in this regard has come under considerable scrutiny. Additional criticisms include the "ceiling effect" and the insensitivity for those patients who walk more than 450 meters. Unfortunately, the alternative end points also have limitations. In addition, the 6-minute walk remains a FDA requirement for pharmacological studies in PAH.
Costs
The relative costs of those tests used to assess baseline function and response to treatment are an ongoing consideration, particularly in the era of declining reimbursement. Serum biomarkers may be the least expensive; eg, brain natriuretic peptide levels can be assessed for approximately $20. Echocardiography and right heart catheterization would represent the other end of the spectrum with costs that generally exceed $350 and $1000 respectively. Medicare reimbursement for a 6MWT is approximately $68. Whether the reimbursement covers the overhead has not been directly studied, but an analysis in our institution seems to indicate that this is not the case, as the cost to perform is approximately $150.

CONCLUSION
The 6MWT is an easy to perform and practical test that has been used in the assessment of patients with a variety of cardiopulmonary diseases including PAH. The correlation with maximal cardiac output renders the test an indirect measure of ventilation function in patients with significant PAH. In addition, the test has been employed in the majority of studies evaluating the efficacy of pulmonary arterial vasodilators and has been demonstrated to correlate with prognosis. Despite the existence of testing guidelines, the test has not been standardized in patients with PAH. In order to improve our understanding and interpretation of the test results in patients with pulmonary vascular disease, this review should provide a sufficient basis for the consistent performance of the 6MWT within an institution.

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Exercise Training and Pulmonary Rehabilitation in the Pulmonary Hypertension Patient

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Recent evidence challenges the traditional wisdom regarding the risks of exercise in PAH patients. Clearly, there are some patients who benefit from the addition of pulmonary rehabilitation to their medical treatment. Still, the details regarding the optimal patient population, timing, and makeup of the program are undefined. As evidence mounts regarding the safety and benefits of an exercise regime in patients with PAH, pulmonary rehabilitation may become another tool to improve the quality of life for these patients.

Exercise training improves outcomes in patients with cardiopulmonary diseases such as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD). Because of this, formal rehabilitation programs are commonly used in management. Although the symptoms of pulmonary arterial hypertension (PAH) are similar to those in both CHF and COPD, data on the effects of exercise in PAH patients are minimal. Historically, exercise was discouraged for PAH patients due to concern that it would induce hypoxemia, arrhythmias, and worsening right ventricular failure. However, results of recent studies have challenged this historical wisdom. Based on early data, the most recent American College of Chest Physicians (ACCP)/American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) evidence-based clinical practice guidelines suggest that pulmonary rehabilitation may be beneficial in PAH patients, although they offered no firm recommendation. Experts in PAH continue to debate the safety versus potential benefit of an exercise program for these patients. The rationale for the ongoing investigation can be better understood by examining respiratory physiology in the patient with PAH.

EXERCISE PHYSIOLOGY IN PAH

One of the earliest symptoms of PAH is dyspnea with exertion. This symptom is related to complex alterations in normal exercise physiology. In response to physical exertion, muscle metabolism increases which then prompts an increase in respiratory rate and cardiac output to optimize oxygen delivery. The normal pulmonary circulation responds to this increased flow by recruiting vascular units and decreasing vascular resistance. These compensatory mechanisms are impaired in the patient with PAH. Cardiopulmonary exercise testing (CPET) allows observation of this physiologic change by measuring the ventilatory equivalent of carbon dioxide (VE/VCO₂), oxygen consumption (VO₂), carbon dioxide production (VCO₂), and anaerobic threshold (AT). Using CPET, we are able to relate the pathophysiology of PAH to the patient’s symptom of dyspnea with exertion.

Pulmonary arterial hypertension is characterized by abnormal remodeling of the adventitial, smooth muscle and intimal layers of the small pulmonary arteries. As disease burden increases, the pulmonary circulation transforms from a high flow/low resistance system to a low flow/high resistance system. This transformation affects exercise capacity in 2 ways. First, pulmonary arteries can no longer vasodilate to accommodate increased flow. Second, there are fewer “unused” and therefore available vascular units for recruitment. In normal controls, the ventilatory equivalent for carbon dioxide (VE/VCO₂) will decrease with exercise as respiratory rate increases and alveolar-capillary units are recruited. In PAH patients, an increase in physiologic dead space, due to decreased perfusion in the remodeled pulmonary capillary bed and resultant ventilation/perfusion mismatch, alters this response. Thus VE/VCO₂ increases in PAH patients commensurate with the severity of disease. Further, right to left intracardiac shunting with exercise in PAH patients with a patent foramen ovale will worsen this abnormal response to exercise. Increased dead space ventilation in PAH patients is also confirmed by measuring the partial pressure of end-tidal CO₂ with exercise (Figure 1). This mismatch between perfusion and ventilation of alveoli limits respiratory efficiency and likely contributes to dyspnea.

The cardiac output response to exercise is also altered in PAH. Cardiac magnetic resonance imaging (MRI) studies reveal an impaired stroke volume response in PAH patients when compared to normal controls. This impairment in stroke volume results from both an increase in pulmonary artery pressure (PAP) with exercise and a decrease in left ventricular volume as the enlarged right ventricle geometrically impairs diastolic filling. This low output state decreases oxygen delivery to the exercising muscle, resulting in lactic acidosis and a further increase in ventilatory drive. Thus, this pathologic response to exercise creates a spiral of increasing respiratory drive and decreasing cardiopulmonary efficiency.

In addition to limitations in cardiac output and pulmonary vascular capacitance, PAH patients also have altered peripheral oxygen extraction. Tolle et al recently compared exercise hemodynamic and CPET parameters in patients with PAH, diastolic heart failure, and systolic heart failure (Figure 2). This comparison revealed a significant decrease in oxygen extraction at maximal exercise in patients with mild PAH when compared to patients with left sided heart failure. The cause of this difference is unclear, but perhaps the ongoing vasculopathy in pulmonary hypertension induces a more
“systemic” inflammation, with distant effects on muscle metabolism. Mainguy et al evaluated exercise capacity, quadriceps strength, enzymatic profiles, and muscle biopsy pathology in 10 patients with idiopathic PAH (IPAH). Pulmonary arterial hypertension patients had a lower proportion of type I muscle fibers, a higher potential for anaerobic metabolism, and lower quadriceps strength than matched controls. These results suggest that skeletal muscle dysfunction may also contribute to dyspnea in patients with PAH.

EXERCISE TRAINING
The observation that exercise limitation in PAH affects quality of life prompts the question of whether this might be amenable to intervention. To this end, recent work has examined whether an exercise training program might be safe and effective in PAH patients. Mereles et al, working in Germany, published the largest work on this subject in 2006. This multicenter study group recruited 30 patients into a 15-week randomized controlled exercise and lifestyle modification protocol. Patients were either classified as having PAH (n=23) or chronic thromboembolic pulmonary hypertension (n=7), were World Health Organization (WHO) functional class II-IV, and had been on a stable medical regimen for at least 3 months.

Patients were randomized into a training group or a sedentary group. Patients in each group were monitored in the hospital for the initial 3 weeks of the protocol. The primary end points of the study were 6-minute walk test (6MWT) distance and health related quality of life as measured by the Short Form Health Survey (SF-36). Secondary end points included Borg dyspnea index, changes in WHO functional class, stress echocardiographic parameters including estimated PAP and right ventricular and atrial areas, and CPET parameters. These end points were evaluated at baseline, Week 3, and Week 15.

The program was intensive and both the control and the intervention groups received a nutritional program, physical therapy, massages, counseling, respiratory training, and muscular relaxation while in the hospital. The intervention group additionally underwent a supervised, 7-day-a-week regimen of 10 to 25 minutes of interval-graded bicycle ergometer training which was limited by peak heart rate <120, SpO₂ <85% and perceived physical exertion. Additionally, they performed 60 minutes of walking on level and uphill ground 5 days per week during which they were accompanied by a physiotherapist and received “mental...
training” to improve their perception of their physical abilities. Five days per week they performed 30 minutes of dumbbell training and 30 minutes of respiratory training. They also participated in yoga and “strengthening of respiratory muscles.” After the 3-week in-hospital program, they were discharged with an individualized training manual and a bicycle ergometer. They were instructed to use the bicycle for a total of 15-30 minutes, 5 times per week, at their target heart rate. They also were instructed to continue their respiratory exercise and dumbbell training every other day. They were monitored by phone during the at-home period. After the initial 15-week period, the sedentary group was offered the same training regimen and 10/15 participated, comprising a secondary training group.

All patients had severe PAH with mean pulmonary vascular resistance of 902±358 dynes·cm⁻⁵ in the sedentary group and 969±44⁴ dynes·cm⁻⁵ in the training group. Baseline WHO functional class was primarily III (73%), with the remainder of patients classified as II (20%) and IV (7%).

The results of this intensive training regimen were significant. At baseline the groups had similar 6MWT distances at 411±86 m in the control group and 439±82 m in the training group (P=0.38). After completion of the 15-week program the mean difference in the 6MWT distance between the groups was 111 m (P<0.001) (Figure 3). The secondary training group also showed 6MWT improvement at 3 weeks and after completion of the program. Quality of life scores were lower in patients at baseline compared with the general population. The physical training program improved the physical and mental component summary scores on the SF-36 and the subscale scores for physical functioning, mental health, and vitality. WHO functional class improved significantly in the training group as did peak oxygen consumption (VO₂ peak 11.4±3.3 ml·min⁻¹·kg⁻¹ vs 15.4±3.7 ml·min⁻¹·kg⁻¹). The ventilatory equivalent of carbon dioxide at anaerobic threshold decreased in the primary training group after 3 weeks but increased in sedentary patients. There were no adverse events during the program such as right heart failure or progression of symptoms or disease.

This was the first prospective, randomized, controlled trial to show that a regimented exercise training program can positively impact quality of life and exercise parameters in patients with PAH. Despite these exciting results, the findings in this study must be interpreted with caution. Improvement in 6MWT distance as a result of training does not indicate improvement in pulmonary hemodynamics, as it might in response to pharmacologic therapy for PAH. In addition, the population studied in the Mereles paper excluded patients with connective tissue diseases.

**CARDIOPULMONARY REHABILITATION**

In 2009, a group in Amsterdam examined the effect of a 12-week outpatient program on 6MWT distance and CPET parameters. This study also examined the effect of strength training by assessing quadriceps function with a hydraulic dynamometer and muscle biopsy at baseline and after training. Additionally, endurance was measured using submaximal exercise with both aerobic and resistance training. All patients in this program were diagnosed and treated for PAH. They attended a training program at a rehabilitation center 3 times per week, which utilized the American Heart Association guidelines for the rehabilitation of chronic heart failure patients. Briefly, this program consisted of cycling and resistance training targeted at the quadriceps. At the end of the trial period, there were no changes in 6MWT distance or peak exercise capacity. However, their exercise endurance time increased and their anaerobic threshold shifted toward a higher workload (32±5 to 46±6 W, p = 0.001). Quadriceps strength increased by 13% (p = 0.005), but there was a larger change.
in muscle endurance at 34% (P = 0.001). Quadriceps muscle biopsy showed increased capillary formation and oxidative enzyme activity after training. This study showed that an outpatient, intermittent program can improve endurance and muscle aerobic capacity.

A similar but smaller study was recently reported from Quebec. In this trial, 5 IPAH patients treated with a single oral agent were recruited into a 12-week outpatient cardiopulmonary rehabilitation program. Baseline 6M WT, CPET, endurance cycle testing, and volitional and non-volitional quadriceps strength at maximal voluntary contraction (MVC) were measured. These measurements were then used to create an exercise prescription for each patient. Patients attended the program 3 times per week, which consisted of: 10-15 minutes of cycling with workload personalized to CPET, resistance exercises consisting of 2 sets of 10-12 repetitions for 6-8 different muscle groups, and 15 minutes of treadmill walking at 85% of mean 6M WT speed. The intensity of the program was then increased as tolerated. The following parameters were measured before and after the program: 6M WT, cycle endurance test, limb muscle cross-sectional area, quadriceps function by maximal voluntary contraction and magnetic stimulation, and muscle biopsy. At the end of the training period, patients exhibited a mean increase of 13% in 6M WT distance and a 53% increase in endurance time. Additionally, VE/VCO2 decreased after training. The proportion of type I muscle fibers decreased, while type II muscle fiber increased and the capillary/fiber ratio increased. The authors postulate that this “less fatigable” muscle profile might contribute to a higher anaerobic threshold after training. This study also suggests that in patients with IPAH, exercise endurance can be improved by exercise training.

The magnitude of the improvement noted in these trials rivals medical therapy. In fact, the STRIDE-1 study group utilized CPET data when evaluating the safety and efficacy of sitaxsentan in PAH. Although the primary end point (peak VO2) was reached for the highest dose of the drug, none of the other CPET parameter changes were statistically significant. Medical therapy is targeted toward the pathology of pulmonary arteriopathy, and should be optimized and stable before increasing cardiopulmonary demand with an exercise program. The addition of exercise training targets cardiovascular fitness and muscle strength, thereby improving oxygen delivery, oxygen uptake, and ultimately endurance.

**FUTURE DIRECTIONS**

These studies reveal that a careful and regimented exercise program may improve endurance and symptoms in PAH patients. Still, many questions remain unanswered regarding the optimization of these programs. These studies included patients who had been on a stable PAH treatment regimen for a number of months. The optimal timing for initiation of a program remains unknown. Additionally, reported programs had varying ratios of strength versus aerobic exercise. Although it is likely that a combination of both strength and endurance training is helpful, the optimal combination is also unknown. Further work is needed to determine if results from studies such as that reported in the Mereles paper can be reproduced completely in the outpatient setting and in broader patient populations. Ongoing work in the area of exercise pathophysiology and programs in patients with PAH will help answer some of these remaining questions.

**REFERENCES**

1. In a 40-year-old patient undergoing exercise testing with measurement of pulmonary arterial pressures to investigate the etiology of dyspnea on exertion, which of the following criteria represents the best indicator of an abnormal pulmonary vascular response pattern?
   a. Mean pulmonary arterial pressure during exercise greater than 30 mm Hg
   b. Estimated right ventricular systolic pressure during exercise greater than 40 mm Hg by echocardiography
   c. Increase in mPAP relative to cardiac output of greater than 2 mm Hg per liter of cardiac output with failure of pulmonary vascular resistance to fall
   d. None of the above

2. A mean pulmonary arterial pressure greater than 30 mm Hg at peak exercise indicates that a patient has pulmonary arterial hypertension.
   a. True
   b. False

3. Pulmonary arterial pressure during exercise in normal individuals is most significantly influenced by which of the following variables?
   a. Older age
   b. Gender
   c. Exercise modality (ie, cycle ergometry vs treadmill)

4. Noninvasive cardiopulmonary exercise testing can distinguish between exercise limitations due to pulmonary arterial hypertension, heart failure with preserved ejection fraction, and preload failure.
   a. True
   b. False

5. Invasive hemodynamic monitoring during cardiopulmonary exercise testing at MGH involves all of the following except:
   a. Pulmonary arterial catheter
   b. Continuous 12-lead EKG recording
   c. Radial arterial catheter
   d. Exercise stress echocardiography
   e. First pass radionuclide ventriculographic scanning

6. What are the results of the noninvasive exercise studies of the cases reviewed in this paper?
   a. Low VO\textsubscript{2}max, early ventilatory threshold, elevated VE/VCO\textsubscript{2}
   b. High VO\textsubscript{2}max, early ventilatory threshold, elevated VE/VCO\textsubscript{2}
   c. Low VO\textsubscript{2}max, late ventilatory threshold, elevated VE/VCO\textsubscript{2}
   d. Low VO\textsubscript{2}max, early ventilatory threshold, decreased VE/VCO\textsubscript{2}
   e. Low VO\textsubscript{2}max, late ventilatory threshold, decreased VE/VCO\textsubscript{2}

7. The 6-minute walk test is commonly used in the evaluation of patients with PAH. Which one of the following statements is most correct?
   a. The minimally important clinical difference between tests is 15 meters
   b. A distance walked of 380 meters indicates a better prognosis
   c. Patients should not be allowed to use oxygen during the test
   d. The technicians performing the test should support the patients by encouraging them to do their best

8. The 6-minute walk test assesses exercise capacity but which of the following is NOT correct?
   a. As right ventricular function deteriorates so does the distance walked
   b. The patient may increase their walk distance with subsequent testing without any associated cardiovascular improvement
   c. The test provides discriminatory information on the exact mechanism limiting exercise capacity
   d. The distance walked directly correlates with oxygen consumption

9. Which of the following physiologic responses to exercise is abnormal in the patient with PAH?
   a. The cardiac output response
   b. The pulmonary vascular response
   c. Peripheral muscle oxygen extraction
   d. All of the above
   e. a and b

10. Which of the following is true regarding supervised exercise programs in patients with PAH?
    a. They improve quality of life
    b. They improve survival
    c. They are unsafe because of the risk of worsening right ventricular failure
    d. They improve endurance
    e. a and d

11. Oxygen extraction at peak exercise is decreased in PAH patients to the same degree as patients with CHF.
    a. True
    b. False
Exercise and PH Project #406802

Individuals wishing CME credit for this self-study activity should read the text, answer the self-assessment examination questions, complete the form below,* and send by US mail or fax to the following address by September 1, 2011. You should receive a score of 70% or higher for CME credit. Your test will be scored and your participation will be entered into the CME records at the University of Michigan Medical School.

Office of Continuing Medical Education
Attn: Pamela Little
Towsley Center—1500 East Medical Center Drive
University of Michigan Medical School
Ann Arbor, MI 48109
Fax: (734) 936-1641

Your certificate will be mailed within 3 weeks of receipt of request.

Self Assessment Answer Key
Circle one correct answer.

1. a b c d  
2. a b  
3. a b c  
4. a b  
5. a b c d e  
6. a b c d e  
7. a b c d  
8. a b c d  
9. a b c d e  
10. a b c d e  
11. a b

Evaluation of CME Activity
(see page 91)

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<tr>
<th>Poor</th>
<th>Satisfactory</th>
<th>Excellent</th>
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1. Extent to which objectives were met

2. Potential impact on your practice

3. Avoidance of commercial bias or influence

4. Your overall evaluation of this self-study activity

Additional comments about this self-study activity:

________________________________________________________________________

________________________________________________________________________

Suggestions for future topics:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

* Self-assessment examination may also be completed online at: http://cme.med.umich.edu
Help your pulmonary hypertension patients gain the knowledge, confidence and hope vital to coping and managing their disease.

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Web and phone support can help.
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www.PHAssociation.org/DiscussionBoards

Toll-free Patient-to-Patient Support:
800-748-7274

Starting a support group has never been easier: From a how-to manual to phone support, PHA works with doctors, nurses and other medical professionals to help start successful groups.

For more information on support groups or to request PHA materials for your office, contact Debbie Castro at Debbie@PHAssociation.org or 301-565-3004 x755.
Simvastatin as a Treatment for PAH

Both researchers and clinicians have shown a significant amount of interest in the potential benefit of HM G-CoA reductase inhibitors (statins) for the treatment of patients with pulmonary arterial hypertension (PAH). The statins, in addition to having cholesterol-lowering benefits, have been shown to possess potent anti-proliferative, anti-thrombotic, and anti-inflammatory cardiovascular properties. Statins have been reported to suppress endothelial and vascular smooth muscle cell responses to injury in animal models. Over the last several years, a series of investigations in animal models of pulmonary hypertension (both the hypoxic-and monocrotaline-rat models) have provided data suggesting possible potential therapeutic benefit for patients with PAH.

In this issue of the Clinical Trials Update, we review the multicenter trial by Wilkins et al.1 which looks into the addition of simvastatin as a treatment for PAH in patients with class II and III symptoms who are already stable on oral therapy. The authors conducted a double-blind, randomized, placebo-controlled trial evaluating the effects of simvastatin added on to optimized therapy in patients with idiopathic PAH (IPAH), associated PAH (APAH) with connective tissue disease, or atrial septal defects (ASDs). Patients were either on a stable dose of phosphodiesterase type-5 (PDE-5) inhibitors or endothelin receptor antagonists or both, plus background therapy. Patients were randomized to receive either simvastatin or placebo for 24 weeks and after that were offered open label simvastatin (40 mg po QD and then titrated up to 80 mg po every day).

The primary outcome measure studied was the change in right ventricular (RV) mass and function, assessed by cardiac MRI. Secondary end points included change in 6-minute walk distance; plasma NO metabolites and cytokines levels as well as biomarkers (NT-proBNP and growth factor-15 [GDF-15]). Quality of life was documented using the Cambridge Pulmonary Hypertension Outcome Review. BORG dyspnea scale was used post 6-minute walk.

At 6 months, the RV mass was shown to decrease in the statin group by 5.2 +/- 11 g (P = 0.045) while the RV mass increased in the placebo group by 3.9 g +/- 14 g. The NT-proBNP significantly decreased during the initial 6 months in the statin group but not in the placebo group. There were no significant changes in other outcome measures (including the 6-minute walk, cardiac index, and cytokines).

From 6 to 12 months, both the RV mass and the NT-proBNP increased back toward baseline in the patients who had been started on the statin and continued on the statin so that there was no longer a difference from baseline. Patients who were started on the statin after placebo showed a stable RV mass and NT-proBNP. As in the first 6 months, there were no significant differences in the secondary outcomes between the 2 groups. There was not a significant reduction in the quality of life score between the patients on the statin and those on the placebo.

In this study, the addition of simvastatin to the treatment of patients with IPAH/hereditary PAH (HPAH) and PAH associated with ASD or connective tissue disease was associated with this reduction in RV mass and NT-proBNP in the first 6 months, but these improvements were not sustained over 12 months.

This study had some limitations. It was a relatively small study. The fact that the statin was added to stable patients who were already on 1 or 2 different classes of treatment (PDE-5 inhibitors and endothelin receptor antagonists) made this small group difficult to interpret. These drugs may all interact with each other as they are all substrates for CYP3A4, which would make this even more difficult to evaluate. A larger study looking at each one individually to evaluate the effects they have on each other would be of interest.

This study’s primary outcome was RV mass. The question arises on how this relates clinically to patients with PAH and the outcomes to which it relates. Even with the decrease in the RV mass, there were no significant changes in the clinical secondary outcomes. Also, as the authors point out, there were no data on the changes in pulmonary vascular resistance and therefore no way to evaluate whether the reduction in RV mass was secondary to a reduction in the resistance.

This study brings up many questions on how the statins may be used in patients with pulmonary hypertension in the future. It provides a launching pad to begin considering how best to study this class of drug in larger and possibly longer studies.

Obesity is an epidemic affecting a staggering proportion of the population worldwide. The US Surgeon General reports that more than 1 billion adults are overweight (body mass index [BMI] 25-29.9 kg/m²) and at least 300 million are categorized as obese (BMI >30 kg/m²). The impact of obesity in the cardiopulmonary system is well recognized. The cardiac structures undergo a variety of adaptations and functional alterations as excessive adipose tissue accumulates, even in the absence of other comorbidities. One fundamental change that occurs with obesity is increased metabolic need. As a result, the circulating blood volume, plasma volume, and cardiac output increase. This leads to an increase in wall tension and induces left ventricular hypertrophy, which results in a decrease in diastolic compliance. At this stage obese patients present with diastolic heart failure accompanied by pulmonary hypertension. Once the left ventricle is no longer able to adapt to the increase in left ventricular filling pressure and enlargement, systolic dysfunction follows with worsening pulmonary hypertension, often accompanied by right heart failure.

The effect of obesity on respiratory physiology is numerous and includes elevated work of breathing in the presence of heightened demand for ventilation. Mechanically, obesity is associated with respiratory muscle inefficiency and diminished respiratory compliance. The decreased functional residual capacity and expiratory reserve volume are associated with the closure of peripheral lung units, ventilation to perfusion ratio abnormalities, and hypoxemia, which is pronounced in the supine position. These chronic abnormalities result in hypoventilation and sleep apnea syndromes with attenuated hypoxic and hypercapnic ventilatory responsiveness leading to hypoxemia, pulmonary hypertension, and progressive disability.

Thus, obesity appears to be the major risk factor in pulmonary hypertension associated with diastolic dysfunction and chronic hypoxemia/hypoventilation, among others. However, there is no definitive evidence to demonstrate direct cause and effect between obesity and pulmonary arterial hypertension (PAH) as shown by the updated consensus document, which does not list obesity as a risk feature for PAH.

This lack of evidence is surprising given the far reaching effects obesity poses on the cardiopulmonary systems. PAH appears to be common among obese patients as demonstrated by its association with appetite suppressant use. One recent study suggests that obesity alone may be a risk factor for PAH. Furthermore, the benefits of weight loss in improving and, in some cases, reversing the symptoms and structural abnormalities associated with PAH have been reported. Patients who underwent bariatric surgery in conjunction with PAH therapy have shown dramatic improvements in exercise performance, hemodynamics, and sleep.

Why is there such paucity of direct evidence linking obesity and PAH? Could it be that BMI, an indirect measure of obesity, appears to be the major risk factor for PAH alone may be a risk factor for PAH. Furthermore, the benefits of weight loss in improving and, in some cases, reversing the symptoms and structural abnormalities associated with PAH have been reported. Patients who underwent bariatric surgery in conjunction with PAH therapy have shown dramatic improvements in exercise performance, hemodynamics, and sleep.

References

Update PHA’s Address
To accommodate program and staff growth, PHA has moved into new space in its current building. Please note that the new address is Suite 1000. The rest of the address and phone numbers remain the same: Pulmonary Hypertension Association, 801 Roeder Road, Suite 1000, Silver Spring, MD 20910-4496. Phone: 301-565-3004.

Clan Receives Award
Stephen Y. Chan, MD, PhD, Instructor of Medicine at Harvard Medical School and Associate Physician, Brigham and Women’s Hospital, Boston, is the recipient of the 2010 Pulmonary Hypertension Association/NHLBI Mentored Clinical Scientist Development Award (K08) for his research on behalf of patients.

PH and . . . Brochure Series Available
PHA launched a new series of brochures about pulmonary hypertension and 6 associated diseases and conditions. The PH and . . . brochures discuss the connection between PH and the following: Hereditary Hemorrhagic Telangiectasia (HHT), HIV, Liver Disease, Methamphetamine Use, Sickle Cell Disease, and Scleroderma. The brochures were written by members of PH Clinicians and Researchers who specialize in the associated conditions and translated into patient-friendly text with the help of PH Resource Network member Michele Gilbert, RN, MSN, APN-C, CCRN, CNN. These brochures are designed to help increase awareness about the prevalence of PH in associated-disease patients and provide needed educational resources for patients and members of the medical community.

The PH and . . . brochures have been produced in two series: one for medical professionals and the other for patients and caregivers and are available online at www.PHAAssociation.org/AssociatedDiseases and www.PHAAssociation.org/Medical/AssociatedDiseases. For more information, contact PHA at 301-565-3004.

PHA’s “Building Medical Education in PH” Partnership
Building Medical Education in PH events are designed to foster partnerships between PHA and PH Centers to promote continuing education in the field of pulmonary hypertension through CME educational events. Upcoming courses are scheduled at:

2nd Annual UNC-Duke Research Triangle Pulmonary Hypertension Symposium
October 22, 2010
The Friday Center

Chapel Hill, N.C.
Email: jennifer_mayfield@med.unc.edu
Call: 919-962-7399

8th Annual Update in Pulmonary Hypertension Institution Affiliation: Tufts University and Medical Center
December 3, 2010
Hyatt Regency Cambridge
Cambridge, Mass.

More information on additional upcoming BME events can be found on the calendar listing at PHA Online University: www.PHAOnlineUniv.org/Calendar. To learn more about partnering with PHA through Building Medical Education in PH for your next CME event, please contact Meghan Finney, Medical Education Program Associate, at 301-565-3004 x 776 or BME@PHAAssociation.org.

New Patient Materials
Newly diagnosed PH patients can receive an Envelope of Hope via their PH physician’s office. With free materials from PHA, it’s never been easier to provide the information and support patients are looking for. All patients need to do is fill out a request postcard, send it to PHA, and they will receive a mailing of educational and support materials. To obtain referral postcards for your office or clinic, contact EOH@PHAssociation.org or call 301-565-3004 x777. PHA membership brochure displays are also available by contacting FPOC@PHAAssociation.org.

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

American College of Chest Physicians Annual Meeting
CHEST 2010
October 30 - November 4, 2010
Vancouver, British Columbia, Canada
www.chestnet.org/accc/chest/chest-annual-meeting

Society of Critical Care Medicine
40th Critical Care Congress
January 15-19, 2011
San Diego, California, USA
www.sccm.org

American Thoracic Society International Conference
May 13-18, 2011
Denver, Colorado, USA
www.thoracic.org
The University of Michigan Medical School and PHA are pleased to announce the second year of this important educational program.

Using a combination of a dynamic didactic presentation with interactive case studies, this program will instruct front-line clinicians in the highest quality of care for patients with PAH. The 30-City Medical Education Program is appropriate for all health care professionals who screen or help care for patients with PAH.

<table>
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<tr>
<th>Programs Scheduled to Date:</th>
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<tr>
<td><strong>Tuesday, October 12</strong></td>
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<tr>
<td>Portland, OR</td>
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<tr>
<td>Catherine J. Markin, MD</td>
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<tr>
<td>Oregon Health and Science University</td>
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<tr>
<td><strong>Wednesday, October 13</strong></td>
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<tr>
<td>Riverside, CA</td>
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<tr>
<td>Ronald J. Oudiz, MD</td>
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<td>The David Geffen School of Medicine at UCLA</td>
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<td><strong>Thursday, October 14</strong></td>
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<tr>
<td>Boise, ID</td>
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<tr>
<td>Lynn M. Brown, MD, PhD</td>
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<td>University of Utah</td>
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<td><strong>Tuesday, October 19</strong></td>
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<tr>
<td>Indianapolis, IN</td>
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<tr>
<td>Omar Minai, MD</td>
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<td>Cleveland Clinic</td>
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<td><strong>Wednesday, October 20</strong></td>
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<tr>
<td>Hershey, PA</td>
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<td>Darren B. Taichman, MD, PhD</td>
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<td>University of Pennsylvania School of Medicine</td>
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<td><strong>Thursday, November 4</strong></td>
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<tr>
<td>San Juan, PR</td>
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<tr>
<td>Franck Rahaghi, MD, MHS, FCCP</td>
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<td>Cleveland Clinic Florida</td>
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<tr>
<td><strong>Tuesday, November 9</strong></td>
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<tr>
<td>Chico, CA</td>
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<tr>
<td>Dana P. McGlothlin, MD</td>
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<td>UCSF School of Medicine</td>
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<tr>
<td><strong>Tuesday, November 9</strong></td>
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<tr>
<td>Long Island, NY</td>
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<tr>
<td>Arunabh Talwar, MD</td>
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<td>Albert Einstein College of Medicine</td>
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<td><strong>Wednesday, November 10</strong></td>
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<tr>
<td>Tucson, AZ</td>
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<tr>
<td>Franz Rischard, DO, MS</td>
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<td>University of Arizona</td>
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<td><strong>Tuesday, November 16</strong></td>
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<td>Greenville, SC</td>
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<tr>
<td>Kristin B. Highland, MD</td>
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<td>Medical University of South Carolina</td>
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<tr>
<td><strong>Thursday, November 18</strong></td>
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<tr>
<td>El Paso, TX</td>
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<tr>
<td>Fernando Torres, MD</td>
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<td>University of Texas Southwestern Medical Center</td>
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“Definitely the BEST presentation I have been to on this topic; guest lecture right to the point/informative/useful”

B.E., Burlington, VT

“Entire program was informative; case studies helped to put into real settings and encouraged use of information gained”

K.F., Morgantown, WV

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A complimentary dinner will be provided.

There is no fee for this program.

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For the treatment of pulmonary arterial hypertension (WHO Group I) patients with NYHA Class III symptoms to increase walk distance

PROSTACYCLIN POWER IS...

INHALE ABLE

The vasodilatory and antiplatelet activities of a prostacyclin analogue

Improvement in 6MWD at peak and trough exposure when added to oral monotherapy

Four times daily dosing during waking hours—treatment timing can be adjusted for planned activities

Patient-friendly delivery with the lightweight, portable, handheld TYVASO Inhalation System

*TYVASO has primarily been studied when added to a phosphodiesterase type 5 (PDE-5) inhibitor or an endothelin receptor antagonist (ETRA)


INDICATION

TYVASO is indicated to increase walk distance in patients with WHO Group I pulmonary arterial hypertension and NYHA Class III symptoms. 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 ≥4% 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.


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For more information, please visit www.tyvaso.com

TYVASO (treprostinil) INHALATION SOLUTION

PROSTACYCLIN MADE PRACTICAL.
BRIEF SUMMARY
The following is a brief summary of the full prescribing information for TYVASO® (treprostinil) Inhalation Solution. Please review the full prescribing information prior to prescribing TYVASO.

INDICATIONS AND USAGE
TYVASO is indicated to increase walk distance in patients with WHO Group I pulmonary arterial hypertension and NYHA Class III symptoms. The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

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

CONTRAINDICATIONS
None.

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

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

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) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

ADVERSE REACTIONS
The following potential adverse reactions are described in Warnings and Precautions:
- Decrease in systemic blood pressure
- 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 rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 12-week placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group I and nearly all NYHA Functional Class III), the most commonly reported adverse reactions to TYVASO included: cough (54%), headache (29%), nausea (22%), flushing (15%), and diarrhea (11%).

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TYVASO n = 115</th>
<th>Placebo n = 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>62 (54)</td>
<td>35 (29)</td>
</tr>
<tr>
<td>Headache</td>
<td>47 (41)</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Throat Irritation/Pharyngitis</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>Vomiting</td>
<td>17 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Syncope</td>
<td>7 (6)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*More than 3% greater than placebo

The safety of TYVASO was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of one year. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo controlled trial.

Adverse Events Associated with Route of Administration
Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngitis, pain, epistaxis, hemoptysis, and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

DRUG INTERACTIONS
Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (TYVASO), however, some of such studies have been conducted with orally (treprostinil diethanolamine) and subcutaneously administered treprostinil (Remodulin®).

Pharmacodynamics
Antihypertensive Agents or Other Vasodilators
Concomitant administration of TYVASO with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension.

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

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

Sildenafil
In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil diethanolamine, no pharmacokinetic interactions between treprostinil and sildenafil were observed.

Effect of Cytochrome P450 Inhibitors and Inducers
In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP3A4.

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil didehydroamine) indicated that co-administration of the cytochrome P450/CYP2C9 enzyme inhibitor gemfibrozil increases exposure (both Cmax and AUC) to treprostinil. Co-administration of the CYP2C9 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C9.

Effect of Other Drugs on Treprostinil
Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

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

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

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

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

Geriatric Use
Clinical studies of TYVASO did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, 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. Uptake 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.

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Rx only July 2009
www.tyvaso.com
Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) in patients with WHO Class II-IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these potential benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

Important safety information
Because of the associated risks, Tracleer may be prescribed only through the Tracleer Access Program.

Potential for serious liver injury (including, after prolonged treatment, rare cases of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring)—Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter.

High potential for major birth defects—Pregnancy must be excluded and prevented through the use of reliable forms of birth control; monthly pregnancy tests should be obtained.

Contraindicated for use with cyclosporine A and glyburide.

Please see brief summary of prescribing information including BOXED WARNING on following pages.
Use in Patients with Pre-existing Hepatic Impairment

Tracleer should generally be avoided in patients with moderate or severe liver impairment. There has been limited experience with maintenance dose in 62.5 mg twice daily. No information about the safety and efficacy of Tracleer in children between the ages of 12 and 18 years.

Use with Ritonavir

Co-administration of Tracleer in Patients on Ritonavir

In patients who have been receiving ritonavir for at least 10 days, start Tracleer at 62.5 mg once daily or every other day based upon individual tolerability [see Drug Interactions].

Co-administration of Ritonavir in Patients on Tracleer

Discontinue use of Tracleer at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume Tracleer at 62.5 mg once daily or every other day based upon individual tolerability [see Drug Interactions].

Dosage Forms and Strengths

Tracleer is available as 62.5 mg and 125 mg film-coated, uncoated tablets for oral administration. 62.5 mg tablets: film-coated, round, biconvex, orange-white tablets, embossed with identification marking “025.” 125 mg tablets: film-coated, oval, biconvex, orange-white tablets, embossed with identification marking “125”.

Contraindications

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. In animal studies, bosentan caused teratogenic effects including malformations of the head, mouth, face, and orofacial and limb vessels. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or other permanent birth control measures, such as their disease progresses.

Dosage and Administration

Recommended Dosing

Tracleer should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of liver injury. Tablets should be administered morning and evening or with or without food.

Required Monitoring

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated.

Dosage Adjustments for Patients Developing Aminotransferase Elevations

The initial dose of Tracleer should be reduced to 62.5 mg twice daily and 7% of PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to ≥3 × ULN were seen in 3% of patients treated with bosentan. The combination of hepatocellular injury (increases in aminotransferases of ≥3 × ULN) and increases in total bilirubin (≥3 × ULN) is a marker for potential serious liver injury.

Elevations of AST and ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with Tracleer.

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 × ULN, treatment with Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

Table 1: Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations ≥3 × ULN

<table>
<thead>
<tr>
<th>ALT/AST Levels</th>
<th>Treatment and monitoring recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 and ≤5 × ULN</td>
<td>Confirm by another aminotransferase test; if confirmed, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate [see below].</td>
</tr>
<tr>
<td>&gt;5 and ≤8 × ULN</td>
<td>Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).</td>
</tr>
<tr>
<td>&gt;8 × ULN</td>
<td>Treatment should be stopped and re-introduction of Tracleer should not be considered. There is no experience with re-introduction of Tracleer in these circumstances.</td>
</tr>
</tbody>
</table>

Use in Females of Childbearing Potential

Initiate treatment in females of childbearing potential only after a negative pregnancy test and only in females who are using two reliable methods of contraception. Females who have had a tubal sterilization or Copper T 380 IUD or LNG 20 μg inserted do not require any other forms of contraception. Effective contraception must be practiced throughout treatment and for one month after stopping Tracleer. Females should seek contraceptive advice as needed from a gynecologist or primary care physician. Urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer [see Boxed Warning, Contraindications, Drug Interactions].
Decreased Sperm Counts

An open-label, single-site, multicenter, safety study evaluated the effect on testicular function of Tracleer 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Sperm counts were evaluated at baseline, 6 months, and various times thereafter due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decrease in sperm count of at least 50% in 25% of the patients enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function.

Decreases in Hemoglobin and Hematocrit

Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease in hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4–12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values < 11 g/dL) were observed in 6% of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin occurred in 2% compared to 1% in placebo-treated patients.

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of bosentan treatment.

During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 78% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

Pulmonary Veno-Occlusive Disease

Should pulmonary veno-occlusive disease occur when Tracleer is administered, the possibility of associated pulmonary veno-occlusive disease should be considered and Tracleer should be discontinued.

Prescribing and Distribution Program for Tracleer

Because of the risks of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.). Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. Information about T.A.P. can be obtained by calling 1-866-228-3084.

To enroll in T.A.P., prescribers must complete the T.A.P. Tracleer (bosentan) Enrollment and Renewal Form (see T.A.P. Tracleer [bosentan] Enrollment and Renewal Form for full prescribing physician agreement) indicating agreement to:

- Read and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
- Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with every patient prior to prescribing Tracleer.
- Review pretreatment liver function tests (ALT/AST/bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
- Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
- Enroll patients in T.A.P. and renew patients’ enrollment annually thereafter.
- Educate and counsel females of childbearing potential to use reliable contraception, as defined on the Tracleer Enrollment and Renewal Form, during treatment with Tracleer and for one month after treatment discontinuation.
- Counsel patients who fail to comply with the program requirements.
- Notify Actelion Pharmaceuticals US, Inc. of any adverse events, including liver injury, and report any pregnancy during Tracleer treatment.

Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer.

ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

- **Potential liver injury** [see Boxed Warning and Warnings and Precautions]
- **Fluid retention** [see Warnings and Precautions]

Clinical Studies Experience

Safety data on bosentan were obtained from 13 clinical studies (9 placebo-controlled and 4 open-label) in 887 patients with pulmonary arterial hypertension and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg twice daily) were administered for up to 2 years.

On Study-351, BREATHE-1 and EARLY.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo</th>
<th>Bosentan N=258</th>
<th>Bosentan N=172</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Respiratory Tract Infection</td>
<td>56</td>
<td>22%</td>
<td>30</td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
<td>15%</td>
<td>25</td>
</tr>
<tr>
<td>Edema</td>
<td>28</td>
<td>11%</td>
<td>16</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>12</td>
<td>5%</td>
<td>8</td>
</tr>
<tr>
<td>Syncope</td>
<td>12</td>
<td>5%</td>
<td>7</td>
</tr>
<tr>
<td>Flushing</td>
<td>10</td>
<td>4%</td>
<td>5</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>4%</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>9</td>
<td>4%</td>
<td>4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9</td>
<td>4%</td>
<td>3</td>
</tr>
<tr>
<td>Liver Function Test Abnormal</td>
<td>9</td>
<td>4%</td>
<td>3</td>
</tr>
<tr>
<td>Palpitations</td>
<td>9</td>
<td>4%</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>3%</td>
<td>6</td>
</tr>
</tbody>
</table>

The concomitant administration of bosentan and cyclosporine A is contraindicated [see Contraindications].

Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when Tracleer is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking Tracleer [see Boxed Warning, Contraindications].

An interaction study demonstrated that co-administration of bosentan and a combination oral hormonal contraceptive produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects.

Cyclosporine A

The concomitant administration of bosentan and cyclosporine A is contraindicated [see Contraindications].

During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. Consequently, Tracleer is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

Glyburide

Increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of Tracleer and glyburide is contraindicated, and alternative hypoglycemic agents should be considered [see Contraindications].

Administration of bosentan decreased the plasma concentrations of glyburide by approximately 50%. The plasma concentrations of bosentan were also decreased by approximately 30%. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A. The possibility of worsened glucose control in patients using these agents should be considered.

Lopinavir/Ritonavir or Other Ritonavir-containing HIV Regimens

In vitro data indicate that bosentan is a substrate of the Organic Anion Transport Protein (OATP), CYP3A, and CYP2C9. Ritonavir inhibits CYP3A and inhibits and induces CYP3A. However, the impact of ritonavir on the pharmacokinetics of bosentan may largely result from its effect on CYP3A.

In normal volunteers, co-administration of Tracleer 125 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily increased the trough concentrations of bosentan on Days 4 and 10 approximately 48-fold and 5-fold, respectively, compared with those measured after Tracleer administered alone.
Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD. The similarity of malformations induced by bosentan to the equivalent of 10.5 g/day in a 70 kg person, plasma concentrations of bosentan in rabbits in vivo were lower than those reached in the rat. Clinical experience with concurrent administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trial due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients.

Digoxin, Nicardipine, and Losartan
Bosentan has no significant pharmacokinetic interactions with digoxin and nicardipine, and losartan has no significant effect on plasma levels of bosentan.

Sildenafil
In normal volunteers, co-administration of multiple doses of 125 mg twice daily bosentan and 80 mg three times daily sildenafil resulted in a reduction of sildenafil plasma concentrations by 62% and increased bosentan plasma concentrations by 50%. These effects were not considered clinically relevant and dose adjustments are not necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

Iloprost
Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD) or in dogs treated up to 12 months at doses as high as 1500 mg/kg/day (50 times the MRHD) for two years but not at doses as high as 1500 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of brain astrogliomas in males at doses as low as 600 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of in vitro tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and an in vivo mouse micronucleus assay), there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology
Bosentan was teratogenic in rats given oral doses 180 mg/kg/day. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face, and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 and 300 mg/kg/day. Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs.

Impairment of Fertility/Testicular Function
The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m2 basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD) and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 90 times the MRHD).

PATIENT COUNSELING INFORMATION
Advises patients to consult the Medication Guide on the safe use of Tracleer.

Important Information
• Monitoring of serum aminotransferases

The physician should discuss with the patient the importance of monitoring of serum amino-

• Pregnancy testing and avoidance of pregnancy

Patients should be advised that Tracleer is likely to cause birth defects based on animal studies.

Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. The patient should contact their physician if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or similar expert as needed.

• Drug Interactions

The physician should discuss with the patient possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.
The information and fellowship I have found in PH Resource Network has been invaluable to my clinical practice. My resources have grown dramatically. I am proud to be a part of this valuable group.

~ Kathleen Hague, RN, BSN

For more program information and to register, please visit the PHA website: www.PHAssociation.org/Preceptorship

Connecting the Links of PH Care

Join the PH Resource Network to directly connect with over 750 of your PH-treating peers who share your commitment to enhance the care for PH patients and change the history of this disease.

As a member of the PH Resource Network, you will:

- Connect with your colleagues through the PH Resource Network email group and the PH Pulse, the PH Resource Network quarterly newsletter.
- Advance your knowledge through PHA’s CME opportunities at PHA’s 9th International PH Conference and Scientific Sessions, PH Resource Network Symposium, live programs and more.
- Become a leader by joining one of the many PH Resource Network committees and share your expertise through PathWriters and the PHA Speakers Bureau.

“The information and fellowship I have found in PH Resource Network has been invaluable to my clinical practice. My resources have grown dramatically. I am proud to be a part of this valuable group.”

~ Kathleen Hague, RN, BSN

Join www.PHAssociation.org/PHRN | Email PHRN@PHAssociation.org | Phone 301-565-3004
Earn CME, find the latest research, and connect with your colleagues

The programs of the PHA Medical Education Fund are made possible through unrestricted educational grants from our sponsors:

- Actelion
- Gilead
- Pfizer
- United Therapeutics

PHA also appreciates the support of the Centers for Disease Control (CDC). This website is supported in part by Grant Number 1U5U51DP001739-01 from the CDC. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC.

Advance Your Career:
Join PH Clinicians and Researchers

Share your commitment to advance the study and treatment of pulmonary hypertension. Become a member of PHA's PH Clinicians and Researchers (PHCR) and connect with more than 450 of your PH-treating colleagues.

As a member of PHCR, you will:
- Reach PHA's 10,000 members by listing your practice on PHA's Find a Doctor database, exclusive to members of PHCR.
- Share case studies and engage in active conversations with members of PHCR on the PHCR email group.
- Share your expertise and add to your CV. Speak at an upcoming PHA program, host a Building Medical Education in PH event or write a guest column for one of PHA's publications.

PHA members receive a registration discount to attend PHA’s 9th International PH Conference and Scientific Sessions, June 25-27, in Garden Grove, Calif.

Join www.PHAssociation.org/PHCR | Email PHCR@PHAssociation.org | Phone 301-565-3004
Co-PaySolutions
benefit has increased!

Beginning February 1, 2010

Monthly out-of-pocket expenses capped at $25 for patients with commercial insurance.

Gilead Sciences is committed to serving the PAH community through improved financial assistance. We understand how important it is for your PAH patients to remain on therapy, and during difficult financial times, every dollar matters that much more.

That is why Gilead is announcing an enhancement to our Co-PaySolutions program—providing significantly improved benefits to those who qualify.

- Capping out-of-pocket expenses at $25 per month (previously $75)
- Providing expanded assistance up to a maximum benefit of $9,200 per year (previously $7,100)

These benefits will automatically be applied through LEAP to patients whose co-pay exceeds $25.

To learn more about Gilead Solutions, call 1-866-664-LEAP, or contact your LEAP Care Manager.
Program Announcement:

New Application Deadline: October 12, 2010  Resubmission Deadline: November 12, 2010

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

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

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

FUNDING:*
The award will be funded by PHA and NHLBI and the K08 and/or the K23 will be awarded in 2010.

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

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

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