Congenital Heart Disease and 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.PHAssociation.org/SLC.

† deceased
Pulmonary Hypertension Associated with Congenital Heart Disease: It’s Not All the Same

With improvements in medical and surgical therapeutics over the past two decades, the number of adults living with congenital heart disease now exceeds the number of children. Whether as a result of excessive pulmonary blood flow in childhood, or related to post-capillary obstruction, many of these adults have associated pulmonary hypertension (PAH-CHD) and require advanced management strategies. The evaluation of adults with PAH-CHD, which is often accompanied by complex cardiac lesions including single ventricle anatomy, can be extremely challenging. Presently, with the emergence of novel targeted PAH agents, medical-surgical approaches to APAH-CHD patients are rapidly evolving. In this edition of Advances, Guest Editor Dr Rich Krasuski calls upon authors to highlight the latest advances in the management of PAH in adults with structural heart disease. From the basics on anatomy for the non-congenital heart expert, to imaging, novel medical and interventional therapeutics, and the importance of transition programs, experts cover it all in this issue.

On a personal note, this edition of Advances represents the final journal published during my term as Editor-in-Chief. I want to extend a tremendous thanks to the editorial board and to Deb McBrine for their dedication and assistance during my term. It is with great pleasure that I am able to hand off the position to a close colleague and friend, Dr Myung Park. Dr Park’s expertise in the field, and enthusiasm for helping the PH community, will undoubtedly serve her well in this new position as Editor-in-Chief. Congratulations, Myung!

Finally, I want to express my deepest gratitude for the years of mentorship by Dr Robyn J. Barst who recently lost her own battle with illness, but won so many for the PH community. While many of us will miss her dearly, I am certain that Dr Robyn Barst’s legacy will continue to impact the field for many years to come.

Signing off,

Erika Berman Rosenzweig, MD
Director, Pulmonary Hypertension Center
Columbia University, College of Physicians and Surgeons

Guest Editor’s Memo

This issue of Advances in Pulmonary Hypertension focuses on the management of patients with congenital heart disease and associated pulmonary hypertension. More than a million adults in the United States have congenital heart defects, and adults now outnumber children with congenital heart defects. Many of these patients present complex cases with unique anatomical defects and very complicated interplay between pulmonary blood flow and pulmonary vascular resistance. Up to 40% of congenital heart patients are at risk for developing pulmonary hypertension and up to 10% actually develop it. Half of these can progress to Eisenmenger syndrome, a condition resulting in profound cyanosis from venous to systemic blood flow, when shunt lesions go unrecognized and untreated.

The goal of the following articles is to provide a broad overview of the congenital heart lesions most likely to result in pulmonary vascular disease, so the pulmonary hypertension specialist can become aware of the presenting features and the unique management strategies required. A multitude of treatments are now available for these patients, including medical therapies targeting the pulmonary vasculature, percutaneous devices that can be used to close abnormal intracardiac and vascular communications, balloons and stents that can be used to increase blood flow when the circulation is compromised, and even catheter-based valve prostheses that can be implanted without requiring surgery. A variety of surgical procedures also exist that can target the many different heart defects and valve abnormalities and dramatically alter the natural history of these disorders. Often what is utilized is a hybrid technique with several different specialists working together to improve the quantity and quality of life for this challenging patient population. It is indeed an exciting time to provide care for this constantly expanding group of patients!

Richard Krasuski, MD
Director of Adult Congenital Heart Disease Services
The Cleveland Clinic
ONLY inhaled prostacyclin analogue approved as an add-on to oral PAH monotherapy

- 52% of patients improved 6MWD by greater than 20 m
- Improvement in 6MWD at peak (20 m) and trough (14 m) exposure

Dosing regimen fits into patients' schedules

- Short treatment sessions: just 2 to 3 minutes, 4x daily
- Set up once daily
  - One plastic ampule per day—no need to replace ampule for each treatment session
  - About 5 minutes a day for device preparation—once in the morning, and the device is ready to go all day
- Treatment timing can be adjusted for planned activities

INDICATION

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

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

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

IMPORTANT SAFETY INFORMATION

- Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System
- The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension
- Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn
- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope

Studied efficacy of Tyvaso was based on improvements in 6-minute walk distance (6MWD), New York Heart Association (NYHA) functional class, and Minnesota Living With Heart Failure (MLWHF) questionnaire scores.

TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=215) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at week 12 (obtained at least 4 hours after study drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.

Adverse events

- 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, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope

STUDY DESIGN: TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=215) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at week 12 (obtained at least 4 hours after study drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.

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.

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


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TYVASO: the ONLY inhaled prostacyclin analogue approved for 4x-daily dosing

Short treatment sessions: just 2 to 3 minutes each

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**INDICATIONS AND USAGE**

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

**WARNINGS AND PRECAUTIONS**

- Patients with Pulmonary Disease or Pulmonary Infections—The safety and efficacy of TYVASO have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.
- Risk of Symptomatic Hypotension—Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with TYVASO may produce symptomatic hypotension.
- Patients with Hepatic or Renal Insufficiency—Treat 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 CYP2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both Cmax and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is not known whether treprostinil at an infusion rate of 10 ng/kg/min. inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

**CONTRAINDICATIONS**

None.

**ADVERSE REACTIONS**

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

- Decrease in systemic blood pressure
- Bleeding

**ADVERSE REACTIONS 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 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions to TYVASO included: cough and throat irritation; headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with TYVASO than with placebo.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**—Use 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.**

**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 older patients.**

**OVERDOSAGE**

In general, symptoms of overdose with TYVASO include flushing, headache, hypertension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.
Summaries and commentaries from the section editors and invited reviewers present a clinical context for practitioners’ application of the latest published research relevant to the care of patients with pulmonary hypertension. In this issue, Kelly Chin discusses the role of computed tomography and 6-minute walk distance in the diagnosis of pulmonary hypertension patients.

**Sugiura T, Tanabe N, Matsuura Y, et al. Role of 320-Slice computed tomography in the diagnostic workup of patients with chronic thromboembolic pulmonary hypertension.** *Chest*. 2012 Oct 22. [Epub ahead of print]

Sugiura et al evaluated the accuracy of 320 slice computed tomography (CT) scanning in patients undergoing evaluation for chronic thromboembolic pulmonary hypertension (CTEPH). Forty-four patients were identified as having probable CTEPH based on VQ scan and echocardiography. Patients then underwent 320 slice CT scan, right heart catheterization, and pulmonary angiography. The CT scans were obtained using 0.5 mm slice thickness with ECG gating, and required 2 gantry rotations in order to simultaneously image the lungs and the entire heart. Two independent reviewers read each CT scan, and their results were compared with pulmonary arteriogram, set as the gold standard test for the analysis.

Overall, CT performed well. The sensitivity of the 320 slice CT scan for detecting lobar PEs was 97%, and the specificity was 97.1%, with excellent inter-observer agreement (Kappa=0.91, Table). At the segmental level, the sensitivity was 85.8% and the specificity was 94.6%, with very good inter-observer agreement (Kappa=0.79). The subsegmental arteries were not included in the analysis, mainly due to a lack of an acceptable reference standard. The authors also attempted to estimate systolic pulmonary arterial pressure (sPAP) by looking at the curvature of the interventricular septum, finding a strong correlation between their measured estimate and the actual sPAP (r=-0.79, P<0.001).

Interestingly, the sensitivity and specificity results were calculated at the level of the individual vessel. In other words, they calculated the number of correctly identified vessels (normal vs clot) in the 344 main and lobar arteries and in the 860 segmental arteries that were evaluated; the number of correct CTEPH diagnoses was not reported. Out of 44 patients, only 18 subsequently underwent pulmonary thromboendarterectomy; the disposition of the other patients was not discussed.

The authors concluded that CT pulmonary angiography was a less invasive alternative to conventional angiography for the diagnosis of CTEPH, but acknowledged that the study was a retrospective, single-center study of a highly selected cohort, and that further study was needed.

Sugiura et al provide an interesting look at how multislice CT may be used in the future, though with several caveats. Notably, the patient population included only those with “suspicion” for CTEPH, so it is impossible to determine what the sensitivity and specificity of the test would be in a less select population, nor is it possible to compare its accuracy vs VQ scan. Additionally, although the accuracy of the specific vessels involved seems to have been quite good, they do not discuss how or whether they used this information in determining “operability,” a critical and challenging aspect of the CTEPH evaluation.

**Table: Summary of pathological vascular findings as delineated by CTPA and PDSA, and statistical analysis of findings in CTPA compared to findings in PDSA**

<table>
<thead>
<tr>
<th></th>
<th>CTPA</th>
<th>PDSA</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>K (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main/lobar arteries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(N=344)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of normal</td>
<td>271</td>
<td>277</td>
<td>97.0</td>
<td>97.1</td>
<td>89.0</td>
<td>99.3</td>
<td>0.91</td>
</tr>
<tr>
<td>vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.86-0.96)</td>
</tr>
<tr>
<td>Chronic thromboembolic</td>
<td>73</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>findings</td>
<td></td>
<td></td>
<td>97.0</td>
<td>97.1</td>
<td>89.0</td>
<td>99.3</td>
<td>0.91</td>
</tr>
<tr>
<td>Segmental arteries</td>
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<td></td>
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<td></td>
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<td>(N=860)</td>
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</tr>
<tr>
<td>Number of normal</td>
<td>661</td>
<td>670</td>
<td>85.9</td>
<td>94.6</td>
<td>81.9</td>
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<td>vessels</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.74-0.84)</td>
</tr>
<tr>
<td>Chronic thromboembolic</td>
<td>199</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>findings</td>
<td></td>
<td></td>
<td>85.9</td>
<td>94.6</td>
<td>81.9</td>
<td>95.9</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: CTPA = Pulmonary angiography on 320-slice CT, PDSA = pulmonary digital subtraction angiography, PPV = positive predictive value, NPV = negative predictive value, K = Cohen’s Kappa, 95%CI = 95% confidence interval. Copyright 2012 by the American College of Chest Physicians. Reprinted with permission.

Correspondence: kelly.chin@utsouthwestern.edu
tion. Importantly, prior studies have suggested that conventional CT angiography is less sensitive than VQ scan in the diagnosis of CTEPH.\textsuperscript{1,2} Further study is needed prior to more widespread adoption of 320 slice CT as either a screening or confirmatory test for CTEPH.


Savarese et al performed a meta-analysis of 22 clinical trials in pulmonary arterial hypertension (PAH) looking at mortality and change in 6-minute walk distance (6M WD). They were specifically interested in whether change in 6M WD predicted survival and other outcomes, such as PAH-related hospital admission. Similar to prior meta-analyses, they found that active treatment led to a reduction in all-cause death (odds ratio [OR] 0.43, P<0.01), and active treatment also reduced hospitalization for PAH and/or lung transplantation (OR 0.44, P<0.01) and the initiation of PAH rescue therapy (OR 0.56, P<0.01). However, they did not identify any relationship between change in 6M WD and outcome. They did find a significant relationship between change in 6M WD and change in pulmonary vascular resistance (r=-0.63, P<0.01). In an accompanying editorial, Dr Stuart Rich reviewed the history of the 6M WD as a primary endpoint in PAH phase III clinical trials, and suggests that now is the time to consider novel clinical trial strategies\textsuperscript{3}.

Saverese et al found that change in 6M WD does not correlate well with mortality and other outcomes. Notably, other studies have reported similar findings, suggesting that achieving a particular walk threshold (＞380-440 meters) is more important than the absolute value of the change in 6M WD achieved.\textsuperscript{4,5}

References
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Thursday, September 26, 2013

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Transitioning the Pediatric Pulmonary Hypertension Patient

Section Editor
Martha Kingman, NP

Beth A. Coleman, RN, CPNP
Senior Instructor, Department of Pediatrics Division of Cardiology Pulmonary Hypertension Program University of Colorado at Children’s Hospital Colorado Aurora, CO

Michelle Calderbank, RN, BSN, CPN
Clinical Nurse Coordinator Pulmonary Hypertension Program Children’s Hospital Colorado Aurora, CO

Advances in disease awareness, earlier diagnosis, and additional therapeutic options for treatment of pediatric pulmonary hypertension (PH) in the last 2 decades have dramatically improved survival, leading to the first generation of pediatric patients surviving to adulthood.1-4 Pediatric care is generally a family-centered approach, whereas adult care is more patient-centered. When patients become young adults they must move from dependency on parental involvement and oversight to independence and individual accountability. It is difficult for young adult patients to navigate this transition successfully without coordinated support from their family, pediatric, and adult care providers.

Recent analyses of pediatric PH within REVEAL and in the Netherlands Registry demonstrate the 2 primary subgroups as idiopathic pulmonary arterial hypertension (IPAH) and PH associated with congenital heart disease. IPAH is seen less often in children, while PH associated with congenital heart disease is seen more often than in adults.4 The proportionately higher incidence of young adults with PH associated with congenital heart disease that will be receiving care through adult PH programs in the future will require incorporating adult congenital heart disease (ACHD)-trained physicians into the adult PH care team. The ACHD community has for-

mally addressed the need to create more structured programs with a recent publication of a best practice statement for managing transition to adulthood for adolescents with congenital heart disease.3 The adolescent medical community has recognized issues around transition for more than 2 decades, including a position paper published by the Society of Adolescent Medicine in 1993.6 Transition practices can be further modeled from large pediatric chronic disease populations that have already piloted and implemented these processes, such as cystic fibrosis and sickle cell disease.7-9

Traditionally, adolescent patients have transferred to adult programs through a “drift-away” model: an incomplete, vague transition from the pediatric team instead of a clear and comprehensive “handoff” to the adult care team.30 The “drift-away” model of transfer has been an unsuccessful transition, leaving young adults struggling to manage their disease and treatment well, and frequently resulting in being lost to follow-up.

Over the past 5 years, the center at Children’s Hospital Colorado has experienced increasing numbers of adolescent PH patients achieving college acceptance, entering the workforce, beginning to live independently, and therefore moving away from their nuclear family and support system. Parallel to this, young adults are required to transition from a dependent role where their parents led interactions with health care providers, coordinated medication refills and dosing, and, for those on invasive therapies, often mixed and changed the infusions daily. In addition to the usual challenges of entering college or the workforce, these young adults suddenly have to take ownership of their disease process, become independent in medication administration, identify changes in clinical symptoms, maintain medication compliance, and learn to access the medical providers and arrange clinic follow-up appointments. These challenges have led to the development of a transition program that will assist providers, young adults, and their families in making a structured yet individualized, comprehensive, and successful transition to an adult program.

Barriers to successful implementation of a transition program include insufficient staffing, lack of identified staff members responsible for transitions, financial challenges, institutional acceptance, and resistance from the adolescents and their parents in transferring to an adult center. Commitment to partnership and open dialogue between pediatric and adult programs is vital for smooth and individualized transitions of care.5,10,11

Key aspects of the transition process include: timing; patient, family, and provider readiness; identification of adult PH care team; successful completion of transition curriculum; and transfer of care (Figure 1). The American Academy of Pediatrics, American Academy of Family Physicians, and the American College of Physicians have recommended that the transition process start as early as 12 years of age, with the physical or absolute transfer of care between 18 and 21 years of age depending on developmental readiness.10 Even before the actual education or curriculum portion of the process begins, the concept should be discussed with the patient and family. This decreases stress of the unknown, as many pediatric patients have built a good rapport with their pediatrician and pediatric care team.

After developmental readiness is assessed and the patient enters the transition process, the curriculum focuses on basic understanding of diagnosis and sequentially builds to medication management,
infusion therapy, and direct interaction with the medical care team. Parents play a critical role in the early stages of the transition process, as they must be committed to the process and willing to start relinquishing control, empowering the patient to work toward independence in health care management. The expected age of transfer, roles, and responsibilities during transition should be identified, discussed, and provided in writing.\(^\text{10}\)

It is important to recognize and discuss patient and parent needs and perspectives during the transition process, understanding that it is complex and potentially emotional for them. Families of chronically ill children have made significant changes and accommodations in their lives to care for their children. The pediatric care team has been a constant, is familiar, and is known. To be successful the young adult has to be the driver throughout the process, nourishing self-management skills and growing autonomy.\(^\text{5}\)

In conclusion, transition planning should be a standard policy in pediatric PH programs to maximize patients’ abil-
Transfer Checklist

- Patient/family and pediatric PH provider determine readiness to transition
- Patient has successfully completed Phases I through VI of transition curriculum
- Adult PH provider identified and notified of transfer referral
- Adult PH Provider has accepted referral and has received transfer referral packet
- Patient has scheduled and completed first Adult PH Clinic visit
- Patient and parents have the Adult PH Program’s contact information
- Including contact process for emergency issues
- Telephone care conference between pediatric and adult providers to discuss issues.
- Confirm transfer of care, complete and hand off successful.
- Patient has contacted all pharmacies, home health, and equipment providers with new PH provider information for future prescription management and care orders.

Figure 2: Transition Checklist.

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 has positively influenced the prognosis and survival of patients with PAH.

This self-study activity is based on 4 articles that review the management of patients with congenital heart disease and pulmonary hypertension.

This activity is jointly sponsored by Washington University School of Medicine 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. Describe the anatomy of the most common congenital heart defects (and their repairs) that are associated with the development of PAH.
2. Demonstrate the importance of simple and advanced imaging technique in adults with congenital heart disease and PH as diagnostic and risk stratifying tools.
3. Understand the complex interplay between pulmonary blood flow and pulmonary vascular resistance and the techniques (medical, catheter-based, and surgical) that are used to modify it.
4. Discuss the clinical studies that have established the basis for pharmacology therapy, and explore the new therapeutic frontiers in patients with congenital heart disease and PH.

Self-Assessment Examination: See pages 196 and 197 for self-assessment questions, answer key, and evaluation form.

Faculty
Chair
Richard A. Krasuski, MD, FACC, FAHA
Director of Adult Congenital Heart Disease Services
Cardiovascular Medicine
Cleveland Clinic Foundation
Cleveland, Ohio

Contributing Authors
Jamil A. Aboulhosn, MD, FACC, FSCAI
Director, Ahmanson/UCLA Adult Congenital Heart Disease Center
Los Angeles, California

Sona V. Babu-Narayan, M RCP, PhD
Royal Brompton and Harefield NHS Foundation Trust
National Heart and Lung Institute
Imperial College London
NIHR Cardiovascular Biomedical Research Unit
Royal Brompton Hospital and Imperial College London
London, United Kingdom

Thomas Bashore, MD
Professor of Medicine
Senior Vice Chief, Division of Cardiology
Duke University Medical Center
Durham, North Carolina

Michael A. Gatzoulis, MD, PhD, FESC, FACC
Royal Brompton and Harefield NHS Foundation Trust
National Heart and Lung Institute
Imperial College London
NIHR Cardiovascular Biomedical Research Unit
Royal Brompton Hospital and Imperial College London
London, United Kingdom

Todd L. Kiefer, MD
Assistant Professor
Division of Cardiology
Duke University Medical Center
Durham, North Carolina

Wei Li, MD, PhD, FESC, FACC
Royal Brompton and Harefield NHS Foundation Trust
London, United Kingdom

Erika B. Rosenzweig, MD
Columbia University College of Physicians and Surgeons
Pulmonary Hypertension Center
New York, New York

Michael B. Rubens, FRCP
Royal Brompton and Harefield NHS Foundation Trust
London, United Kingdom

Giancarlo Scognamiglio, MD, PhD
Royal Brompton and Harefield NHS Foundation Trust
London, United Kingdom

Warren A. Zuckerman, MD
Columbia University College of Physicians and Surgeons
Pulmonary Hypertension Center
New York, New York

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 Washington University School of Medicine and the Pulmonary Hypertension Association. Washington University School of Medicine is accredited by the ACCME to provide continuing medical education to physicians.

Credit Designation: Washington University School of Medicine designates this enduring material for a maximum of 2.0 AMA PRA Category 1 Credits. Physicians should claim only the 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 196 to help physicians review important points. A form is also included on page 197 for physicians to evaluate the CME activity. Completion of this activity involves reading the journal and completing the self-assessment examination and evaluation form with a passing grade of 70% or higher, which may take up to 2 hours. Credits for this self-study program are available from May 31, 2013 through April 30, 2014. There is no fee for this program. Please note that this self-study program may also be viewed online at https://cme-online.wustl.edu/pha.

Accreditation Statement: Department of Continuing Medical Education, Washington University School of Medicine, Campus Box 8063, 660 South Euclid Avenue, St. Louis, MO 63110

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.
Anatomy of Congenital Heart Disease Lesions Associated With Pulmonary Arterial Hypertension

Todd L. Kiefer, MD
Assistant Professor
Division of Cardiology
Duke University Medical Center
Durham, NC

Thomas Bashore, MD
Professor of Medicine
Senior Vice Chief, Division of Cardiology
Duke University Medical Center
Durham, NC

Pulmonary arterial hypertension (PAH) is one of the well-characterized sequelae. It is particularly common with unrepaired large left to right shunt lesions that occur distal to the tricuspid valve. Despite prior cardiac surgery, some patients have residual defects that contribute to the development of PAH. The diagnosis of PAH requires right heart catheterization and is defined as a mean pulmonary artery (PA) pressure greater than 25 mm Hg, with a pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure less than 15 mm Hg, and a pulmonary vascular resistance (PVR) greater than 3 Wood units.

It is estimated that overall 5%-10% of patients with congenital heart disease and as many as 30% of unrepaired patients have PAH. When PAH does occur in conjunction with congenital heart disease, it is associated with increased morbidity and mortality. However, the outcome and response to vasodilator therapies is much better for the cohort with congenital heart disease than for all other etiologies of PAH.

The pathophysiology leading to the development of PAH in congenital heart disease patients is related to increased pressure and blood flow in association with a left to right shunt lesion. This scenario is common in a large, uncorrected ventricular septal defect (VSD) or patent ductus arteriosus (PDA), and in surgically constructed shunts where the pulmonary vasculature is exposed to aortic systolic pressure. Alternatively, pre-tricuspid valve shunts, which are low-pressure lesions associated with increased volume circulating through the right ventricle (RV) and pulmonary circulation, such as atrial septal defects (ASD) and partial anomalous pulmonary venous return (PAPVR), lead to PAH much less often.

Over time these shunt lesions lead to distinct changes in the pulmonary arteries with the development of plexiform lesions and subsequent increases in PA pressures and PVR. This often results in right ventricular dysfunction, and in some cases the PA pressures increase, reversal of shunting from net left to right to net right to left occurs with notable cyanosis and the onset of Eisenmenger syndrome. One rationale for early surgical or percutaneous repair of congenital cardiac disease is to prevent the onset or avoid the progression of PAH.

In this review, we will focus on the anatomy of the various congenital cardiac lesions that are associated with PAH. There are several congenital lesions that produce pulmonary venous hypertension, such as pulmonary veno-occlusive disease, cor triatriatum sinister, mitral valve abnormalities, and other left-sided obstructive lesions (coarctation of the aorta and supra-, sub-, and valvular aortic stenosis), but these lesions produce a different pathophysiology and will not be the focus of this discussion.

A VSD is a common form of congenital heart disease with an estimated prevalence of 3 per 1000 in children and 0.3 per 1000 adults, as some VSDs close spontaneously during childhood into adulthood. It is also the most common congenital cardiac lesion associated with PAH in a Dutch registry. There are multiple types of VSDs depending on their location: membranous or perimembranous, muscular, inlet and outlet varieties (doubly committed or infundibular) (Figure 1). Often more than 1 defect in the ventricular septum is present. Anatomically, a membranous VSD is bordered by the membranous portion of the ventricular septum, the aortic valve, and the tricuspid valve. In some cases, the septal leaflet of the tricuspid valve will cover this defect and form a “windsock” deformity with ventricular systole. Often the windsock is fenestrated with left to right shunting of blood from the left ventricle (LV) to the RV. At times, the septic tricuspid leaflet can fuse with the membranous ventricular septum, leading to closure of the defect and obliteration of shunting.

Muscular VSD, as the name suggests, is surrounded by myocardium and can be located anywhere in the ventricular septum. There are often multiple VSD sites in a given patient. An inlet VSD is bordered by the mitral valve, the tricuspid valve, and the muscular septum. Given this location, it is a part of the spectrum of the atrioventricular (AV) canal or AV septal defect, previously referred to as endocardial cushion defects, and is often associated with trisomy 21 (Down syndrome). The inlet VSD is most commonly associated with PAH, with nearly 40% of such patients developing PAH. Finally, an outlet VSD, also referred to as an infundibular, doubly committed, or supracristal VSD with its location superior to the crista supraventricularis, is surrounded by ventricular...
septum, aortic valve, and pulmonic valve. It is important to recognize that any type of VSD may occur either in isolation or with other congenital abnormalities.

The size of a VSD (small vs large) is clinically often estimated, especially in children, by the ratio of the diameter of the VSD to the diameter of the aortic annulus. Defects that are less than or equal to 25% of the diameter of the aortic annulus (usually less than 1 cm) are designated as small, restrictive defects. In general, the smaller size limits flow and left-to-right shunt magnitude. In this scenario, the development of PAH is much less likely. Conversely, a large defect is defined as having a diameter greater than 75% of the diameter of the aortic annulus (usually greater than 1 cm). Given the larger defect and lack of restriction to flow, the pulmonary arterial bed is exposed to a greater degree of systemic LV systolic pressure, and the subsequent development of PAH is much more common.

Atrial septal defects are another common form of congenital heart disease. However, PAH develops less commonly (10%) with this lesion than in post-tricuspid valve shunt lesions in which the pulmonary vascular bed is exposed to higher pressures as well as the increased shunt volume. Five subtypes of ASD have been described: secundum (75%), primum (15%), and superior sinus venosus (10%) are the most common. Less common are the unroofed coronary sinus and the inferior sinus venosus defect (Figure 2). A secundum ASD is characterized by a defect in the fossa ovalis region (generally central region) of the atrial septum. The primum ASD involves the inferior aspect of the atrial septum near the atrioventricular valves. If a concomitant inlet VSD is present, then the defect is classified as an AV septal defect (see previous section on VSD subtypes). In addition, the primum ASD is often associated with an abnormality in the anterior mitral valve leaflet termed a cleft mitral valve, which is associated with varying degrees of mitral regurgitation. The sinus venosus ASD is divided into 2 anatomic subtypes: a superior sinus venosus defect and an inferior sinus venosus defect. The superior sinus venosus ASD involves a defect in the superior aspect of the atrial septum at the junction of the roof of the atria and the entrance of the superior vena cava into the right atrium (RA). A superior sinus venosus ASD is associated with greater than 90% of cases with PAPVR of the right upper pulmonary vein, which aberrantly drains into the RA instead of the left atrium. The inferior sinus venosus ASD is defined by a defect in the interatrial septum inferiorly near the junction with inferior vena cava.

Partial anomalous pulmonary venous return functions as a low-pressure, pre-tricuspid valve shunt lesion, which serves to volume load the RV and pulmonary circulation in a similar manner to an ASD. It is also a rare lesion, with autopsy studies demonstrating an incidence of 0.6%-0.8%. Likewise, in addition to the previously discussed association of superior sinus venous ASD and right upper pulmonary vein anomalous return, there is an association in 5%-10% of cases of secundum ASD with PAPVR. A nomalous pulmonary venous return also occurs at an increased frequency in patients with Turner syndrome.

There are multiple variations of PAPVR in terms of the anatomic location of the vein and number of veins involved and location of anomalous venous attachment/drainage. Anomalous veins may drain into the right atrium, left innominate vein, coronary sinus, superior vena cava, or the inferior vena cava (Scimitar syndrome) (Figure 3). Given that PAPVR is an uncommon lesion, an accurate population level estimate of association with PAH is not available. However, multiple case reports have been pub-

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**Table: Risk for development of PAH with various shunt lesions**

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
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<tbody>
<tr>
<td>• Secundum ASD</td>
<td>• Sinus venosus ASD</td>
<td>• Large, unrestricted VSD or PDA</td>
</tr>
<tr>
<td>• Partial anomalous pulmonary venous return</td>
<td>• Cooley-Waterston shunt</td>
<td></td>
</tr>
<tr>
<td>• Small, restrictive VSD</td>
<td>• Pott’s shunt</td>
<td>• Primum ASD</td>
</tr>
<tr>
<td></td>
<td>• AV septal defect</td>
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</table>
lished describing PAH due to PAPVR in the absence of other congenital anomalies. The pathophysiology is similar to an isolated ASD, and thus a small percentage of patients with this pathology may develop PAH.

A PDA is another post-tricuspid valve, high-pressure to low-pressure shunt lesion that may lead to subsequent PAH. An essential component of fetal circulation and physiology, the ductus arteriosus usually closes during the first few days after birth. However, in some individuals the ductus does not close and persists as a congenital PDA. This represents 5%-10% of all congenital abnormalities.10 From an anatomic perspective, the fetal ductus arteriosus and persistent PDA are a funnel-like connection from the thoracic aorta to the main pulmonary artery. The development of PAH is related to the size of the PDA and the amount of shunt. In some series, the PDA accounts for 20% of cases of congenital heart disease-related PAH.11

An aortopulmonary (AP) window is a rare congenital abnormality that is similar to a PDA, but differs in anatomic location. It is an anatomic connection between the ascending aorta and the main PA, and is usually large and unrestricted in terms of allowing high-pressure systemic flow into the pulmonary vasculature. This facilitates and accelerates the development of PAH and often progression to Eisenmenger syndrome if not surgically corrected at an early age.

Truncus arteriosus is a rare type of congenital heart disease characterized by a common great vessel originating from the heart and the PAs and coronaries arising from the ascending vessel. There are 2 classification systems, the system of Collett and Edwards12 and the Van Praagh and Van Praagh13 system used to describe the relationship between the aorta and the PA. A VSD is essentially universal. This form of congenital heart disease is always diagnosed shortly after birth and unrepaired leads to severe PAH and Eisenmenger physiology. In adults with prior surgical repair for truncus arteriosus, residual shunt may exist and lead to PAH.

Double-outlet right ventricle (DORV) is another rare expression of congenital heart disease characterized by the origin of both great vessels from the morphologic RV, along with a VSD to allow oxygenated systemic blood from the LV, albeit mixed with venous return in most cases, to reach the aorta. Double-outlet right ventricle represents a broad spectrum of anatomy and pathophysiology depending on the location of the VSD in relation to the great vessels (subaortic, subpulmonic, doubly committed, or remote).14 Furthermore, the clinical presentation may vary from that of an isolated VSD, to transposition with a VSD, to tetralogy of Fallot-like, to single-ventricle physiology in the case of a remote VSD.

Figure 2: Anatomic locations of ASD subtypes.

Figure 3: Anatomic variants of partial anomalous pulmonary venous return.
The subaortic subtype of DORV is most common, accounting for approximately 50% of cases. The subaortic DORV subtype also has the strongest association with development of PAH given pathophysiology similar to a large VSD. Pulmonary arterial hypertension may also occur in the unrepaired subpulmonic DORV subtype if there is not RV outflow or pulmonary valve level obstruction to minimize pulmonary blood flow. In one recent series from a database of patients with adult congenital heart disease, 17% of patients with the diagnosis of DORV were noted to have PAH.

Some patients with congenital heart disease have had a surgical shunt to increase flow into the pulmonary circuit when the congenital abnormality prevented adequate pulmonary perfusion. These are generally palliative shunts as a bridge to complete surgical repair. As such, surgical shunts would often be ligated or taken down at the time of subsequent cardiac surgery. However, it is not uncommon to encounter an adult patient with a patent surgical shunt. Through the 1960s and 1970s, as surgical experience with congenital heart defects grew, it was discovered that these palliative high-flow, high-pressure shunts that delivered systemic blood flow to the lungs commonly resulted in PAH.

The first surgical shunt, referred to as a Blalock-Taussig (BT) shunt, was performed in 1944. The BT shunt was constructed from connection of the right subclavian artery to the right PA (Figure 4). The original BT shunt evolved through several modifications, including use of the left side and a synthetic conduit (modified Blalock shunt) to connect the subclavian artery to the PA, which preserved the subclavian artery and circulation to the upper extremity along with control over flow to the lung via diameter of the conduit.

Subsequently, Dr. Willis Potts performed a surgical procedure connecting the descending thoracic aorta to the left PA, which became known as a Potts shunt (Figure 4). In a similar manner, Dr. David Waterston devised a surgery whereby an anastomosis between the posterior aspect of the ascending aorta and the right PA was created (Figure 4). This is commonly known as a Cooley-Waterston shunt. Less frequently used as a palliative shunt was the central shunt, or a surgically created equivalent of the congenital AP window, in which an anastomosis was made between the ascending aorta and the main PA. The Potts and Waterston surgical shunts have a much stronger propensity to produce PAH than the Blalock shunts due to less restrictive flow into the PA from the aorta. For that reason, they were abandoned in favor of the Blalock approach.

Eisenmenger syndrome is the end-stage result of long-standing PAH. It has a prevalence of approximately 8%-10% in patients with congenital heart disease. The pathophysiology involves the progression of irreversible PVR to the point at which PA pressures are greater than systemic aortic pressures and a shunt lesion that was originally left to right reverses in direction of blood flow right to left. With the onset of right to left shunting, cyanosis is apparent. In cases of a PDA, differential cyanosis may be observed due to the anatomic location of the shunt with cyanotic lower extremities and normal appearing upper extremities. Moreover, Eisenmenger syndrome is associated with a variety of other end-organ system complications. Once PA systolic pressure and/or PVR is greater than two thirds of systemic values, and certainly when Eisenmenger syndrome with right to left shunting is present, surgical intervention to correct the underlying cardiac pathology is generally contraindicated.

In conclusion, several anatomic forms of congenital heart disease can lead to PAH. In particular, pressure and volume loading left to right shunt lesions (post-tricuspid valve) in contradistinction to only volume loading left to right shunt lesion (pre-tricuspid valve) are much more likely to cause PAH. From an epidemiologic perspective, unrepaired VSD and PDA are 2 of the more common lesions that will be complicated by pulmonary hypertension. The management of patients with congenital heart disease is complex, and pulmonary hypertension experts should work closely with cardiologists who have specialized training in adult congenital heart disease in order to optimize outcomes for patients with PAH related to congenital heart disease.

References
The Essential Role of Imaging in the Evaluation of Patients With Pulmonary Arterial Hypertension in Association With Congenital Heart Disease

Giancarlo Scognamiglio, MD, PhD,
Sonya V. Babu-Narayan, MRCP, PhD,
Michael B. Rubens, FRCR,
Michael A. Gatzoulis, MD, PhD, FESC, FACC,
Wei Li, MD, PhD, FESC, FACC,
Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom

CLASSIFICATION OF PAH-CHD
The heterogeneity of cardiac morphology and its functional consequences require a customized classification, including a detailed description of cardiac morphology, previous surgical and/or catheter intervention/s, and current functional and hemodynamic status of the patient.

LEFT TO RIGHT SHUNTS
Left to right shunts are the most common substrate for PAH-CHD, accounting for approximately 38% of patients with CHD and pulmonary hypertension (PH) in a recent report from Canada. This group includes patients with Eisenmenger syndrome, where the development of PAH occurs in the presence of a nonrestrictive left to right shunt—intracardiac (usually post-tricuspid) or extracardiac. In about 50%-70% of cases, patients develop irreversible and progressive pulmonary vascular disease in the first few years of life, resulting eventually in reversal of blood flow through the shunt and cyanosis. Examples of these lesions are large ventricular septal defects (VSD), patent ductus arteriosus (PDA), complete atrioventricular septal defects (AVSD), truncus arteriosus, or functionally univentricular hearts without pulmonary stenosis. In cardiac lesions with a left to right shunt at the pre-tricuspid level, ie, patients with large atrial septal defects (ASD) with initial volume and not pressure overload, the development of pulmonary vascular disease is less frequent and later in life. Only one-tenth to one-fifth of patients with a hemodynamically important and large interatrial communication will eventually develop pulmonary vascular disease, mostly in late adulthood.

FONTAN CIRCULATION
Pulmonary arterial hypertension can also complicate other subgroups of CHD, both in their natural history and after surgical repair; such an example of the unique features of the pulmonary circulation in CHD is represented by the Fontan “circulation,” where systemic venous return is directed to the lungs without an interposed ventricular pump (Figure 1). At first glance, it may appear to be out of line with the classical definition of PAH (increased pulmonary vascular resistance [PVR] of greater than 3 Wood units per meter squared or MPAP of more than 25 mm Hg). However, there is evidence of an abnormal pulmonary vascular bed in these patients, as suggested by an abnormal response to exogenous nitric oxide administration. We submit, herewith, that patients with the Fontan circulation should be considered in the PAH-CHD group, as even a minimal increase in PVR can have a major adverse effect on the pulmonary circulation and thus cardiac output given the absence of a subpulmonary ventricle. Based on these considerations, a more refined classification of PAH that coexists with CHD has been proposed to better address this rather heterogeneous patient group that cannot be assumed to be similar in terms of pathophysiology and hemodynamics (Table 1).

ROLE OF IMAGING
Multimodality imaging plays a key role in assessing and managing patients with PAH-CHD. It is important to recognize the strengths/weaknesses and the complementary nature of different imaging modalities as well as the complex nature of the diagnostic questions that need to be addressed.

In this review, we will focus on the imaging tools commonly employed to evaluate PAH in CHD patients and their relative contribution to diagnostic assessment, evaluation of the functional and hemodynamic impairment, and longer-term prognostication.

ECHOCARDIOGRAPHY
Transthoracic echocardiography (TTE) is the first-line cardiovascular imaging modality in the assessment of patients with various types of PAH because it is easy to apply, relatively inexpensive, and provides accurate information on cardiac anatomy and physiology.

In the setting of PAH-CHD, TTE is particularly suitable for the real-time interrogation of structural abnormalities as well as hemodynamic disturbances. In the majority of these patients, TTE allows the evaluation of cardiac anatomy (ie, orientation and veno-atrial, atrioventricular, and ventriculo-arterial connections), the morphology of cardiac structures, ventric-
The presence of shunt lesions, and hemodynamic assessment (eg, severity of valvular regurgitation and evaluation of shunts and velocities across obstructive lesions).7

In addition, in the context of PAH-CHD, TTE is especially helpful in providing information on the following aspects:

- Pulmonary artery pressure
- Right ventricular (RV) involvement
- Prognostication/outcome

### Pulmonary Artery Pressure

**Pulmonary artery systolic pressure.** Pulmonary artery systolic pressure (PASP) can be estimated using tricuspid regurgitation (TR) velocity (V) by applying the Bernoulli equation \[ \text{PASP} = 4V^2 + \text{estimated right atrial (RA) pressure, where V is the average peak TR velocity}. \] In patients with CHD, PASP can also be calculated using maximum flow velocity across a VSD or an aortopulmonary shunt (PDA, Blalock-Taussig shunt) \( \text{(PASP} = \text{systolic blood pressure} - 4V^2) \).8-9

A few aspects must be kept in mind to ensure accurate estimates of PASP.

- Although PASP measured by echocardiography correlates relatively well with PASP measured invasively, Bland-Altman analysis in the clinical setting demonstrates that large (10-20 mm Hg) differences between invasive and noninvasive PASP are common. The most common causes of inaccurate estimation of PASP include an incomplete Doppler envelope, resulting in underestimation of pressure or an overestimate of RA pressure from inferior vena cava diameter and collapsibility.10

### Table 1: Proposed classification of PAH in the setting of congenitally malformed hearts as based on circulatory pathophysiology (modified from 6). Abbreviations: ASD, interatrial communication; AVSD, atrioventricular septal defect; (i)PAH, (idiopathic) pulmonary arterial hypertension; PVR, pulmonary vascular resistance; PDA, patent arterial duct; POF, patent oval foramen; PVH, pulmonary venous hypertension; VSD, ventricular septal defect.

<table>
<thead>
<tr>
<th>Significant shunting lesions</th>
<th>iPAH-like lesions</th>
<th>PAH due to past or present PVH</th>
<th>Eisenmenger physiology</th>
<th>Fontan-like physiology</th>
<th>Unilateral PAH</th>
<th>Hypoplastic PA system</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) For corrective surgery, PVR is low and presents no problem</td>
<td>a) Small unoperated lesion (eg, POF, ASD, VSD, PAD) not hemodynamically related to PAH</td>
<td>a) After corrective surgery of pulmonary venous stenosis or aortic/mitral valvar disease or coarctation, with normal wedge pressure and left ventricular function</td>
<td>a) Classical Eisenmenger physiology: no subpulmonary outflow obstruction; predominantly right to left shunting at atrial, ventricular, or arterial level, no intraventricular mixing</td>
<td>a) After Fontan operation with the right atrium being incorporate</td>
<td>a) Due to a surgical shunt previously created to increase pulmonary blood flow, which has led to significant PAH on that side</td>
<td>a) After corrective surgery of tetralogy of Fallot without major anatomical obstructions of the pulmonary vascular system, and PAH</td>
</tr>
<tr>
<td>b) For corrective surgery, PVR elevated, risk increased but accepted</td>
<td>b) Small residue after corrective surgery of a shunting lesion, not hemodynamically related to PAH</td>
<td>b) PAH due to left ventricular dysfunction with abnormal wedge pressure and increased PVR</td>
<td>b) Functionally univentricular physiology: no sub-pulmonary outflow obstruction; systemic desaturation is due to intraventricular mixing</td>
<td>b) Fontan with a lateral or extracardiac conduit, right atrium excluded, no fenestration</td>
<td>b) Due to congenital origin of one pulmonary artery or of major collateral vessels from the aorta, causing PAH</td>
<td>b) After corrective surgery of pulmonary atresia without major anatomical obstructions of the pulmonary vascular system, and PAH</td>
</tr>
<tr>
<td>c) For corrective surgery, PVR elevated, risk too high, not operable</td>
<td>c) After corrective surgery of pulmonary venous stenosis or aortic/mitral valvar disease or coarctation, with normal wedge pressure and left ventricular function</td>
<td>c) Anatomy as above</td>
<td>c) Anatomy as above</td>
<td>c) Anatomy as above</td>
<td>c) Anatomy as above</td>
<td>c) Anatomy as above</td>
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</table>

**Figure 1:** The Fontan operation and its various modifications. (a) Classic Fontan operation. (b) Lateral tunnel with fenestration, (c) extracardiac Fontan. f, fenestration; IVC, inferior vena cava; PA, pulmonary artery; RA, right atrium; SVC, superior vena cava. (Reprint from Gatzoulis MA, Webb GD, Daubeny PEF. Diagnosis and Management of Adult Congenital Heart Disease. Oxford, UK: Churchill-Livingstone. 2003; page 85.)
The right ventricular systolic pressure (RVSP) calculated from TR velocity may only be taken as the PASP in the absence of RV outflow obstruction. In CHD, more care should be taken to exclude any obstruction along the pulmonary pathway, especially after pulmonic valve surgery or in patients with previous systemic to pulmonary shunts. In some cases, peripheral or segmental pulmonary stenosis may also be present; this will require complementary imaging such as cardiovascular MRI to delineate.

Velocity measurements are angle dependent. Tricuspid regurgitant jets should be taken from multiple acoustic windows (apical 4-chamber views, RV inflow, and off axis if necessary) with accurate transducer angulation in order to obtain a parallel intercept angle between the ultrasound beam and jet to avoid underestimation. In some cases of trivial regurgitant jet and suboptimal continuous-wave Doppler spectrum, the injection of contrast agents (agitated saline, sonicated albumin, or air-blood-saline mixture) may be required to achieve clear delineation of the jet envelope.

Close relationship between PASP and RV cardiac output exists. In cases of “end-stage” PAH, where both advanced RV dysfunction and increased PVR cause a significant reduction in stroke volume, PASP may appear “pseudonormalized” as a consequence of the low driving pressure generated by the failing RV. Underestimation of RV pressure may also occur with the development of diastolic RV dysfunction, characterized by high RA pressure and a stiff RV.

Furthermore, in cases of severe TR the peak velocity may underestimate the trans-tricuspid pressure gradient because of early equalization of pressure between RA and RV, leading to truncation of the Doppler envelope.

Pulmonary artery mean and end-diastolic pressure. Mean pulmonary artery pressure and pulmonary end-diastolic pressure (PADP) are especially useful when TR velocity cannot be obtained or when further information is required. A jet of pulmonary regurgitation, present in the majority of patients with PAH-CHD, permits the measurement of the end-diastolic pulmonary pressure using the modified Bernoulli equation: 

$$\text{PADP} = 4 \times (\text{end-diastolic pulmonary regurgitant velocity})^2 + \text{RA pressure}.$$ 

Similarly, MPAP can be determined from early peak pulmonic regurgitation velocity using the modified Bernoulli equation and adding the estimated RA pressure. Mean pulmonary artery pressure can also be estimated by using pulmonary acceleration time (AT) measured from the onset of RV ejection to peak pulmonary flow velocity (Figure 2). Generally, the shorter the AT, the higher the PVR and hence the pulmonary artery pressure. A value <105 ms is suggestive of PH. Mean pulmonary artery pressure can also be derived by regression formulas where: 

$$\text{MPAP} = 79 - (0.45 \times \text{AT})\text{.}$$ 

The same authors also found that in patients with ATs <120 ms, the formula 

$$\text{MPAP} = 90 - (0.62 \times \text{AT})\text{.}$$

performed better. In addition to AT, the shape of the flow wave is of interest, as PH is associated with a deceleration of flow in mid systole (notching). In the presence of increased PVR and low arterial compliance, pulse wave reflection has greater magnitude and propagates more rapidly, arriving at the right ventricular outflow tract (RVOT) during systole.

In patients with a Fontan circulation, as previously discussed, even a minor increase in pulmonary artery pressure may have significant hemodynamic consequences on the Fontan circulation. Conventional diagnostic criteria for PAH cannot be applied in this type of circulation. Information about MPAP in this setting can be derived from mean flow velocity across a fenestration between the Fontan or total cavopulmonary connection pathway and the atria; when such a fenestration is
present and can be interrogated by echo Doppler [MPAP = 4 V² + left atrial (LA) mean pressure]. If this value is more than 17 mm Hg, it is highly suggestive of PAH.

Comprehensive diagnosis of PAH-CHD should combine Doppler pressure measurements with other accompanying echocardiographic features such as ventricular size and systolic function, as it is the RV that plays the key role in determining clinical presentation and prognosis in PAH-CHD.

Assessment of RV Morphology and Function

Right ventricular morphology. Normally the RV is a thin-walled chamber. In most forms of PAH, as a result of chronic progressive pressure loading, progressive RV remodelling occurs, initially in the form of hypertrophy and later as dilatation, along with progressive contractile impairment and, eventually, RV failure.

Compared to the patients with other forms of PAH, Eisenmenger syndrome hemodynamics and resulting RV remodelling are distinctly different. In adults with Eisenmenger syndrome with post-tricuspid defects and 2 ventricles, the RV often appears greatly hypertrophied with no significant dilatation. This unique physiopathologic adaptive model is explained by the preservation of a “fetal-like” phenotype without loss of RV hypertrophy and the presence of a ventricular communication, allowing both ventricles to function as a single entity.

In contrast, adults with PH and a pre-tricuspid shunt (ie, ASD) show greater LA, RA, and RV dilatation. It can therefore be postulated that loss of RV hypertrophy during infancy, lack of a training effect on the RV during childhood, and the absence of a ventricular communication that pairs the 2 ventricles functionally likely explain the differing RV response.

Eccentricity index. In patients with PAH, the high RV pressure may reduce the trans-septal pressure gradient between the 2 ventricles and leads to the frequently observed flattening of the intraventricular septum (IVS). M-mode analysis, with its high temporal resolution, can accurately estimate differences in the timing of leftward IVS shift during the cardiac cycle. Two-dimensional echo permits the quantification of the septal deformation using the eccentricity index, measured from a parasternal short axis view at the level of the chordae tendineae as the ratio of the left ventricle (LV) dimension parallel and perpendicular to the IVS respectively. It is usually measured both at end diastole and end systole with a normal value of 1.0, which occurs when the LV cavity maintains a round and symmetrical configuration on short-axis imaging. Mild, moderate, and severe septal bowing is represented by values of 1.1–1.4, 1.5–1.8, and >1.8.

LV filling abnormalities. Intraventricular septum deformation also alters LV shape, size, and diastolic filling. Thus, a common echocardiographic finding in these patients is blunted early diastolic filling of the LV, which in this scenario is not indicative of LA hypertension, but instead represents a marker of abnormal ventriculo-ventricular interaction. In fact, increased RV pressure and prolonged RV systole cause early diastolic reversal of the IVS. As a result, early diastolic transmural filling is reduced and redistributed to late diastole.

Right ventricular function. Assessment of RV function is the single most important aspect of the echocardiographic examination in patients with PAH, because symptoms and outcome both depend on the ability of the RV to adapt to an increased pulmonary vascular load.

Right ventricular dysfunction is challenging to quantify on echocardiography. All available acoustic windows and views should be used to provide complementary information and allow for a comprehensive assessment. Qualitative assessment of function based on visual inspection is commonly used in practice, but is limited by a significant interobserver variability, which is especially problematic when assessing relative changes in RV function in the same patient.

Tricuspid annular plane systolic excursion. Differences in muscle fiber orientation of the RV suggest that longitudinal shortening plays a greater role in RV emptying than in the LV. This predominantly longitudinal contractile pattern of the RV can be easily obtained.

Tricuspid annular plane systolic excursion (TAPSE) is the longitudinal systolic displacement of the RV base toward the RV apex and has been shown to correlate strongly with RV ejection fraction (EF). Tricuspid annular plane systolic excursion can be derived using 2D guided M-mode (Figure 3a), is simple and highly reproducible, and has been recommended by American Society of Echocardiography (ASE) guidelines as part of routine echocardiographic evaluation. Normal values vary between 2.3 cm–2.6 cm, with a TAPSE of 2.0 cm likely representing the lowest acceptable normal value. Values in the range of 1.8 cm–2.0 cm, 1.6 cm–1.8 cm, and <1.6 cm are consistent with mild, moderate, and severe RV systolic dysfunction.

A significant limitation of TAPSE in PAH-CHD is that it is highly load dependent, such that it may become pseudonormalized in the presence of significant ventricular volume loading, such as with left to right shunting or severe TR.

Tissue Doppler imaging. Analogous to TAPSE, systolic wave velocity by tissue Doppler imaging (TDI) is a measure of longitudinal myocardial contraction. Tissue Doppler imaging like TAPSE is load dependent and may become pseudonormal under conditions of increased ventricular volume loading. Mean value in normal controls is approximately 15 cm/s at the annulus, with a lower accepted reference limit of normal of 10 cm/s.

Fractional area change. A more quantitative approach of assessing RV function is to measure the RV functional area change (FAC), [(end-diastolic area - end-systolic area)/(end-diastolic area)] × 100, which has demonstrated a close correlation with RV EF by MRI. It is obtained by tracing areas of the RV at end diastole and end systole from the apical 4-chamber view beneath the trabeculations. Unfortunately, incomplete visualization of the RV cavity, especially when the RV is dilated, as well as difficulties in endocardial definition lead to relatively poor reproducibility, thus making it an unreliable tool for serial assessment.

Myocardial performance index. The myocardial performance index (MPI), also known as the Tei index, provides a
global assessment of both RV systolic and diastolic function. It can be calculated either from Doppler imaging (apical 4-chamber view for the tricuspid inflow pattern and the parasternal short-axis RVOT view for the determination of ejection time) or from TDI (single image from the lateral annulus of the tricuspid valve), according to the formula: $\text{MPI} = \frac{\text{isovolumic contraction time} + \text{isovolumic relaxation time}}{\text{RV ejection time}}$.

Values greater than 0.40 by pulsed-wave Doppler or greater than 0.55 by tissue Doppler signify RV dysfunction. It has a good reproducibility, does not rely on geometric assumptions, and can be applied even in the presence of a suboptimal acoustic window. On the other hand, it is relatively load dependent and unreliable when RA pressure is elevated. Right ventricular ejection time, a component of MPI, has been shown to increase on targeted therapy for PAH.

**Total isovolumic time.** The total isovolumic time (t-IVT), which represents the sum of both isovolumic relaxation time (IVRT) and isovolumic contraction time (IVCT), can be calculated by subtracting filling time and ejection time from RR interval. It can be expressed as seconds per minute when calculated using the following formula: $\text{t-IVT} = 60 - ([\text{ejection time} \times \text{heart rate}/1000] + [\text{total filling time} \times \text{heart rate}/1000])$.

Total isovolumic time is the time during the cardiac cycle heart neither ejecting nor filling. It is the total wasted time. In patients with increased pulmonary artery pressure, reduced pulmonary artery compliance will limit RV ejection time and prolonged tricuspid regurgitation duration will result in shortened filling time. Therefore, t-IVT will be significantly prolonged, and as a consequence stroke volume and hence cardiac output decreases. Total isovolumic time can be used for monitoring disease progression and assessing prognosis.

**Advanced right ventricular imaging.** Speckle tracking—strain and strain rate examine the deformation and rate of deformation of the myocardial segments. These represent a method of assessing intrinsic RV myocardial contractility that is less load dependent, but currently remain outside the standard echocardiographic protocols due to the lack of normative data and high interobserver variability.

Real time 3-dimensional echocardiography can overcome the limitations of 2D echo in the assessment of RV volumes and EF. Three-dimensional echocardiographic RV volumes are comparable to those derived by MRI, although little data exist for significantly dilated or dysfunctional ventricles. Technologies, able to create a 3D model of the RV by a post-processing analysis of anatomical landmarks identified in any 2D view, are currently under investigation in an ongoing study in PAH.

**Echocardiographic Predictors of Clinical Outcome**

Different echocardiographic variables have been demonstrated to yield prognostic information that may guide clinical management. From the current literature, and according to the European Society of Cardiology (ESC) guidelines, the echocardiographic assessment of RV function is important. The right ventricular systolic area (RVSA) assessed by M-mode imaging, the tricuspid annular plane systolic excursion (TAPSE) assessed by M-mode imaging, and the right ventricular fractional area change (RVFAC) assessed by tissue Doppler imaging are some of the echocardiographic predictors of clinical outcome. A low TAPSE, RVSA, or RVFAC is associated with a higher risk of adverse events, including hospitalization, death, and heart failure.

**Figure 3:** (a) TAPSE by M-mode recording. (b) Kaplan-Meier curve for TAPSE. Patients with TAPSE <15 mm had higher mortality rates than patients with TAPSE ≥15 mm. (Reprinted with permission from Moceri P, Dimopoulos K, Liodakis E, et al. Echocardiographic predictors of outcome in Eisenmenger syndrome. *Circulation*. 2012;126:1461-1468.)
cardiographic indices most closely associated with unfavorable outcome, including RA area index, diastolic eccentricity index, pericardial effusion, MPI, and TAPSE, are all indicators of RV decompensation. However, prognosis is significantly affected by the etiology of PAH. Patients with Eisenmenger syndrome exhibit a better prognosis compared with idiopathic PAH and connective tissue disease-associated PAH. Patients may survive decades after the initial diagnosis of PAH-CHD, even before the advent of advanced targeted PAH therapy. As mentioned before, the difference in outcome is thought to be related to better adaptation of the RV to systemic or high pulmonary artery pressure. In support of this view, we have recently demonstrated that the longitudinal function of the RV is preserved or mildly impaired in the majority of patients with Eisenmenger syndrome, and that even though RV dilation was prevalent, it was less severe than that described in idiopathic PAH and was not related to adverse outcome.29

Right ventricular long axis function (TAPSE). Right ventricular longitudinal contraction in Eisenmenger patients has been shown to be an independent prognostic factor, both in our cohort, where even small reductions in TAPSE were associated with adverse outcome (Figure 3b), and in another recent prospective study from Van De Bruaen and colleagues where TAPSE <15.9 mm was predictive of lower event-free survival and higher all-cause mortality.30

Ratio of RV effective systolic to diastolic duration. The duration of TR, a marker of impaired adaptation to pressure overload and of RV failure, is strongly related to outcome. In fact, in these cir-

Figure 4: (a) Measurement of effective RV systolic and diastolic duration on trans-tricuspid Doppler. (b) Measurement of RA area on 2D echocardiogram. (c) Time-dependent receiver operating characteristic curves at 1.5 years for the echocardiographic composite score (TAPSE <15 mm, ratio of RV effective systolic to diastolic duration ≥1.5, right atrial area ≥25 cm², RA/LA area ratio ≥1.5). (Reprinted with permission from Moceri P, Dimopoulos K, Liodakis E, et al. Echocardiographic predictors of outcome in Eisenmenger syndrome. Circulation. 2012;126:1461-1468.).

CME Section

176 Advances in Pulmonary Hypertension
cumstances RV filling time is limited by prolongation of TR in presystole and/or early diastole, and cardiac output may consequently decrease. In order to improve the diagnostic power of echo in Eisenmenger patients, a ratio of RV effective systolic to diastolic duration can be calculated (Figure 4a). Durations of systole and diastole can be measured from the clearest Doppler signal of TR from the apical view. Effective systolic duration is measured from the onset to the end of TR. Effective diastolic duration is measured from the end of TR to the onset of the subsequent TR signal. A ratio $\geq 1.5$ is an independent predictor of outcome.29

Right atrial area and ratio of RA to LA area. Parameters reflecting high central venous pressure have also been shown to predict mortality in PAH. Right atrial dilation is a reflection of long-standing pressure overload and ensuing heart failure. Quantitative assessment of RA size is performed from the apical 4-chamber view (Figure 4b). Right atrial measurements are obtained at the end of ventricular systole, when chamber size is maximal. Right atrial area is usually measured, as it has been reported to predict adverse outcome in the setting of PAH. Eisenmenger patients with pre-tricuspid shunts, who are thought to have a worse prognosis compared with those with post-tricuspid shunts,31 are expected to have larger atria because of the long-standing shunt at the atrial level. Right atrial dilation, beyond being a marker of right-sided overload and possibly stiffness of a hypertrophied RV, is also a predisposing factor for arrhythmias. Mortality risk is significantly increased when RA area is $\geq 25$ cm$^2$ or RA/LA ratio is $\geq 1.5$.29

All the parameters discussed above have their limitations when used in isolation. Comprehensive assessment with a combination of multiple parameters provides the most accurate prognostication.

In our cohort, a composite score based on these strong echocardiographic predictors of outcome (TAPSE $<15$ mm, ratio of RV effective systolic to diastolic duration $\geq 1.5$, RA area $\geq 25$ cm$^2$, and RA/LA area ratio $\geq 1.5$) identified patients with more than 3-fold increased risk of death at 1.5 years, with a very high area under the curve on receiver operating curve (Figure 4c).

CHEST RADIOGRAPHY AND CARDIAC COMPUTED TOMOGRAPHY

A plain chest x-ray provides a record of cardiac size, which in the CHD population as a whole carries prognostic significance.32 The typical changes of PAH on the chest x-ray are enlargement of the central pulmonary arteries with relative pruning of the distal vessels. There may also be signs of specific chamber enlargement or other features to suggest a particular underlying defect (Figure 5).

Although disadvantaged by the need for ionizing radiation and contrast, computed tomography (CT) has an important part to play in the investigation of PAH-CHD, as it provides information on cardiac chambers, great arteries, lung vasculature, and parenchyma and mediastinal structures in a single acquisition with high spatial resolution.33 This is particularly the case when acoustic windows have been poor (limiting echocardiography), lung disease is present, or devices such as pacemakers prevent cardiovascular magnetic resonance (CMR) scanning.

Similar features of cardiac physiology associated with PAH described previously can also be identified using cardiac CT. Communications between chambers can be visualized and the direction of shunt inferred by the direction of contrast (Fig-

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**Figure 5:** Chest x-ray of a patient with ASD and PH. The main pulmonary artery (long arrow) and its main branches are enlarged, and the peripheral pulmonary vessels by comparison are “pruned.” The heart is enlarged and the shape suggests right heart enlargement. The aortic knuckle (short arrow) is small—a feature typical of ASD.

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CME Section
Although excellent at providing anatomical detail, it is generally not the modality of choice for providing functional data. If necessary, biventricular function can be assessed, though this necessitates greater radiation exposure to capture information throughout the cardiac cycle.

The CT pulmonary angiogram is the test of choice to assess the proximal and distal pulmonary arteries noninvasively. In doing so, pulmonary artery dilatation can be identified as well as the presence of thrombus, which may form in situ due to sluggish blood flow in an inflamed pulmonary vascular bed rather than being embolic in origin (Figures 6b and c).

High-resolution CT scanning provides valuable information on lung parenchyma, which can be abnormal in patients with CHD because of bronchiectasis or hypoplasia. It may also detect parenchymal changes due to PAH, for example, ground glass changes, nodular opacities, and serpiginous intrapulmonary vessels. In those with chronic thromboembolic PH, it may also identify within the lung tissue hemorrhage, infarction, or a mosaic pattern (due to heterogeneous lung perfusion). High-resolution CT has a vital role in identifying patients with pulmonary veno-occlusive disease, where advanced therapies might be harmful. The key features of this rare entity on CT are interlobular septal thickening, ground glass shadowing, and adenopathy.

When contrast is enhanced, this technique is particularly adept in the assessment of extracardiac features, particularly native or surgically fashioned systemic to pulmonary shunts. Collateral vessels are readily identified. These include dilated bronchial arteries (a feature commonly seen in PAH) or bypassing vessels in cases of pulmonary venous occlusion.

An analytic technique called fractal analysis has been studied to determine whether the degree of branching within the pulmonary arteries of children and young adults with PAH, half of whom had CHD, could be used as a noninvasive
Figure 7: Representative examples of segmented pulmonary artery masks, and below them the derived skeletonized representations for patients with mild, moderate, and severe PH. (Reprinted with permission from Moledina S, de Bruyn A, Schievano S, et al. Fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension: A proof of principle study. *Heart*. 2011;97:1245-1249.).

Figure 8: (A) Cardiovascular magnetic resonance still systolic frame from balanced steady-state free precession cine image demonstrating a large PDA (asterisk) measuring 13 mm diameter. The pulmonary artery is severely dilated with maximum diastolic diameter 50 mm. The RV is severely hypertrophied. (B) A corresponding in-plane phase velocity map is shown, and blood flow is demonstrated to be predominantly from the main pulmonary artery to the aorta in systole.
measure of PH (Figure 7). This index compared well with conventional markers of disease severity such as functional class, 6-minute walk test distance, and indexed PVR, and predicted death among the cohort [HR 5.6 (95% CI 1.2 to 25; \(P = 0.027\)])

CARDIOVASCULAR MAGNETIC RESONANCE
Cardiovascular magnetic resonance has the major advantage of being able to image in any plane with high spatial and temporal resolution without requiring ionizing radiation. As repeated examinations become common, the latter characteristic is particularly beneficial for patients with PAH-CHD.

In order to optimize image quality, breath holding is required. This may be problematic for some patients with PAH-CHD. In addition, pacemakers/devices currently represent a contraindication to routine CMR.

CMR acquisition and subsequent analysis of a stack of contiguous cine image covering the whole heart from base to apex provides the gold standard assessments of right and left ventricular size and function, especially so for heavily trabeculated RVs. However, analysis remains operator dependent.

Using both cine imaging and in-plane flow mapping, intracardiac shunts can be easily identified and quantified. By comparing the ratio of flow through the pulmonary
artery to that in the aorta using flow mapping, Qp:Qs can be determined and aortic flow mapping can be used to determine cardiac output. Tricuspid and pulmonary regurgitation can be assessed with cine imaging, through-plane and in-plane flow.

With the addition of contrast enhanced magnetic resonance angiography, extracardiac shunts (Figures 8a and b) as well as the pulmonary vasculature can be delineated. Septal motion can be qualitatively noted on cine imaging just as in echocardiography.

Late gadolinium enhancement for myocardial tissue characterization has been applied to PAH and typically demonstrates areas of enhancement at the RV-LV insertion point. Histological data, however, support the concept that the myocardial disarray at these sites is a normal feature of insertion-region anatomy exaggerated in PH by the hypertrophy of the RV. Significant efforts have been given over to noninvasively assessing pulmonary pressures using CMR with indices such as RV mass, septal deviation, pulmonary artery stiffness, and more recently 4-dimensional flow patterns (Figure 9). Of the longer established measures, none has emerged as a reliable measure in patients with PAH. Moreover, none have been routinely tested in a CHD population where the presence of pre-existing RV hypertrophy, septal defects, shunts, and arterial abnormalities may confound many of these parameters.

In the setting of a hybrid CMR interventional lab, PVR derived from the Fick method has been shown to be inaccurate in conditions of high pulmonary blood flow or increased oxygen concentration. With promising results, the same technique has been used to show that PVR can be determined noninvasively in a small cohort with mainly atrial and ventricular septal defects. A pulmonary flow of 6.05 l/min/m² or a Qp/Qs ratio ≤ 2.5/1 had a specificity of 100% for predicting PVR of ≤ 3.5 W/m² on receiver-operator characteristic analysis.

**CMR Assessment of Treatment and Prognosis**

The main measure used in clinical practice and as a trial endpoint in PAH is the 6-minute walk test. However, this has faced considerable criticism given its limitations and failure to demonstrate a relationship with clinical endpoints. This has spurred investigation into alternative surrogates, one of which has been RV mass as assessed by CMR. This measure, when employed after medical and surgical therapies, has been shown to reflect improvements in indices of remodelling.

Cardiovascular magnetic resonance has also been used to prognosticate in patients with PAH. Right ventricular dilatation and impaired systolic RV function as well as increased degrees of pulmonary artery stiffness are predictors of a poor outcome in PAH. Unfortunately, data specific to PAH-CHD have yet to be published.

**CMR in Eisenmenger Syndrome**

Cardiovascular magnetic resonance in Eisenmenger syndrome occasionally correctly defines the precise nature and functional significance of the underlying CHD. In surgically palliated patients, CMR can be used to assess the presence and patency of surgical shunts. It is also useful for assessment of other relevant extracardiac features such as PDA or aortopulmonary collaterals. The central pulmonary arteries should be imaged for presence of aneurysmal dilatation, poor expansibility, sluggish flow, and in situ rather than thromboembolic pulmonary arterial thrombus.

**CONCLUSION**

In summary, multimodality imaging plays a major role in assessing patients with PAH-CHD in terms of anatomy, physiology, presence, extent and progression of PAH, and RV function. Different imaging modalities come with strengths and weaknesses, and physicians and imaging specialists should be aware of their complementary and prognostic role, as to provide the optimal therapy and outcomes for the patient with PAH-CHD.

**References**

15. Dabestani A, Mahan G, Gardin JM, et al. Eval-
Pulmonary arterial hypertension with increased PVR is a frequent complication of CHD, known as associated pulmonary arterial hypertension (APAH)-CHD.1,2 This results from pulmonary vascular remodeling due to nonrestrictive, shunt-related increases in pulmonary blood flow (PBF) and/or exposure to increased pulmonary artery pressure (PAP) and sheer stress.3 While the currently accepted definition of PAH no longer includes elevated PVR, it is very important to determine PVR when evaluating a patient with APAH-CHD, as an isolated elevation in PAP with normal PVR may occur with increased PBF and can be amenable to surgery as opposed to representing true pulmonary vasculopathy. Therefore, these authors continue to use the classic definition of PAH when evaluating APAH-CHD, which includes a mean PAP ≥25 mm Hg with normal left-sided filling pressures (left ventricular end-diastolic pressure or pulmonary capillary wedge pressure = 15 mm Hg) and an elevated PVR (PVR indexed to body surface area [PVRi] > 3 Wood units [WU/m²]).4,5 In cases of APAH-CHD, it is also important to differentiate PAH from pulmonary venous hypertension, in which there is increased PAP in the setting of elevated left-sided filling pressures and normal PVR, or a mixed picture with elevation of PAP, left-sided filling pressures, and also PVR. It is critical to distinguish between patients with PAH, pulmonary venous hypertension, and mixed disease (PAH/PVH), as the treatments for these various forms of disease not only vary, but targeted medical therapies may be unsafe in patients with associated postcapillary pulmonary hypertension.

As more patients with CHD are surviving into adulthood, APAH-CHD has become an important medical management issue. The development of PAH in the setting of CHD is partly dependent on the type and size of the cardiac defect, as well as other predisposing environmental and genetic factors. Post-tricuspid valve lesions such as ventricular septal defect (VSD) and patent ductus arteriosus (PDA) are more prone to the development of PAH than pre-tricuspid valve lesions such as atrial septal defect (ASD).6 With progression of disease in these patients, cyanosis eventually develops as a result of reversal of left to right shunting, and this is known as Eisenmenger syndrome.7 It is generally believed that in order to avoid the development of pulmonary vascular disease (PVD), nonrestrictive post-tricuspid defects such as large VSDs and PDA's should be repaired prior to 1 or 2 years of age, while ASDs may be repaired later in childhood. In addition, there are more complex cardiac defects that are associated with the early development of PAH. These include truncus arteriosus, transposition of the great vessels (especially in the presence of a VSD), and complete atrioventricular septal defect (especially in the setting of trisomy 21). If these defects are not repaired within the first few weeks of life, severe PVD will almost invariably develop.8

The clinical presentation of APAH-CHD can be divided into 4 physiologic subtypes (Table). This clinical classification becomes very important in the management of these patients, as treatment strategies are not necessarily the same for each subtype. The latter 2 categories, PAH in the setting of small defects and PAH after corrective cardiac surgery, are physiologically analogous to idiopathic PAH (IPAH), with respect to the lack of a complete atrioventricular septal defect (especially in the setting of trisomy 21). These patients are likely at increased risk for more rapidly progressive RV failure and worse outcomes than those patients with adequate RV “pop-off.” The medical approach in these patients does not differ from that of other forms of WHO Group 1 PAH, although there are less controlled data on the use of targeted PAH therapies available for such patients.

During the last 2 decades there have been significant improvements in the treatment and outcomes of patients with WHO Group 1 PAH. Nine medications have become available in the United States to target 3 main pathways involved in the pathophysiology of PAH: the pros-tacyclin, endothelin, and nitric oxide path-

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Key Words—associated PAH, Eisenmenger syndrome, endothelin receptor agonist, phosphodiesterase-5 inhibitors, prostanooids
Correspondence: wz2116@columbia.edu
Table: Clinical classification of congenital systemic-to-pulmonary shunts associated with PAH. From Simonneau, et al. 2009

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Eisenmenger syndrome</td>
<td>Patients with unrepaired systemic-to-pulmonary shunts resulting from large nonrestrictive defects leading to a severe, progressive increase in PVR, bidirectional shunting, and ultimately reversed shunting with central cyanosis.</td>
</tr>
<tr>
<td>PAH with moderate to large defects</td>
<td>PVR is mildly to moderately increased, systemic-to-pulmonary shunt is still present, and no cyanosis is present at rest.</td>
</tr>
<tr>
<td>PAH with small defects</td>
<td>Smaller defects generally include VSD ≤1 cm and ASD ≤2 cm, and clinical picture is similar to IPAH.</td>
</tr>
<tr>
<td>PAH following corrective cardiac surgery</td>
<td>CHD has been corrected, but PAH is present either immediately after surgery or recurs several months or years after surgery in the absence of significant residual shunts.</td>
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PAH therapies are often used in the treatment of APAH-CHD patients, as well. However, the absence or small percentage of APAH-CHD patients included in these drug trials underscores the need for future studies designed specifically to study this heterogeneous patient population. Medical management of APAH-CHD patients within the first 2 subtypes of APAH-CHD (Table), those with ES and those with PAH in the setting of unrepaired moderate to large defects, requires additional attention to the impact of residual shunting on medical management. The clinical picture within these groups of patients spans a wide range, and at either end of the spectrum, medical decision making is relatively straightforward. At one end, an infant with a large nonrestrictive VSD will have elevated PAP and normal PVRI (≤3 WU/m²), and can be treated with surgical closure of the shunt with little fear that PAP will remain elevated postoperatively.

On the opposite end of the spectrum are patients with severe pulmonary vasculopathy, or ES, demonstrated by shunt reversal, low PBF, and cyanosis in the setting of elevated PAP and high PVR. In these patients with significantly elevated PVR and reversal of shunting, surgical closure would not be advisable; however, these patients may benefit from some of the newer targeted PAH medical therapies. With advances made in targeted PAH therapies, the concept of a combined medical-surgical approach has also become more feasible for subgroup 2 patients (PAH with moderate to large defects in whom PVR is at least mildly increased, systemic-to-pulmonary shunt is still prevalent, and no cyanosis is present at rest), with optimization first medically prior to consideration of surgery. In addition, the idea of a partial repair has emerged in which a fenestration, most commonly an interatrial communication, is left by the surgeon to serve as a “pop-off valve” for the RV. This determination of operability is one of the more challenging and more important aspects of the management of patients with APAH-CHD.
comparison of hemodynamics between disparately sized patients.18

During evaluation of a systemic-to-pulmonary shunt, if there is no evidence of pulmonary venous hypertension once baseline data are collected and PVRI is >3 WU/m², acute vasodilator testing should be performed with inhaled nitric oxide or intravenous epoprostenol, during which another full hemodynamic assessment should be performed. Separate assessment with 100% oxygen may be performed, as well. An extensive review of hemodynamic parameters in determining operability in APAH-CHD was recently published by Giglia and Humpl.19 The authors acknowledged limitations to many of the studies reviewed, and were clear that any parameters be used as a guide within the context of the complete clinical picture. PVRI values in the range of 6 to 8 WU/m² or lower are generally considered operable.19 The ability to lower PVRI to 6 WU/m² or lower with vasodilator testing with inhaled nitric oxide +/− oxygen has been associated with better outcomes, as well.20-22 Additionally, a >10% decrease in PVR and PVR/SVR ratio in response to acute vasodilator testing, with a final PVR/SVR ratio of <0.3 are predictive of better postoperative outcomes.23,24

Due largely in part to advances in targeted PAH therapies and studies demonstrating improved hemodynamics in APAH-CHD patients with such therapies, there is an evolving role for a combined medical-surgical approach to those patients that are either borderline operable, or in some cases initially inoperable.25-28 It is reasonable to treat with targeted therapies for a period of months and reevaluate by catheterization, sometimes requiring serial reevaluations. If medical treatment of a patient with a shunt and moderate PVD is effective, PVR will lower and result in increased PBF. As a result, surgical measures may actually be necessary to protect the pulmonary vasculature from the development of further damage.

Cardiac catheterization alone, however, cannot determine operability, since catheterization data are often obtained under “ideal” resting conditions. While a patient at rest may seem to be operable, with a minor respiratory illness and hypoxic vasoconstriction, it may become evident that a shunt should not be closed, or at least not completely. A thorough medical history and physical examination, and exercise testing when possible, play important roles in the determination of operability. Important elements of the history include age, type of CHD, and time of and circumstances surrounding diagnosis. The importance of the type of CHD has been previously discussed; and in general, the earlier a shunt lesion is diagnosed, the more likely the patient is operable. In addition, a history of cyanosis and/or dyspnea with exertion is important. Signs of cyanosis such as blue lips or nail beds with exercise, clubbing, and erythrocytosis also help provide a complete picture to determine operability.

**EISENMENGER SYNDROME**

In 1897, Viktor Eisenmenger first described a 32-year-old patient who died of massive hemoptysis and had a VSD on postmortem examination. The term “Eisenmenger syndrome” was coined by Paul Hamilton Wood in 1958 to define the condition of increased PAP and PVR in relation to a VSD with resultant shunt reversal and cyanosis. Subsequently, ES has been used to describe any CHD or shunt between the great arteries with resultant increase in PVR and shunt reversal.29 Advances in CHD diagnosis and cardiac surgery, especially during infancy and early childhood, have helped to increase the number of CHD patients surviving into adulthood, and decrease the number of patients with ES in the Western world. Only around 5% of adults with CHD will develop PAH.30 However, in developing countries where patients seek medical care later in life, ES still remains a significant problem. The worldwide prevalence of PAH in adults with CHD has recently been estimated at between 1.6 and 12.5 million, with 25% to 50% presenting with ES.31 In Latin America, the prevalence of advanced APAH-CHD relative to IPAH at cardiovascular centers is between 2:1 and 3:1.32 Although life expectancy is reduced in ES, it is significantly better than IPAH, with many patients surviving into their third and fourth decades,33 and even some into their seventh decade.33,34 More than 40% of subjects are expected to be alive 25 years after diagnosis.7,35 There is some bias in these data as many patients were from the era prior to targeted PAH therapies. As a result, many who died early of severe hypoxemia and RV failure due to advanced ES may not have been included. However, with advances in targeted therapies, the hope is for future improvements to these numbers, supported by a recent study predicting 5-year survival of 95.3% in children with ES.36

**Conventional Therapies for Eisenmenger Syndrome**

Historically, treatment options for ES patients had been limited to palliative therapies and heart-lung transplantation or lung transplantation with surgical correction of a simple shunt. Currently, conventional management is used in combination with targeted PAH therapies. Commonly used conventional therapies may include digoxin, diuretics, and anticoagulation, as well as antiarrhythmics when warranted, although none of these agents have been shown to improve survival in ES. Although supporting evidence is not particularly strong, digoxin is generally used for right heart failure.37 Diuretics are often employed in this situation, as well; however, they should be used cautiously, as they may reduce plasma volume in patients with erythrocytosis, and also lead to dehydration. Anticoagulation in ES patients is a debatable subject due to increased risks of pulmonary artery thrombosis as well as hemoptysis, stroke, and hemorrhage.37 Although the benefit of anticoagulation in IPAH patients has been demonstrated,38,39 no such data exist in ES patients. Given the potential complications, the decision to anticoagulate should be made carefully on an individual, case-by-case basis. Long-term use of oxygen is often employed in ES patients; and while it may be associated with improvement in subjective status, no survival benefit has been reported.37,40

ES patients that are chronically cyanotic may develop secondary erythrocytosis. With hemoglobin above 20 g/dL, hyperviscosity symptoms may develop,
including headache, fatigue, and difficulty concentrating. Phlebotomy, combined with isovolumic fluid replacement, is reserved only for patients with symptomatic hyperviscosity and no iron deficiency or dehydration.\textsuperscript{41,42} Iron deficiency, often missed in this patient population due to the requirement of a relatively high resting hemoglobin in the setting of chronic cyanosis, is associated with lower event-free survival and higher mortality in ES patients, and should be treated when recognized.\textsuperscript{41,43}

**Targeted Therapies for Eisenmenger Syndrome**

There are emerging data on the use of all 3 main classes of targeted PAH therapies (prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors) for the treatment of ES patients. As opposed to APAH-CHD with moderate PVD, ES patients are unlikely to experience a significant decrease in PVR that would be enough to reverse shunting and allow for surgical correction of CHD. The aim of targeted therapies in these cases is to improve exercise tolerance, hypoxemia, physical capacity, and ultimately survival.

Intravenous epoprostenol has been used in pediatric PAH,\textsuperscript{44} and specifically in APAH-CHD,\textsuperscript{9,45} leading to improvements in functional capacity, hemodynamics, and survival. In 1999, Rosenzweig et al reported the first benefit of PAH-targeted therapy of any form in this patient population, with improvements in cardiac index, PVR, and quality of life in 20 patients with APAH-CHD.\textsuperscript{9} Similarly, in 2003, Fernandes et al demonstrated improvements in functional capacity, oxygen saturation, and hemodynamics in 8 ES patients using epoprostenol.\textsuperscript{45} Treatment with epoprostenol requires use of a permanent central venous catheter, which can be problematic in the setting of right to left shunt due to the potential for thromboembolic events. In addition, systemic and local complications may include infections, sepsis, and line breakage with drug interruption. Treprostinil, a similar and longer-acting prostanoïd, can be delivered either intravenously, subcutaneously, or by inhalation, and offers potential advantages over epoprostenol in terms of a longer half-life and mode of delivery. Although efficacy and safety has not been fully established in this patient population, open-label multicenter trials involving the intravenous and subcutaneous formulations have included patients with APAH-CHD,\textsuperscript{10,46} and the inhaled formulation has recently been FDA-approved for use in patients in WHO Group 1.

The first randomized, double-blind, placebo-controlled study in ES patients was the BREATHE-5 trial, which investigated the efficacy and safety of the dual endothelin receptor antagonist bosentan in adult ES patients.\textsuperscript{13} It remains the only trial of its kind dedicated solely to the ES population. During the 16-week study, bosentan significantly reduced PVR and improved PAP and exercise capacity compared to placebo.\textsuperscript{13} Longer-term data from the follow-up portion of the study demonstrated continued improvements in exercise capacity and functional class over an additional 24 weeks.\textsuperscript{15} Safety findings were of particular importance, given the potential for worsening of right to left shunting in the face of decreased SVR with vasodilator therapies. There was no significant difference in oxygen saturation change between the bosentan and placebo groups during the study period. In addition, there was a worsening of PVR in the placebo group, underscoring the progressive nature of untreated ES. Smaller-scale, open-label studies demonstrated sustained effects over longer periods of time using bosentan in the ES population.\textsuperscript{47-49} The selective endothelin receptor antagonist ambrisentan offers potential advantages over bosentan given its selectivity for the endothelin-A receptor, which demonstrates vasoconstrictor effects. Although less studied, ambrisentan has also been noted to be safe and efficacious in APAH-CHD and ES.\textsuperscript{28}

Oral sildenafil is the most widely used of the phosphodiesterase-5 inhibitors in the treatment of PAH, and has been used in pediatric and APAH-CHD, with benefits on exercise capacity and hemodynamics demonstrated.\textsuperscript{26,30,51} Singh et al performed a randomized, placebo-controlled, double-blind, crossover study in 10 IPAH and 10 ES patients in 2006, and found that sildenafil significantly improved functional status, exercise capacity, and PAP compared to placebo.\textsuperscript{50} Similarly, a recent prospective, open-label, multicenter study out of China on 84 ES patients demonstrated safety and improved functional status, exercise capacity, oxygen saturation, PAP, and PVR after 12 months of sildenafil therapy.\textsuperscript{14} Sildenafil also comes in an intravenous form, and there may be a role for its use peripheratively in the intensive care setting. The longer-acting, once-daily dosed tadalafil is less well studied than sildenafil; however, a recent randomized, placebo-controlled, double-blind, crossover study in ES patients also demonstrated safety and short-term improvements in exercise capacity, functional class, oxygen saturation, and hemodynamics after 6 weeks of therapy.\textsuperscript{52}

Due to the progressive nature of PAH and the efficacy limitations of each of the drug classes, one of the mainstays of the treatment of PAH has become combination therapy. In this manner, drugs with different mechanisms of action may provide an additive effect, or even the same effect at lower doses. Although data are limited in ES patients, in 2010, Larsen et al performed a randomized, placebo-controlled, double-blind, crossover study evaluating the effect of combination therapy with bosentan and sildenafil in 21 ES patients.\textsuperscript{53} In this study, patients were treated with bosentan for 9 months and were then treated for 3 months with sildenafil or placebo, followed by a 3-month crossover. They found improvements in exercise capacity and hemodynamics after treatment with bosentan, but no further benefit after addition of sildenafil, although there was an increase in oxygen saturation and the combination was well tolerated. The future of PAH therapy in ES patients certainly involves evaluation of such combination therapies, as well as studies evaluating cutting-edge, targeted PAH therapies such as oral prostacyclin (selexipag), tissue-targeting endothelin receptor antagonist (macitentan), receptor tyrosine kinase antagonist (imatinib), and soluble guanylate cyclase inhibitor (riociguat).\textsuperscript{54} Over the last decade, the outlook for the ES patient has gone
from a “hands-off” strategy to a hopeful one, in the form of targeted PAH agents that may lead to improvements in functional status, exercise capacity, and survival. Further study in clinical trials will be essential for optimization of medical therapies for APAH-CHD over the next decade.

CONCLUSIONS
While PAH associated with CHD is classified with many other subgroups as Group 1 pulmonary hypertension, this group is very heterogeneous in terms of anatomic, physiologic, and clinical features. Improvements in diagnosis and surgery for CHD have dramatically improved the short- and long-term outlook for patients with APAH-CHD. Although advancements in noninvasive imaging such as echocardiography have helped in the evaluation of this patient population, the importance of cardiac catheterization cannot be overstated in helping with management. In addition, the newer targeted PAH therapies appear to have short-term benefits in these patients, but require further investigation, and their use in patients with borderline hemodynamics has paved the way for a combined medical-surgical approach to management in select patients.

Reference
The Role of Catheter-Based and Surgical Treatments in Patients With Congenital Heart Disease and Pulmonary Hypertension

Jamil A. Aboulhosn, MD, FACC, FSCAI
Director, Ahmanson/UCLA Adult Congenital Heart Disease Center
Los Angeles, CA

This manuscript is intended to provide a brief overview of the indications for and outcomes of surgical and transcatheter interventions for congenital heart disease and pulmonary hypertension (PH). Pulmonary hypertension is frequently encountered in children and adults with congenital heart disease and is most commonly related to large "central" shunts, ie, those occurring at the ventricular or great arterial level (Figure 1). If uncorrected early in infancy or childhood, large central shunts result in increased pulmonary blood flow, left heart volume overload, PH, and heart failure. If the child survives this initial period of volume overload and heart failure, they will very likely develop effacement of the normal pulmonary arterial architecture and severe elevations in pulmonary arterial resistance, eventually resulting in cyanosis and Eisenmenger syndrome.1

Pre-tricuspid valve shunts, ie, those at the atrial and/or venous level, are typically not associated with severe PH in infancy and childhood, although progressive PH with age often occurs. Indications for surgical or transcatheter closure include evidence of right heart volume overload, arrhythmias, mild to moderate PH, and decreased functional capacity (Table 1).2 Doppler echocardiography is indispensable as a cost-effective tool for the noninvasive evaluation of hemodynamics and shunt fractions.3,4 Invasive cardiac catheterization is reserved for the subset of patients in whom inadequate acoustic windows limit the utility of transthoracic echocardiography or those in whom pulmonary vascular resistance or chamber pressures must be measured directly. Cross-sectional imaging techniques using computed tomography or magnetic resonance imaging are also widely used in the noninvasive assessment of anatomy and function.5

SURGICAL INTERVENTIONS
Operative interventions to palliate or repair the congenital lesions were originally devised to address physiologic issues, specifically to increase or diminish the supply of blood to the pulmonary circulation. The early era of congenital cardiac surgery is marked by giant leaps forward in the physiologic treatment of lesions. For example, patients with pulmonary atresia or single ventricle defects underwent placement of an arterio-pulmonary shunt, a wave of surgical innovation initiated by the famed Blalock-Taussig shunt, a subclavian to pulmonary artery connection supplying a controlled volume of arterial blood to the pulmonary arterial circulation (Figure 2).6 Residual hemodynamic defects are often present in operated patients and are a major cause of progressive deterioration that may not become evident for decades after surgery. Residual hemodynamic defects may be amenable to further surgery or transcatheter intervention. Reoperations in adults with congenital heart disease are common and provide particular challenges.7 The risks of reoperation are often greater than for the primary procedures, requiring careful entry into the chest with extensive dissection of scar tissue and longer cardiopulmonary bypass times and greater use of blood products.8 Careful preoperative planning should include an in-depth understanding of the underlying cardiovascular anatomy and the alterations caused by previous surgical intervention. Computed tomography or magnetic resonance angiography may be utilized to determine the anatomic relationships and quantify the proximity of the heart to the sternum; sternal entry is particularly risky when a high pressure ventricle, great artery, or conduit lies immediately posterior to the sternum. In patients with complex congenital heart disease, specifically those with cyanotic lesions, definitive "correction" may not be possible until the anatomy and physiology have been opti-

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Correspondence: JAboulhosn@mednet.ucla.edu

Figure 1: Types and locations of congenital cardiac defects.

Figure 2: Tricuspid atresia and pulmonary atresia. Surgical arterio-pulmonary shunts placed to increase pulmonary blood flow. The classic BT (Blalock-Taussig), Waterston, and Pott’s shunts are of historical importance and may be present in adults, but are no longer in clinical use for a variety of reasons, including difficulty in controlling pulmonary blood flow and the development of PH. The central and modified BT shunts are made of synthetic materials and are used in the current surgical era.
mized by 1 or more “palliative” procedures. In patients with known PH, modulation of pulmonary arterial resistance with inhaled nitric oxide or parenteral prostacyclin therapy is indicated in the perioperative period. The decrease in systemic arterial resistance and systemic blood pressure encountered with prostacyclin therapy can be counteracted with selective alpha 1 agonists or vasopressin in hypotensive patients.

Heart and heart-lung (block) transplantation are ultimate therapeutic options in patients who continue to deteriorate with optimal medical therapy and have no other good reparative surgical or interventional options. Compared with adult recipients, patients with adult congenital heart disease experience higher post-heart transplantation mortality and retransplantation. Patients with Eisenmenger syndrome may be offered lung transplantation with repair of the cardiac defect or heart-lung transplantation. The success of either approach in these patients has been limited. Given the advancements in the management of PH and the limited success of these operations, mainly the sickest patients who fail to stabilize or improve on pulmonary arterial vasodilator therapy are considered candidates. The potential roles of ventricular assist devices and the total artificial heart in congenital patients are currently being investigated with promising early results.

**TRANSCATHETER INTERVENTIONS**

Major advances in percutaneous transcatheter interventions have been made over the past 25 years in the field of congenital heart disease. Improvements in device, imaging, and catheterization technologies and procedural techniques have brought interventional cardiology to the forefront as a therapeutic intervention that may delay or obviate surgery. A adult congenital cardiac catheterizations today are often performed solely for reparative or palliative transcatheter interventions. Interventional catheterization has largely replaced surgery as the treatment of choice for a number of congenital cardiovascular conditions, including secundum atrial septal defect (ASD) (Figures 3 and 6), patent ductus arteriosus (Figure 5), and ventricular septal defect (VSD) closure (Figure 4). Careful patient selection and imaging are imperative to the safety and success of transcatheter procedures.

**SPECIFIC LESIONS**

**Atrial Septal Defect**

Atrial septal defects are commonly encountered and occur in one-third of adults with congenital heart disease. Various types exist: secundum ASD is the most common, accounting for 75% of defects. Ostium primum defects, often accompanied by endocardial cushion defects and inlet-type VSDs, occur in 20% of cases. Sinus venosus defects (usually superior)

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Table 1: Indications for intervention in congenital shunt defects.

<table>
<thead>
<tr>
<th>Defect</th>
<th>Indications for Intervention</th>
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| Secundum ASD            | Qp:Qs >1.5:1  
RVE, RAE  
Mild-Mod Pulmonary HTN:  
PAP <2/3 systemic  
PVR <2/3 systemic  
Paradoxical Embolism  
SVT/DOE |
| Patent Foramen Ovale    | Paradoxical Embolism (not prevented by antiplatelet/antithrombotic Rx)                      |
| Ventricular Septal Defect | Qp:Qs >1.5:1  
LAE, LVE  
Mild-Mod Pulmonary HTN:  
PAP <2/3 systemic  
PVR <2/3 systemic  
DOE  
AR |
| Patent Ductus Arteriosus | Qp:Qs >1.5:1  
Mild-Mod Pulmonary HTN:  
PAP <2/3 systemic  
PVR <2/3 systemic  
LAE, LVE  
SVT/DOE  
Any PDA? |

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**Figure 3:** A) Transthoracic echo with color Doppler, modified parasternal long-axis view demonstrating a complex secundum type atrial septal defect (ASD) (vertical white arrows) that has multiple fenestrations and a left to right shunt. The right atrium (RA) and right ventricle (RV) are dilated. B) Post-transcatheter ASD closure with 2 Amplatzer septal Occluder devices. Left ventricle (LV), tricuspid valve (TV).
occur in 5% of patients; the rarest type is the coronary sinus ASD (Figure 1).

Atrial septal defects often go unrecognized for the first 2 decades because of the indolent clinical course and benign findings on physical examination. Initial diagnosis in adulthood is common and survival into adulthood is the rule. However, life expectancy is not normal in the unpaired patient, with mortality increasing by 6% per year after age 40.\textsuperscript{17,18} Progressive symptoms of dyspnea on exertion and palpitations frequently occur in adulthood and are caused by increasing right sided chamber enlargement, PH, right ventricular failure, tricuspid regurgitation, and atrial arrhythmias. The degree of left to right shunt may increase with age as left ventricular compliance decreases and systemic arterial resistance increases after the fourth decade. Paradoxical embolism may occur.

Surgical repair has been performed for over 40 years and has been efficacious and safe provided the pulmonary arterial resistance is not severely elevated.\textsuperscript{16,19} Several studies have shown improvement in functional capacity, reduced arrhythmia risk, and reduced incidence of PH after surgical or transcatheter closure, including in those with small defects (\(<1\) cm), older patients, and asymptomatic individuals.\textsuperscript{20-23} Predictors of increased surgical mortality include: older age at operation, advanced heart failure (NYHA III or IV), Qp:Qs >2.5:1, pulmonary artery systolic pressure >40 mm Hg, and increased pulmonary arterial resistance.\textsuperscript{24} The exclusion of patients with severe PH from defect closure may eventually be obviated by pulmonary artery vasodilator therapy with prostaglandins, endothelin blockers, and phosphodiesterase type 5 (PDE-5) inhibitors that may reduce pulmonary arterial pressure and resistance permitting shunt closure in these patients.\textsuperscript{25,26} Severe PH in patients with ASD probably represents the coincidence of idiopathic PH or PH secondary to another process (eg, scleroderma) and ASD.\textsuperscript{1} Unlike patients with large unoperated nonrestrictive central shunts (eg, VSD) who experience PH from birth and develop pulmonary vascular disease within the first few years, patients with large ASD of similar shunt magnitude do not necessarily develop severe PH and right to left shunting or the onset of PH is delayed into late adulthood. That being said, a large ASD may contribute to the development of PH, but may not be the sole cause of the underlying pulmonary vascular disease in a cyanotic patient. Patients with trisomy 21 (Down syndrome) may develop accelerated pulmonary vascular disease in the presence of ASD (primum or secundum).

Transcatheter device closure of secundum type ASD was first performed in 1976 by King and Mills.\textsuperscript{27} Advancements in biocompatible materials, device design, and catheterization technology have led to the availability of a variety of occlusion devices.\textsuperscript{28-30} Prosthetic devices are now available in a range of sizes and can be delivered through a variety of venous access sites, including the femoral vein.\textsuperscript{31} The most commonly used devices are the Amplatz septal occluder (Abbott Vascular, Abbott Park, IL) for atrial septal defects and the Cardiac Plug Pro vascular stop (Boston Scientific, Natick, MA) for ventricular septal defects.\textsuperscript{32,33} The device is deployed percutaneously using a delivery system and is closed in the catheterization laboratory or operating room. The device is often deployed with the assistance of contrast angiograms to ensure correct positioning. The device is then released, and the sheath is withdrawn. The device is then expanded, and its position is verified with fluoroscopy and cineangiography. The occluder is then released, and the sheath is withdrawn. The device is then expanded, and its position is verified with fluoroscopy and cineangiography. The device is then released, and the sheath is withdrawn.
devices (Figures 3 and 6). Transcatheter device closure compares favorably with surgical closure in terms of long-term outcome and is associated with shorter hospital stays and fewer post-procedural complications. Transcatheter device closure techniques have supplanted surgery at many institutions as the method of choice for ASD closure in properly selected patients; complications are rare. Short-term complications have included device embolization, aortic root or atrial wall perforation, and cardiac tamponade. Mid- and long-term complications include thrombus formation, device erosion into the aortic root, atrial dysrhythmias, and infective endocarditis. The use of platelet inhibitors for at least 6 months following device closure is recommended to decrease the risk of device thrombosis. The long-term outcomes of device closure using the Amplatzer septal are equivalent to long-term surgical results. Older patients with abnormal left ventricular compliance or restrictive physiology may have a significant increase in left heart filling pressure following ASD closure. Balloon test occlusion of the ASD with simultaneous measurement of pulmonary artery occlusion pressure or direct measurement of left ventricular diastolic or left atrial pressure may be revealing. Manual fenestration of commercially available devices allows for a small “pop-off” for decompression (Figure 6).

**Ventricular Septal Defect**

Isolated VSD is the most commonly encountered form of congenital heart disease in the pediatric population; most are small and close spontaneously. The spectrum of isolated residual VSD encountered in the adult patient usually consists of:

1. Small restrictive defects or defects that have closed partially with time. The pulmonary vascular resistance is not significantly elevated and the left to right shunt magnitude is mild (Qp:Qs ≤ 1.5:1).
2. Large nonrestrictive defects in cyanotic patients who have developed Eisenmenger syndrome, with systemic pulmonary vascular resistance and shunt reversal (right to left).
3. Patients with moderately restrictive defects (Qp:Qs ≥ 1.6:1 and ≤ 2:1) who have not undergone closure for some reason. These patients often have mild to moderate PH.
4. Patients who have had their defects closed in childhood. These patients may have VSD patch leaks.

Small restrictive defects of the muscular or membranous septum may be watched conservatively without need for operative intervention. Six percent of patients with small supracristal or perimembranous defects may develop aortic valve prolapse and resultant aortic regurgitation that may be progressive. The prolapsing aortic valve cusp (usually the right coronary cusp) may partially or completely close the VSD. Aortic valve repair or replacement may be necessary in patients with aortic regurgitation who develop exertional symptoms or progressive left ventricular dilation. In a long-term follow-up registry, the overall survival rate was 87% for all patients with unoperated VSD at 25 years. For patients with small defects (Qp:Qs < 1.5 and low pulmonary artery pressure), the survival rate was 96%; patients with moderate and large defects fare worse, with 25-year survival of 86% and 61%, respectively. Those with cyanosis (Eisenmenger’s complex) had a much lower 25-year survival of 41.7%.

In patients with large nonrestrictive VSD, pulmonary vascular disease begins at birth or soon afterwards with abnormal vascular remodeling; eventually, if the defect is not repaired, the pulmonary arterial resistance exceeds the systemic arterial resistance resulting in right to left shunting and cyanosis, the condition known as Eisenmenger syndrome. Early attempts at surgical closure of central shunts in patients with Eisenmenger syndrome were met with an unacceptably high risk of mortality and the practice was quickly abandoned. Thereafter, the condition was deemed “irreversible”; however, this common wisdom is now being challenged. There is ample evidence that pulmonary vasodilators result in improved pulmonary blood flow, improved functional capacity, and may improve survival in patients with Eisenmenger syndrome. Although isolated cases and small series of successful defect closure in Eisenmenger syndrome have been published, the majority of cases are deemed too high risk and closure is contraindicated. Larger defects may be repaired in the absence of severe PH and severely elevated pulmonary vascular resistance, which incurs a high perioperative risk (Table 1). Postoperative life expectancy is not normal but has improved over the past 50 years with improved surgical techniques and experience. Postoperative conduction defects
are common but complete heart block is rare in the current era. Transcatheter device occlusion of muscular and perimembranous VSD is feasible and trials demonstrate a good safety and efficacy profile (Figure 4).\textsuperscript{52-55} Complete heart block has been noted to occur in up to 6% of children and 1% of adults.\textsuperscript{52,55} Hybrid techniques, those involving surgical and transcatheter components, are being increasingly applied and may obviate the need for cardiopulmonary bypass. They are especially attractive for defects that may prove challenging to close via transcatheter techniques; those involving surgical and transcatheter techniques alone or in infants with concerns over vascular access.\textsuperscript{56,57} Patients with small restrictive defects (Qp:Qs = 1.5:1 and low pulmonary artery pressure) are generally asymptomatic and do not require intervention unless they have aortic regurgitation or infective endocarditis.\textsuperscript{2}

**PATENT DUCTUS ARTERIOSUS**

The ductus arteriosus is an essential communication during fetal life that (along with the foramen ovale) allows oxygenated maternal blood to be directed to the systemic circulation, thus avoiding the high resistance, kinked and collapsed, fetal pulmonary arterial circulation. Within 48 hours of birth, and under the influence of higher oxygen levels in the newborn as compared to the fetus in utero, the ductus arteriosus begins to close. In a small subset of human beings, occurring either spontaneously or more rarely as part of a family cluster, the ductus arteriosus remains open and is appropriately named a PDA. Patent ductus arteriosus is associated with other congenital malformations such as VSD or coarctation of the aorta. Those born at high altitude, presumably due to the lower oxygen tension, have a higher prevalence of PDA. The consequences of a PDA are largely dependent on the size of the duct and the magnitude of the shunt; very small PDA with negligible shunts are rarely problematic and do not result in PH or heart failure, but are rarely associated with endarteritis. Large defects with a Qp:Qs of \( \geq 1.5:1 \) often result in left sided volume overload and progressive increases in pulmonary arterial pressure and resistance. If unrepaird surgically or via transcatheter techniques, these defects often result in Eisenmenger syndrome with suprasystemic pulmonary arterial resistance and shunt reversal. Given that the location of the PDA is usually beyond the takeoff of the left subclavian artery, the deoxygenated pulmonary arterial blood shunts to the lower body resulting in differential cyanosis (Figure 7). Indications for surgical or transcatheter closure are similar to those for ASD and VSD (Table 1). Patients with severe PH without reactivity to pulmonary vasodilators or improvement with transient balloon occlusion are generally not considered candidates for PDA closure; however, there is a growing body of evidence that responsiveness to treatment with pulmonary vasodilators may facilitate subsequent defect closure using a variety of commercially available Nitinol devices.\textsuperscript{58-60}

**CONCLUSION**

Pulmonary hypertension is often present in patients with native or operated congenital heart disease. The care of these patients is often challenging given the degree of heterogeneity of native defects, including variations in defect location, size, shunt magnitude, shunt direction, co-existent conditions, the presence of multiple defects, and a wide spectrum of potential anatomic variations. The clinician seeking to provide care to this population should be familiar with the various surgical and transcatheter interventions that are currently utilized, their outcomes, potential complications, and expected sequelae. The indications and contraindications to surgical or transcatheter interventions in patients with PH and congenital heart disease are outlined. The outcomes of surgical and transcatheter procedures in appropriately selected patients are usually excellent.

**References**


1. Aggressive monitoring for the development of PAH should occur in Fontan patients because:
   a. They often have a mean pulmonary pressure >25 mm Hg at right heart catheterization
   b. An Eisenmenger physiology is associated in most cases
   c. A conduit obstruction may lead to cardiac decompensation
   d. Even slight increase in PVR may have significant hemodynamic consequences

2. Which of the following forms of congenital heart disease is most likely to lead to the development of PAH?
   a. Partial anomalous pulmonary venous return without repair
   b. Secundum atrial septal defect without repair
   c. An unrestricted ventricular septal defect without prior repair
   d. Patent foramen ovale without repair

3. A 30-year-old woman is diagnosed with a membranous VSD. She undergoes echocardiographic imaging evaluation and an invasive hemodynamic study. The hemodynamic study demonstrates pulmonary artery pressures of 110/50 mm Hg. Her central aortic pressure is 100/60 mm Hg. A pulmonary venous oximetry sample has a saturation of 95% and her femoral artery oximetry sample has a saturation of 86%. There is severe pulmonary regurgitation, as well. Which of the following is correct regarding treatment?
   a. Closure of the VSD is indicated
   b. PAH vasodilator therapy only is indicated
   c. Heart transplantation should be considered
   d. She should have pulmonary valve replacement

4. Which of the following is the most common subtype of ASD?
   a. Muscular
   b. Outlet
   c. Secundum
   d. Sinus venosus
   e. Membranous

5. Echocardiographic indicators of poor outcomes in patients with Eisenmenger syndrome are:
   a. Pericardial effusion + low TAPSE
   b. Low TAPSE + shortened RV filling time + increased RA area/LA area
   c. Pericardial effusion + low TAPSE + shortened RV filling time
   d. Bi-atrial enlargement

6. In Eisenmenger patients, the presence of RV late gadolinium enhancement at cardiac MRI:
   a. Is a pathologic finding in any cases
   b. Is usually located at the apex
   c. Is a normal feature typically evident at the insertion points
   d. When present at the insertion points is an indicator of poor outcome

7. Catheter-based interventions are available for all of the following lesions except:
   a. Secundum atrial septal defect
   b. Muscular ventricular septal defect
   c. Ostium primum atrial septal defect
   d. Patent ductus arteriosus

8. In a 4-month-old infant with APAH-CHD due to a nonrestrictive VSD, what would you most expect hemodynamics to resemble on cardiac catheterization?
   a. Elevated pulmonary artery pressure, normal wedge pressure, elevated pulmonary blood flow, normal pulmonary vascular resistance
   b. Elevated pulmonary artery pressure, elevated wedge pressure, normal pulmonary blood flow, normal pulmonary vascular resistance
   c. Normal pulmonary artery pressure, normal wedge pressure, normal pulmonary blood flow, normal pulmonary vascular resistance
   d. Elevated pulmonary artery pressure, normal wedge pressure, normal pulmonary blood flow, elevated pulmonary vascular resistance

9. The BREATHE-5 trial involving which endothelin receptor antagonist was the first randomized, double-blind, placebo-controlled drug trial conducted solely on Eisenmenger patients?
   a. Sildenafil
   b. Bosentan
   c. Ambrisentan
   d. Treprostinil

Disclosures
(continued from page 165)
sented. To be disclosed to participants are all personal financial relationships with a com-mercial interest whose products are relevant to the content of this CME activity. It is the policy of Washington University School of Medicine, Continuing Medical Education, to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All faculty participating in this activity are expected to disclose to the audience any financial interest or other potential conflict. Each author was asked to complete a disclosure information form for this activity. Disclosures are reported below:

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CME Reviewers
W. Edwin Dodson, MD, Associate Vice Chancellor and Associate Dean for Admissions and Continuing Medical Education, Professor of Pediatrics and Neurology, Washington University School of Medicine.

Murali Chakinala, MD, Associate Professor, Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine.
Congenital Heart Disease and Pulmonary Hypertension

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Circle one correct answer.

1. a b c d
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3. a b c d
4. a b c d
5. a b c d
6. a b c d
7. a b c d
8. a b c d
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Poor Satisfactory Excellent

1. Extent to which objectives were met

   1  2  3  4  5

2. How would you rate the course overall

   1  2  3  4  5

3. How helpful was the information presented

   1  2  3  4  5

4. Was the activity free of commercial bias? Yes No

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Management of PAH in Adults with Congenital Heart Disease: Impact and Dilemmas

Guest editor Richard Krasuski, MD, convened a group of experts by telephone on January 17, 2013, to discuss current trends in diagnosis and treatment of pulmonary hypertension among patients with congenital heart disease. Joining the call were Professor Maurice Beghetti, Head of Pediatric Subspecialties, Division Head of Pediatric Cardiology Unit, Children’s University Hospital, Geneva, Switzerland; Curt Daniels, MD, Director, Adolescent and Adult Congenital Heart Disease Program Nationwide Children’s Hospital, The Ohio State University, Columbus, Ohio; Wayne J. Franklin, MD, Texas Children’s Hospital, Houston; and Michael J. Landzberg, MD, Associate Director, Adult Pulmonary Hypertension Program and Director, Boston Adult Congenital Heart Program, Boston Children’s Hospital.

**Dr Krasuski:** We are here today to discuss the impact and dilemmas in the management of pulmonary arterial hypertension (PAH) in adults with congenital heart disease (ACHD). There are now up to a million ACHD patients, and we believe that up to 40% of these patients are at risk for PAH; 10% of ACHD patients will actually develop PAH. So we’re talking about 100,000 such patients existing in the United States alone, and possibly up to 40,000 that have developed Eisenmenger syndrome. So it’s a large and growing group and an exciting and challenging field to practice in. It’s very impressive in terms of what’s happened in the last decade or 2, regarding the development of multifaceted management strategies for these people. I am going to begin by asking the following question of this prestigious panel: “how can we best identify those patients with congenital heart disease who have pulmonary hypertension and who might be candidates for some of the therapeutic interventions that we now have available?”

**Dr Daniels:** We know a group of patients from the large congenital heart disease population, who are higher-risk patients. Those are patients who have shunt lesions and some of our more complex lesions. So these are the patients we must be aware of as having the potential to either have pulmonary hypertension or develop pulmonary hypertension. Then we also have to be aware, as an educational point to ourselves and our community, but also other cardiologists and even possibly pulmonologists who see patients, to rule out pulmonary hypertension or evaluate for pulmonary hypertension because patients may be completely repaired and still develop pulmonary hypertension. We know a percentage of patients, even if they have shunts closed, even at what we consider an earlier age, still may develop pulmonary hypertension down the road as an adult. There are risk factors that lead to those with shunt lesions and complex congenital heart disease that makes them more vulnerable to develop pulmonary hypertension, such as timing of when a septal defect was closed, surgical shunts that may have been placed, length of time with a shunt before they had a complete repair. So we have to be aware that the congenital heart disease population as a whole is at risk, but there are certain patients, certain populations within the congenital heart disease population, that are at higher risk for developing pulmonary hypertension, and be aware and able to evaluate those patients, looking specifically for signs, symptoms of pulmonary hypertension.

**Dr Landzberg:** What Curt identified were findings that many of us, as congenital heart disease docs, would recognize, but I wonder if we can extend that a little bit. For the general practitioner or for the internist who is out there, if one is fortunate enough to have the preoperative history on these folks, we could say that, almost everybody’s at risk but, in particular, folks who may have had preprocedural large-volume shunting. Maybe if you had ventricular dysfunction going into the shunt repair. If you had a lot of volume coming back to your left side of your heart, as well, that’s a sign that someone may be at increased risk for the development of pulmonary hypertension after closure. I think many of us will see arrhythmia as a preoperative arrhythmia or postoperative arrhythmia as a sign that the patient may be having increased risk for developing pulmonary hypertension. Persistent RV dysfunction, functional decline, just in general, if someone’s not doing well with congenital heart disease afterwards, that puts the thought into my head, could this person have pulmonary hypertension, and just age alone. So I think that anyone that’s not doing well, anyone that’s getting older, anyone that has heart muscle dysfunction, I’m thinking has the potential for pulmonary hypertension.

**Dr Beghetti:** I think you both raise a very important point. So we may ask adult physicians to see these patients and refer to “adult congenital heart disease.” I think one important point that you both raised is that we need to know what happened at an early age, especially in the ones that had surgery, and then come back to the adult clinic with PH later in life. And I think the
transition and the connection between the pediatric cardiology and the adult cardiology with regard to these patients is very important, to be sure that we have the data on what happened and how the decision was done to do the surgery, to close the shunt, and exactly what Mike just raised now: if there were specific problems that can be identified and indeed, the risk factors for this population, and then identify the risk factors that will allow you to identify the patients that are at high risk to develop postoperative pulmonary hypertension. Because I think in our database now, what we see is that the Eisenmenger population is an old population. We should see fewer of these patients. But the growing population is patients with PH after repair. And so we need to identify these patients and the risk factors for these patients.

Dr Krasuski: I completely agree. Between a randomized trial and several prospective registries, we’ve accumulated quite a bit of data about Eisenmenger patients. But as time goes on, hopefully we can identify and intervene in these patients early enough to prevent them from developing Eisenmenger physiology. We have developed trials focused on Eisenmenger syndrome, including the published BREATHE-5 study and newly enrolling MAESTRO trial. These are randomized, placebo-controlled trials examining the role of pharmacologic therapy. But for patients with earlier forms of PAH, how can we apply these data to them? Should we be more aggressive at earlier stages of the disease? And how can we apply what’s been learned in other etiologies of pulmonary hypertension to our ACHD patients?

Dr Beghetti: Eisenmenger patients and the ones who present with PH after complete repair may be a bit different. For the Eisenmenger patients, as you said, the MAESTRO will include patients with, I would say, functional class II, which would be considered as mildly symptomatic, and we’ll see what happens with this population. I think the other group appears really quite affected with the preliminary result we have. And with the group that presents with PH after repair, it seems, even if we do not have still all the data, that we need to be a bit more aggressive with this population, compared to Eisenmenger patients. Even if we think we still need to have more data on Eisenmenger patients to see also the benefit from early aggressive therapy.

Dr Daniels: I agree. I think that finding a patient with complete repair of a shunt, for instance, who has developed pulmonary hypertension, has the pathophysiology of advancing pulmonary hypertension. And so far, there is no evidence to the contrary, to believe that this particular patient population is not going to follow a pathway with a closed, repaired shunt, almost similar to an idiopathic PH patient. Of course, we don’t know this and we know the Eisenmenger population has a very different course in terms of their prognosis. But the patient with a closed, repaired shunt, and found later to have pulmonary vascular disease, we have to believe this is an advancing disease process. We certainly see that as we follow patients now, we’re collecting more information. Therefore, we have to believe that early therapy is quite important and not waiting until they are more symptomatic, which we all know means that the right ventricle is becoming more dysfunctional from a systolic and diastolic and a compliance standpoint. So early treatment certainly seems to be the best course of action for these patients.

Dr Franklin: I think that the Eisenmenger data for us, specifically in Houston, have been very helpful the past few years. Because in the past, where I think we would just start them on maybe one medicine and that was all. Often these are Down syndrome patients. I think now we’ve been more aggressive to try to get them on advanced therapies, whether it’s 2 drugs or 3 drugs. Usually it’s 2; often they do not tolerate 3 drugs. But I also agree with Curt closely that the ones that we think are repaired, we’re still following every year. And I think maybe we should think about starting them earlier on therapy. So I think there has been the real emphasis on early detection now, as well.

Dr Krasuski: Let me shift gears a little bit and ask the group to briefly discuss what type of workup they do in the newly diagnosed ACHD-PH patient. So you have a patient who has a congenital heart lesion and develops pulmonary hypertension, though not yet Eisenmenger syndrome. What types of studies should we perform to look for other sources of pulmonary hypertension? Should we be doing a full pulmonary workup for these patients, such as VQ scanning and pulmonary function testing? Bloodwork assessing for collagen vascular disease? Sleep-disordered breathing workup? What is your standard practice in these patients? Particularly in this era of cost containment, do you run the whole gamut and follow the same algorithm as for any newly diagnosed PH patient? Or do you focus on what you think the most likely etiology is?

Dr Daniels: Before we address this, let me shift back a little bit. There were a couple of things that folks mentioned that gave me a bit of a twitch, only because it underscored that we’re missing some data or there are some additional data out there that may be
Dr Daniels: I would completely agree. And I think Dr Beghetti: I definitely agree with that, because therapies. Other contributors that have their own independent diseases—there are way too many times that we find despite the fact that somebody has congenital heart disease after a repair. The REVEAL dataset makes me worry. It’s clearly in a patient population that came to advanced heart—pulmonary hypertension clinics rather than adult congenital heart disease clinics, but it was suggested a terrible prognosis in that small patient group. But there are 2 ongoing registries in this country that are going to hopefully define that for us. And as part of those registries, we are mandating exactly what you mentioned, Rich, that we go through the full evaluation. Our patients with congenital heart disease have many other triggers for pulmonary hypertension. So I’m a big fan of a full and complete evaluation, despite the fact that somebody had a shunt to begin with and despite the fact that somebody has congenital heart disease—there are way too many times that we find other contributors that have their own independent therapies.

Dr Beghetti: I definitely agree with that, because you can have a congenital heart defect and also have other triggers or other risk factors. And that’s extremely, extremely important to know. On top of this, it’s extremely important also to re-cathe the patients, for the reasons that Mike raised before, to be sure that there is not a combination of pre- and postcapillary pulmonary hypertension, and also to see if there are any clots in the lung. Because they had surgery, sometimes they have catheters in place for a long time after surgery. So I think definitely we need to begin to look at everything before starting these therapies, because otherwise you will blame the therapy for not working, but maybe that’s because the indication was not exactly the one you thought. And the complete workup should help make the diagnosis correctly.

Dr Daniels: I would completely agree. And I think to bring it back to a specific patient population that we all see is the atrial septal defect (ASD) patient. A patient with an ASD that’s been closed or even remains open and has pulmonary hypertension, this is a population we all see. We’re not sure many times is the ASD truly causing the pulmonary vascular disease or an innocent bystander, or possible a contributor. And so I think this highlights, at least for me in the evaluation and workup, we do need to perform a complete workup, even on our congenital heart disease patients, not knowing if this is cause and effect or an innocent bystander. We don’t want to miss a diagnosis, as Maurice says, go down the wrong pathway in terms of our therapies when we should have been looking in a different direction.

Dr Krasuski: Those are all excellent points. Now, Maurice, you alluded to the importance of heart catheterization and potentially repeat heart catheterization while on therapy to assess therapeutic response. What about performing hemodynamic challenges in the cath lab? How often do you do vasodilator challenges, fluid challenges, and other such studies to assess the physiological response? Do you reserve such procedures to the first catheterization or is it worth reassessing?

Dr Beghetti: I tend to do complete caths all the time, including vasoreactivity testing. It’s not because I think that I will find the patients becoming reactive, because this is extremely, extremely uncommon. But based on some data coming from Belgium, from the group of (s/l Vander Butz), and also from (s/l Mikhaila Douto) in Italy, this could be a good way to identify some risk factors for this population. When you still have some reactivity, it seems based on these 2 studies that the patient may have a better outcome. They also may have a better response to some of the therapies, because there is some vasodilatory reserve. So that may be the reason to assess vasodilatory reserve. I think the fluid challenge, especially if the patient is older or if there is some history of ventricular dysfunction, can unmask diastolic dysfunction, and I think that’s very important to know in our population. I think maybe we mismanage these kinds of things in some of our patients. In terms of follow-up caths, I think it’s important to do follow-up caths in the population where there is closed shunt in PH. That will be exactly the same follow-up that you do in idiopathic PH. In Eisenmenger syndrome, and I’m sure that Mike will have strong ideas on that, the problem is to reproduce the data properly and really be sure that you can compare data from cath to cath. And sometimes it’s not easy because these caths with open shunts are sometimes a bit difficult, as you all know. So I think you need also to adapt a little bit to the population that you follow.

Dr Landzberg: All of us in this group perform catheterizations. And have different opinions about how often to cath, but I think we all probably share the opinion that cath plays a vital role. The number of times that we find something unexpected at a cath in somebody who has congenital heart disease and pul-
Pulmonary hypertension is far too often. And I would say that, as we’ve underscored before in terms of the many triggers to pulmonary hypertension development, our patients are prone to pericardial construct and have reasons to have pulmonary venous stenosis, restrictive myocardial disease, other unexplained or unexpected pulmonary arterial stenoses. And so I underscore that during the very first catheterization, it’s critical to do a full, complete angiographic, hemodynamic, multiple maneuver catheterization. I have been amazed at the more than rare patient that is responsive to pulmonary vasodilator acute therapy, and I know that we all believe slightly differently in terms of whether or not somebody can respond to a calcium antagonist in our population or should respond. In the same breath, I agree that it’s vitally important to know whether or not somebody is responsive. It tells you something about their prognosis as well. My toughest point is what about serial catheterizations? And this applies to the patient with idiopathic disease, as well as to our own patients. There is so much hour-to-hour variation of the hemodynamics of our patients, in a normal host, or a patient with pulmonary hypertension that small differences, even small to moderate differences, don’t necessarily tell us a lot, but there are still key prognosticators that we get from hemodynamics. I often repeat caths, but I have no idea how often it should be. Certainly, when there is a functional decline, that’s a marker for us to go back and reassess hemodynamics.

**Dr Daniels:** I completely agree. The first cath is critical. And this is where the data are so important that it’s accurate and done with detail and in an organized fashion. You know, for the audience that will be reviewing this roundtable discussion, many may not be congenital heart disease experts in performing cardiac catheterizations on patients with shunts. And I would emphasize the point of collaborating with congenital heart disease experts with cardiac catheterization data, because collecting data in a correct fashion will make the difference between which pathway you will go with that particular patient, whether it’s pulmonary hypertension-specific therapy, whether it’s deciding to close the shunt, whether it’s deciding therapy should be headed toward heart failure, diastolic dysfunction. And so it’s critically important that the correct information is obtained, under the right conditions. The oxygen saturation data: is the patient on supplemental oxygen? That the vasodilator trial is done correctly. Because this is the one shot in the catheterization lab to obtain correct information. So I would emphasize, even if you are in a center that performs cardiac catheterization for pulmonary hypertension, but maybe not specifically for congenital heart disease, collaboration with congenital heart disease experts is critical to obtain the correct data.

**Dr Krasuski:** It’s great to hear such a strong consensus on the importance of hemodynamically defining the disorder and properly collecting the data. This really sets you on the proper path toward appropriate therapy. My next question is: “how do you follow ACHD-PH patients in terms of assessing their disease progression and response to treatment?” The 6-minute walk has gotten kind of a black eye recently as a surrogate for outcomes in pulmonary hypertension. Do you guys regularly measure the 6-minute walk in your CHD-PH patients? Do you utilize metabolic stress testing? Do you measure biomarkers? Do you regularly perform echocardiograms? We’ve already discussed catheterization and the importance of potentially repeating it at some point, though we may differ perhaps in what we believe the appropriate interval should be. When you see your patients back in clinic, what are those essential tools that you use to assess how the patient is doing and how successful therapy has been?

**Dr Franklin:** It’s interesting, Rich. The 6-minute walk, as you mentioned, has been controversial lately. But I still use it. I still use it for enrolling patients and starting therapy and monitoring patient responses. The test is easy to do. It’s a good, sustainable test, if you will. But I also use echo; I use saturations. Some of our patients that are pretty debilitated are not able to do even a submaximal stress test. So that’s where I think the 6-minute walk continues to be very useful. It would be interesting to see what the group consensus is about repeat catheterization. I usually will save that until there’s either some unusual response, or the patient is not responding, or I’m going to start a second drug, or it’s been a year and the patient may be a surgical candidate, or something like that. But I tend to use more of the noninvasive measures, rather than cathing them more than once or twice.

**Dr Beghetti:** Yeah, that’s what I said before. I think we should clearly differentiate Eisenmenger and non-Eisenmenger patients. I think repeating caths in Eisenmenger, again it’s very difficult to see a major difference. And there is always some risk to redo the cath in this population; you never know what can happen. So I think I would do exactly what you say. If the patient is not responding as you expected or you plan maybe to add another drug, that is one of the good reasons to repeat the cath. But if an Eisenmenger patient is doing well, I would not do repeated routine cath. This may be different in a closed shunt.
centers are following exactly the same approach if a patient is doing perfectly well with all the noninvasive assessment, they would keep the cath only for patients that have inadequate response to treatment. And I would do exactly as you said, a 6-minute walk test, saturation at rest and at end of exercise, BNP, echo and a function class assessment. I still think the functional class one can gain from discussing with the patient is sometimes just as helpful. It’s simple but still very helpful in these patients. I think the CPET for the Eisenmenger patient is a bit of a tricky test, even if it becomes a little more used in the other populations. I think in the very blue patient, it’s very difficult to have reliable data.

Dr Daniels: I would pose to the group that one of the aspects that we are most concerned with is right ventricular performance. And certainly, newer data seem to suggest that maybe we should be looking at the right ventricle in a different way. Certainly, we all look at our patients with echocardiograms on some regular basis. I find the echocardiogram for PH probably to be the least helpful in following patients, just because most patients with advanced disease, and certainly with Eisenmenger patients, we really do not gain much information beyond what everybody’s mentioned: how they are feeling clinically, their oxygen saturation data, exercise data. But certainly evaluating the right ventricular systolic function is an important parameter that we probably should be following more closely. And whether or not that allows us to change our therapy, add therapy, consider other therapies may be important for the future. In our Eisenmenger patients, we do have a difficult time in the cath lab, I agree. And a difficult time really with obtaining accurate and consistent data. I’d be interested to see what others think.

Dr Beghetti: MRI should be one of the options.

Dr Krasuski: With regard to MRI and some of the other novel, newer techniques for disease assessment, such as strain imaging on echo, is there anything that you all see that will change how we practice in this patient population? Maybe there are some biomarkers you all see that will change how we practice in this. Maybe there are some biomarkers you all see that will change how we practice in this, such as strain imaging on echo, is there anything that you all see that will change how we practice in this patient population? Maybe there are some biomarkers you all see that will change how we practice in this.

Dr Landzberg: Let’s focus on MR and anatomy. Our world of congenital heart disease underscores that the progressive decline or the ability of the patient to succeed with pulmonary vascular disease is in part related to the pulmonary vascular bed and in part related to the supporting structures that mount the flow to the pulmonary vascular bed. And so that the standard right ventricle in idiopathic pulmonary arterial hypertension or acquired PAH is very different for our patients who often don’t have a normal ventricle, don’t have a normal atrioventricular valve, or don’t have a normal conduit system in terms of passage of preload to the subpulmonary ventricle. So I think that understanding how that ventricle is doing, not just from a hemodynamic standpoint but from an imaging standpoint, is particularly valuable in the management, but also in the primary classification of what’s going on. So MR for us, and Curt, I’m glad you underscored it, is an increasingly valuable aspect of not just the management but also in terms of the very classification of our patients.

Dr Krasuski: Would someone want to comment on the routine measurement of natriuretic peptides?

Dr Beghetti: I measure them, but I’m a bit careful. I think the data that has just been published by the (s/l Brompton) group is very interesting. But I think that sometimes you have to be very careful not to over rely on the BNP values. We still have to learn about how this works. In patients that have Eisenmenger, some renal dysfunction, that are using diuretics. Sometimes doing a BNP during the day, in the morning or in the evening, you may have surprise that the level is a bit different, if it’s before or after Lasix dose, depending of the renal function in your patient. And so I think we need to learn a little bit more. But the data coming out from some studies are quite interesting. And definitely in the MAESTRO trial, we would like to measure that in a standardized way, to see if in a standardized way in a large cohort of patients, this can be used to address if the treatment is or is not working.

Dr Landzberg: Is it reasonable to say, Maurice, that most of us will collect natriuretic peptide will use it as part of the assessment, but none of us will take it in isolation? And I think that the recent data would underscore that it’s an important part of the mix, but not to be taken in isolation.

Dr Beghetti: Definitely. That’s exactly what I meant.

Dr Daniels: And I would agree, it’s a part of the follow-up and evaluation of our patients, a perfect way to say it but not the sole decision maker about adding additional therapy or changing therapy, but it’s added to our process of evaluation.

Dr Krasuski: In our program we collect a lot of data at each clinical visit. We look at functional status, natriuretic peptides, echoes, and 6-minute walks. One of the things that I like to examine is the general trend
in each of these. I’ve found that taking patients to the catheterization laboratory is most helpful for clarification of the disease state when there are conflicting data. If all the data are heading in the wrong direction, I’m fairly confident that our chosen clinical strategy is probably not right. When there are, for instance, improvements in the 6-minute walk and functional state but the natriuretic peptides are increasing, then I’ll start thinking about some of the things that Maurice mentioned: maybe it’s the measuring technique or the time of day when the measurement was made. But if I have more conflicting data, like evidence that the right heart is failing despite no worsening of the patient reported function state, then this is the time where catheterization may be most helpful—to know which direction the hemodynamics (pressures and pulmonary/systemic blood flows) are going. So why don’t we now move into how we approach these patients therapeutically? Let’s start by reviewing lifestyle modification. I think one of the areas that has always been controversial, and where we’re learning more that some of the recommendations we made in the past weren’t correct, is exercise. What do you tell your patients, particularly the ones that have pulmonary hypertension and congenital heart disease, about exercise? Do you encourage them to participate in programs? What kinds of restrictions do you place?

**Dr Daniels:** Well, we will at our center encourage patients with new diagnosis of pulmonary hypertension, whether it’s congenital heart disease or not, to initially be involved in a rehab program. It’s difficult in the United States to have patients approved through insurance companies for cardiac rehab, so many of our patients will go through pulmonary rehab. With a pulmonary hypertension diagnosis, they can proceed with pulmonary rehabilitation, which I think allows them to begin an exercise program, and allows them to have confidence in what they’ll be able to do. And as they hopefully improve on therapy, they’ll be able to accelerate their own exercise performance. So I guess as an opener, I would say that we try to incorporate an exercise program into the pulmonary hypertension population, and the congenital heart disease patients fall into this mix.

**Dr Beghetti:** When you consider again the Eisenmenger and the closed shunt, do you give the same possibility of exercise to both? Or you would advise them differently?

**Dr Daniels:** Well, I would say we’re a little more cautious with Eisenmenger patients, only from the standpoint of some of the isometrics. There’s always some component of isometrics with a rehab program.

**Dr Daniels:** I think we are a little less willing to freely open the door to the isometric program that’s part of rehab with the Eisenmenger population. That is probably the only difference and caveat. But otherwise, the aerobic performance, the aerobic activity, we prescribe in a similar fashion.

**Dr Landzberg:** The pulmonary rehab that you mention, Curt, is so attuned to what our patients can and should be doing in terms of their mixed diseases that are going on, in terms of both pulmonary parenchyma, Bellows, and peripheral musculature. Those programs are often well designed to what our patients need. It really is remarkable at how the referring clinician population frequently is so concerned about our patients going to physical therapy and rehab and yet the patients so desperately welcome it. And there are accruing data, not just for the idiopathic pulmonary arterial hypertension population but also for the congenital heart disease population, which you underscored, Curt. It’s now a routine part of all of our practices to have patients with congenital heart disease, associated pulmonary hypertension, go for rehab. It’s one of the first, if not the first things that we do.

**Dr Daniels:** Maurice, what do you do?

**Dr Beghetti:** So, it’s a bit difficult to send them to cardiac rehab. And so the pulmonary hypertension center is run in the adult field by pulmonologists and we’re working together. So it seems that the possibility from this side is a little bit better. The only concern that sometimes they have, and as we are not directly involved, is the saturation of the patients. And did you need to teach a little bit the people taking care of them to not be too scared about the saturation? Because if you send them to the pulmonary rehab, where they’re used to stress a little bit if the sats go below 90, just imagine when they have patients sitting in the low 70s—so that’s more the physician, the nurses, and the technicians that you need to teach sometimes about the disease.

**Dr Daniels:** Yes. Good point. Education for the rehab program for these particular patients is key.

**Dr Krasuski:** With regard to oxygen saturations, what are your individual practices in terms of prescribing oxygen? Do you recommend it for all patients going through rehabilitation? Focusing on the Eisenmenger patient, I think we all recognize that the data here are very, very limited and that perhaps we’ve been overzealous with oxygen. Certainly, we have all experienced one of our Eisenmenger patients getting

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*“It’s critical to do a full, complete angiographic, hemodynamic, multiple maneuver catheterization.”*  
Dr Landzberg
admitted to the hospital overnight; and when we walk in room on the following morning, the patient is on 100% oxygen by non-rebreather mask. We obviously have work to do in terms of educating our nursing staff and other physicians that take part in the care of our patients. What do you recommend in terms of oxygen prescriptions and the use of supplemental oxygen at night and during exercise?

**Dr Beghetti:** I would like to answer before Michael, because I know that he has strong ideas about that. I would say that I don’t know. But what I’m sure is that the workup of the lungs of these patients should be done, because that may help you to decide if the patient needs or does not need oxygen. Because if he or she has some restrictive disease, restrictive lung disease, or some gas exchange problem, I think that’s very important to know. Because in this population, there may be a good chance that oxygen may help. And then there’s maybe a population that oxygen may not help. And that’s why we still have a lot of controversy about the use of oxygen in this population. But I’m sure that Michael will comment on that.

**Dr Landzberg:** All of us respect the work that was done by Julio Sandoval in Mexico City, who has taught us much about pulmonary arterial hypertension. The study that most people refer back to is a very small study that relates to nocturnal oxygen use in chronically cyanotic patients with general heart disease. It’s a difficult study to extrapolate from. And without being controversial, I would suggest exactly as Maurice said. The key here is to assess the underlying pulmonary parenchymal and Bellows disease that so many of our patients have. I don’t restrict oxygen away from our patients, but I put it into the mix if they have combined disease.

**Dr Daniels:** And I think also since our population is different, many of them would have had open-heart surgery. They would have had surgical procedures, a sternotomy. We know now from our congenital heart disease data that many of our patients have restrictive lung disease. And so they do have limitations of their lung capacities, which in many cases will lead to areas of lung that do not participate in oxygen exchange in a normal fashion or the capacity at which we consider to be normal. So a workup of lung disease is important. And I think all of us have found patients, that surprisingly, do feel better on oxygen can exercise longer and do perform better. And at the end of the day, it is all about patients’ feeling better and improving their quality of life. And so it’s important, I think, to assess whether or not patients that are desaturated need oxygen, whether they respond to oxygen. Do they feel better with oxygen? Does it improve their quality of life? And I guess to be quite frank, we many times will allow patients to make that decision. You know, if you feel better on oxygen and you’re able to exercise and your quality of life improves, then that’s fine. If you really don’t feel better and the chore of having oxygen, carrying oxygen actually worsens your quality of life and we really do not see a response, then obviously we wouldn’t prescribe oxygen.

**Dr Beghetti:** Yes, we need to remember that sometimes they’ve had several surgeries. And so they may have chest deformity, not only lungs, chest deformity. And it is well known that cyanotic patients sometimes have scoliosis. So if you had the chest deformity because of the surgery, the scoliosis, and maybe some lung disease, clearly you will find some patients that after the complete lung workup, they will require oxygen.

**Dr Franklin:** Yes, that’s a good point, too. It’s something that we struggle with, here in Houston. Because I generally don’t necessarily start oxygen. But that said, I have patients who’ve come to me on oxygen and I don’t necessarily stop it, either from their pulmonologist or the prior cardiologist that I’ve inherited from. But to Curt’s point, I’d say yes, some patients feel better on it. Rich, I think you mentioned the nocturnal oxygen. Some patients use it at night and they just feel more rested in the morning. Who knows if that’s placebo effect or not. But, like Curt said, quality of life is important, too. But I tend to not necessarily start oxygen if I’m going to start patients on an exercise regimen, per se.

**Dr Krasuski:** There is a growing body of literature, Wayne, as you’re alluding to, that patients with pulmonary hypertension have sleep-disordered breathing. So it certainly makes sense that the ACHD patients with pulmonary hypertension behave similarly and may therefore benefit from nocturnal oxygen. I wanted to bring up another controversial topic: anticoagulation. How do we handle that in our ACHD-PH patients? It’s interesting that this controversy has existed for over 2 decades and I’m not sure we’re any smarter about this now. I want to know what this expert panel thinks in terms of how we should utilize anticoagulation and what type of impact we make when we do so.

**Dr Daniels:** Personally separate the Eisenmenger cyanotic patient from the noncyanotic patient. I guess even though it is controversial, I still follow some pretty general rules until I see data otherwise. And the general rules that I continue to follow is if they’re a
patient that is cyanotic, this brings a whole host of other hematologic issues of cyanosis, but if they’re a noncyanotic patient, a congenital heart disease patient with pulmonary hypertension, then I typically follow the general rules, which is prescribing anticoagulation, unless a contraindication. The cyanotic patient becomes much more difficult and somewhat more controversial. I do not prescribe anticoagulation for a cyanotic Eisenmenger patient, because of the concern, and certainly we see bleeding diathesis. The cyanotic patient has polycythemia, and typically bleeding disorder that aren’t always completely worked out, but certainly we know that this is the case. And in those patients, unless there is a strong reason to prescribe anticoagulation, such as pulmonary emboli or atrial arrhythmias, the bleeding risk outweighs preventive anticoagulation.

Dr Landzberg: I think for the last 20 years, I’ve taught every fellow that if Curt Daniels says something that you need to totally disregard anything I’ve ever said and listen to what Curt says.

Dr Daniels: Until now. (laughter)

Dr Landzberg: On the same hand, what’s underscored in terms of the population of folks who take care of them, the data that are out there, are quite interesting in this very question, because here are centers that are so aligned with each other. And I actually thought Curt was going to say the exact opposite of what he said, because in the practice here, I will tend to use anticoagulation as the last therapy to add onto the patient with a closed shunt who’s not cyanotic, because I think the data are the least there, and I try to get those patients onto every other therapy where I might have some data or some cohort observational studies, at the least. And it’s the patients with Eisenmenger syndrome that I’m the most concerned with. I know that there are data in terms of prothrombosis; those data are strong. Granted, exactly what Curt said, the data that say that we make a difference with anticoagulation are unknown, but I worry in particular about them. So with the same data, we can argue both sides frequently. But I’ll go back to the very first part of my statement, which was if Curt said something, that’s what I would argue.

Dr Beghetti: I think this underscores the problem we have. We absolutely do not know. And that’s the problem. For example, as a pediatrician, for my idiopathic PH in pediatrics, usually I don’t anticoagulate unless they have a severe RV dysfunction. There is no science behind that, but the problem is that the risk of bleeding in a young patient is pretty high because they’re still very active. And so we rely more on experience than on real data for this anticoagulation approach. And I think in both patients, idiopathic PH and Eisenmenger. And I don’t see how we will indeed design any study at the current time that would help us to really decide for that, unless some of you have an idea. But I think it will be very difficult now to do the study in this population.

Dr Daniels: It certainly will be very important to, as a registry, to try to gather more data on Eisenmenger patients. Who is on anticoagulation? What is their outcome? What is the risk? I mean, it’s an incredibly heterogeneous population, so it will be very difficult to find information, except for observational registry. But, you know, Mike’s point is, of course, a good one. The risk with Eisenmenger is thromboembolic, but they also develop hemoptysis. Clinically I have seen a greater incidence of hemoptysis than thromboembolic events. So it’s an incredibly tough balance. Any scientific evaluation of that population says we see clotting and we see bleeding. And so it makes it very difficult to know what is the proper approach.

Dr Franklin: Very good points. Maybe registries will be the answer. Because I certainly go both ways, but I probably tend to not anticoagulate. I guess no hard data either way. And I tend to think iatrogenic bleeding, whether it’s hemoptysis or what have you, is probably worse. And so I tend to not. But hopefully, we’ll get smarter about this as some of these registries come through.

Dr Krasuski: I would add that one group I regularly anticoagulate are the Eisenmenger patients with indwelling lines for intravenous therapies.

Dr Beghetti: Definitely, yeah.

Dr Krasuski: This also applies to the same group of patient with pacemakers or defibrillators. These are patients in whom I am worried about the risk for paradoxical embolization. All the points on anticoagulation are well taken. I particularly like the way that Mike was able to explain how you could use the data to argue each side of whether or not to anticoagulate in Eisenmenger and CHD-PAH patients.

Dr Krasuski: We’ve unfortunately run out of time, though we have covered many of the topics I wanted to discuss. Let me try to partially summarize our discussion for some “take-home” points. We first discussed the at-risk population. That there are certain groups of patients in whom we’re worried about the development of pulmonary hypertension. Patients...
with larger shunts (natural or surgically created), older patients, those with ventricular dysfunction early on, and patients who had lesions repaired later in life. These are the patients in whom we don’t want to miss the opportunity to screen for PAH. We should be aware of this complication even in the patients that have been previously repaired—this is a very important point for the care providers that don’t routinely follow congenital heart patients—having a complete anatomical repair does not always equal a lifetime free of complications. And pulmonary hypertension is a very important complication. We discussed the approach to workup in these patients. The consensus was that a thorough workup is incredibly important, because we have a tendency to lump patients together who may not respond the same way to therapy. The more we know about certain characteristics such as their lung status, the better we’ll be able to adapt our therapeutic approach and improve outcomes. The importance of catheterization was emphasized. We each come from the vantage point that all perform heart catheterization. We all agreed that an initial hemodynamic assessment for any of the patients who is going to undergo selective pulmonary therapies is absolutely critical. And that it really sets the patient on the proper path for treatment. We were a little conflicted when discussing if and when we should take the patient back to the cath lab. Our agreement was that recatheterization in the patient with Eisenmenger syndrome who is doing well is unnecessary. For the patient with a corrected shunt, we would be a little bit more likely to reassess hemodynamics, particularly if there are any conflicting data about their clinical status. We talked a little bit about natriuretic peptides. They may be an exciting marker to follow, as is MRI for the assessment of ventricular function. In terms of our therapeutic approach to patients, we all mentioned how important exercise is and that’s an important first step in getting patients on the road to feeling better. All of us kind of mentioned the struggle, particularly with insurance companies, that we’ve each had in getting patients into cardiac rehab. Pulmonary rehabilitation may be an alternative pathway for getting patients properly regimented to start exercising again. The use of oxygen should depend upon whether underlying lung disease is present. There are plenty of patients with congenital heart defects who also have restrictive lung disease and other pulmonary problems, so it’s important we properly assess those patients. We don’t want to necessarily restrict their oxygen, particularly if it helps them feel better, but supplemental oxygen at this point, particularly in the Eisenmenger patient, remains fairly controversial. Our discussion of anticoagulation illustrated that we haven’t gotten very far in research in this area, and we have not come up with any good guidelines for who should be anticoagulated. Because the opinion is so strong among physicians who treat CHD-PAH, we absolutely need to collect these data in our registries. Perhaps we won’t be able to do a randomized trial, but through the newer registries that all of you are part of on this board, we may be able to better answer this question in the future. We only talked a little bit about selective pulmonary vasodilator therapy for these patients. The trend appears toward more aggressive use of combination therapy at an earlier stage in the disease process. I think you guys did a fabulous job, and my job as moderator was pretty easy with such a terrific group of panelists. Are there any other final parting comments or anything that we missed today that we should have covered?

**Dr Daniels:** I would just say, Rich, it was an outstanding discussion and I think important for the audience, the topics and the synopsis you just provided really goes to the importance of this educational experience and this opportunity for those that are going to be reviewing our roundtable discussion. So thanks, Rich, for putting it together. And I thank my colleagues for their expert opinion.

**Dr Beghetti:** I have one additional comment. I think the discussion was very interesting for one more reason. You may have noticed, and it’s not to minimize the role of the new targeted therapies, because I think these therapies have started again to work on these patients, but we almost did not discuss these new therapies. And we discussed that we still need to understand what happened to our patients and that we need to very well work up our patients before using these therapies. That’s a very strong message of this roundtable.

**Dr Landzberg:** The study of pulmonary hypertension really began with congenital heart disease and its understanding and the pulmonary vasculature. I personally think that our collaboration with our colleagues who study solely pulmonary arterial hypertension is very rich. Future understanding of the coupling between the right (pulmonary) ventricle and the other supporting structures in the arterial vasculature is really going to lay the foundation for better understanding of this disorder.
Congenital Heart Disease With Associated Pulmonary Arterial Hypertension. Who and When to Operate: A Therapeutic Dilemma

Section Editor
Myung H. Park, MD

Usha Krishnan, MD
Associate Director, Pulmonary Hypertension
Pediatric Cardiology
Columbia University Medical Center
New York, New York

In countries with easy availability of surgical care for congenital heart disease, most patients undergo surgery at an appropriate age before development of pulmonary vascular disease. However, there is an increasing population of children and young adults with previously undiagnosed or unoperated congenital heart disease. The responsibility of deciding who is operable and whether treatment modalities can reverse vascular changes enough to convert a previously “borderline or inoperable” patient to being a surgical candidate often rests with the pulmonary hypertension specialist.1-3 Indeed, studies have shown that operating on patients with high pulmonary vascular resistance (PVR) makes the prognosis significantly worse than the natural history of leaving them without surgery. Cardiac catheterization still remains the gold standard for deciding on operability of these patients.1,2 One must have a clear mental distinction between elevated pulmonary pressures (as in large left to right post-tricuspid shunts) and elevated PVR, which implies distal vascular changes. Children with large left to right shunts and heart failure symptoms with increased pulmonary blood flow will clearly benefit from early surgery. Patients with large defects and PVR equal to or more than systemic vascular resistance (SVR) will have reversed shunts (Eisenmenger syndrome) and are inoperable. Patients with elevated but subsystemic PVR and therefore smaller left to right shunts are the subjects of the therapeutic dilemma. Must one treat with pulmonary vasodilators first and then recheck hemodynamics and operate if suitable— or just leave them alone and manage as early Eisenmenger syndrome?3 What is the long-term outcome of survivors of this strategy?

Clinical clues to increasing PVR can be sought by careful history taking. An infant with a large left to right shunt is usually undernourished, has feeding problems and irritability, may become diaphoretic with crying, and may have recurrent respiratory infections. Then, as the child grows, if pulmonary vascular disease develops, these symptoms of increased pulmonary blood flow gradually disappear and the child starts catching up on growth and appetite and becomes less tachypneic. This is the honeymoon period, when the parents are lulled into a false sense of security that their child is cured of the heart disease, until the shunt reverses as PVR becomes more than the SVR and the child initially gets blue with exercise, and later is cyanosed all the time.

Different defects develop pulmonary vascular disease at different times.1,3 Complex congenital heart defects like transposition of great arteries, truncus arteriosus, and endocardial cushion defects (especially with Down syndrome) almost always develop increased PVR in infancy.3 Many children with large defects at the ventricular or great artery level develop vascular changes in the first 2 years of life, unlike atrial defects, where the majority of patients have near normal PVR well into adulthood. A gain, there is a subgroup of patients with atrial shunts who present with elevated PVR at a very early age, and are thought to possibly be patients with idiopathic pulmonary arterial hypertension (IPAH) with an associated atrial shunt. The goal in managing patients with left to right shunts is to diagnose these lesions early and intervene before development of irreversible pulmonary vascular disease. Patients with significant shunts (Qp/Qs >2:1) at the ventricular (VSD) or great artery level (PDA or A.P. window) should be operated in infancy to prevent vascular disease. Patients with atrial septal defects (ASD) are managed differently. Most patients with moderate secundum ASDs can be treated in the interventional cardiac catheterization laboratory, using devices to close the defect. Careful preprocedure evaluation involves sizing of the defect by prior echocardiography, as well as by balloon sizing using transesophageal echocardiographic guidance during cardiac catheterization, ensuring adequate rims to seat the device and avoiding interference with surrounding structures. A major part of this decision making can be done by transthoracic echocardiogram before taking the patient for the procedure. Patients with sinus venosus, coronary sinus, and primum ASDs are not amenable to transcatheter closure and need to undergo surgical repair. Patients with smaller ASDs with no evidence of right sided volume overload by echocardiogram are usually not at risk for developing PAH, endocarditis, or heart failure and do not need to be closed. The only indications for closure of a small atrial defect or patent foramen ovale would be in an adult with recurrent strokes without other etiologies, or people who train to be deep sea divers (to prevent reverse shunting and catastrophic events).

Evaluation in the cardiac catheterization laboratory should involve very careful assessment of baseline hemodynamics with at least 3 complete right and left heart saturation and pressure runs (Table 1). Hemodynamic calculations include pulmonary and systemic blood flow (Qp and Qs), pulmonary and systemic resistances (PVR and SVR) at baseline, and with acute vasodilator testing (AVT) using inhaled nitric oxide (INO). [A cute va-
soresponsiveness is defined as reduction of mean pulmonary artery pressure by at least 10 mm to a value /H1102140 mm with an increased or unchanged cardiac index. 4-6 There are several issues that the clinician has to be aware of while performing and interpreting cardiac catheterization data. Snapshot hemodynamic studies are greatly influenced by sedation, general anesthesia, airway and lung parenchymal issues, stress (of intubation), catecholamines, and variations in acid-base balance, especially in young children under general anesthesia. Several studies have demonstrated benefits of treating Eisenmenger patients with advanced therapies. It is thought that their antiproliferative effects lead to reverse remodeling in the pulmonary circulation and may eventually cause reduction in PVR and improve right ventricular hypertrophy.1 Perhaps treating borderline patients with pulmonary vasodilators for a finite period of time and reassessing their hemodynamics would reduce their PVR enough to make them candidates for shunt closure. Since short-term improvements in these patients may not translate into long-term survival benefit, partial closure of the defect in highly selective patients with improved hemodynamics on treatment and continuing pulmonary vasodilator therapy seems an attractive prospect and merits further investigation. Larger and longer-term studies using these strategies will be required before one can be sure of the right approach for these patients, but the availability of newer drugs holds a promise for the future.

References

Table 1: Formulae for calculation of shunts and resistances using hemodynamic data

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Q_p = \frac{\text{VO}_2}{(\text{PVO}_2 - \text{PAO}_2)})</td>
<td>Pulmonary blood flow</td>
</tr>
<tr>
<td>(Q_s = \frac{\text{VO}_2}{(\text{Aortic} - \text{Mixed Venous Saturation})(\text{Oxygen Capacity})})</td>
<td>Systemic blood flow</td>
</tr>
<tr>
<td>(Q_{ep} = \frac{\text{VO}_2}{(\text{Pulmonary Vein} - \text{Mixed Venous Saturation})(\text{Oxygen Capacity})})</td>
<td>Effective pulmonary flow</td>
</tr>
<tr>
<td>(L-R \text{ Shunt} = Q_p - Q_{ep})</td>
<td>Left-to-right shunt</td>
</tr>
<tr>
<td>(R-L \text{ Shunt} = Q_s - Q_{ep})</td>
<td>Right-to-left shunt</td>
</tr>
<tr>
<td>(Q_p/Q_s = \text{Aortic} - \text{Mixed Venous Saturations/Pulmonary Vein} - \text{Pulmonary Artery Saturation})</td>
<td>Pulmonary vascular resistance</td>
</tr>
</tbody>
</table>

Abbreviations: \(\text{VO}_2\) = oxygen consumption; \(Q_p\) = pulmonary blood flow; \(Q_s\) = systemic blood flow; \(Q_{ep}\) = effective pulmonary flow; \(\text{PVO}_2\) = pulmonary vein \(\text{O}_2\) content; \(\text{PAO}_2\) = pulmonary artery \(\text{O}_2\) content; \(m\text{PAP}\) = mean pulmonary artery pressure; \(m\text{AoP}\) = mean aortic pressure; \(m\text{RAP}\) = mean right atrial pressure; \(m\text{PVP}\) = mean pulmonary venous (or pulmonary artery wedge) pressure; saturation \(P\text{VR}\) = pulmonary vascular resistance; \(SVR\) = systemic vascular resistance.

While breathing 100% O₂, one must include dissolved oxygen in the calculation of oxygen content, using the equation "dissolved Oxygen = 0.03*PO₂.

\(P\text{VR} = \frac{m\text{PAP} - m\text{PVP}}{Q_p}\)  
\(SVR = \frac{m\text{AoP} - m\text{RAP}}{Q_s}\)  
Oxygen capacity = 13.6*Hemoglobin(gm/dl).

While breathing 100% O₂, one must include dissolved oxygen in the calculation of oxygen content, using the equation "dissolved Oxygen = 0.03*PO₂.
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ADCIRCA® (tadalafil) tablets is a phosphodiesterase 5 inhibitor (PDE-5i) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

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Pulmonary Arterial Hypertension: ADICRA is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults with mean pulmonary artery pressure ≤ 25 mm Hg at rest and ≤ 30 mm Hg during exercise, who have symptoms of heart failure, to improve clinically meaningful functional capacity and to delay the clinical progression of PAH. ADICRA was effective when added to pre-existing background therapy in patients with PAH who were not responsive to initial therapy with calcium-channel blockers. ADICRA was not effective when added to patients who were taking an endothelin receptor antagonist. This drug is not recommended for use in combination with an endothelin receptor antagonist and a prostanoid. ADICRA was not effective in patients with PAH due to HIV infection.

CONTRAINDICATIONS

Concomitant Organic Nitrates: Do not use ADICRA in patients who are using any form of organic nitrate, either regularly or intermittently. ADICRA potentiates the hypotensive effect of nitrites. The potential for this interaction is thought to result from the combination of effects of nitrates and ADICRA on the nitric oxide/cGMP pathway. Hypersensitivity Reactions: ADICRA is contraindicated in patients with a known serious hypersensitivity to tadalafil (ADICRA or CIALIS). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects: Discuss with patients the appropriate control of blood pressure or blood pressure enhancers and the impact of anginal chest pain requiring nitroglycerin following intake of ADICRA. At least 48 hours should elapse after the last dose of ADICRA before taking nitroglycerin. If a patient has taken ADICRA, has not ingested nitroglycerin and is undergoing medical supervision with appropriate hemodynamic monitoring, patients who experience anginal chest pain after taking ADICRA should seek immediate medical attention. PDE5 inhibitors, including tadalafil, have mild systemic vasodilator properties that may result in transient decreases in blood pressure. Prior to prescribing ADICRA, carefully consider whether patients with underlying cardiovascular disease could be adversely affected by such vasodilator effects. Patients with severely impaired autonomic function and with the potential for reflex tachycardia (e.g., orthostatic hypotension), and patients who have disease states that might predispose them to priapism (such as sickle cell disease, multiple myeloma, or leukaemia), or in patients with anatomic deformations of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease). ADICRA should be used with caution in patients who have preexisting cardiovascular disease that might predispose them to priapism (such as sickle cell disease, multiple myeloma, or leukaemia), or in patients with anatomic deformations of the penis (such as angulation, cavernosal fibrosis, or Peyronie’s disease). ADICRA use with Alpha Blockers and Antihypertensives — PDE5 inhibitors have not been studied. Inform patients about the potential for drug-to-drug interactions. Co-administration of ADICRA in Patients on Ritonavir — In clinical trials: a small number of patients who were specifically excluded from the PAH clinical data on administration of ADICRA to patients with severe hepatic cirrhosis have not been studied. Avoid use of ADICRA. ADICRA Effects on the Effect: Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non–arteritic anterior ischemic optic neuropathy (NAION), a disease of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors. It is not possible to determine whether these events are related to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors. Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and these patients are not recommended. Hearing Impairment: Physicians should advise patients to seek immediate medical attention in the event of sudden decrease or loss of hearing. These events (e.g., tinnitus and dizziness), have been reported in temporal association to the intake of PDE5 inhibitors, including ADICRA. 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: Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADICRA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADICRA not to take CIALIS or other PDE5 inhibitors. Prolonged Erection: There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of drugs. Priapism may result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention. ADICRA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell disease, multiple myeloma, or leukaemia), or in patients with anatomic deformations of the penis (such as angulation, cavernosal fibrosis, or Peyronie’s disease). Effects on Bleeding: PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADICRA has not been administered to patients with bleeding disorders or significant active peptic ulcer disease. ADICRA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

ADVERSE REACTIONS

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

- Hypotension
- Vision loss
- Hearing loss
- Priapism
- Clinical Trials Experience:

- Cardiovascular adverse events (≥5% in patients taking ADICRA 40 mg group and occurring more frequently than with placebo).

- TABLE 1: Treatment-Emergent Adverse Events Reported by ≥5% of Patients in ADICRA and More Frequent than Placebo by 2%
are using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Alpha-Blockers — PDE5 inhibitors, including ADCIRCA, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin. Antihypertensives — PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo. Alcohol — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure–lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations. Potential for Other Drugs to Affect ADCIRCA: Ritonavir — Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir. Other Potent Inhibitors of CYP3A — Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and irtraconazole, avoid use of ADCIRCA. Potential Inducers of CYP3A — For patients chronically taking potent inducers of CYP3A such as rifampin, avoid use of ADCIRCA.

Potential for ADCIRCA to Affect Other Drugs: Cytochrome P450 Substrates — Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoenzymes (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan). Aspirin — Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin. P-glycoprotein (e.g., digoxin — Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

USE IN SPECIFIC POPULATIONS
Pregnancy: Pregnancy Category B — Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed. Non-teratogenic effects — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance. Nursing Mothers: It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman. Pediatric Use: Safety and effectiveness of ADCIRCA in pediatric patients have not been established. Geriatric Use: Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered. Renal Impairment: For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis. Hepatic Impairment: Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child–Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child–Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients.

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

Clearing the Fog: PH-Associated Diseases
If your patients are juggling multiple conditions associated with pulmonary hypertension, you know that managing their care can be overwhelming for them and their families. Now there’s some clarity: In PHA’s new video series, your patients can hear stories from fellow PH patients living with associated diseases and the healthcare professionals who treat them.

Learn more at:
www.PHAssociation.org/PHPlus

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

PH Pulmonary Hypertension Association
Empowered by hope
Help Your Patients and Caregivers Connect to Support
PHA offers monthly telephone support groups for patients, caregivers, and parents. We make it easy for you to share this resource with your patients: you can sign up for email alerts, download a postcard as a PDF, or request printed postcards for your clinic at www.PHAssociation.org/TelephonePostcards. Your patients can also find a support group in their community by going to www.PHAssociation.org/FindaSupportGroup.

New Resources on PVD and Right Ventricular Dysfunction
Sessions from the September 2012 Keystone Symposium, titled “Pulmonary Vascular Disease and Right Ventricular Dysfunction: Current Concepts and Future Therapies,” are now on PHA Online University. Organized by Drs. Georg Hansmann of Hannover Medical School, Stephen L. Archer of Queen’s University, and Margaret R. MacLean of the University of Glasgow, this conference gathered basic and clinical researchers in pulmonary vascular disease and right ventricular dysfunction. Recordings cover topics such as cell phenotype and function in PAH, right ventricle and pulmonary circulation in PAH, right ventricle failure in PAH, and more. The recordings are at www.PHAOnlineUniv.org/KeystoneSymposium.

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

PHA Launches Major Campaign for Early Diagnosis
Lynn Brown, MD, campaign chair

Images of zebras and their stripes have been cropping up more frequently among professionals who treat pulmonary hypertension (PH). They’ve appeared in this and other issues of Advances, for instance, and on buttons given out at medical meetings. Expect the zebra to proliferate in diverse primary and specialty care circles, as well, as PHA carries out its new zebra-themed Sometimes it’s PH campaign for early diagnosis in the US and global health communities.

Physicians on PHA’s Board of Trustees suggested the zebra emblem to reverse the culture and right ventricular dysfunction. Recordings cover topics such as cell phenotype and function in PAH, right ventricle and pulmonary circulation in PAH, right ventricle failure in PAH, and more. The recordings are at www.PHAOnlineUniv.org/KeystoneSymposium.

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Sometimes it’s PH

Hearing Hoof Beats:
The Latest on the Sometimes it’s PH Campaign

The campaign’s central message is: “Sometimes dyspnea, chest pain, and other widespread symptoms may lead you to conclude it’s asthma, chronic obstructive pulmonary disease (COPD), obesity, or lack of fitness. But sometimes it’s not. Sometimes it’s PH.”

Sometimes it’s PH responds to a call to action from a November 2011 white paper, Pulmonary Arterial Hypertension: Recommendations for Improving Patient Outcomes, written under PHA’s leadership by a group of PH experts from around the globe. Data cited included a finding from the REVEAL Registry that the mean duration between symptom onset and confirmed diagnosis by right heart catheterization is 2.8 years and has scarcely improved in more than 2 decades. The paper concluded that delays in diagnosis of PH and referral to specialized care are now the main barriers to better patient outcomes. Optimal care, noted in the paper, is collaboration between primary and specialty care providers.

PHA’s 5-year campaign will teach health care professionals to consider a PH diagnosis when symptoms warrant and to team up earlier with specialized PH physicians who can confirm diagnosis and offer a wider range of treatment, clinical trials, and patient support networks. The campaign will educate medical professionals by publishing articles in professional journals, placing news stories, developing new forums for educating about early diagnosis and referral, exhibiting and speaking at medical and allied health meetings, and joining with key professional and advocacy organizations on education and communication initiatives that reach their members.

At this early stage, the campaign’s activities have included the creation of a Web site devoted to the campaign, www.SometimesItsPH.org, the release of a 60-second video spot accessible through that site, and outreach to health care media. We have formed leadership committees composed of PH physicians and allied health professionals. Each committee will guide activities in 1 of the 3 campaign approaches: educating, communicating with health professionals, and forming collaborative relationships with key professional associations.

This column will appear in future issues of Advances to provide updates on Sometimes it’s PH. Keep an eye on this bold and important new PHA initiative.
Sometimes symptoms indicate asthma or COPD. But sometimes they don’t.

When learning to diagnose, doctors are taught that hoof beats suggest horses, not zebras. But a rare disease like pulmonary hypertension is like a zebra among horses.

Those expecting common diseases often overlook the zebras. As a result, many PH patients have been misdiagnosed repeatedly before getting the treatment they need. Even worse, almost three-quarters of patients have advanced PH by the time they are diagnosed.

The Pulmonary Hypertension Association is taking unprecedented action to change that. Our Sometimes it’s PH campaign promotes early diagnosis among primary and specialty care providers. Join us.

www.SometimesItsPH.org
Program Announcement:

New Application Deadline: June 12, 2013
New Application Deadline: October 12, 2013
Resubmission Deadline: July 12, 2013
Resubmission Deadline: November 12, 2013

PULMONARY HYPERTENSION ASSOCIATION (PHA)

National Heart, Lung, and Blood Institute (NHLBI)

Jointly Sponsored

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

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

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

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

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

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

* Restrictions apply. Please see complete announcement at the website listed above.
Host a Free PHA On-Demand Event at Your Institution

Bring free PAH medical education to your community. PHA’s On-Demand initiative enables medical professionals to choose a program, topic, speaker, format, and date, and PHA takes care of the rest. Learn more about the On-Demand Program: www.PHAssociation.org/OnDemand.

- I would like to receive a complimentary copy of the Pulmonary Hypertension: Cases, Controversies and Conundrums CD-ROM.
- I would like to receive a complimentary copy of the 2010 Pulmonary Hypertension Scientific Sessions DVD.
- I would like to receive a quarterly, complimentary copy of Advances in Pulmonary Hypertension.
- I would like to receive notification when the online edition of Advances in Pulmonary Hypertension is available.
- I would like to receive notification when new PH webinars and online courses are offered.

Name ___________________________ Title ___________________________
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Address ___________________________________________________________
City ___________________________ State ______ ZIP ___________
Phone ___________________________________________________________
E-mail address ________________________________

Winter 2013
Help Patients Find You!

As PHA strives to better serve our constituents, we are committed to making sure our Find a Doctor Directory, located at www.PHAssociation.org/FindADoctor, provides the most current information for patients. The Find a Doctor Directory is PHA’s premier resource for patients seeking PH-treating physicians, and being listed in the directory is a benefit available only to members of PH Clinicians and Researchers (PHCR). To ensure your listing is complete and correct, make sure your online profile is updated.

Current members: To update your listing in the Find a Doctor Directory, please visit www.PHAssociation.org/PHCR/ProfileUpdate.

Lapsed members: To renew your membership, please visit www.PHAssociation.org/PHCR/Renew.