ISSN 1933-088X

Advances in Pulmonary Hypertension

Vol 22, No 1; 2023

Official Journal of the Pulmonary Hypertension Association

The Fruits of Research in PH

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

Advances in
Pulmonary Hypertension
Official Journal of the Pulmonary Hypertension Association

PUBLISHER
Pulmonary Hypertension Association
Matt Granato, LL.M., MBA, President and CEO

PHA OFFICE
Pulmonary Hypertension Association
8401 Colesville Road, Suite 200
Silver Spring, MD 20910
301-565-3004; 301-565-3994 (fax)
Advances@PHAssociation.org

PUBLISHING OPERATIONS
Kara Kopchinski,
Managing Editor

Advances in Pulmonary Hypertension is available online at www.AdvancesinPH.org.

Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

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

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

***Advances in Pulmonary Hypertension*'s Web Platform**

Advances in Pulmonary Hypertension is available at www.AdvancesinPH.org. This site offers enhanced capabilities including a dedicated DOI and cross-referencing potential, as well as other features valuable to practitioners, researchers, and educators. Registration is recommended to access all site features and benefits.

We are thrilled to bring this issue of *Advances in Pulmonary Hypertension* to you, which highlights some of the fruits of basic and clinical research in pulmonary hypertension. We have invited accomplished PH experts to help us navigate through some of the increasingly complex challenges in the diagnosis and treatment of PH. First, we have included all the scientific abstracts presented at the PHA 2022 International Pulmonary Hypertension Conference.

Next, Drs. Jennifer Keen, Nadine Al-Naamani, and Corey Ventetuolo provide a focused review on emerging therapies for the management of pulmonary arterial hypertension (PAH). They summarize selected and most promising novel pharmaceuticals currently on the horizon and in clinical trials that are targeting new pathways in PAH.

In August of 2022, the European Society of Cardiology and the European Respiratory Society published guidelines for the diagnosis and management of pulmonary hypertension (PH). This recent guideline now lowers the pulmonary vascular resistance from > 3 Wood units down to >2 Wood Units to meet the criteria for pre-capillary PH. Drs. Bradley Maron and Georgios Triantafyllou take us back to 1973, when the diagnosis of PH only required a mean PAP of >25 mmHg, and then review the subsequent literature that forms the basis for the revised definition. Dr. Robert Frantz provides a counterpoint to the lowering of the upper limit of PVR by highlighting the problems with the revised definition of pre-capillary PH, and how it might be practically implemented in clinical practice. Finally, Drs. Vallerie McLaughlin, Marc Humbert, Charles Burger, and Hilary DuBrock discuss the pros and cons of these new guidelines in-depth in a roundtable format.

We immensely thank all of our contributing authors for sharing their experience and insights. We sincerely hope you enjoy reading this issue of *Advances in Pulmonary Hypertension*.

Thenappan Thenappan, MD
Division of Cardiology, Department of Medicine, Lillehei Heart Institute, University of Minnesota Medical School, Minneapolis, Minnesota

Ronald Oudiz, MD
Lundquist Institute for Biomedical Innovation, Division of Cardiology, Harbor–UCLA Medical Center, Torrance, California

PHA 2022 International Pulmonary Hypertension Conference Abstracts

BOSENTAN DECREASES RIGHT VENTRICULAR SYSTOLIC PRESSURE AND PRO-BRAIN NATRIURETIC PEPTIDE LEVELS IN INFANTS WITH PULMONARY HYPERTENSION

Lily M. Landry
Department of Pediatrics, Division of Pediatric Cardiology University of Mississippi Medical Center, Jackson, MS, USA

Andrew C. Burks
School of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

Onyekachukwu Osakwe
Department of Pediatrics, Division of Pediatric Cardiology, University of Mississippi Medical Center, Jackson, MS, USA

Jarrod D. Knudson
Department of Pediatrics, Division of Pediatric Critical Care, University of Mississippi Medical Center, Jackson, MS, USA

Christopher L. Jenks
Department of Pediatrics, Division of Pediatric Critical Care, University of Mississippi Medical Center, Jackson, MS, USA

Category: Clinical Science
Selected Areas: Pediatrics, Therapeutic Strategies

Background: Pulmonary hypertension (PH) is a rare and potentially fatal disease in children if left untreated. Emerging therapies, including bosentan, a dual endothelin receptor antagonist (ERA), have shown significant benefits in the adult PH population; however, few studies have assessed the efficacy and safety of ERAs in infants and young children.
Methods: Our study was a single-center retrospective analysis of patients <2 years of age with a confirmed diagnosis of PH and started on bosentan therapy between 2017 and 2020. Twelve cases met eligibility criteria. Demographic (Table 1), laboratory, echocardiographic, and cardiac catheterization data were analyzed (Tables 2–4).
Results: With treatment, there was a statistically significant decrease in mean right ventricular systolic pressure estimated by the tricuspid regurgitation jet (79 ± 23 mm Hg reduced to 52 ± 25 mm Hg; *P* value <0.001) and pro-brain natriuretic peptide levels (21071 reduced to 2037; $P < 0.001$). Additionally, improvement and eventual normalization of right ventricular function and septal geometry was seen within the first 4 months of therapy (Figure). Patients who underwent cardiac

Table 1. Descriptive Statistics

Patient characteristic	Value (n = 12)[a]
Male	9 (75)
Female	3 (25)
Gestational age at birth, wk	31.8 ± 6 (23.4–40)
Birth weight, g	1759 ± 1106 (660–3580)
Ethnicity	
African American	7 (58)
Caucasian	5 (42)
Etiology of PH, mo	
Chronic lung disease alone	1 (8)
Congenital heart disease alone	1 (8)
Mixed lung and heart disease	10 (83)
Age at diagnosis, mo	3.6 ± 2.4 (0–7.2)
Age at time of bosentan initiation, mo	9.6 ± 4.4 (3–17.8)
Time from diagnosis to initiation of bosentan therapy, mo	6.0 ± 5.2 (0.3–17.8)
ICU survival	7 (58)
Hospital survival	7 (58)

ICU, intensive care unit; PH, pulmonary arterial hypertension.
[a]Data are shown as n (%) or mean ± SD (range).

Table 2. Change in Echocardiographic Parameters with Treatment

Parameter	Baseline (n = 12)[a]	Posttreatment (n = 11[b])	*P*value
Right ventricular function			
Normal	6 (50)	11 (100)	0.04
Mildly depressed	4 (33)	0 (0)	<0.01
Moderately depressed	2 (17)	0 (0)	<0.01
Interventricular septal position			
Normal	0 (0)	4 (36)	0.09
Flat in systole	2 (17)	3 (27)	1.00
Flat in diastole	0 (0)	1 (10)	1.00
Flat in systole and diastole	5 (42)	3 (27)	0.66
Bowing into the left ventricle in systole	5 (42)	0 (0)	0.04
RVSP from TR, mm Hg	79 ± 23 (40–120)	52 ± 25 (23–100)	<0.001
Left ventricular ejection fraction, %	77 ± 10 (58–88)	71 ± 9.6 (59–88)	0.50

RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation jet.
[a]Data are shown as n (%) or mean ± SD (range).
[b]One patient died prior to getting a posttreatment echocardiogram.

 DOI:10.21693/1933-088X-22.1.4

Table 3. Change in Catheterization Parameters with Treatment

	Baseline (n = 7)[a]	Posttreatment (n = 4)	*P* value	95% confidence interval
Parameters				
PVRi (Wood units × m^2)	5.06	3.14	0.140	–0.77 to 4.62
SVRi (Wood units × m^2)	10.7	11.4	0.811	–7.80 to 6.27
PVR/SVR ratio	0.54	0.34	0.253	–0.17 to 0.57
Mean pulmonary artery pressure, mm Hg	34.4	31.0	0.443	–5.67 to 12.9
Diastolic pulmonary pressure, mm Hg	21.0	16.0	0.018	1.06–8.94
Transpulmonary gradient, mm Hg	23.7	18.7	0.183	–2.79 to 12.8
Diastolic pulmonary gradient, mm Hg	9.5	7.0	0.403	–3.87 to 8.87

PVRi, indexed pulmonary vascular resistance; PVR/SVR, pulmonary vascular resistance to systemic vascular resistance; SVRi, indexed systemic vascular resistance.

[a]Data are shown as mean values.

Table 4. Change in Laboratory Values with Treatment

Laboratory value	Baseline (n = 12)[a]	Posttreatment (n = 12)	*P* value	95% confidence interval
Pro-BNP	21071	2037	<0.001	4655–33413
Hemoglobin	11.09	11.95	0.161	–2.07 to 0.36
Platelet count	269.75	259.24	0.732	–51.3 to 72.3
AST	52.1	45.54	0.359	–7.78 to 20.9
ALT	43.3	32.96	0.137	–3.46 to 24.1

ALT, alanine aminotransferase; AST, aspartate transaminase; Pro-BNP, pro-brain natriuretic peptide.

[a]Data are shown as n (%) or mean ± SD (range).

catheterization after therapy initiation (n = 4) demonstrated hemodynamic improvements; however, only the decrease in diastolic pulmonary pressure was statistically significant (*P* value = 0.018). No significant difference in hemoglobin, platelet count, or liver function tests was observed between groups.

Conclusions: In conclusion, these data suggest that bosentan may be an effective and relatively safe treatment option for children <2 years of age with PH. Further long-term randomized control studies are necessary to validate the potential clinical benefit of using this drug therapy in young children.

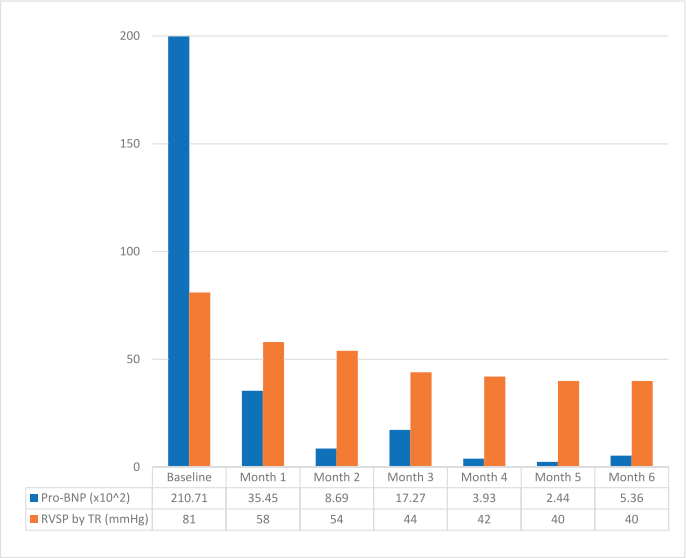


Figure 1: Pro-brain natriuretic peptide and right ventricular systolic pressure trends by month. Pro-BNP, pro-brain natriuretic peptide; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation jet.

CONCOMITANT MEDICATION USE IN TREATMENT JOURNEY OF PULMONARY ARTERIAL HYPERTENSION PATIENT: A CANADIAN RETROSPECTIVE CLAIMS ANALYSIS

Essam Ibrahim
Janssen Inc., Toronto, Ontario, Canada

Assem Al-Akabawi
Janssen Inc., Toronto, Ontario, Canada

Moses Dawodu
Janssen Inc., Toronto, Ontario, Canada

Juejing Ling
IQVIA Solutions Canada Inc., Kirkland, Quebec, Canada

Irene Wang
IQVIA Solutions Canada Inc., Kirkland, Quebec, Canada

Brad Millson
IQVIA Solutions Canada Inc., Kirkland, Quebec, Canada

Category: Clinical Science
Selected Areas: Databases and Registries

Background: The current standard of care for pulmonary arterial hypertension (PAH) is combination therapy, which imposes pill burden on PAH patients who live with multiple comorbidities. This study aims to understand the concomitant medication use in treatment journey of Canadian PAH patients.

Methods: Patients initiating PAH therapy (index) from September 1, 2016, to August 31, 2019, were selected in the Ontario Drug Benefits (ODB), Régie de l'assurance maladie du Québec (RAMQ), and IQVIA Canadian Private Drug Plan (PDP) databases. Medication prescriptions 5-year prior and 1-year postindex were tracked. Concomitant medication

analysis used ODB and PDP; prescriber specialty analysis used PDP database.
Results: A total of 1019 patients were included from ODB (N = 481), PDP (N = 422), and RAMQ (N = 116). Tadalafil (61%) and sildenafil (22%) were most prescribed at index. One year prior to index, 75% and 30% of patients with concomitant medications (N = 828) were on 5+ and 10+ concomitant medication classes, respectively. From 5 years prior to the 1-year postindex, the proportion of cardiovascular medications use declined (16% versus 13%), while that of diuretics use increased (10% versus 16%). Compared with the year prior, prescriptions of rescue treatment decreased 1 year postindex (926 versus 763). Here, 72% of patients (N = 300) were prescribed by general practitioner (GP) before index, while prescribers of cardiovascular and respiratory medications shifted from GP to specialist postindex. Among the top 3 prescribers, females had a significant reduction in the number of concomitant medications postindex, while males trended the opposite way.
Conclusions: This study shows the complex treatment journey of Canadian PAH patients and highlights the need to reduce pill burden and improve disease management.

WORLD DRUG RETENTION AND INITIATION OF COMBINATION DRUG THERAPY FOR PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION IN CANADA

Essam Ibrahim
Janssen Inc., Toronto, Ontario, Canada

Assem Al-Akabawi
Janssen Inc., Toronto, Ontario, Canada

Moses Dawodu
Janssen Inc., Toronto, Ontario, Canada

Juejing Ling
IQVIA Solutions Canada Inc., Kirkland, Quebec, Canada

Jillian Murray
IQVIA Solutions Canada Inc., Kirkland, Quebec, Canada

Brad Millson
IQVIA Solutions Canada Inc., Kirkland, Quebec, Canada

Category: Clinical Science
Selected Areas: Databases and Registries

Background: Treatment guidelines for pulmonary arterial hypertension (PAH) recommend combination therapy in most patients. This study evaluated retention of PAH drugs and time-to-initiation of combination drug therapy with macitentan and selexipag in Canada.
Methods: Patients claiming PAH drugs from January 2017 to March 2021 were identified in the Ontario Drug Benefits (ODB), Régie de l'assurance maladie du Québec (RAMQ), and IQVIA Canadian Private Drug Plan (PDP) databases. Drug retention was calculated for patients submitting claims 12 months following treatment index (March 2019 to February 2020 [PDP, ODB]; January to December 2019 [RAMQ]). Treatment was considered first line if patients were treatment naïve with >180 days of claims history. Time-to-initiation of combination therapy was calculated for macitentan+PDE5i and selexipag-containing therapies.
Results: Around 2150 patients claimed PAH drugs annually, with averages of 1000 (PDP), 900 (ODB), and 250 (RAMQ). Most patients were female (65%–77%) and aged 45+ years (69%–85%). The 12-month retention was greatest for macitentan in PDP (67%) and RAMQ (88%), and tadalafil (78%) in ODB. Of patients on macitentan or selexipag, approximately 79% and 95% were on combination therapy (2+ drugs) in 2020, respectively. In 2020, 12%–17% of patients were on macitentan combination therapy (3+ drugs), and 43%–69% were on selexipag combination therapy (3+ drugs). In 2020, mean time-to-initiation was 4–5 months for macitentan+PDE5i and 17–23 months for selexipag-containing therapies (Table).
Conclusions: Real-world data from Canada shows that most PAH patients on macitentan or selexipag are on combination therapies. Time-to-initiation was 4–5 months for macitentan+PDE5i, and 17–23 months for selexipag-containing combination therapies. This study shows the complex treatment journey of Canadian PAH patients and highlights the need to reduce pill burden and improve disease management.

Table 1. Annual Average Time (mo) From First-Line PAH Treatment to Selexipag- and Macitentan-Combination Therapy, 2017–2021

	Selexipag combination therapy			Macitentan combination therapy	
Source	ODB	PDP	RAMQ	PDP	RAMQ
2017	N/A	17.0	16.5	6.8	4.4
2018	24.0	21.0	18.7	4.3	3.0
2019	24.3	17.0	28.2	4.3	3.1
2020	17.8	17.0	22.8	5.1	4.2
2021 YTD	30.3	19.0	15.5	7.4	4.6

RATIONALE AND DESIGN OF THE RIOCIGUAT USERS (ROAR) REGISTRY

Roxana Sulica
Pulmonary Critical Care and Sleep Division, NYU Grossman School of Medicine, NYU Langone Health, New York, NY, USA

Stacy Mandras
AdventHealth Transplant Institute, Orlando, FL, USA

Chad Miller
Piedmont Physicians, Pulmonary Hypertension/Pulmonary Critical Care Medicine, Piedmont Healthcare, Austell, GA, USA

R. James White
University of Rochester Medical Center, Rochester, NY, USA

Nick H. Kim
Division of Pulmonary and Critical Care Medicine, University of California San Diego, La Jolla, CA, USA

Sameer Bansilal
Bayer US, LLC, Whippany, NJ, USA

Vicki Poon
Bayer US, LLC, Whippany, NJ, USA

Daniel Johnson
Bayer US, LLC, Whippany, NJ, USA

Valerie Carvajal
Bayer US, LLC, Whippany, NJ, USA

Murali Chakinala
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Washington University at Barnes-Jewish, St. Louis, MO, USA

Category: Clinical Science
Selected Areas: Databases and Registries, Quality of Life, Therapeutic Strategies

Background: Initial pulmonary arterial hypertension (PAH) treatment has evolved from monotherapy to combinations of approved drug classes. Riociguat was approved for PAH based on the PATENT study, which studied it as monotherapy or in sequential combination with an endothelin receptor antagonist (ERA) or nonparenteral prostanoid. PATENT and REPLACE gave substantial data on riociguat combinations, but there are no US-based registry data on riociguat.
Methods: ROAR (NCT04813926; funder: Bayer US, LLC) is a US-based, multicenter, prospective, observational registry of adults with PAH who are riociguat-naïve or who initiated riociguat 90 days previously. Data will be collected at standard-of-care visits (usually every 3–6 months) for 24 months or until 30 days after discontinuing riociguat. Planned enrollment: 500 patients (~50 sites). The primary objective is to study safety and effectiveness of riociguat as first-line therapy or combined with an ERA and/or prostanoid. Secondary objectives include safety and effectiveness of first-line riociguat versus transition from a phosphodiesterase-5 inhibitor, and the importance of treatment sequence. Effectiveness outcomes include change from baseline to months 6 and 12 in 6-minute walk distance, biomarkers, clinical PAH risk scores, hemodynamics (right heart catheterization), echocardiography, laboratory tests, and New York Heart Association and World Health Organization functional class. Patient-reported outcomes will be assessed at baseline, month 6, and month 12. Primary safety endpoints are incidence of selected adverse events and serious adverse events through 24 months. ROAR began recruitment in July 2021.
Results: By January 13, 2022, 35 patients were enrolled.
Conclusions: Interim baseline data will be presented.

UNDERSTANDING DRIVERS AND BARRIERS TO PARTICIPATION IN CLINICAL TRIALS FOR PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

Sandeep Sahay
Houston Methodist Hospital, Houston, TX, USA

Elizabeth Aselage
Gossamer Bio, Inc., San Diego, CA, USA

David F. Harris
Insight & Measurement, LLC, Durham, NC, USA

Marie Mascia-Rand
Project Breathless, Princeton, NJ, USA

Rob Roscigno
Gossamer Bio, Inc., San Diego, CA, USA

Erin Elman
Gossamer Bio, Inc., San Diego, CA, USA

Stephen C. Mathai
Johns Hopkins University School of Medicine, Baltimore, MD, USA

Category: Clinical Science
Selected Areas: Databases and Registries

Background: Ongoing trials of therapies targeting drivers of disease are key to improving outcomes in patients with pulmonary arterial hypertension (PAH), but enrollment is challenging. Factors affecting enrollment in PAH trials are not well characterized. We conducted a survey to identify factors that encourage or discourage trial participation by PAH patients.
Methods: A survey was administered through Rare Patient Voice, an online platform used by >100 000 patients and

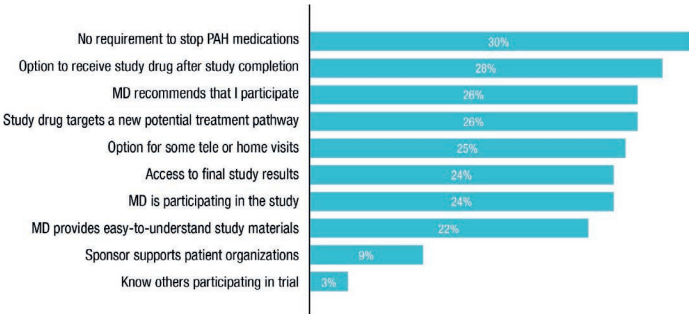


Figure 1: Top factors encouraging participation in clinical trials.

caregivers, to gather demographics, trial considerations, and preferences for health care provider (HCP) communication. Eligible participants were >21 years old, treated with 1 PAH medication, had a self-reported PAH diagnosis for 6 months, and had never participated in a clinical trial. The protocol was approved by a central institutional review board, and participants provided informed consent.

Results: One hundred two patients completed the survey. Average age was 51.4 years, average time from PAH diagnosis was 8.3 years, and 69% reported stable disease. Fifty-three percent and 37% of respondents were *very interested* and *somewhat interested* in trial participation, respectively, yet 75% reported not having a discussion about trial participation with HCPs. Over 90% reported they would welcome such a discussion. Factors encouraging trial participation are summarized (Figure).

Conclusions: While PAH patients are interested in clinical trial enrollment, awareness regarding trial opportunities is lacking. Other barriers to participation include concerns regarding maintenance of current therapy and providers and a desire to continue study drug after trial completion. Further education is needed for patients and clinicians to encourage trial participation.

IMPROVING THE USE OF RISK ASSESSMENTS FOR PULMONARY ARTERIAL HYPERTENSION: A QUALITY IMPROVEMENT INITIATIVE AT A PULMONARY HYPERTENSION SPECIALTY CLINIC

Janice E. Heffernan
Rush University College of Nursing, Northwestern Memorial Hospital Pulmonary Department, Chicago, IL, USA

Jacquelynne Messinger
Formerly Bluhm Cardiovascular Institute, Pulmonary Vascular Disease Program, Chicago, IL, USA

Michael J. Cuttica
Division of Pulmonary and Critical Care Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Ruben Mylvaganam
Division of Pulmonary and Critical Care Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

David Pugh
Pulmonary Vascular Disease Program, Northwestern Medicine, Chicago, IL, USA

Yasmin Raza
Bluhm Cardiovascular Institute, Feinberg School of Medicine, Northwestern University, Feinberg School of Medicine, Northwestern Medicine, Chicago, IL, USA

Ambalavanan Arunachalam
Division of Pulmonary and Critical Care Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: The most recent pulmonary arterial hypertension (PAH) guidelines stress the importance of multiparameter risk assessments to classify disease severity and guide management decisions. However, formal risk assessment tools are often underused in clinical practice, leading to missed op-

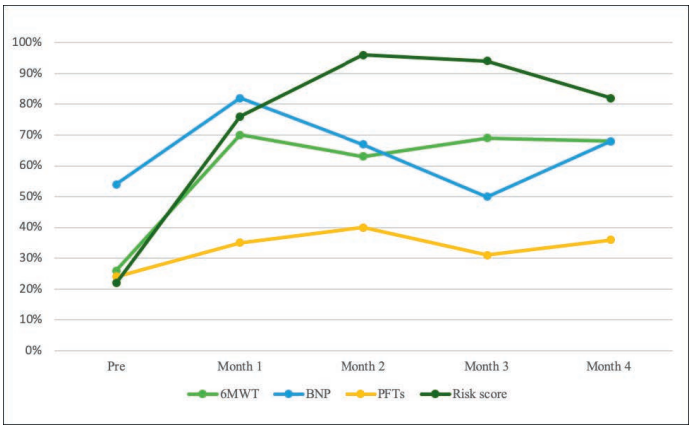


Figure 1: Risk assessment and variable documentation by month.

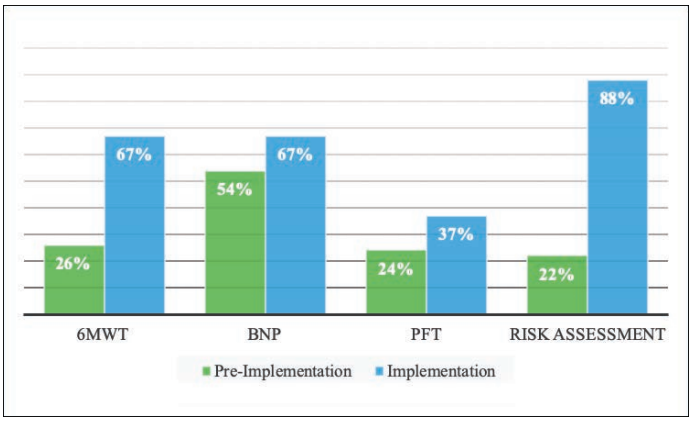


Figure 2: Chart audit results.

portunities to escalate pharmacotherapy and other supportive measures, which may prevent clinical deterioration.
Methods: A retrospective chart review was conducted to understand the frequency of risk assessment documentation at a large pulmonary hypertension (PH) specialty clinic. Electronic medical record (EMR) modifications, including a REVEAL 2.0 flowsheet and quick text, were implemented to support provider use of a formal risk assessment tool. An education session for providers focused on the new EMR features and the collection of key variables necessary for accurate risk assessments. A separate training for medical assistants reviewed the organization's 6-minute walk test (6MWT) protocol. Throughout the project period, audit and feedback cycles were used to measure and communicate progress toward outcome objectives.
Results: During the 4-month implementation period, documentation of risk assessments improved from 22% to 88%. The percent of patients with a 6MWT documented in the previous 6 months increased from 26% to 67%. The collection of brain natriuretic peptide values and pulmonary fitness tests also improved (Figures 1 and 2).
Conclusions: EMR integration of a preferred risk assessment tool paired with evidence-based quality improvement methods is an effective strategy to increase provider use of PAH risk assessments in a real-world setting. More research is needed to understand how this increased collection of risk assessments affects management decisions. The effects of risk stratification on the selection and timing of pharmacotherapy is of particular interest.

CASE STUDIES ON OUTCOME OF CONGENITAL HEART DEFECTS ATTRIBUTED TO TIMING OF SCREENING AND INTERVENTION

Anam Pyakurel, MBBS
Pulmonary Hypertension Association Nepal, Urlabari, Nepal
Civil Service Hospital, Kathmandu, Nepal

Sahadev Bidari, MBBS
Pulmonary Hypertension Association Nepal, Urlabari, Nepal
Greencity Hospital, Kathmandu, Nepal

Prasansha Thapa, MBBS
Pulmonary Hypertension Association Nepal, Urlabari, Nepal
Birat Nursing Home, Biratnagar, Nepal

George Bush Jung Katwal, MBBS
Pulmonary Hypertension Association Nepal, Urlabari, Nepal
Annapurna Neurological Institute And Allied Sciences, Kathmandu, Nepal

Chooda M. Khanal, PhD
Pulmonary Hypertension Association Nepal, Miami, FL
Florida International University, Miami, FL

Lava Timsina, PhD
Pulmonary Hypertension Association Nepal, Miami, FL
Indiana University, Indianapolis, IN

Roshan Khatiwada, MBBS
Pulmonary Hypertension Association Nepal, Miami, FL
Himal Hospital, Kathmandu, Nepal

Category: Case Report
Selected Areas: Diagnosis or Screening and Physiologic Studies; Diseases and Conditions Associated with PH; Quality of Life

Background: Congenital heart defects (CHDs) are the most common types of birth defects (1% of births per year in the United States). Among babies with CHD, 1 in 4 presents critical CHD with a need for surgery in infancy. In this study, we highlight the importance of screening camp and early intervention in pulmonary arterial hypertension (PAH) cases secondary to CHDs in rural settings of Nepal.
Methods: Series of comprehensive cardiac screening camps were conducted in different parts of rural Nepal. In this paper, we present clinical symptoms, diagnosis, surgical management, and follow-up outcomes of 2 PAH cases secondary to CHD who were screened at one of the cardiac camps and referred to and reevaluated in tertiary cardiac centers.
Results: The first case of an 11-year-old female who was referred from the screening camp was managed surgically in 37 days of screening, had a favorable outcome, and was doing well during follow-up, whereas the second case of a 22-year-old male managed surgically after 9 months of screening had an unfavorable outcome of death on the first postoperative day. The difference in time to surgical management in both cases was attributed to several factors: patient's age, awareness and their socioeconomic factors, and clinical heterogeneity in consensus recommendation and practices in government facilities in Nepal.
Conclusions: Cardiac screening camp in rural settings of developing countries like Nepal may help in early diagnosis and prevention of cardiac related morbidity and mortality. Early diagnosis and hence management of CHD facilitated through cardiac screening camp can save many more lives of children living with CHDs if conducted effectively with continuity of care at regular follow-up intervals.

PHASE 1, OPEN-LABEL STUDY OF INHALED SERALUTINIB TO ASSESS POTENTIAL EFFECTS ON THE PHARMACOKINETICS OF CYTOCHROME P450 AND TRANSPORTERS

Jack Li
Gossamer Bio, Inc., San Diego, CA, USA

Matt Cravets
Gossamer Bio, Inc., San Diego, CA, USA

Emanuel DeNoia
ICON Clinical Research, LLC, Gaithersburg, MD, USA

Debbie Slee
Gossamer Bio, Inc., San Diego, CA, USA

Lawrence S. Zisman
Gossamer Bio, Inc., San Diego, CA, USA

Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Seralutinib is an inhaled small-molecule kinase inhibitor specifically developed for the treatment of pulmonary arterial hypertension (PAH), with an optimized kinase specificity profile that targets PDGFRa/β, CSF1R, and c-KIT, and modulates BMPR2. Targeting these pathways may reverse pulmonary vascular inflammation, cellular proliferation, and fibrosis. In addition, by directly targeting the diseased lung, inhaled seralutinib limits systemic exposure. Based on in vitro predictions and given that multi-agent regimens are often required in treating PAH, we evaluated the potential for drug-drug interactions (DDIs) with inhaled seralutinib.
Methods: Twenty-four healthy adults received a cocktail of probe substrates: caffeine (CYP1A2), montelukast (CYP2C8), flurbiprofen (CYP2C9), midazolam (CYP3A), digoxin (P-gp), and pravastatin (OATP1B1/1B3) with or without seralutinib. Pharmacokinetics and safety were evaluated.
Results: Geometric least square mean ratios for Cmax and AUC of probe substrates with and without seralutinib are shown. Seralutinib is a moderate CYP3A inhibitor per the effect on midazolam (Figure).
Conclusions: Based on the moderate effect, seralutinib is not expected to cause clinically relevant DDIs with most PAH drugs that are CYP3A substrates (tadalafil, riociguat, bosentan, and macitentan); these drugs may be co-administered without dose modification. In the case of sildenafil, dose adjustments should be considered based on risk-benefit assessment. In addition, clinically relevant DDIs with substrates of CYP1A2, CYP2C8, CYP2C9, CYP2C19, P-gp (except for digoxin), or OATP1B1/1B3 are not anticipated. Seralutinib was well tolerated with or without co-administered agents.

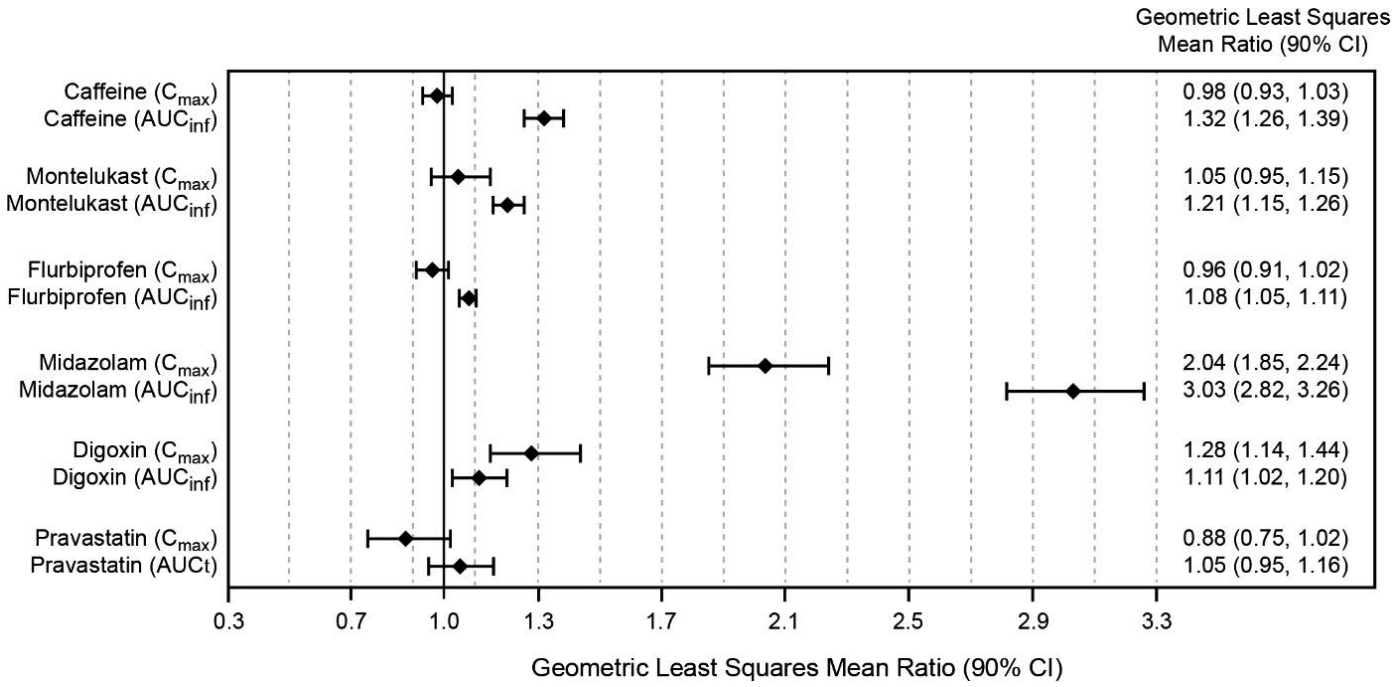


Figure 1: Forest plot of geometric least square (LS) mean ratios of plasma pharmacokinetics (PK) parameters of probe substrates and metabolites (PK population).

EVIDENCE OF TARGET ENGAGEMENT AND PATHWAY MODULATION: BIOMARKER ANALYSIS OF THE PHASE 1B INHALED SERALUTINIB STUDY

Robin Osterhout
Gossamer Bio, Inc., San Diego, CA, USA

Kristin B. Highland
Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA

Robert P. Frantz
Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

David Nickle
Gossamer Bio, Inc., San Diego, CA, USA

John McConnell
Norton Pulmonary Specialists, Louisville, KY, USA

Charles D. Burger
Division of Pulmonary, Allergy, and Sleep Medicine, Mayo Clinic, Jacksonville, FL, USA

Robert F. Roscigno
Gossamer Bio, Inc., San Diego, CA, USA

Matt Cravets
Gossamer Bio, Inc., San Diego, CA, USA

Ramona McCaffrey
Gossamer Bio, Inc., San Diego, CA, USA

Jack Li
Gossamer Bio, Inc., San Diego, CA, USA

Lawrence S. Zisman
Gossamer Bio, Inc., San Diego, CA, USA

Jean-Marie Bruey
Gossamer Bio, Inc., San Diego, CA, USA

Luke S. Howard
Imperial College Healthcare NHS Trust, London, UK

Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Seralutinib is an inhaled small-molecule kinase inhibitor which selectively targets PDGFRa/β, CSF1R, and c-KIT signaling implicated in pulmonary arterial hypertension (PAH) pathobiology. An approximately 30× higher lung than plasma exposure and extended lung target engagement (TE) in preclinical studies suggest that pharmacodynamic activity in the human lung is expected at the dose levels studied. We evaluated changes in exploratory peripheral biomarkers of TE and mechanism of action in PAH subjects.
Methods: In a phase 1b multicenter, randomized, placebo-controlled study, subjects with PAH were randomized 3:1 to receive inhaled seralutinib up to 90 mg BID or placebo for 14 days. Whole blood and serum samples were collected at screening and day 14 for biomarker analysis: pretreatment, 5 minutes, and 2 hours posttreatment. A novel whole blood CSF1R internalization assay was developed to assess TE. Epigenetic immunoprofiling assays and RNAseq were performed.
Results: Eight subjects received seralutinib (n = 6) or placebo (n = 2). Seralutinib was well tolerated at doses up to 90 mg BID. Seralutinib inhibited CSF1R internalization at 5 minutes but not 2 hours postinhalation relative to baseline, consistent with its short half-life in peripheral circulation. Transcriptomics data at day 14 identified treatment-associated shifts in 779 genes. An epigenetic signal suggestive of increasing FOXP3+ Tregs:CD4+ T cells following treatment was also observed.
Conclusions: Preliminary biomarker findings support TE and downstream effects in the periphery that suggest target modulation by seralutinib in PAH patients. Seralutinib is being evaluated as a new treatment for patients with PAH receiving standard of care (SOC) background therapies in a recruiting phase 2 study (NCT04456998).

A PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INHALED SERALUTINIB FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION: A TRIAL IN PROGRESS

Robert P. Frantz
Mayo Clinic, Rochester, MN, USA

Luke S. Howard
Imperial College Healthcare NHS Trust, London, UK

Vallerie V. McLaughlin
University of Michigan, Ann Arbor, MI, USA

Olivier Sitbon
Université Paris-Saclay, Le Kremlin-Bicêtre, France

Roham T. Zamanian
Stanford University, Menlo Park, CA, USA

Raymond L. Benza
Ohio State University, Columbus, OH, USA

Kelly Chin
UT Southwestern Medical Center, Dallas, TX, USA

Richard Channick
UCLA Medical Center, Los Angeles, CA, USA

Matt Cravets
Gossamer Bio, Inc., San Diego, CA, USA

Jean-Marie Bruey
Gossamer Bio, Inc., San Diego, CA, USA

Erin Elman
Gossamer Bio, Inc., San Diego, CA, USA

Robert Roscigno
Gossamer Bio, Inc., San Diego, CA, USA

David Mottola
Gossamer Bio, Inc., San Diego, CA, USA

Lawrence S. Zisman
Gossamer Bio, Inc., San Diego, CA, USA

Hossein-Ardeschir Ghofrani
Justus-Liebig University Giessen, Giessen, Germany

Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Seralutinib is a potent, clinical-stage kinase inhibitor for treatment of patients with pulmonary arterial hypertension (PAH). It selectively targets PDGFRa/β, CSF1R, and c-KIT signaling implicated in PAH pathobiology, and modulates BMPR2. Seralutinib is delivered with a discreet, hand-held dry powder inhaler to directly target the diseased lung to limit systemic exposure and thereby potentially improve efficacy and tolerability. A phase 2 study is ongoing (TORREY; NCT04456998).

Methods: TORREY is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of inhaled seralutinib in adult subjects with World Health Organization Group 1 pulmonary hypertension (PH). Patients with Functional Class II or III PAH on therapy with a pulmonary vascular resistance (PVR) ≥400 dyn·s/cm^5 are eligible. The planned treatment period is 24 weeks, with a target enrollment of 80 patients. The primary endpoint is change in PVR measured by right heart catheterization from baseline to 24 weeks. The key secondary endpoint is change in 6-minute walk test (6MWT) from baseline to 24 weeks. Two substudies will explore novel endpoints. In the heart rate monitoring substudy, the effect of seralutinib on cardiac effort during 6MWT will be assessed. The computerized tomography substudy will examine the effect of seralutinib on pulmonary vascular remodeling by quantifying changes in pulmonary arterial blood volume. Exploratory biomarkers will be evaluated for target engagement and response to treatment.
Conclusions: This abstract was previously presented at the ISHLT2021 Annual Meeting and Scientific Sessions (Frantz et al., *J Heart Lung Transplant*. 2021;40(4 Suppl):S107. doi:10.1016/j.healun.2021.01.346).

CASE STUDY: PORTOPULMONARY HYPERTENSION

Rosemarie Gadioma, ANP
New York Presbyterian Weill Cornell, New York City, NY, USA

Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: Portopulmonary hypertension is pulmonary arterial hypertension (PAH) in portal hypertension. Pulmonary hypertension (PH) is classified in five groups: Group 1 is PAH with several etiologies including idiopathic, heritable PAH, collagen vascular disease, congenital heart disease, HIV, drugs, or portopulmonary hypertension. Group 2 is PH owing to left heart disease. Group 3 is PH owing to lung disease. Group 4 is chronic thromboembolic PH (CTEPH). Group 5 is miscellaneous cause of PH.
Methods: Portal hypertension develops in the setting of cirrhosis, extrahepatic portal vein thrombosis, or schistosomiasis. This results in the resistance to portal blood flow leading to complications such as ascites and variceal bleed. Portopulmonary hypertension affects up to 6% of patients with advanced liver disease.
Results: (Case) A 66-year-old woman with newly diagnosed PH World Symposia on Pulmonary Hypertension Group 1 with history of chronic Hepatitis C (HCV; status post Epclusa February through August 2020) and alcohol-related cirrhosis complicated by ascites and hepatopulmonary syndrome, hypertension, and diabetes type 2 was being evaluated for liver transplant. She had an echocardiogram which showed moderate PH. She was then referred after cardiac catheterization which showed systemic level PH. She was started on AMBITION medications with subsequent severe migraine headaches. She had gained fluid weight and was then admitted for further management.

PATIENT-REPORTED VERSUS CLINICIAN-ASSESSED FUNCTIONAL CLASS IN THE ADAPT PULMONARY ARTERIAL HYPERTENSION REGISTRY

Karim El-Kersh
University of Nebraska Medical Center, Omaha, NE, USA

Hilary DuBrock
Mayo Clinic, Rochester, MN, USA

Stephen Mathai
Johns Hopkins University School of Medicine, Baltimore, MD, USA

Melisa Wilson
AdventHealth, Orlando, FL, USA

Stephanie Hwang
University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC, USA

Table 1. Comparison of World Health Organization Functional Classification (WHO-FC; Completed by Clinician) and Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR; Completed by Patient)

	WHO-FC (Completed by clinician)	PH-FC-SR[1] (Completed by patient)
Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.	I have pulmonary hypertension, but my physical activity is not limited. I can do my day-to-day physical activity (e.g. household tasks, go to work, go to the store) and my usual exercise without getting short of breath or feeling tired or experiencing chest pains or feeling like I may faint.
Class II	Patients with pulmonary hypertension resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.	I have pulmonary hypertension and my physical activity is slightly limited. I feel comfortable at rest. I can do my day-to-day physical activity (e.g. household tasks, go to work, go to the store) but it makes me feel short of breath or tired or have chest pains or feel like I may faint.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.	I have pulmonary hypertension and my physical activity is noticeable limited. I feel comfortable at rest. I can do the type of physical activity I have to do on a day-to-day bases (e.g. bathing, dressing, preparing meals) but it makes me feel short of breath or tired or have chest pains or feel like I may faint.
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.	I have pulmonary hypertension and almost any physical activity makes me feel short of breath or tired or have chest pains or nearly faint. I frequently experience swollen ankles. I may have a bloated stomach. I may get short of breath or tired even when resting. I experience increasing amounts of discomfort with any physical activity.

[1]Highland KB, Crawford R, Classi P, et al. *Health Qual Life Outcomes.* 2021;19(1):202. Published 2021 Aug 24.

Table 2. Baseline Characteristics of Patients in Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR) Substudy From the ADAPT Registry

Patient Characteristics	n = 18
Age, mean (S.D.)	65 (15.2) years
Female sex – no. (%)	12 (67%)
Race/Ethnicity – no. (%)	
White	15 (83%)
Black/African American	2 (11%)
Asian	1 (6%)
Highest level of education– no. (%)	
High school diploma or equivalent	3 (17%)
Some college, no degree	5 (28%)
Associate degree	2 (11%)
Bachelor's degree	5 (28%)
Master's degree	1 (6%)
Professional or doctoral degree (PhD, MD, JD, PharmD, etc.)	1 (6%)
Prefer not to answer	1 (6%)
Working status at baseline – no. (%)	
Working full-time (≥40 hours per week)	6 (33%)
Working part-time (<40 hours per week)	3 (17%)
Disabled, permanently or temporarily	6 (33%)
Retired	3 (17%)
Time since PAH diagnosis, mean (S.D.)	5.7 (3.6) years
PAH classification – no. (%)	
Idiopathic	11 (61%)
Associated with connective tissue disease	4 (22%)
Associated with drug or toxin exposure	2 (11%)
Heritable	1 (6%)
PAH background medications – no. (%)	
None	4 (22%)
ERA only	2 (11%)
PDE-5i / sGCS only	3 (17%)
ERA + PDE-5i / sGCS	9 (50%)
6MWD at baseline, mean (S.D.)	424.1 (100) m
BNP at baseline, mean (S.D.) (n = 9)	107.4 (144.0) pg/mL
NT-proBNP at baseline, mean (S.D.) (n = 8)	1221.1 (1431.0) pg/mL

Note: table includes only patients with matched assessments of PH-FC-SR and WHO-FC.

Scott Seaman
United Therapeutics Corporation, Research Triangle Park, NC, USA

Meredith Broderick
United Therapeutics Corporation, Research Triangle Park, NC, USA

Kristin Highland
Cleveland Clinic, Cleveland, OH, USA

Category: Clinical Science
Selected Areas: Databases and Registries, Diagnosis or Screening and Physiologic Studies, Diseases and Conditions Associated with PH

Background: The World Health Organization Functional Classification (WHO-FC) measures pulmonary arterial hypertension (PAH) symptom severity and activity limitations. The Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR) is an adapted version of the WHO-FC for patient self-completion (Table 1). PH-FC-SR can provide longitudinal monitoring when collecting clinician-rated FC may not be feasible or practical. The study aimed to determine if patient-reported PH-FC-SR agreed with clinician-assessed WHO-FC.
Methods: ADAPT is a real-world registry of PAH patients taking oral treprostinil. An optional substudy in ADAPT collected PH-FC-SR and WHO-FC at baseline, week 24, and week 52. Patient responses were blinded to study team members assessing WHO-FC. PH-FC-SR and WHO-FC were matched if both patient and clinician completed the FC survey within 30 days of each other. Agreement between PH-FC-SR and WHO-FC was assessed.
Results: There were 27 matched assessments from 18 unique patients at 9 sites. Baseline characteristics include socioeconomic and PAH disease statuses (Table 2). Twenty-four of 27 (89%) matched assessments were completed on the same day (Table 3). Twenty-three of 27 (85%) patient and clinician scores were the same. Two patients underreported and 2 patients overreported PH-FC-SRs compared with matched clinician assessments

(unique patients, Table 3).

Conclusions: This is the first study assessing agreement between WHO-FC and PH-FC-SR. Patients from different sites with a range of PAH disease and socioeconomic statuses successfully matched clinician-assessed FC reports, supporting validity of use in clinical practice for longitudinal, at-home monitoring.

Table 3. Matched Patient-Reported Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR) and Clinician-Assessed World Health Organization Functional Classification (WHO-FC) Survey Responses. Discordant Assessments Are Italicized and Bolded

Observation #	Patient	Patient-Reported (PH-FC-SR)	Clinician-Assessed (WHO-FC)	Time between surveys (days)	Time of Assessment
1	A	CLASS III	CLASS III	0	Baseline
2	B	CLASS II	CLASS II	0	Baseline
3	B	CLASS II	CLASS II	0	Follow Up 1
4	***C***	***CLASS II***	***CLASS I***	***7***	***Baseline***
5	C	CLASS I	CLASS I	0	Follow Up 1
6	***D***	***CLASS II***	***CLASS III***	***0***	***Baseline***
7	E	CLASS II	CLASS II	0	Baseline
8	F	CLASS II	CLASS II	0	Baseline
9	***F***	***CLASS IV***	***CLASS II***	***0***	***Follow Up 1***
10	G	CLASS II	CLASS II	0	Baseline
11	H	CLASS II	CLASS II	16	Baseline
12	I	CLASS I	CLASS I	0	Baseline
13	I	CLASS I	CLASS I	0	Follow Up 1
14	I	CLASS I	CLASS I	0	Follow Up 2
15	J	CLASS II	CLASS II	0	Baseline
16	***K***	***CLASS III***	***CLASS IV***	***0***	***Baseline***
17	L	CLASS II	CLASS II	0	Baseline
18	L	CLASS II	CLASS II	0	Follow Up 1
19	M	CLASS II	CLASS II	0	Baseline
20	M	CLASS II	CLASS II	0	Follow Up 1
21	N	CLASS I	CLASS I	0	Baseline
22	O	CLASS I	CLASS I	0	Baseline
23	P	CLASS I	CLASS I	0	Baseline
24	P	CLASS I	CLASS I	0	Follow Up 2
25	Q	CLASS II	CLASS II	0	Baseline
26	Q	CLASS II	CLASS II	0	Follow Up 2
27	R	CLASS II	CLASS II	2	Baseline

Class I = No limitation of physical activity, Class II = Slight limitation of physical activity, Class III = Marked limitation of physical activity, and Class IV = Inability to carry out any physical activity.

SAFETY AND EFFICACY OF RT234 VARDENAFIL INHALATION POWDER ON EXERCISE PARAMETERS IN PULMONARY ARTERIAL HYPERTENSION: PHASE 2 DOSE-ESCALATION STUDY DESIGN

Raymond L. Benza
The Ohio State University Wexner Medical Center, Columbus, OH, USA

Veronica Franco
The Ohio State University Wexner Medical Center, Columbus, OH, USA

Mandar A. Aras
University of California San Francisco, San Francisco, CA, USA

Leslie Spikes
University of Kansas Medical Center, Kansas City, KS, USA

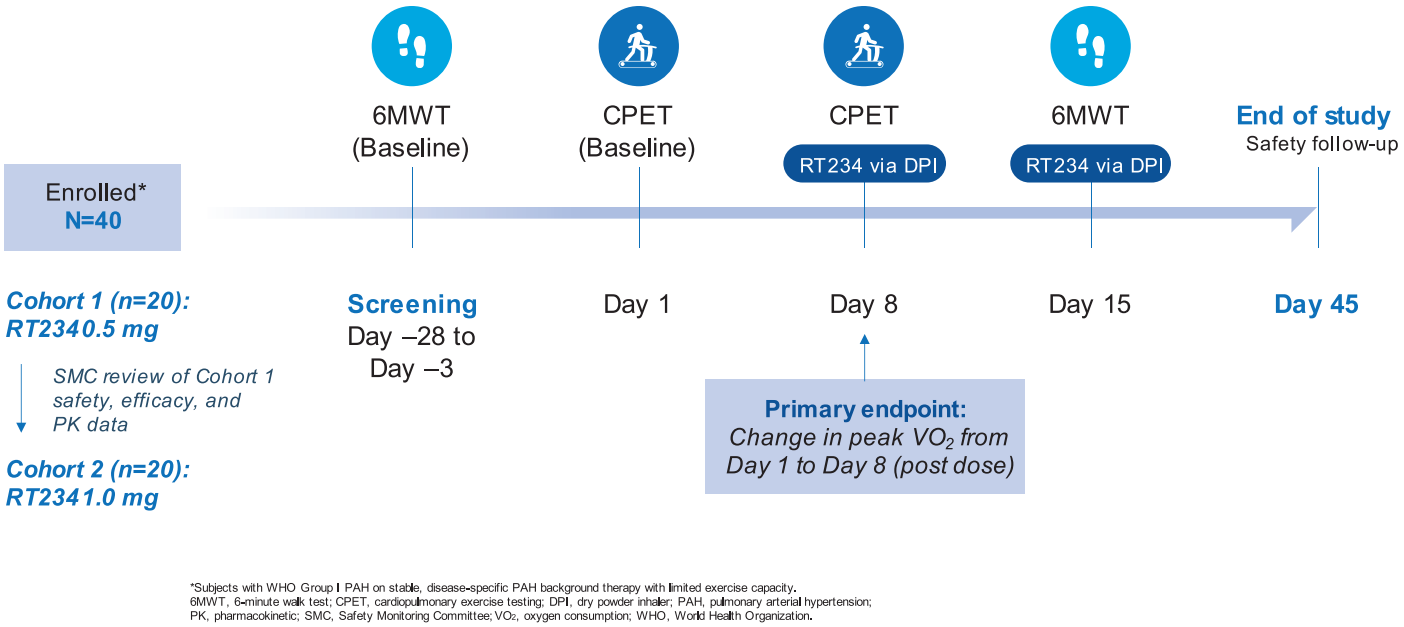
Daniel Grinnan
Virginia Commonwealth University School of Medicine, Richmond, VA, USA

Kevin Corkery
Respira Therapeutics Inc., Albuquerque, NM, USA

Carol Satler
Respira Therapeutics Inc., Albuquerque, NM, USA

Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is currently managed using chronic, scheduled treatments to improve exercise capacity and delay clinical worsening. Availability of an as-needed (PRN) treatment may further enhance patient quality of life by rapidly resolving symptoms associated with physical activity. RT234 is a drug and device combination of vardenafil hydrochloride and the novel axial oscillating sphere dry powder inhaler that is suitable for PRN use and has the potential to improve exercise capacity, physical activity, and associated symptoms (ie, dyspnea).
Methods: The CL202 study (NCT04266197; Sept 2020-Dec 2023 [expected completion]) is a multicenter, open-label, dose-escalation, phase 2b study designed to evaluate the safety and efficacy of RT234 on exercise parameters assessed by cardiopulmonary exercise testing (CPET) and 6-minute walk distance (6MWD) in patients with PAH (Figure).
Results: Up to 40 adult patients with right heart catheterization—confirmed World Health Organization Group 1 PAH on stable oral PAH-specific (=2) and/or inhaled



*Subjects with WHO Group I PAH on stable, disease-specific PAH background therapy with limited exercise capacity.
6MWT, 6-minute walk test; CPET, cardiopulmonary exercise testing; DPI, dry powder inhaler; PAH, pulmonary arterial hypertension; PK, pharmacokinetic; SMC, Safety Monitoring Committee; VO_2, oxygen consumption; WHO, World Health Organization.

Figure 1: CL202 study design.

therapy are being enrolled in 2 successive dose cohorts (0.5 mg; 1.0 mg). A safety monitoring committee will decide whether to proceed with the 1.0 mg cohort or terminate the study. Safety measures include adverse events (at each of 2 single-dose treatment days and for 30-day follow-up) and acute physical and cardiac effects. Efficacy measures include changes in peak oxygen capacity (Vo_2; primary endpoint) and exertional symptoms from baseline (day 1) to 15 minutes postdose during CPET on day 8, and change in 6MWD from baseline (screening, day –28 to day –3) to 15 minutes postdose on day 15.

Conclusions: Exploratory endpoints include pharmacokinetics and exposure-response analyses. The results of the CL202 study are expected to inform the design of phase 3 trials of RT234.

THYROID STORM FROM GRAVES' DISEASE ASSOCIATED WITH SEVERE PULMONARY HYPERTENSION AFTER PULMONARY THROMBOENDARTERECTOMY FOR CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Evan Carabelli MD
Temple University Hospital, Philadelphia, PA, USA

Philip Lavenburg DO
Temple University Hospital, Philadelphia, PA, USA

Riyaz Bashir
Temple University Hospital, Philadelphia, PA, USA

Paul Forfia
Temple University Hospital, Philadelphia, PA, USA

William Auger
Temple University Hospital, Philadelphia, PA, USA

Vladimir Lakhter
Temple University Hospital, Philadelphia, PA, USA

Frances A. Rogers
Temple University Hospital, Philadelphia, PA, USA

Lori Warren
Temple University Hospital, Philadelphia, PA, USA

Estefania Oliveros Soles
Temple University Hospital, Philadelphia, PA, USA

Anjali Vaidya
Temple University Hospital, Philadelphia, PA, USA

Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: While pulmonary hypertension (PH) is often cured in chronic thromboembolic PH (CTEPH) after pulmonary thromboendarterectomy (PTE), there is a risk of recurrent PH after PTE in a minority of patients.
Methods: (Case) A 50-year-old female with hypertension and hysterectomy for fibroids presented with dyspnea, severe PH and right ventricular (RV) dysfunction. Ventilation-perfusion scan (Figure 1), computed tomography angiography (CTA), and pulmonary angiography (Figure 2) revealed multiple areas of severe thromboembolic disease. She underwent urgent PTE (Figure 3) with markedly improved hemodynamics, albeit warranting resumption of sildenafil early postop. Six months postop, she developed worsening dyspnea and was restarted on 3-drug PH therapy. One year postop she had severe PH

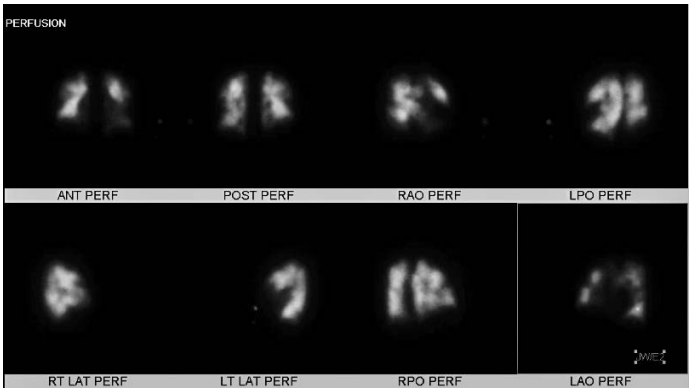


Figure 1: Preoperative perfusion scan demonstrating multiple unmatched perfusion defects in the right upper, right lower, left upper, and left lower lobes. ANT, anterior; LAO, left anterior oblique; LAT, lateral; LPO, left posterior oblique; LT, left; PERF, perfusion; POST, posterior; RAO, right anterior oblique; RPO, right posterior oblique; RT, right.

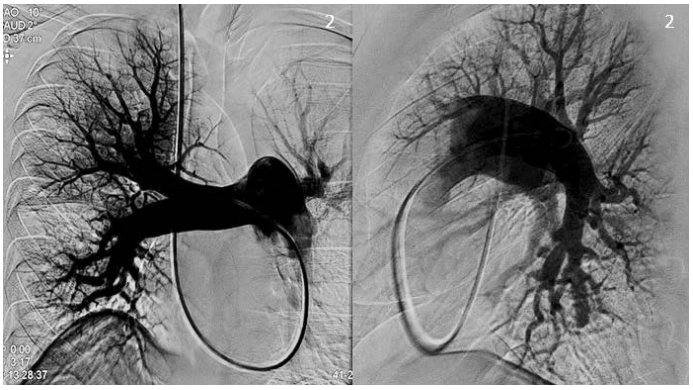


Figure 2: Preoperative pulmonary angiogram. (**Left**) Anterior-posterior view of selective right main pulmonary angiogram and (**Right**) lateral view of selective left main pulmonary angiogram showing obstructive lesions in multiple, bilateral lobar, and segmental branches.

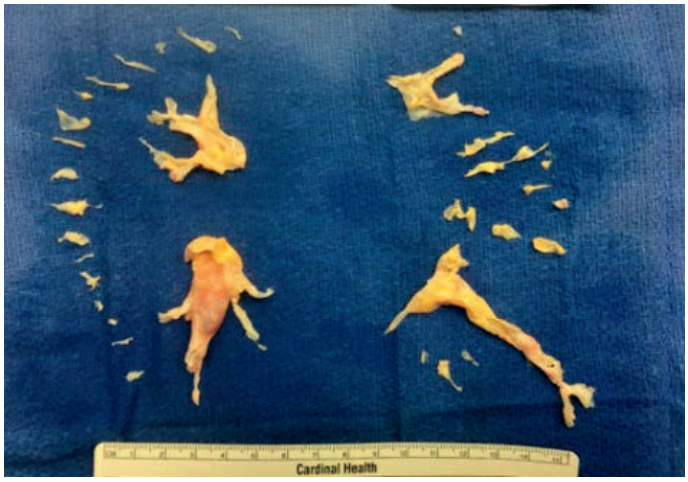


Figure 3: Clot specimen removed from pulmonary thromboendarterectomy.

despite high-dose combination PH therapy and underwent balloon pulmonary angioplasty (BPA). Ongoing fatigue and dyspnea prompted readmission 1 month later.

Results: (Decision making) Severe PH post-PTE and post-BPA should prompt consideration of PH etiologies beyond thromboembolic disease. She was noted to have persistent sinus tachycardia, bounding arterial pulses, hyperreflexia, and hyperdynamic findings on echo-Doppler (Figure 4). Thyroid studies revealed severe thyrotoxicosis leading to a diagnosis of Graves' disease. She was treated with methimazole, iodine, and steroids followed by thyroidectomy with substantial improvement in symptoms and improved RV function by echo.

Conclusions: While PH after PTE is generally related to thromboembolic disease, it may not always be. Clinical assessment of PH after PTE should include careful consideration and evaluation for thyroid disease and the broad range of medical conditions known to be associated with PH.

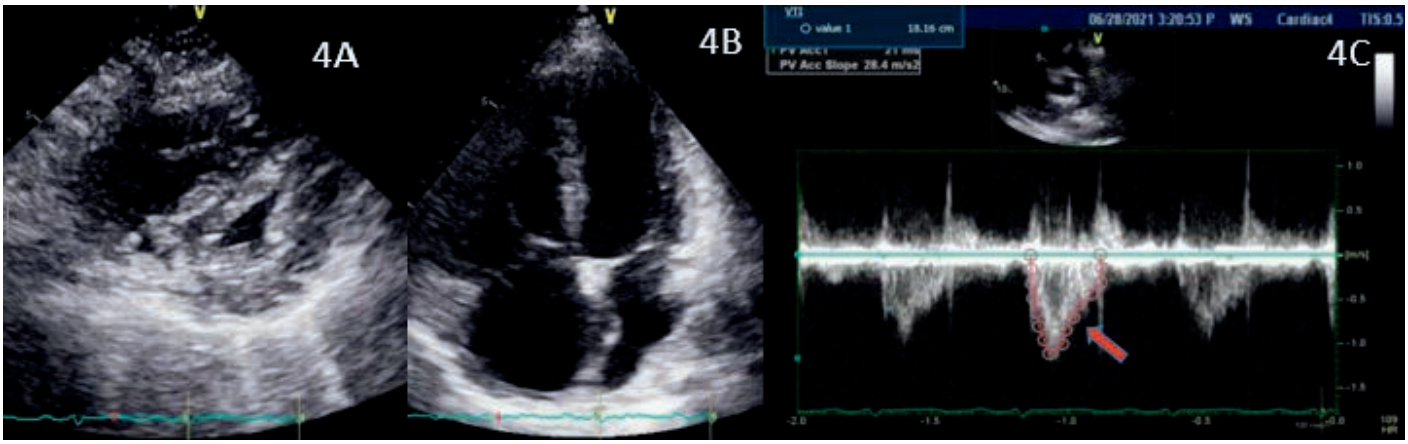


Figure 4: (**A**) Hyperdynamic LV and systolic interventricular septal flattening. (**B**) RV enlargement and dysfunction, RA dilatation and right-to-left interatrial septal bowing. (**C**) PW Doppler of the RVOT. Short acceleration time and late systolic notching (red arrow). LV, left ventricular; PW, pulsed-wave; RA, right atrial; RV, right ventricular; RVOT, RV outflow tract

ACUTE HEMODYNAMIC IMPROVEMENT IN CHRONIC PULMONARY ARTERIAL HYPERTENSION ON DUAL THERAPY FOLLOWING RT234 INHALATION

Anne Keogh
St Vincent's Hospital, Darlinghurst, NSW, Australia

Nathan Dwyer
Royal Hobart Hospital, Hobart, TAS, Australia

Eugene Kotlyar
St Vincent's Hospital, Darlinghurst, NSW, Australia

David Kaye
The Alfred Hospital, Melbourne, VIC, Australia

Category: Clinical Science
Selected Areas: Quality of Life, Therapeutic Strategies

Background: RT234 is an inhaled formulation of phosphodiesterase type-5 inhibitor (PDE5i) vardenafil, in development for episodic symptoms of pulmonary arterial hypertension (PAH). This phase 2a escalating-dose trial evaluated acute changes in pulmonary vascular resistance (PVR) and other hemodynamic (HD) parameters in PAH patients on stable maintenance dual therapy.
Methods: Three cohorts received RT234 0.2, 0.6, or 1.2 mg during right heart catheterization.
Results: Of 14 subjects, age was 54 ± 14 years (79% female) and functional class was 2 (57%), 3 (36%), or 4 (7%). In the 0.2, 0.6, and 1.2 mg cohorts, respectively, mean PVR was 635 ± 344, 469 ± 431, and 579 ± 337 dyn·s/cm^5 at baseline and decreased by −6.6% (−22.2 to 2.7), 23.7% (−44.7 to −18.6), and −16.0% (−22.7 to −10.5) postinhalation. With 0.6 and 1.2 mg, PVR fell >10% at 5 minutes, a reduction sustained for 60 minutes. PVR/systemic vascular resistance ratio changed by −8.0% (−27.1 to 14.1), −18.4% (−37.8 to 0.9), and −11.9% (−23.9 to −0.3) for the 0.2, 0.6, and 1.2 mg doses, indicating the 0.6 mg dose may offer the greatest pulmonary selectivity. No clinically significant changes in systemic blood pressure or heart rate were observed. Change in PaO_2 was +1.8% (−13.5 to 27.4), +8.1% (−13.5 to 22.6), and +4.3% (−1.4 to 9.9) for the 3 doses. Improvements in pulmonary HD with 0.6 mg RT234 were on par with 20 mg oral vardenafil, with less systemic hypotension and higher oxygenation. The only treatment-related adverse events (AEs) were mild headache and mild throat irritation, each in a single subject. No respiratory AEs occurred. RT234 produced rapid reduction in PVR, sustained for 60 minutes, and was well tolerated (Figure).
Conclusions: The optimally effective RT234 dose appears to be 0.6 mg. RT234 is suited for as-needed or preemptive PAH therapy.

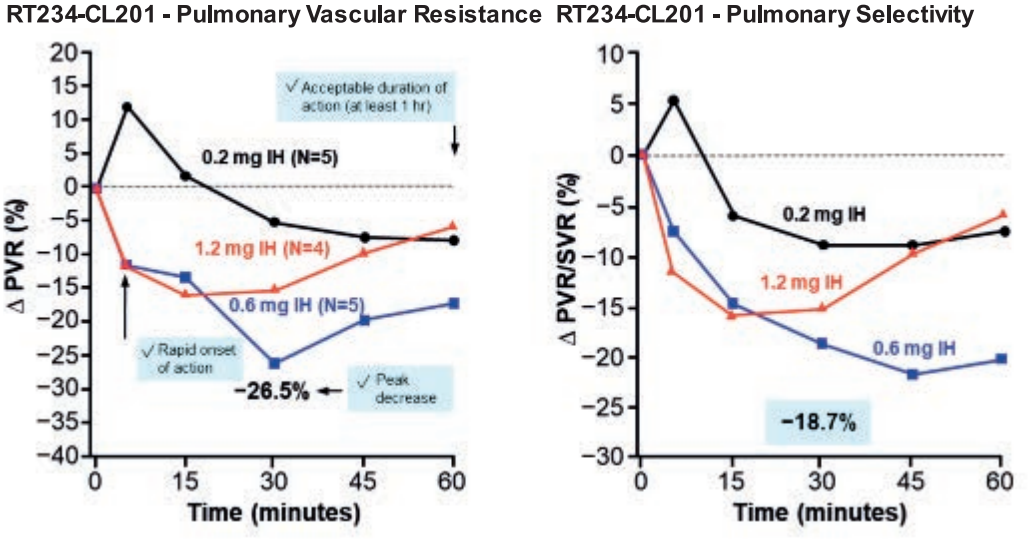


Figure 1: Hemodynamic outcomes: pulmonary vascular resistance and pulmonary selectivity up to 60 minutes post-RT234 dose.

SOCIAL DETERMINANTS OF HEALTH IN PULMONARY ARTERIAL HYPERTENSION: A CLINICIANS' PERSPECTIVE

Vijay R. Nadipelli
BPharm, MS, Thomas Jefferson University, Philadelphia, PA, USA

Karim El-Kersh, MD
University of Nebraska Medical Center, Omaha, NE, USA

Willie H. Oglesby, PhD, MBA
Thomas Jefferson University, Philadelphia, PA, USA

Jean M. Elwing, MD
University of Cincinnati, Cincinnati, OH, USA

Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH, Effect of COVID and Telemedicine on PH Management, Quality of Life

Background: Social determinants of health (SDOH) can affect the vulnerable pulmonary arterial hypertension (PAH) population, especially during the COVID-19 pandemic. Providers' understanding of SDOH at the point of care and their potential effect is unknown.

Methods: Semistructured virtual interviews of US health care providers (HCP) at pulmonary hypertension (PH) centers and an association were conducted (January and February 2022). A trained interviewer sought participants' perspectives of SDOH in PAH and its effect. Transcripts were developed and analyzed for key themes to assess potential policy implications.

Results: Participants served a large PAH population (Tables 1 and 2) and demonstrated high awareness of SDOH and its effect on treatment and outcomes. Patients' socioeconomic status, health insurance, education, health literacy, employment, housing, food security, transportation, and family support were reported to affect health and well-being. Further complicated by COVID-19-related social isolation, mental health and substance abuse were cited as contributing to significant inequities in care provision and outcomes. While telemedicine helped HCPs manage patients remotely during the pandemic, there was a concern for patients with limited access to this medium. Participants reported not formally screening for SDOH. With the recognition and the desire to act upon health inequities afforded by SDOH, HCPs felt that it was

Table 1. Participant and Pulmonary Hypertension Practice Characteristics[a]

Participant characteristics	(N=18)
Specialty n, (%)	
Pulmonologist	13 (72%)
Cardiologist	4 (22%)
Patient Advocate	1 (6%)
Experience treating PH-PAH population (years)	(n=17)
Average	19.3 years
Total	328 years
Range	6-37 years
Geographic Location n, (%)	
Northeast	8 (44%)
Southeast	1 (66%)
Northcentral	1 (66%)
Southcentral	2 (11%)
West	6 (33%)
PH Practice Characteristics [a]	(n=17)
Practice Setting n, (%)	
PHA Accredited PHCC	15 (83%)
Non-Accredited PHC	2 (11%)
PH Association	1 (6%)
PH Treating, Care and Research Professional Staff (n, range)	
Physicians	4 (2-9)
Nurses	2.3 (0-6)
Others	2 (0-4)
Quality of Life Assessment Tool Use n, (%)	
Yes	5 (29%)
No	12 (71%)
Risk Assessment Tool Use n, (%)	
Yes	16 (94%)
No	1(6%)
PHAR Participation n, (%)	
Yes	11 (65%)
No	6 (35%)
PHAR Patients Enrolled in Participating Sites	
Average	67
Range	2-300
Total	740

[a] Estimates based on study participant awareness and experience; PH=Pulmonary Hypertension; PAH= Pulmonary Arterial Hypertension; PHCC=Pulmonary Hypertension Care Center; PHC=Pulmonary Hypertension Center; PHAR=Pulmonary Hypertension Association Registry

Table 2. Pulmonary Arterial Hypertension Patient Population Characteristics Across Centers (n = 17)[b]

Number of patients	
Average	321
Total	5470
Range	125-600
Average Age (years, range)	52 (35-65)
Gender (%)	
Female	73%
Male	27%
Race (%)	
Caucasian	61%
African American	22%
Hispanic	12%
Asian	5%
Employment Status (%)	
Employed	43%
Unemployed	34%
Retired	23%
Health Insurance Status (%)	
Public	51%
Private	42%
Uninsured	7%
PAH Type (%)	
Idiopathic	39%
Associated	45%
Drug & toxin	11%
Heritable	5%
WHO Functional Class (%)	
FCI	7%
FCII	45%
FCIII	40%
FCIV	8%
PAH Therapy (%)	
Monotherapy	11%
Double therapy	52%
Triple therapy	37%
Average Time to Diagnosis (years)	1.5 years

[b] Estimated based on study participant awareness and experiences; PAH=Pulmonary Arterial Hypertension; WHO=World Health Organization; FC =Functional Class

vital for their centers to have a dedicated PH social worker and support staff to optimize care and outcomes.
Conclusions: Participants were highly aware of the importance of SDOH in PAH patients. An approach that integrates SDOH in care management, streamlined through institutional policy, could minimize disparities contributing to improved health care access, outcomes, and quality of care.

SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF TREPROSTINIL PALMITIL INHALATION POWDER: A PHASE 1 RANDOMIZED, DOUBLE-BLIND, SINGLE-DOSE, AND MULTIPLE-DOSE STUDY

Fraz A. Ismat
Insmed Incorporated, Bridgewater, NJ, USA

Helen Usansky
Insmed Incorporated, Bridgewater, NJ, USA

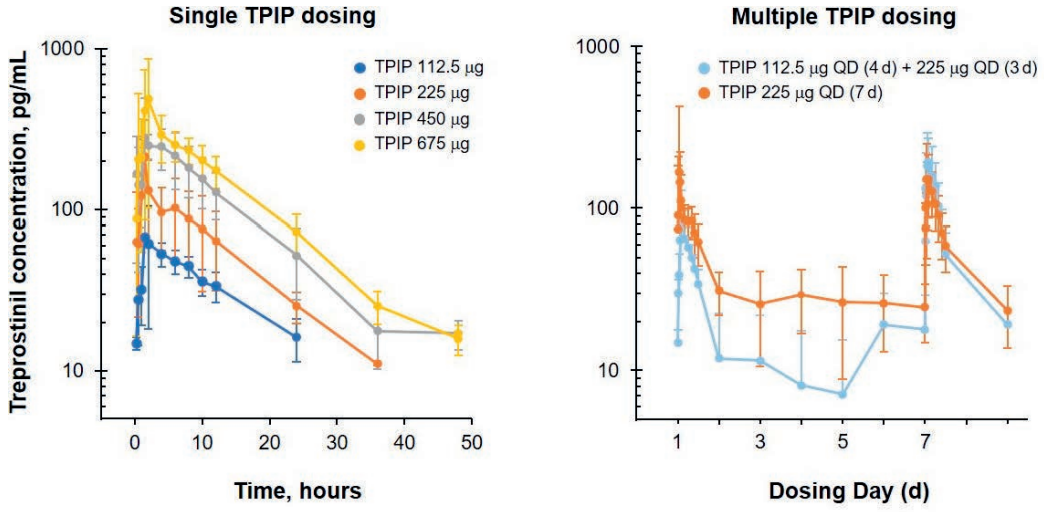
Shilpa Dhar Murthy
Insmed Incorporated, Bridgewater, NJ, USA

Jun Zou
Insmed Incorporated, Bridgewater, NJ, USA

Ariel Teper
Insmed Incorporated, Bridgewater, NJ, USA

Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Use of treprostinil (TRE) in pulmonary arterial hypertension (PAH) is limited by a short half-life ($t_{1/2}$) and dose-limiting treatment emergent adverse events (TEAEs). Treprostinil palmitil inhalation powder (TPIP) is a dry powder formulation of a TRE prodrug.
Rationale: To examine the safety, tolerability, and pharmacokinetics (PK) of single- and repeat-dose administration of once-daily (QD) TPIP.
Methods: Healthy adults received single doses of 112.5, 225, 450, or 675 mg (n = 6/dose) or placebo (n = 2) or multiple doses of 225 mg QD × 7 days (n = 6) or 112.5 mg QD × 4 days, then 225 mg QD × 3 days (n = 6), or placebo × 7 days (n = 4).
Results: Forty-one of 42 participants completed the study. Of single-dose participants, 70.8% (n = 17/24) experienced a TEAE versus 0% of placebo (0/2); cough (42.3%), dizziness (26.9%), throat irritation (19.2%), nausea (15.4%), and hypotension (15.4%) were most common. Of multiple-dose participants. 83.3% (n = 10/12) had a TEAE versus 50.0% of placebo (2/4); cough (58.3% TPIP versus 50.0% PLA), headache (50.0% versus 0%), nausea (33.3% versus 0%), and dizziness (25.0% versus 0%) were most common. TEAEs were mild in 69.0% (29/42) and moderate in 16.7% (7/42), with no severe or serious TEAEs. Titration of TPIP had fewer TEAEs in multiple QD dosing. TRE exposure was dose proportional, and steady-state accumulation was insignificant. Elimination $t_{1/2}$ was 8.7–11.6 hours after a single dose and 6.8–8.8 hours after multiple QD dosing (Figure).
Conclusions: TPIP was generally safe and well tolerated in healthy volunteers, with a PK profile that supports QD dosing. TEAEs were dose related and attenuated with titration.



QD, once daily; TPIP, treprostinil palmitil inhalation powder.

Figure 1: Treprostinil plasma concentrations following single and multiple once-daily (QD) treprostinil palmitil inhalation powder (TPIP) dosing.

PATHOLOGY PREDIAGNOSIS: A CASE REPORT OF RARE HISTOLOGICAL FINDINGS IN EXERCISE-INDUCED PULMONARY HYPERTENSION

Kelsey Cramer, MSN, DNP, AGACNP
Medical College of Wisconsin, Milwaukee, WI, USA

Linus Santo Tomas, MD
Pulmonary and Critical Care Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

David Ishizawar, MD
Cardiology, Advanced Heart Failure, Medical College of Wisconsin, Milwaukee, WI, USA

Category: Case Report
Selected Areas: Diagnosis or Screening and Physiologic Studies, Diseases and Conditions Associated with PH, Therapeutic Strategies

Background: (Case) A 49-year-old man with dyspnea and concerns for graft versus host disease after receiving a hematopoietic stem cell blood transplant for acute myeloid leukemia underwent a video-assisted thoracoscopic surgery (VATs) lung biopsy and was found to have pulmonary vascular remodeling, but preop right heart catheterization (RHC) had demonstrated normal hemodynamics. A repeat RHC with supine bicycle exercise study demonstrated exercise induced pulmonary hypertension (EiPH) with a mPA-CO slope of 3.1 mm Hg/L/min (Table 1). He was treated with riociguat and followed with cardiopulmonary exercise testing (CPET) which demonstrated gradual improvements even after he decided to wean off riociguat (Table 2). Repeat echocardiogram testing demonstrated still normal estimated pulmonary artery systolic pressure 23 mm Hg once weaned off riociguat.
Results: (Discussion) EiPH is felt to demonstrate an early spectrum of pulmonary vascular disease, but without consensus on exercise methodology and/or diagnostic criteria, it can be challenging to diagnose. Data on treatment of EiPH are even more limited. Our case demonstrated a mPA-CO slope

Table 1. Right Heart Catheterization Measurements

	Pre-op Right heart Catheterization	Exercise Right Heart Catheterization	
		Resting baseline	Peak Exercise
Right atrium (mm Hg)	2	4	9
Mean PA (mm Hg)	21	25	52
PA occlusion pressure (mm Hg)	3	11	8
Transpulmonary gradient (mm Hg)	18	14	44
Fick CO/CI (L/min, L/min/m^2)	6.80/3.48	5.37/2.63	Not calculated
Thermo CO/CI (L/min, L/min/m^2)	7.50/3.84	5.77/2.83	14.40/7.06
Pulmonary vascular resistance (Wood units)	2.4-2.7	2.4-2.6	3.1

Table 2. Cardiopulmonary Exercise Tests

			Riociguat Weaning	
	Baseline	**Riociguat 2.5 mg TID**	**Riociguat 1.5 mg TID**	**Riociguat stopped**
Time from baseline (months)	N/A	11	26	31
Time from prior study (months)	N/A	11	15	5
Workload (METS)	4.3	7.5	7.8	8.5
RER	1.18	1.01	1.14	1.09
VO_{2max} (mL/kg/min)	15.2	26.1	27.2	29.9
V_E/V_{CO2} slope	45.2	34.5	32.8	22.5
V_D/V_T ratio baseline	0.21	0.25	0.27	0.15
V_D/V_T ratio exercise	0.15	0.07	0.10	0.06
FVC (L, % predicted)	3.77 L, 77%	4.32 L, 89%	4.40 L, 91%	4.77 L, 89%
FEV1 (L, % predicted)	3.00 L, 78%	3.29 L, 87%	3.30 L, 88%	3.76 L, 90%
FEV1/FVC ratio	80%	76%	75%	79%
MVV (L/min, %)	108 L/min, 71%	85 L/min, 57%	132 L/min, 89%	129 L/min, 109%

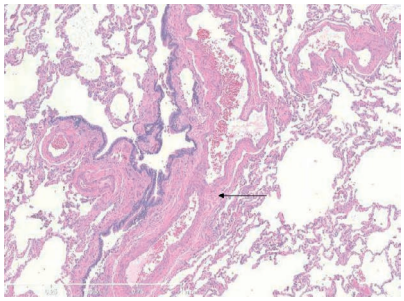


Figure 1: Hematoxylin and eosin stained histologic section of the lung showing thick wall pulmonary arteries. Note the septa (black arrow). The background lung parenchyma exhibits normal architecture, with no evidence of interstitial lung disease.

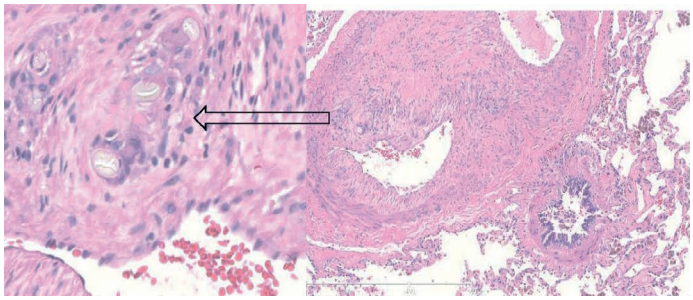


Figure 2: Hematoxylin and eosin section showing pulmonary artery with thickened wall containing basophilic nonpolarizable material and associated foreign body-type giant cell reaction (black arrow).

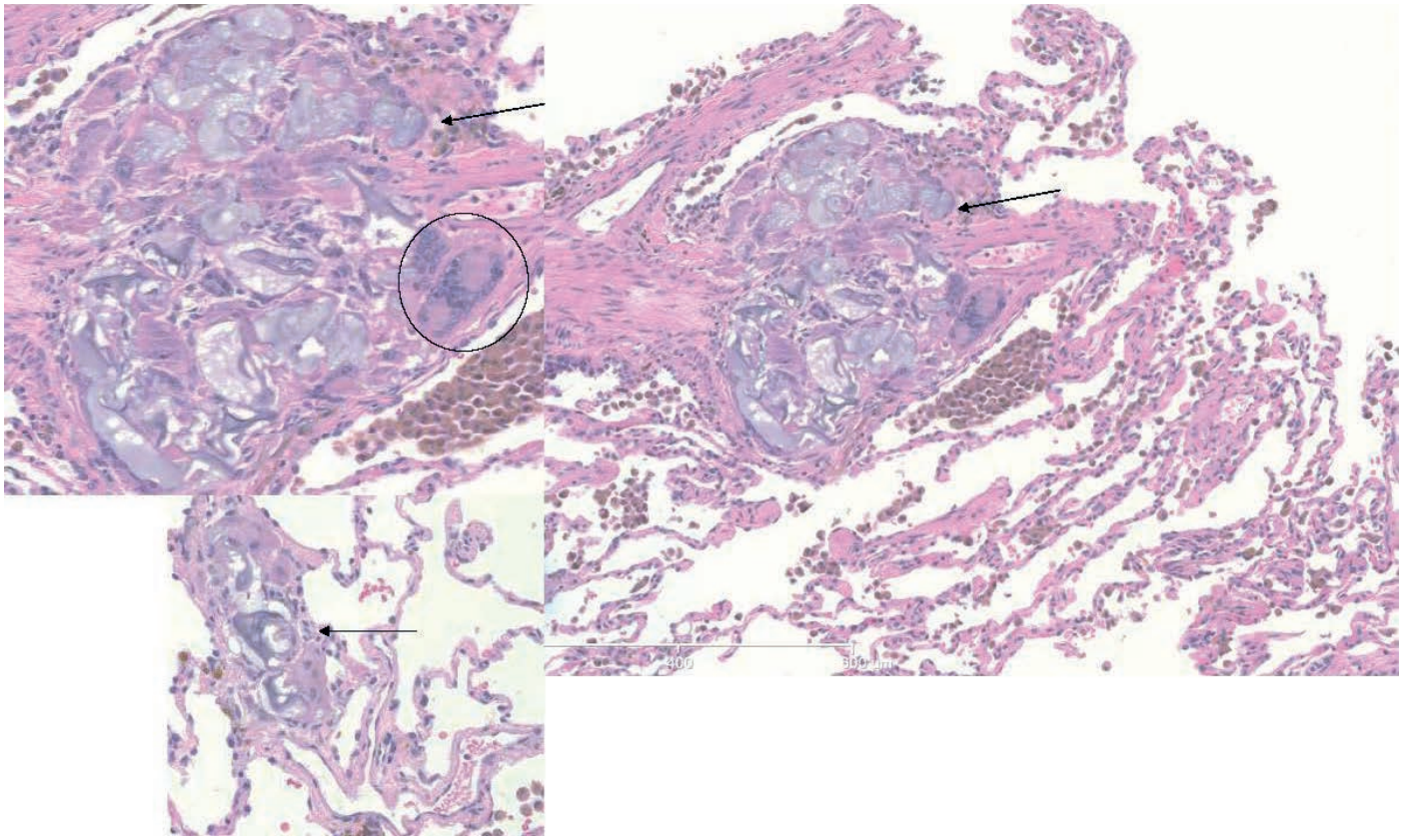


Figure 3: Hematoxylin and eosin sections showing pulmonary vessels with basophilic nonpolarizable material plugging their lumens (black arrows). This also associated with foreign body-type giant cell (circle) reaction.

> 3 mm Hg/L/min, felt to be an indicator of reduced pulmonary vascular distensibility. Furthermore, this case reinforces the importance of identifying and treating pulmonary vascular disease at its earlier disease spectrum (Figures 1–3).

Conclusions: Our case uniquely presents a histopathologic basis for EiPH demonstrating early pulmonary vascular changes on lung biopsy.

LONG-TERM EFFECTS OF ORAL TREPROSTINIL IN SUBJECTS WITH PULMONARY ARTERIAL HYPERTENSION: FREEDOM-EV OPEN-LABEL EXTENSION STUDY

R. J. White
University of Rochester, Rochester, NY, USA

M. Broderick
United Therapeutics Corportation, Durham, NC, USA

C. Q. Deng
United Therapeutics Corportation, Durham, NC, USA

R. Grover
United Therapeutics Corportation, Durham, NC, USA

L. Holdstock
United Therapeutics Corportation, Durham, NC, USA

A. Khan
Oregon Health and Science University, Portland, OR, USA

G. Meyer
Complexo Hospitalar Santa Casa de Porto Alegre, Porto Alegre, Brazil

B. Ng
Nepean Hospital, Sydney, Australia

T. Pulido
Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico

Y. Rao
United Therapeutics Corportation, Durham, NC, USA

I. Saib
United Therapeutics Corportation, Durham, NC, USA

P. Sepulveda
Pontifica Universidad Catolica de Chile, Santiago, Chile

Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Oral treprostinil (TRE) is approved to treat pulmonary arterial hypertension (PAH). FREEDOM-EV established 3 times daily (TID) TRE to delay disease progression when added to oral monotherapy. Data reported here are from subjects who transitioned to an open-label extension (OLE) study after experiencing a clinical worsening event (CWE) during the parent study or at parent study closure.

Table 1. Participant Baseline and Week 48 Characteristics, Assessments, and Reasons for Discontinuation (Observed Data Only Without Imputation)

Treatment assignment, FREEDOM-EV		Placebo (PBO)		Oral Treprostinil (TRE)	
Status at end of FREEDOM-EV		Had CWE	No CWE	Had CWE	No CWE
Baseline, N		108	150	66	144
Completed Week 48 (% baseline), N		67 (63%)	122 (81%)	46 (72%)	132 (92%)
Age at Baseline (years): Mean (SD)		49 (15)	46 (14)	48 (16)	46 (15)
Female		78%	82%	80%	78%
Dose (mg): Mean (SD)	Baseline	--	--	5.5 (3.3)	5.6 (3.4)
	Week 48	5.7 (3.8)	3.6 (2.5)	6.1 (3.6)	6.1 (3.6)
FC, Baseline	I	0 (0%)	19 (13%)	1 (2%)	21 (15%)
	II	13 (12%)	**108 (72%)**	3 (4%)	**101 (70%)**
	III	**83 (78%)**	23 (15%)	**52 (79%)**	22 (15%)
	IV	11 (10%)	0 (0%)	10 (15%)	0 (0%)
FC, Week 48	Improved	**28 (44%)**	14 (12%)	**18 (41%)**	12 (9%)
	Stable	34 (53%)	**102 (84%)**	25 (57%)	**103 (79%)**
	Worsened	2 (3%)	6 (5%)	1 (2%)	15 (12%)
FC, Change from baseline*		P<0.0001	P=0.07	P<0.0001	P=0.56
NT-pro-BNP (pg/ml): Mean (SD)	Baseline	3891 (4987)	1108 (2092)	4729 (12988)	754 (1642)
	Week 48	2262 (3318)	655 (1249)	2867 (4209)	713 (1061)
	Mean (SD) Change from baseline **	-793 (2391) P<0.03	-140 (1128) P=0.19	-86 (4083) P=0.9	-3.9 (1316.5) P=0.97
6MWD (m): Mean (SD)	Baseline	301 (116)	450 (96)	288 (138)	448 (84)
	Week 48	402 (96)	460 (91)	382 (83)	446 (91)
	Mean (SD) Change from baseline **	85 (100) P<0.0001	6 (54) P=0.19	56 (117) P<0.006	-7 (52) P=0.85
Key Reasons for Discontinuation before Closure, N (%)	Death	29 (27%)	14 (9%)	21 (32%)	4 (3%)
	Progressive disease	12 (11%)	0 (0%)	8 (12%)	0 (0%)
	Adverse event	23 (22%)	17 (11%)	8 (12%)	17 (11%)

*** p-values are calculated from McNemar's test; ** p-values are calculated from paired t-test**

Methods: Subjects attended visits at baseline (start of OLE) and every 12 weeks until voluntary discontinuation or study closure. Efficacy measures included 6-minute walk distance (6MWD), World Health Organization Functional Class (FC), and plasma NT-pro-BNP level (week 48 only).
Results: Of 690 FREEDOM-EV subjects, 470 enrolled in the OLE: 258 previously assigned placebo (PBO) and 212 assigned TRE. Baseline characteristics, dosing, and key data are presented in the Table. Mean 6MWD increased significantly from baseline in subjects initially assigned PBO with a CWE in the parent study (85 ± 100 m). NT-pro-BNP decreased significantly in previous PBO subjects with CWE. FC improved in >40% of previous PBO subjects with CWE. Discontinuations from the study due to adverse events were most common in previous PBO patients with CWE (22%). No new safety signals were observed.
Conclusions: Subjects starting TRE after CWE had a significant increase in 6MWD, improved FC, and reduced NT-pro-BNP 48 weeks after starting TRE, whereas those without CWE had small improvements in all efficacy measures after initiating TRE. These data are consistent with the placebo-controlled FREEDOM-EV results and suggest that TRE was effective in a group of higher-risk PBO subjects who had just had a CWE.

PULMONARY HYPERTENSION AND CANTÚ SYNDROME

Kristen Wallace
Department of Pediatric Pulmonology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

Nidhy Varghese
Department of Pediatric Pulmonology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH; Pediatrics

Background: Cantú syndrome has been associated with pulmonary hypertension (PH), but case reports describe it as an infantile condition, often in conjunction with a patent ductus arteriosus (PDA). Here, we present the case of an adolescent with new-onset PH in the setting of Cantú diagnosis.
Methods: (Case) An adolescent male presented after unwitnessed syncopal event and 1-month history of exertional dyspnea and orthopnea. Review of symptoms was remarkable only for nausea, emesis, fatigue, dry nighttime cough, and bilateral leg swelling for a few weeks. Of note, mother's pregnancy was complicated by polyhydramnios requiring multiple amniocenteses and delivery at 36 weeks due to macrosomia. He had a 2-week neonatal intensive care unit admission for respiratory distress and underwent surgical closure of large PDA at 6 weeks of age. His medical history included hypotonia, short stature (recently started on growth hormone), diabetes, elevated body mass index, learning disability, and attention deficit hyperactivity disorder on methylphenidate. Chest x ray showed significant cardiomegaly and chest computed tomography scan had dilation of the pulmonary arteries. Echocardiogram revealed a large pericardial effusion with severe PH. Initial brain natriuretic peptide (BNP) level was elevated to 168 pg/mL. He was tachycardic, mildly hypertensive, and admitted to the intensive care unit for further evaluation and monitoring. Cardiac catheterization revealed mean pulmonary artery pressure 44 mm Hg, wedge pressure 18 mm Hg, and pulmonary vascular resistance 4.3 Wood units, on 50% FiO_2 and nitric oxide (iNO). He was carefully transitioned from iNO to sildenafil therapy and started on diuretics with improvement. As part of the workup for PH, a sleep study revealed moderate obstructive sleep apnea (oAHI: 8.26/hour), which improved with auto-positive airway pressure (PAP) therapy, 5–10 cm H_2O. Genetic studies were also sent, part of our protocol for idiopathic PAH, and supported by distinct facial features. A mutation in the ABCC9 gene resulted, confirming the diagnosis of Cantú Syndrome. He has since been transitioned to tadalafil as an outpatient, and most recent echocardiogram shows improvement in right ventricular function.
Results: (Discussion) Cantú syndrome, also known as hypertrichotic osteochondrodysplasia, is an autosomal dominant genetic condition associated with a gain of function mutation in the ABCC9 or KCNJ8 gene, which encode regulatory and pore forming subunits of ATP-sensitive potassium (K-ATP) channels, respectively. The mechanism of PH development in patients with Cantú syndrome is likely multifactorial, related to obesity effects, obstructive sleep apnea, and risk for effusions. Although K-ATP channelopathy has been associated with development of PH, typically decreased potassium channel activity causing vasoconstriction is seen. In Cantú syndrome, it is the converse: Increased channel activity leads to vasodilation of smooth muscle, compensatory cardiac hypertrophy, and increased cardiac output. The association of PH and Cantú-related channel disease is therefore not clear, and further mechanistic studies are needed. To our knowledge, this is the first noninfantile Cantú syndrome patient with PH. Cantú syndrome patients are reported to develop PH during infancy, perhaps related to PDA physiology, and there is improvement with resolution of the PDA. Although our patient did have a PDA, he did not have any evidence of PH on infantile or childhood studies. Therefore, we hypothesize that PH development in our patient was secondary to the cumulative effect of several risk factors, including Cantú syndrome, obstructive sleep apnea, exposure to methylphenidate therapy, and exposure to growth hormone. This case illustrates the importance of monitoring patients with this syndrome for the development of PH as they grow older and develop other comorbidities. We also highlight the potential for stabilization and improvement of PH with phosphodiesterase inhibitors.
Conclusions: PH should be considered when a patient Cantú syndrome presents with cardiopulmonary issues regardless of age. Further studies are warranted to examine the link between the 2 conditions.

FACEMASKS AND WALK DISTANCE IN PULMONARY ARTERIAL HYPERTENSION PATIENTS

Scott A. Helgeson, MD
Division of Pulmonary & Critical Care Medicine, Mayo Clinic, Jacksonville, FL, USA

Hollie Saunders, MD
Division of Pulmonary & Critical Care Medicine, Mayo Clinic, Jacksonville, FL, USA

Charles D. Burger, MD
Division of Pulmonary, Allergy & Sleep Medicine, Mayo Clinic, Jacksonville, FL, USA

John E. Moss, MD
Division of Pulmonary & Critical Care Medicine, Mayo Clinic, Jacksonville, FL, USA

Tonya K. Zeiger, RRT
Division of Pulmonary, Allergy & Sleep Medicine, Mayo Clinic, Jacksonville, FL, USA

Bryan J. Taylor, PhD
Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, FL, USA

Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies, Effect of COVID and Telemedicine on PH Management

Background: Facemask wearing is a key control measure to prevent transmission of SARS-CoV-2. However, widespread face mask use has proven challenging. Frequently asserted reasons for noncompliance with facemask wearing include heightened breathlessness and carbon dioxide retention and/or hypoxemia, especially during exertion. Our objective was to evaluate whether facemask wearing affected distanced covered, rating of perceived exertion (RPE), and arterial oxygen saturation (SpO_2) during a 6-minute walk test (6MWT) in patients with pulmonary arterial hypertension (PAH).

Methods: Forty-five patients being treated for Group 1 PAH and who performed a 6MWT without (Test 1) and with (Test 2) a facemask between October 2019 and October 2020 (ie, be-

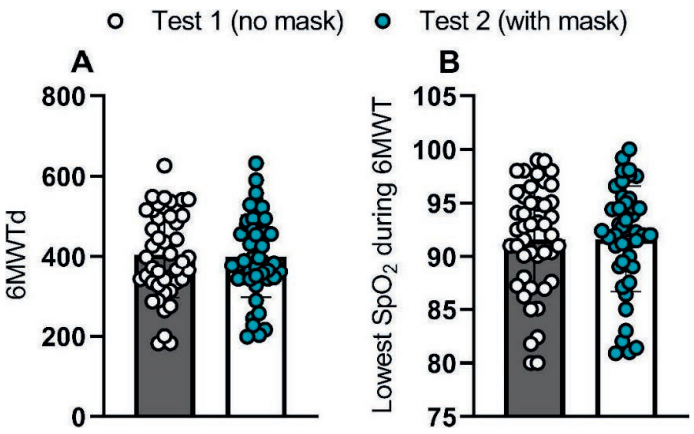


Figure 1: Group mean (solid bars) and individual patient 6-minute walk test distance (6MWTd) and lowest arterial oxygen saturation (SpO_2) during 6-minute walk tests without (Test 1, white circles) and with a facemask (Test 2, blue circles).

Table 1. Descriptive Characteristics, Clinical Data, and Submaximal Cardiopulmonary Exercise Test (CPET) Responses

Demographics				
Age, y	60 ± 11			
Sex	Male	9 (20.0%)		
	Female	36 (80.0%)		
Race	White	39 (86.7%)		
	Black	4 (8.9%)		
	Asian	2 (4.4%)		
Ethnicity	Not Hispanic	41 (91.1%)		
	Hispanic	4 (8.9%)		
BMI	26.8 ± 4.9			
PAH subgroup				
1.1; Idiopathic	18 (40.0%)			
1.2; Heritable	2 (4.4%)			
1.4.1; Connective tissue disease	24 (53.3%)			
1.4.4; Congenital heart disease	1 (2.2%)			
Clinical Data	**Test 1**		**Test 2**	***P*-value**
NYHA/WHO FC				.93
	I	4 (8.9%)	5 (11.1%)	
	II	17 (37.8%)	16 (35.6%)	
	III	24 (53.3%)	24 (53.3%)	
6MWTd, m	405 ± 108		400 ± 103	.81
6MWT SpO_2, %	92.8 ± 3.4		93.3 ± 3.3	.55
RPE, Borg CR10	2.5 ± 1.7		2.5 ± 2.1	.91
REVEAL Lite 2 score	8.2 ± 2.9		8.4 ± 2.8	.80
BNP, pg.mL	175 ± 342		188 ± 342	.86
RVSP, mmHg	55.7 ± 15.8		54.8 ± 16.0	.80
TAPSE, cm	2.0 ± 0.4		2.0 ± 0.5	.74
RV enlargement				.82
	None	14 (31.8%)	17 (37.8%)	
	Mild	18 (40.9%)	15 (33.3%)	
	Moderate	7 (15.9%)	9 (20.0%)	
	Severe	5 (11.4%)	4 (8.9%)	
RV dysfunction				.97
	None	25 (55.6%)	25 (55.6%)	
	Mild	11 (24.4%)	11 (24.4%)	
	Moderate	5 (11.1%)	6 (13.3%)	
	Severe	4 (8.9%)	4 (8.9%)	
Submaximal CPET	**Test 1**		**Test 2**	***P*-value**
Resting SpO_2, %	96 ± 3		96 ± 3	.48
$\dot{V}_E/\dot{V}CO_2$ slope	38.0 ± 9.7		38.7 ± 11.1	.74
$\Delta P_{ET}CO_2$, mmHg	2.2 ± 2.1		2.1 ± 2.0	.88

6MWTd, six-minute walk test distance; SpO_2, arterial oxygen saturation; RPE rating of perceived exertion; BNP, brain natriuretic peptide; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle.

fore and after implementation of a facemask mandate) were included.
Results: At both time points, all patients also underwent a submaximal cardiopulmonary exercise test, echocardiogram, and blood laboratory tests, with a REVEAL Lite 2.0 score calculated (Table). The 6MWTs were performed 81 ± 51 days apart. All patients were clinically stable at both testing timepoints. 6MWT distance was not different between Test 1 versus Test 2 (405 ± 108 m versus 400 ± 103 m, $P = 0.81$; Figure). Similarly, both end-test RPE and lowest SpO_2 during the 6MWT were not different in Test 1 versus Test 2 (RPE: 2.5 ± 1.7 versus 2.5 ± 2.1, $P = 0.91$; SpO_2 nadir: 93 ± 3.4% versus 93.3 ± 3.3%, $P = 0.55$; Figure).
Conclusions: Wearing a facemask had no discernable effect on the arterial oxygen saturation and perceptual responses to exercise or exercise capacity in patients with moderate-to-severe PAH. Wearing a facemask appears to be safe in PAH patients, even during exercise.

AN INNOVATIVE APPROACH TO ENSURING SAFE MANAGEMENT OF INFUSED PROSTACYCLIN THERAPY. A QUALITY IMPROVEMENT PROJECT

Amy Chybowski, NP
UW Health, Madison, WI, USA

Debra Dalsing, RN, MSN, CNML
UW Health, Madison, WI, USA

Tracy Kussmaul, MSN, RN-BC
UW Health, Madison, WI, USA

Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is a rare, incurable disease that leads to right heart failure. One treatment for PAH is continuous subcutaneous (SQ) or intravenous (IV) prostacyclin infusion. These specialized therapies are potent vasodilators, some with very short half-lives, such that any interruption in the infusion can lead to serious injury or death. Direct management by a pulmonary hypertension (PH) team in the ambulatory, emergency room, inpatient, and procedural areas is essential. The purpose of this quality improvement project was to improve patient safety through creation of a best practice advisory (BPA) alert within the electronic medical record (EMR) of patients with PAH receiving an infused prostacyclin.
Methods: Using FOCUS PDCA, the PH team identified the need to ensure all health care professionals (HCPs) are alerted when a patient they encounter is receiving an infused prostacyclin. This would mitigate erroneous manipulation of the infusion by untrained HCPs and ensure the PH team is involved in clinical management, regardless of how or why the patient is seeking access to care.
Results: In collaboration with Clinical Knowledge Management and Nursing Informatics, a BPA was created (Figure). It launches upon opening the EMR of an individual with an infused prostacyclin on their active medication list. The BPA states the patient is receiving a prostacyclin infusion, interrupting the infusion could cause serious injury or death, and the PH team must be contacted. The BPA must be acknowledged by the HCP prior to proceeding into the EMR. Education was provided by the PH team to HCPs working in the Access Center, Department of Emergency Medicine, and Anesthesia.
Conclusions: The BPA has enhanced patient safety and could be explored at other PH centers.

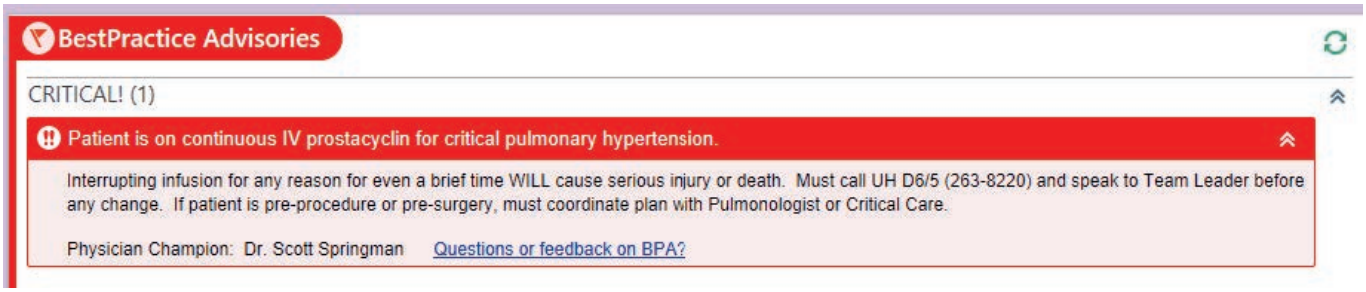


Figure 1: Screenshot of the BPA that launches upon opening the EMR of a person receiving infused prostacyclin therapy.

PULMONARY ARTERIAL HYPERTENSION RISK ASSESSMENT GENOMIC MODEL USING BAYESIAN NETWORK

Charles Fauvel, MD
Internal Medicine Department, Division of Cardiovascular Medicine, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Amy Webb, PhD
Department of Biomedical Informatics, The Ohio State University, Columbus, OH, USA

Zilu Liu, MS
Department of Statistics, The Ohio State University, Columbus, OH, USA

Shili Lin, PhD
Department of Statistics, The Ohio State University, Columbus, OH, USA

Priscilla Correa-Jaque, BMS
Internal Medicine Department, Division of Cardiovascular Medicine, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Raymond Benza, MD
Internal Medicine Department, Division of Cardiovascular Medicine, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Category: Clinical Science
Selected Areas: Databases and Registries

Background: Accurate risk assessment is essential to making individualized treatment decision in pulmonary arterial hypertension (PAH) patients, yet existing probabilistic risk assessment models are insufficient since they do not include contemporary genomic and imaging biomarkers. We aimed to build a risk assessment

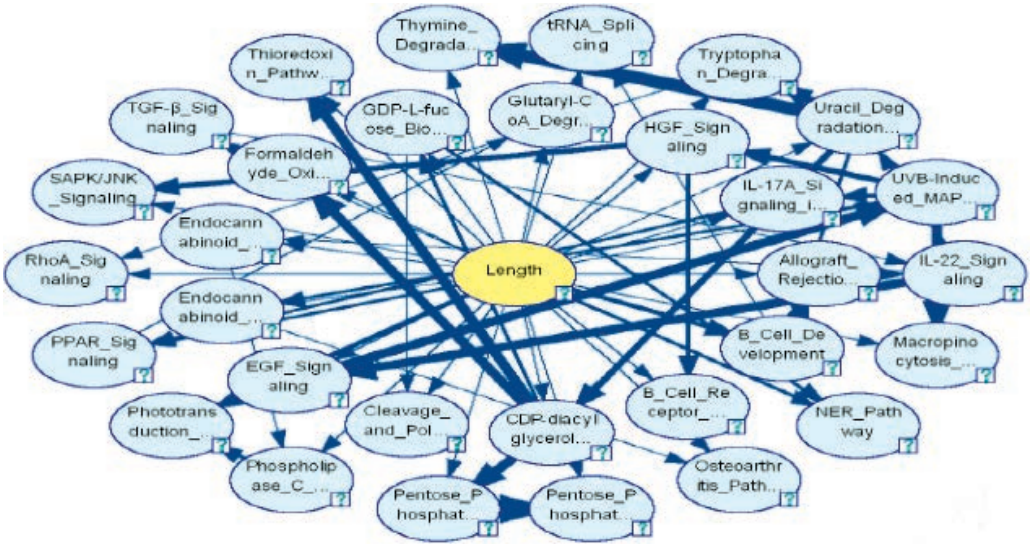


Figure 1: Genomic model Bayesian network.

PATHWAYS RED: short-term survival BLUE: long-term survival	Endothelial dysfunction	Vascular smooth muscle cell hyperplasia and proliferation	Inflammation and dysimmunity	Genetic and microenvironmental factors (DNA damage, ROS…)	Metabolism switch and/or dysfunction	RV hypertrophy / adaptation
TGF-β signaling	x	x	x		x	
SAPN/JNK signaling	x	x	x			
RhoA signaling	x	x	x	x		
PPAR signaling				x		
Phototransduction signaling			x	x		x
Phospholipase C signaling	x	x	x			
Pentose phosphate pathway		x			x	
Pentose phosphate pathway (oxidative branch)				x	x	
Osteoarthritis pathway			x			
NER pathway				x		
Macropinocytosis signaling			x			
IL-22 signaling		x		x		
UVB induced MAPK signaling				x		
Uracil degradation				x		
Tryptophan degradation		x				
tRNA splicing		x		x		
Thymine degradation				x		
Thioredoxin pathway		x		x		
GDP-L-fucose biosynthesis					x	
Formaldehyde oxidative pathway				x	x	
Endocannabinoid neuronal pathway	x	x	x			
Endocannabinoid cancer inhibition pathway						
EGF signaling		x				
Cleavage and polyadenylation of pre-mRNA				x		x
CDP-diacyl glycerol biosynthesis		x			x	
B-cell development			x			
B-cell receptor signaling			x			
Allograft rejection			x			
IL-17A signaling		x				
HGF signaling		x				x
Glutaryl-CoA degradation					x	

Figure 2: Link between each pathway and PAH natural course.

genomic model using a Bayesian network (BN) for PAH patients.
Methods: After performing a whole genome sequencing on 325 samples, variants were filtered for quality, assigned to genes, and filtered for function and population frequency. Retaining PAH patients that survived past 7 years or died prior to 5 years left 221 samples for analysis (mean age = 54 years, 50% idiopathic PAH, 81% of female). Ingenuity pathways analysis was used to generate a list of pathways containing >1 mutated gene from our dataset.
Results: Thirty-one pathways which were significantly (Fisher exact test $P < 0.05$) associated with long-term (>7 years) versus short-term (<5 years) survival were retained. Finally, a BN model, showing interdependency (arrow direction) and association weight (arrow thickness) between the 31 selected pathways and length of survival was built. The 10-fold cross-validation area under the curve averaged 0.75. Using already published peer-reviewed articles, we were able to link each of the 31 pathways to the natural history of PAH including endothelial dysfunction, vascular smooth muscular cell proliferation, inflammation and dysimmunity, genetic and environmental factors, metabolism dysfunction, and right ventricular effect (Figures 1 and 2).
Conclusions: Using a BN, we were able to provide the first PAH risk assessment genomic model including 31 pathways that may be related to the natural PAH course.

PULMONARY ARTERIAL HYPERTENSION RISK ASSESSMENT MODEL USING RANDOM FORREST AND BAYESIAN NETWORK

Liu Zilu
Department of Statistics, The Ohio State University, Columbus, OH, USA

Fauvel Charles
Cardiovascular Medicine Division, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Lin Shili
Department of Statistics, The Ohio State University, Columbus, OH, USA

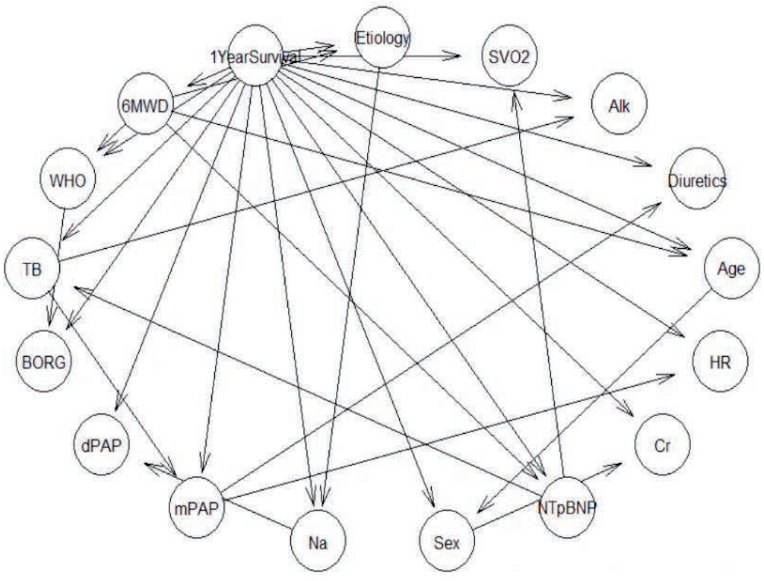
Correa-Jaque Priscilla
Cardiovascular Medicine Division, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Amy Webb
Department of Biomedical Informatics, The Ohio State University, Columbus, OH, USA

Raymond Benza
Cardiovascular Medicine Division, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH

Background: Existing risk assessment models in pulmonary arterial hypertension (PAH) are powerful in predicating survival, yet they are limited in accounting for the internal relationships among variables since they typically assume the independence between variables and their linear association with outcomes. To break free of these limits, we aimed to build a clinical risk assessment model using machine learning methods.
Methods: We harmonized clinical data measured at baseline from 7 adult PAH trials: GRIPHON, SERAPHIN, EARLY, COMPASS-2, COMPASS-3, MAESTRO, and TRANSIT-1. The harmonized data comprised 2870 subjects (mean age = 43



Variable	Thresholds
Age	Male: ≤ 65 / > 65, Female: ≤ 50 / > 50
6MWD (m)	> 440 / 440-200 / < 200
TB (mg/dl)	< 1 / 1-1.5 / > 1.5
BORG	≤ 2 / 2-5 / > 5
SVO2 (%)	> 65 / 60-65 / < 60
Na (mEq/L)	< 135 / 135-145 / > 145
dPAP (mmHg)	≤ 14 / > 14
mRAP (mmHg)	≤ 6 / 6-13 / > 13
Alk (UI/l)	≤ 150 / > 150
Cr (µmol/L)	≤110 / >110
NTpBNP (ng/l)	< 300 / 300-1400 / > 1400
HR (bpm)	≤ 90 / > 90
WHO	I, II, III, IV
Sex	Male, Female
Diuretics	Yes, No
Etiology	Collagen vascular disease, Congenital heart disease, Connective tissue disease, Drugs and toxins, HIV, Idiopathic or familiar

Figure 1: Bayesian network predicting 1-year survival using selected clinical variables.

years, 77% female, 50% idiopathic or familial PAH) and 125 clinical variables, with a mortality rate being 14%. We split the data into 80% as the training dataset and 20% as the test dataset.
Results: Using the training data, we studied variable importance in predicting time to mortality by implementing Random Forest. Sixteen variables with importance values >0.0015 were selected to construct a Bayesian network (BN; Figure) in predicting the 1-year survival status (primary outcome). The thresholds to discretize continuous variables were determined based on clinical knowledge. The BN obtained an area under the curve (AUC) of 0.85 validated using the test dataset. In 5-fold cross-validation, the average AUC was 0.77.
Conclusions: Machine learning provides new powerful methods to build PAH risk assessment models, taking the interdependence among variables into account.

EFFECTS OF FACE-TO-FACE EDUCATIONAL NURSING SUPPORT ON PATIENT COMPLIANCE WITH ORAL PULMONARY ARTERIAL HYPERTENSION THERAPIES

Evangelia Sourounis, PharmD
CVS Health, Northbrook, IL, USA

Pavlo Kyrychenko, PhD
CVS Health, Northbrook, IL, USA

Elisea Avalos-Reyes, PhD
CVS Health, Northbrook, IL, USA

Denise Bagford, BSN, RN, CRNI
CVS Health, Northbrook, IL, USA

Rashmi Grover, PharmD
CVS Health, Northbrook, IL, USA

Lucia Feczko, RPh
CVS Health, Northbrook, IL, USA

Category: Clinical Science
Selected Areas: Databases and Registries, Therapeutic Strategies

Table 1. Baseline Characteristics

	Study (N = 107)	Control (N = 213)	p-value
Age, mean (SD)	65.1 (15.1)	55.1 (21.1)	**0.0001**
Gender male, N (%)	49 (45.8)	57 (26.8)	**0.0006**
Median income in the patient household area, mean (SD)	$52,061 ($24,577)	$52,669 ($20,285)	0.8141
College degrees in the patient household area, mean rate (SD)	15.8% (8.0%)	15.4% (7.4%)	0.6120
African-American, mean rate (SD)	18.7% (25.6%)	18.5% (24.9%)	0.2749
Asian, mean rate (SD)	2.3% (3.4%)	4.3% (9.4%)	**0.0331**

Table 2. Medication Characteristics by Group

6-month*	Study (N = 107)	Control (N = 213)	p-value
Fill Count	5.1	4.5	**0.0016**
Medication possession ratio (MPR)	86.4%	75.0%	**0.0013**
First Fill Drop Off Rate	2.7%	5.7%	0.1438

* Controlled for patients' characteristics through the regression model

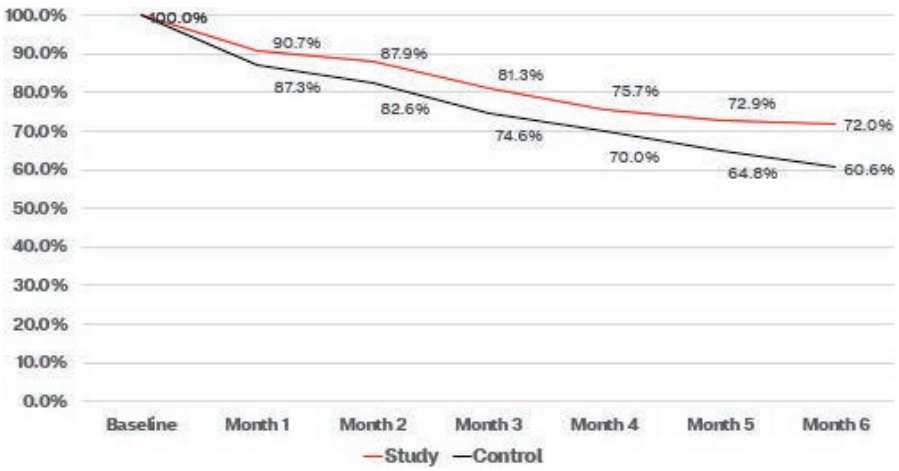


Figure 1: Persistency comparison of nurse-supported therapy versus control.

Background: Therapies currently available to treat pulmonary arterial hypertension (PAH) patients do not reverse the disease; however, they improve pulmonary hemodynamics and offer symptomatic relief and lengthen the time to clinical worsening. These therapies do not come without their challenges, which include side effects and compliance with challenging titration regimens. Health care professionals (HCPs), particularly nurses, play a significant role in improving patient medication adherence. The purpose of this study is to determine the effect that in-home, face-to-face nursing visits have on optimal adherence to oral PAH therapies.
Methods: We identified patients who received an oral PAH drug (riociguat, selexipag, or treprostinil) supported by a nursing program (study group) and patients who received an oral PAH drug (bosentan, ambrisentan, or macitentan) not supported by a nursing program (control group) using CVS Health pharmacy data from January 1, 2018, to June 30, 2019. A logistic regression model examined demographic and medication factors associated with adherence (Table 1).
Results: From January 2018 to June 2019, we identified 107 patients in the study group and 213 patients in the control group. After 6 months, patients in the study group reported 0.6 more fill counts (5.1 versus 4.5; $P < 0.01$), an 11% higher medication possession ratio (MPR; 86.4% versus 75.0%; $P < 0.01$), and higher rates of persistence (72.0% versus 60.6%; $P < 0.05$) than those in the control group. First-fill discontinuation rate was 3% higher (2.7% versus 5.7%; $P = 0.14$) in the control group and more likely to discontinue therapy in the first 6 months following the index fill (HR = 1.52; $P = 0.06$; Table 2, Figure).
Conclusions: Patients supported by nursing had significantly higher adherence.

ESTROGEN PARADOX IN METHAMPHETAMINE (MA)-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION IN ANIMAL MODEL USING BINGE-CRASH MA ADMINISTRATION

Prangthip Charoenpong, MD, MPH
Division of Pulmonary and Critical Care, Department of Medicine, Louisiana State University Health Science Center—Shreveport, Shreveport, LA, USA

Sonia Tindel, RN
Division of Pulmonary and Critical Care, Department of Medicine, Louisiana State University Health Science Center—Shreveport, Shreveport, LA, USA

Kevin Murnane, PhD
Department of Pharmacology, Toxicology & Neuroscience, Louisiana State University Health Science Center—Shreveport, Shreveport, LA, USA

Nicholas Goeders, PhD
Department of Pharmacology, Toxicology & Neuroscience, Louisiana State University Health Science Center—Shreveport, Shreveport, LA, USA

Robert Walter, MD, MPH
Division of Pulmonary and Critical Care, Department of Medicine, Louisiana State University Health Science Center—Shreveport, Shreveport, LA, USA

Category: Basic Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Estrogen paradox describes the increased incidence of pulmonary arterial hypertension (PAH) while having better outcomes in women and female animals. There are limited data suggesting that effects of amphetamine may be modified by sex in several cardiovascular outcomes. We hypothesize the effects of methamphetamine (MA) on the pulmonary vasculature are modified by sex in the binge-crash model of MA administration.
Methods: Experimentally naïve male and female Wistar rats will be used in the study. During a 96-hour procedure of the binge-crash model of MA administration, they will be housed in experiment chamber and will be returned to temperature- and humidity-controlled animal facility for 72 hours. Rats will be trained to self-administer MA by pressing one of the response levers. At the end of the exposure period (8 weeks), the animals will be euthanized, and lungs and hearts collected for histological evaluation and right ventricular/left ventricular septum (RV/LVS) weight ratio measurements. The lungs will be inflated and fixed in formalin overnight. The left lung will be blocked and embedded in paraffin. All sections will be cut and stained with hematoxylin and eosin.
Results: Preliminary data showed that MA-exposed male rats had more inflammation—demonstrated by congestion—than control female and MA-exposed female rats. The arteriolar wall was found to be thinner in MA-exposed female rats than control female rats and MA-exposed male rats (Figure)
Conclusions: Preliminary data demonstrated congestion and arteriolar wall changes in MA-exposed rats, more prominent in male rats. This may suggest estrogen paradox phenomenon in MA-PAH from the binge-crash model.

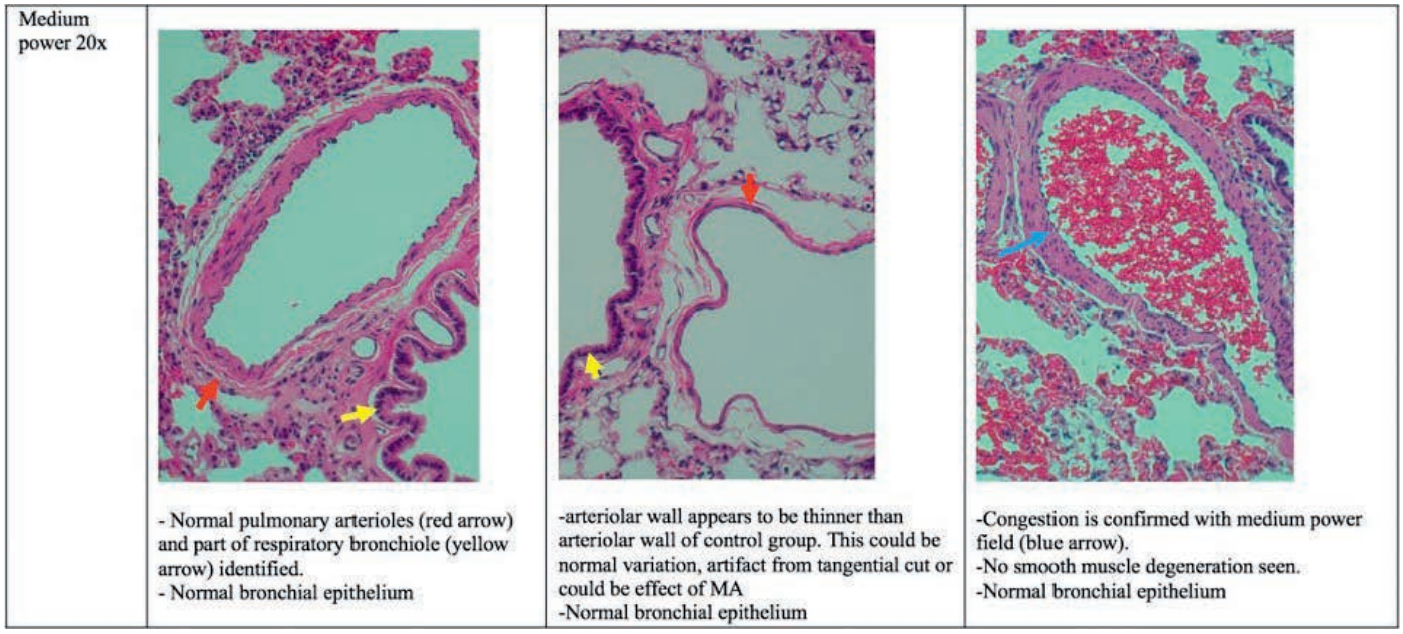


Figure 1: Ateriolar wall changes and congestion in methamphetamine (MA)-exposed rats.

LUNG TRANSPLANT OUTCOMES IN PATIENTS WITH PULMONARY VENO-OCCLUSIVE DISEASE

Prangthip Charoenpong, MD, MPH
Division of Pulmonary and Critical Care, Department of Medicine, Louisiana State University Health Science Center—Shreveport, Shreveport, LA, USA

Sonia Tindel, RN
Division of Pulmonary and Critical Care, Department of Medicine, Louisiana State University Health Science Center—Shreveport, Shreveport, LA, USA

Robert Walter, MD, MPH
Division of Pulmonary and Critical Care, Department of Medicine, Louisiana State University Health Science Center—Shreveport, Shreveport, LA, USA

Category: Clinical Science
Selected Areas: Databases and Registries, Diseases and Conditions Associated with PH

Background: Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension. Most patients need lung transplantation (LTx) as a curative treatment. Previous authors showed that PVOD patients had higher waitlist mortality than pulmonary arterial hypertension (PAH) patients. However, there are no reports on outcomes of LTx in this population. We would like to compare LTx outcomes between PVOD and idiopathic PAH (IPAH) patients.

Methods: This is a retrospective observational study. Patients with a diagnosis of PVOD and PAH underwent LTx between 2005 and 2018 were identified from SRTR database. Numerical data were reported in mean ± SD. Categorical data were reported in count and percent. *T*-tests and χ^2 tests were performed to compare variables between 2 groups. Survival was compared using the Kaplan-Meier (K-M) method.
Results: Sixty-one PVOD patients and 970 PAH patients who underwent LTx were identified. Patients with PVOD had significant lower posttransplant systolic, diastolic, and mean pulmonary artery (PA) pressure and higher cardiac output. Lung allocation score (LAS) at matching were not significantly different. PVOD patients had shorter time on the waiting list (152.7 versus 337.6, $P < 0.01$). The proportion of patients requiring extracorporeal membrane oxygenator (ECMO) post-LTx were higher in the PVOD group (13.11% versus 4.23%, $P < 0.01$). The proportion of patients developing primary graft dysfunction (PGD) was lower in the PVOD group (37.5% versus 61.93%, $P = 0.056$). There was no difference of length of stay, FEV1, FVC, PCO_2 post-LTx, or acute rejection. Survivals were not different using the K-M method ($P = 0.33$; Figure).
Conclusions: PVOD patients had shorter waiting time than PAH patients, suggestive of higher disease severity in PVOD than IPAH. Though more PVOD patients required ECMO support postoperative, long-term outcomes were not different.

	IPAH(970)	PVOD(61)	p-value
Recipient age (year)	39.84±16.27	39.87±21.55	0.99
Gender (F)	654(67.42%)	35(57.38%)	0.11
BMI	24.04±5.06	24.35±5.1	0.64
Post Ltx PASP (mmHg)	88.63±22.79	71.14±22.58	<0.01
Post Ltx PADP (mmHg)	40.01±13.7	34.76±13.49	<0.01
Post Ltx mPAP (mmHg)	57.5±16.36	47.38±16.65	<0.01
Post Ltx PCWP (mmHg)	12.69±7.6	11.39±7.67	0.24
Post Ltx Cardiac output	4.3±1.54	4.79±2.03	0.03
Previous cigarette smoking	186(38.11%)	29(47.54%)	0.16
LAS at matching	45.82±14.28	47.04±14.79	0.53
Time on wait list (days)	337.56±511.14	152.7±263.34	<0.01
Ischemic time (hours)	5.18±1.51	5.69±1.91	0.01
On ECMO after lung transplant	41(4.23%)	8(13.11%)	<0.01
Acute rejection	62/528(11.74%)	10/61(16.39%)	0.29
Post Ltx HD	141/896(15.74%)	7/61(11.48%)	0.37
reintubated	160/519(30.83%)	20/61(32.79%)	0.75
PGD	109/176(61.93%)	6/16(37.5%)	0.056
Length of stay	35.71±41.35	33.38±33.40	0.67
FEV1 post Ltx (%predicted)	68.49±19.78	70.9±17.31	0.39
FVC post Ltx (%predicted)	75.53±18.84	79.1±18.93	0.19
PCO2 post Ltx (%predicted)	35.79±9.77	36.04±9.14	0.86

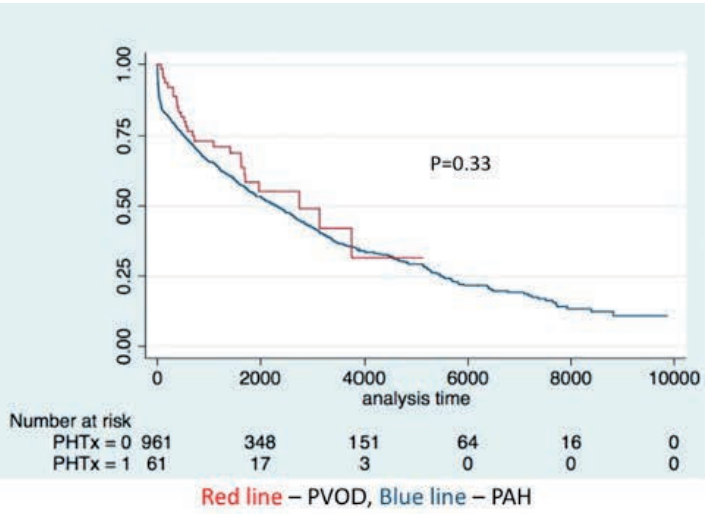


Figure 1: (**Left**) Patient data and (**Right**) Kaplan-Meier survival estimates.

AN UNUSUAL CASE OF CEREBRAL EMBOLISM AFTER INITIATION OF SELEXIPAG FOR SARCOIDOSIS-RELATED PULMONARY HYPERTENSION

Naoya Inoue, MD
Department of Cardiology, Chutoen General Medical Center, 1-1 Shobugaike, Kakegawa city, Shizuoka prefecture, Japan

Shuji Morikawa, MD
Department of Cardiology, Chutoen General Medical Center, 1-1 Shobugaike, Kakegawa city, Shizuoka prefecture, Japan

Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: Pulmonary hypertension is a rare complication of sarcoidosis. Herein, we present the case of a 63-year-old female with a diagnosis of ocular and cutaneous sarcoidosis who developed shortness of breath and was referred to our department to rule out cardiac sarcoidosis.
Methods: Swan-Ganz catheterization was performed, and she was diagnosed with pulmonary arterial hypertension and started on selexipag.
Results: A few days after starting treatment, she presented with hemiplegia and was diagnosed with cardiogenic cerebral embolism by magnetic resonance imaging. As there was no evidence of preexisting intracardiac thrombosis, we suspected unusual cerebral embolism. Echocardiography revealed a deep venous thrombus (DVT), and a bubble study showed a right-left shunt through a patent foramen ovale (PFO) (Figures 1–4).
Conclusions: Based on the above, we concluded that the initiation of selexipag improved pulmonary blood flow and caused unusual cerebral embolism. This report highlights the importance of confirming PFO and DVT before starting treatment for pulmonary hypertension.

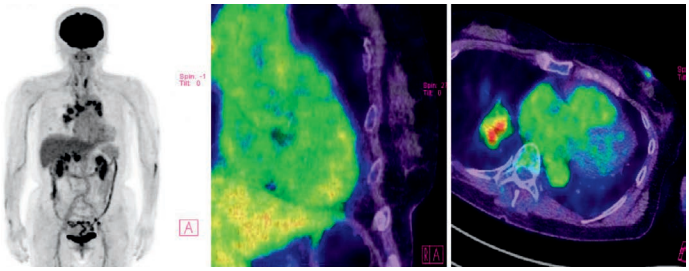


Figure 1: 18F-fluorodeoxyglucose-positron emission tomography/computed tomography scan showed accumulation in enlarged lymph nodes (red nodule) in the hilar region of the longitudinal lung, but no abnormal accumulation in the myocardium.

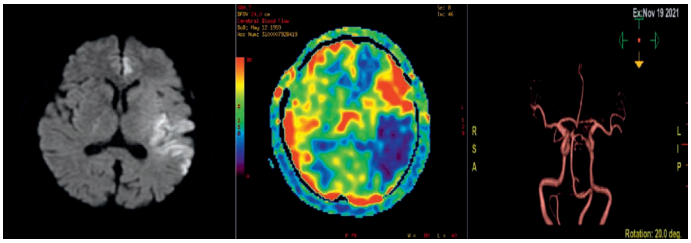


Figure 2: A head magnetic resonance imaging (MRI) scan showed acute infarction in the left frontal and parietal lobes.

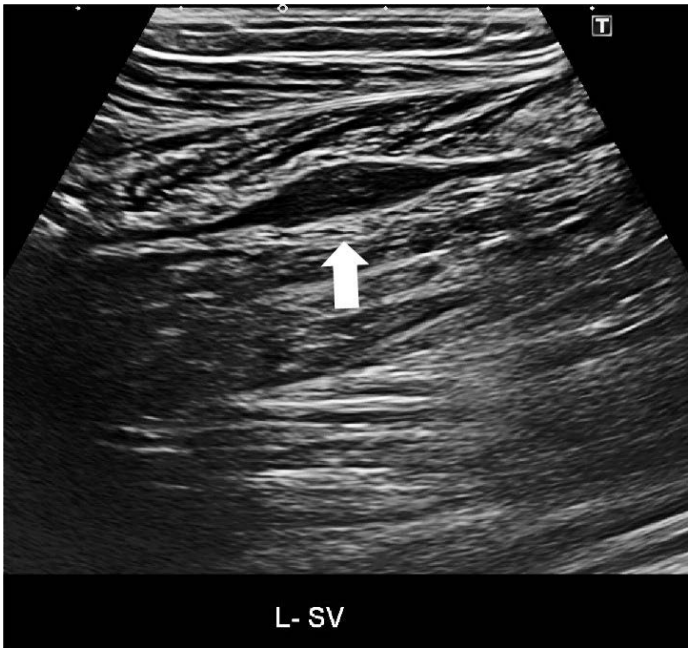


Figure 3: Echocardiography of the lower extremities showed thrombus formation (white arrow) mainly in the left soleus vein.

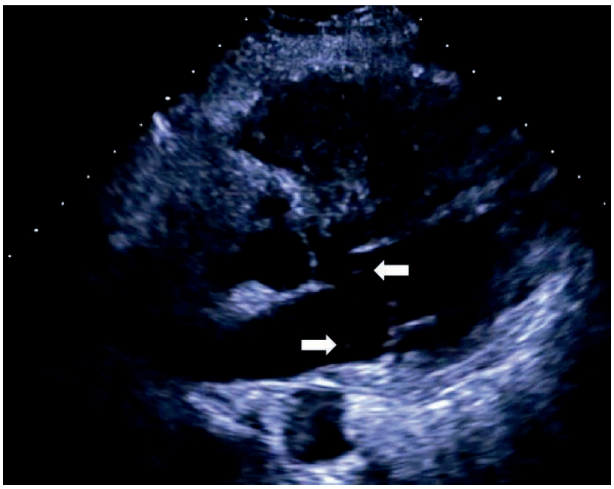


Figure 4: The microbubble (white arrows) test showed a right-left shunt that may have been mediated by the opening of the foramen ovale.

RKER-012, A NOVEL ACTIVIN RECEPTOR TYPE IIB LIGAND TRAP, REDUCED CARDIAC AND PULMONARY PATHOLOGY IN A SUGEN-HYPOXIA MODEL OF PULMONARY ARTERIAL HYPERTENSION

Keith Babbs
Keros Therapeutics, Lexington, MA, USA

Chris Materna
Keros Therapeutics, Lexington, MA, USA

Elliott Fisher
Keros Therapeutics, Lexington, MA, USA

Jasbir Seehra
Keros Therapeutics, Lexington, MA, USA

Jennifer Lachey
Keros Therapeutics, Lexington, MA, USA

Category: Basic Science
Selected Areas: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is characterized by elevated pulmonary vascular resistance resulting in impaired cardiac output and right ventricle (RV) overload. PAH is associated with imbalanced TGF-β signaling, including insufficient activation of SMAD1/5/9. In preclinical studies and clinical trials, rebalancing SMAD signaling with an activin receptor type IIB (ActRIIA) ligand trap has shown benefit but can also increase red blood cells (RBCs), a potentially dose-limiting effect for PAH. KER-012 is an investigational modified ActRIIB ligand trap designed to target ActRII signaling to favor SMAD1/5/9, potentially rebalancing signaling without affecting RBCs.
Methods: We evaluated a research form of KER-012 (RKER-012) to prevent pulmonary and RV dysfunction in a sugen-hypoxia (SH) rat model of PAH. On day 1, 2 groups of Sprague Dawley rats received a single subcutaneous (SQ) dose of SUGEN5416 and were placed in a hypoxic environment (10%–12% O_2). For 3 weeks, SH rats received either vehicle (VEH) or 10 mg/kg RKER-012 twice weekly SQ. A third group serving as healthy controls received VEH twice weekly and remained in a normoxic (NX) environment.
Results: Relative to NX rats, VEH-treated SH rats (VEH-SH) had significantly increased systolic pulmonary arterial pressure (sPAP) and Fulton index (FI; ps < 0.0001), and a trend for increased RBCs ($P = 0.06$), potentially a compensatory response to hypoxia. Relative to VEH-SH, RKER-012 treatment significantly reduced sPAP (–44.5%) and FI (–28.0%; ps < 0.001), with no observed additional change in RBCs.
Conclusions: These results demonstrate that RKER-012 prevented pulmonary and RV dysfunction without affecting RBCs in a rat PAH model. We believe these results provide early evidence that KER-012 has the potential to treat human PAH without a potentially dose-limiting RBC effect.

PROVIDING INNOVATIVE CARE FOR PULMONARY ARTERIAL HYPERTENSION WITHIN THE INTEGRATED HEALTH SYSTEM-OWNED SPECIALTY PHARMACY

Kerry Mello-Parker, PharmD, MBA
Shields Health Solutions, Stoughton, MA, USA

Stacy Walton, RN, BSN
Shields Health Solutions, Stoughton, MA, USA

Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH, Quality of Life, Therapeutic Strategies

Background: The integrated health system-owned specialty pharmacy provides an innovative approach to providing high touch service for patients living with rare disease and complex conditions. The physical presence of an in-clinic patient liaison promotes direct provider engagement, and the fully integrated patient management platform enables clinical pharmacists and nurses to follow a patient's journey across the continuum of care.
Methods: The integrated health system-owned specialty pharmacy is uniquely positioned to clinically manage rare and complex disease states, such as pulmonary arterial hypertension (PAH). Patient liaisons, clinical pharmacists, and nurses play integral roles in onboarding PAH patients and monitoring progress across their clinical journey.
Results: Using standardized, validated assessment tools such as EmPHasis-10, clinical pharmacists and nurses review patient-reported outcomes specific to PAH and assess patient quality of life. Clinicians perform an individualized risk stratification for each patient and adjust the cadence of follow-up assessments based on disease severity. For patients who report the severest of symptoms, clinicians work directly with the provider and the care team to adjust medications and address potential medication nonadherence concerns.
Conclusions: Since several of the medications used in the treatment of PAH require Food and Drug Administration Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use, the integrated pharmacy care model also encompasses manufacturer data reporting, REMS program compliance, and desktop audit support. For these medications, early results demonstrate 100% REMS audit compliance, attributed to a dedicated clinical team and full integration with the health system electronic medical record.

CLINICAL PRESENTATION AND HEMODYNAMICS OF ADULTS WITH EISENMENGER SYNDROME AND PULMONARY ARTERIAL HYPERTENSION AFTER DEFECT CLOSURE

S. Gratsianskaya
Federal State Budget Organization "National Medical Research Center of Cardiology" of Ministry of Healthcare of the Russian Federation, Scientific Research Institute of Clinical Cardiology of A.L. Myasnikov, Department of Pulmonary hypertension and Heart Diseases, Moscow, Russia

Z. Valieva
Federal State Budget Organization "National Medical Research Center of Cardiology" of Ministry of Healthcare of the Russian Federation, Scientific Research Institute of Clinical Cardiology of A.L. Myasnikov, Department of Pulmonary hypertension and Heart Diseases, Moscow, Russia

T. Martynyuk
Federal State Budget Organization "National Medical Research Center of Cardiology" of Ministry of Healthcare of the Russian Federation, Scientific Research Institute of Clinical Cardiology of A.L. Myasnikov, Department of Pulmonary hypertension and Heart Diseases, Moscow, Russia

Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH

Background: To assess clinical, functional, and hemodynamic characteristics of patients with pulmonary arterial hypertension (PAH) associated with congenital heart defect (CHD) and Eisenmenger syndrome (ES) in comparison with patients with PAH after defect closure.
Methods: Here, 56 patients (mean age = 39.1 ± 14.3 years, 46 women): 30 patients with PAH-CHD and ES and 26 patients with PAH after defect closure from the Russian National Registry of Patients with PAH (NCT03707561) were followed for 24 months. Clinical parameters, 6-minute walk test, echocardiogram, and right heart catheterization (RHC) were prospectively recorded.
Results: The age at the onset of symptoms in PAH-CHD and ES was 18.2 ± 15.1 years versus 32.9 ± 14.9 years in PAH after defect closure ($P = 0.003$). The mean time from the occurrence of complaints until the final diagnosis was 36 months for ES and 9 months for PAH after defect closure ($P = 0.0006$). The mean age of atrial septal defect correction was 50 years. Mean time to development of PAH was 4 years. The mean age of ventricular septal defect and patent ductus arteriosus correction was 5 years. Mean time to development of PAH was 20 years. The main complaints were dyspnea (95%) in both groups, but in the ES group, hemoptysis (13%, $P = 0.03$) and weakness (31%, $P = 0.02$) were significantly more frequent. According to echocardiogram, patients with ES had significantly greater right ventricular hypertrophy, higher mean pulmonary arterial pressure (PAP), and patients with PAH after defect closure had the lowest tricuspid annular plane systolic excursion (TAPSE) and the greatest dilatation of right atrium and vena cava inferior. According to RHC, mean PAP and pulmonary vascular resistance were significantly higher in patients with ES. The survival rate of patients with ES was better than with PAH after defect closure (80.5% and 47.9%, respectively).
Conclusions: Our data suggest that adults with ES have more favorable hemodynamic profiles which may result in better prognoses than adults with PAH after defect closure.

IMAGING FINDINGS OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION—A PICTORIAL ESSAY

Krittika Teerapuncharoen
Biological Sciences Division, The University of Chicago, Chicago, IL, USA
Division of Respiratory Disease and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Kavitha Selvan
Section of Pulmonary and Critical Care Medicine, Department of Medicine, The University of Chicago, Chicago, IL, USA

Remzi Bag
Biological Sciences Division, The University of Chicago, Chicago, IL, USA
Section of Pulmonary and Critical Care Medicine, Department of Medicine, The University of Chicago, Chicago, IL, USA

Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening complication of pulmonary embolism (PE). Delay in diagnosis and treatment is associated with poor outcomes. CTEPH is underreported due to nonspecific signs and symptoms, underuse of ventilation-perfusion (VQ) scans, and underrecognition of CTEPH signs on computed tomography pulmonary angiogram (CTPA) and computed tomography (CT).
Methods: Using our image library, we will discuss findings and provide clinical correlation for our cohort of CTEPH patients.
Results: Signs of preexisting CTEPH include findings of chronic PE (eccentric filling defect, abrupt tapering, stenosis ± poststenotic dilatation, webs or bands, calcified thrombus, and dilated bronchial arteries) on CTPA and findings related to pulmonary hypertension (right ventricular hypertrophy, right atrial dilatation, flattening of the interventricular septum, pulmonary artery dilatation, and mosaic attenuation) on CT.

If signs of CTEPH plus acute PE are visualized, acute-on-chronic events should be suspected. In situ pulmonary artery thrombosis, pulmonary artery sarcoma, tumor emboli, and pulmonary vasculitis are all CTPA CTEPH mimickers. A positive VQ scan for CTEPH differs from acute PE and includes at least 1 segmental or larger mismatched perfusion defect. As mismatched perfusion defects can be found in many other conditions altering pulmonary blood flow, further imaging correlation is necessary.

Conclusions: The presence of CT signs or a positive VQ scan should prompt a referral for CTEPH confirmation and evaluation for treatment, including pulmonary endarterectomy. The precise interpretation and early recognition of radiographic signs of CTEPH are essential to improve outcomes.

HYPOXIC PULMONARY HYPERTENSION RESULTS IN EXPANSION OF RIGHT VENTRICULAR CCR2+ MACROPHAGES

Sue Gu, MD
University of Colorado School of Medicine, Division of Pulmonary Sciences and Critical Care Medicine, Aurora, CO, USA
National Jewish Health, Department of Pediatrics, Denver, CO, USA
Cardiovascular Pulmonary Research Laboratory, University of Colorado School of Medicine, Department of Pediatrics-Critical Care Medicine, Aurora, CO, USA

Claudia Mickael, PhD
University of Colorado School of Medicine, Division of Pulmonary Sciences and Critical Care Medicine, Aurora, CO, USA

Linda Sanders, BS
University of Colorado School of Medicine, Division of Pulmonary Sciences and Critical Care Medicine, Aurora, CO, USA

Ronald Vagnozzi, PhD
University of Colorado School of Medicine, Division of Cardiology, Aurora, CO, USA

Delaney Swindle, MS
Cardiovascular Pulmonary Research Laboratory, University of Colorado School of Medicine, Department of Pediatrics-Critical Care Medicine, Aurora, CO, USA

David Irwin, PhD
Cardiovascular Pulmonary Research Laboratory, University of Colorado School of Medicine, Department of Pediatrics-Critical Care Medicine, Aurora, CO, USA

Peter Henson, PhD
National Jewish Health, Department of Pediatrics, Denver, CO, USA

Kurt Stenmark, MD
Cardiovascular Pulmonary Research Laboratory, University of Colorado School of Medicine, Department of Pediatrics-Critical Care Medicine, Aurora, CO, USA

Category: Basic Science
Selected Areas: Diseases and Conditions Associated with PH

Background: Macrophages play critical roles in tissue homeostasis and response to disease and may provide novel therapeutic targets in right heart failure. We hypothesize that the right ventricle (RV) contains macrophage populations at steady state that orchestrate the RV adaptation to pulmonary hypertension.

Methods: C57BL/6J mice at 8–10 weeks were placed in hypobaric hypoxia at 18000 feet or in normoxia at sea level for 4 or 21 days. We measured hemodynamics, resecting the RV and left ventricle (LV), and identified populations of CCR2+ and CCR2− macrophages using flow cytometry.

Results: The RV contained a higher proportion of CCR2+ macrophages than the LV at steady state (43% versus 9.3%, $P < 0.0001$), 4-day hypoxia (37% versus 12.6%, $P = 0.0014$), and 3-week hypoxia (54.5% versus 20%, $P = 0.0007$). After 3-week hypoxia, mice developed pulmonary hypertension with RV systolic pressure of 36 mm Hg versus 24 mm Hg in normoxic mice ($P < 0.0001$) and a trend toward RV hypertrophy with increased Fulton index (0.48 versus 0.32, $P = 0.08$). Three-week hypoxic mice had significantly increased RV macrophages per milligram tissue compared with normoxic mice (224.8 versus 63, $P = 0.03$), particularly in the CCR2+ subset of macrophages (132.5 versus 31.3, $P = 0.03$; Figure).

Conclusions: The RV in homeostasis and hypoxia contains a higher proportion of CCR2+ macrophages than the LV. Chronic hypoxic pulmonary hypertension results in an expansion of all macrophages, particularly CCR2+ macrophages, in the RV which we posit play a role in RV adaptation to pulmonary hypertension.

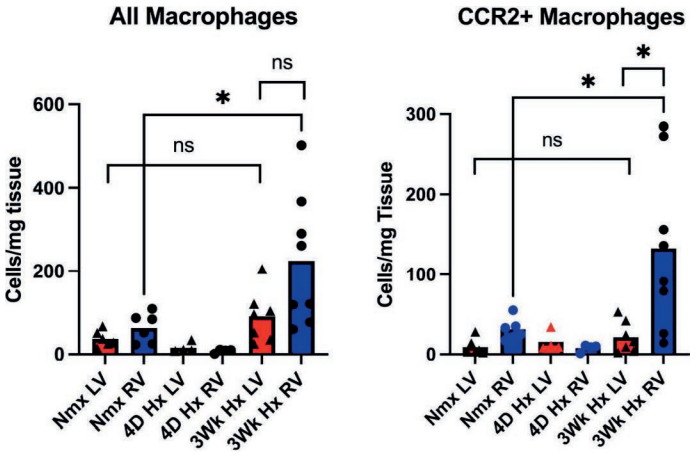


Figure 1: (**Left**) All cardiac macrophages and (**Right**) subset of CCR2+ macrophages quantified by flow cytometry. 3Wk Hx, 3-week hypoxia; 4D Hx, 4-day hypoxia; LV, left ventricle; Nmx, normoxia; RV, right ventricle.

DEFINING METHAMPHETAMINE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION IN AN ACADEMIC MEDICAL CENTER

Ayedh K. Alamri
Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Dominique Ingram
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Nathan D. Hatton
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, USA

Emily M. Beck
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, USA

Jennalyn D. Mayeux
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, USA

Dana Klanderud
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, USA

Christy L. Ma
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Ben Sadeh
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Brittany Penn
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

John J. Ryan
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Category: Clinical Science
Selected Areas: Databases and Registries, Diseases and Conditions Associated with PH

Background: Methamphetamine prevalence has been increasing through the last decade and is associated with multiple cardiovascular complications, including pulmonary arterial hypertension (PAH). In this abstract, we are aiming to define methamphetamine-PAH to find out the rate of hospitalizations, mortality, and quality of life.
Methods: Investigators at the University of Utah Pulmonary Hypertension Program enrolled adults diagnosed

Table 1. Baseline Characteristics of Methamphetamine-Induced Pulmonary Arterial Hypertension Group

	Pulmonary arterial hypertension patients, n (%) (N = 67)
Age groups	
25–64	61 (91)
65–74	5 (75)
Deceased	1 (1.5)
Sex	
Male	33 (49.3)
Female	34 (50.7)
Ethnicity	
Not Hispanic or Latino	62 (92.5)
Hispanic or Latino	3 (4.5)
Unknown	2 (3)
Substance abuse history:	
Methamphetamine	55 (82.1)
Methamphetamine and heroin	5 (7.5)
Methamphetamine and cocaine	7 (10.4)
Past medical history	
HTN	25 (37.3)
Atrial fibrillation	7 (10.4)
Hyperlipidemia	17 (25.4)
Diabetes mellitus	15 (22.4)
Chronic kidney disease	9 (13.4)
COPD	9 (13.4)
CVA	1 (1.5)
Smoking	20 (29.9)
Cardiovascular medications	
B-blockers	14 (20.9)
Angiotensin converting enzyme inhibitors	7 (10.4)
Angiotensin II receptor blockers	9 (13.4)
Loop diuretics	55 (82.1)
Mineralocorticoid receptor antagonists	27 (40.3)
SGLT-2 inhibitor	4 (6)
Pulmonary arterial hypertensions medications	
Calcium channels blockers	8 (11.9)
Endothelin receptor antagonist	40 (59.7)
Phosphodiesterase-5 inhibitor	56 (83.6)
Guanylate cyclase stimulator	3 (4.5)
Prostacyclin agonist	11 (16.4)
Prostacyclin analogues	9 (13.4)

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HTN, hypertension.

Table 2. Hemodynamics for Methamphetamine-Induced Pulmonary Arterial Hypertension Group

Pressure	Mean	Median	Mode	Standard deviation
Right atrial pressure, mm Hg	10.4844	10.0000	7.00	5.79269
Mean pulmonary artery pressure, mm Hg	47.8788	48.5000	50.00	13.84587
Pulmonary capillary wedge pressure, mm Hg	13.8333	12.0000	12.00	6.55998
Pulmonary vascular resistance, Wood units	25.7483	8.8500	3.60	125.79573
Cardiac output, L/min/m^2	19.8244	4.4400	3.40	122.39368
Cardiac index, L/min/m^2	2.4598	2.4000	1.90	0.77376
Tricuspid annular plane systolic excursion, mm	18.9400	18.0000	18.00	5.76273
Left ventricle ejection fraction, %	64.7016	67.0000	55.00	10.84341

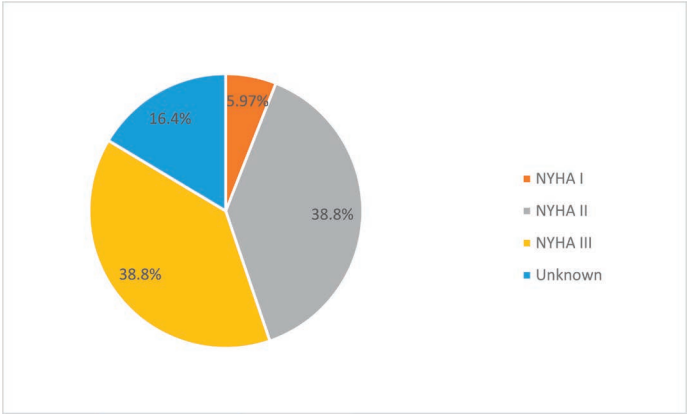


Figure 1: New York Heart Association class for methamphetamine-induced pulmonary arterial hypertension group.

with World Health Organization Group 1 PAH, toxin induced, who were seen between August 2020 and December 2021 in a program-specific registry. Their exposure histories were collected through structured interview and questionnaires, and their hemodynamic criteria were recorded. A total of 67 patients with methamphetamine-associated PAH were enrolled within the University of Utah Registry.

Results: Of the 67 patients enrolled, 50.7% were female, 91% were between the ages of 25 and 64. In 82.1% of patients, there was a history of methamphetamine use only (Table 1). The remaining 17.9% had a history of methamphetamine use and either cocaine or heroin. Most of the patients had Functional Class II–III (Figure). Hypertension was seen in 37.3%, hyperlipidemia in 25.4%, and 22.4% had a history of type 2 diabetes mellitus (Table 2).

Conclusions: In this United States Pulmonary Hypertension Association-accredited academic medical center, there are significant numbers of patients with methamphetamine-associated PAH. Published literature currently lacks large multicenter studies on methamphetamine-associated PAH and factors that affect the progression of this disease.

CONTRASTING PULMONARY ARTERIAL HYPERTENSION PHENOTYPES IN A PULMONARY HYPERTENSION ASSOCIATION-COMPREHENSIVE CARE CENTER VERSUS UNITED STATES NATIONAL REGISTRY DATA

Dominique Ingram
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Ayedh K. Alamri
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Brittany Penn
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Jennalyn D. Mayeux
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, USA

Christy Ma
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Dana Klanderud
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, USA

Ben Sadeh
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Emily Beck
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, USA

Nathan D. Hatton
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, USA

John J. Ryan
Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Category: Clinical Science
Selected Areas: Databases and Registries; Diagnosis or Screening and Physiologic Studies; Effect of COVID and Telemedicine on PH Management

Background: The phenotype of pulmonary arterial hypertension (PAH) continues to evolve. In this study, we report the characteristics of patients seen in an academic medical center for PAH from August 2020 through November 2021 and contrast those with nationally reported data.
Methods: Investigators at the University of Utah PAH center prospectively enrolled adults diagnosed with World Health Organization Group 1 PAH who were seen between August 2020 and November 2021 in a registry. A total of 251 patients were enrolled within the University of Utah PAH Registry (Table 1).
Results: Of the 251 patients enrolled, the most common etiology was associated-PAH (APAH), accounting for 72% of the population (Figure, Table 2, Table 3). The second largest etiology was idiopathic PAH (IPAH) at 26%. Of the total population with APAH, 36% of cases were noted as secondary to connective tissue disease, and 35% were toxin induced (26% and 25% of the total population, respectively). The remainder of patients were familial PAH and other subgroups of PAH. This contrasts significantly with the percentages reported by the United States Pulmonary Hypertension Registry, among others, where 51% are IPAH, and toxin-APAH accounts for only 18%. Of note, 8% of the patients enrolled in the University of Utah Registry were not on PAH-specific therapies. This contrasts with the published national registries, where nonadherence is <1%.
Conclusions: In a US academic medical center, the PAH population contrasts with traditional reported percentages of etiology of PAH. APAH,

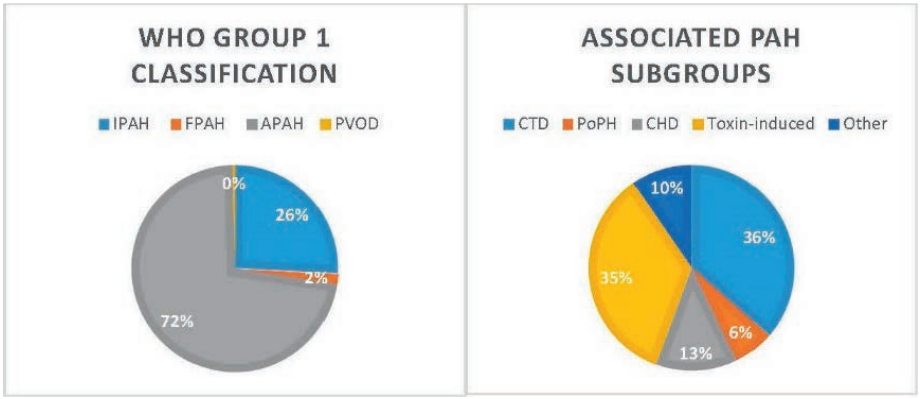


Figure 1: (**Left**) Classification of World Health Organization (WHO) Group 1 at enrollment in the University of Utah Pulmonary Arterial Hypertension (PAH) Registry based on clinical criteria. These classifications were idiopathic (IPAH), familial (FPAH), associated (APAH), and pulmonary veno-occlusive disease (PVOD). (**Right**) APAH was further classified as the following: connective tissue disease (CTD), portopulmonary hypertension (PoPH), congenital heart disease (CHD), toxin induced, and other (HHR, HIV, and hematologic malignancy).

Table 1. Total Patients Enrolled on Therapy for Pulmonary Arterial Hypertension (PAH) by Medication Class

Variable	Oral Therapy				Prostacyclin Pathway			
	CCB	PDE-5 Inhibitor	ERA	Riociguat	Selexipeg	Oral Treprostinil	Inhaled Troprostinil	Injectable Treprostinil
Overall, N=231	31 (13.4)	212 (91.8)	141 (61)	8 (3.5)	38 (16.5)	2 (0.9)	3 (1.3)	26 (11.3)
Monotherapy	0	73 (34.4)	5 (3.5)	1 (12.5)	0	0	0	0
Combination, Dual Oral Therapy (a)	0	74 (34.9)	76 (53.9)	3 (37.5)	0	0	0	0
Combination, Oral/Prostacyclin (b)	0	10 (4.7)	0	0	6 (15.8)	0	0	4 (15.4)
Combination, Triple Therapy (c)	0	55 (25.9)	60 (42.6)	4 (50)	32 (84.2)	2	3	22 (84.6)

Data are presented as n (%). CCBs were not included in combination therapy categories. Injectable treprostinil accounts for both intravenous and subcutaneous administration. (a) 2 of 3 oral therapies (ERA, PDE-5, riociguat); (b) 1 oral therapy and one prostacyclin pathway; (c) triple therapy consisting of 2 oral therapies and 1 prostacyclin pathway. CCB, calcium channel blocker (eg, amlopidine, nifedipine); ERA, endothelin receptor antagonist (eg, ambrisentan, macitentan); PDE-5 inhibitor, phosphodiesterase-5 inhibitor (eg, sildenafil, tadalafil).

Table 2. Demographic Data and Characteristics of Subjects at Time of Enrollment According to Classification

Characteristic	All Patients	IPAH	FPAH	PVOD	APAH
Patients	251	65	4	1	182
Age Group					
25-64 y	152 (60.56)	32 (49.23)	2 (50)	1 (100)	117 (64.3)
65-74 y	62 (24.7)	16 (24.6)	0	0	45 (24.7)
> 75 y	28 (11.16)	15 (23.1)	2 (50)	0	13 (7.14)
Deceased	7 (2.79)	0	0	0	7 (3.85)
Female sex	180 (71.71)	52 (80)	4 (100)	1 (100)	124 (68.13)
Race					
Asian	4 (1.59)	1 (1.54)	0	0	3 (1.65)
Black	6 (2.39)	0	0	0	6 (3.30)
Native American/Alaskan	5 (1.99)	1 (1.54)	0	0	4 (2.20)
Pacific Islander	2 (0.8)	0	1	0	1 (0.55)
White	217 (86.45)	58 (89.23)	3	1	156 (85.71)
Other	17 (6.77)	5 (7.69)	0	0	12 (6.59)
Hispanic or Latino ethnicity	19 (7.57)	7 (10.29)	0	0	12 (6.59)
BMI, kg/m²	30 ± 7.17	31.66 ± 6.76	35.36 ± 6.46	37.22	29.29 ± 7.18

Presented as % or mean ± standard deviation

not IPAH, accounts for most cases. This may reflect regional variation or practice patterns. This study is limited by the lack of genotyping.

Table 3. Diagnostic Data Including Right Heart Catheterization Hemodynamics, Functional Class, and 6-Minute Walk Distance (6MWD) at Time of Enrollment According to World Health Organization (WHO) Group 1 Classification

Characteristic	All Patients	IPAH	FPAH	PVOD	APAH
Functional class	n= 251	n = 65	n= 4	n=1	n= 182
I	11 (4.38)	3 (4.6)	0	0	8 (4.4)
II	147 (56.57)	45 (69.2)	2 (50)	0	101 (55.5)
III	62 (24.7)	12 (18.5)	1 (25)	1	51 (28)
IV	8 (3.19)	0	0	0	8 (4.4)
not available	20 (7.97)	5 (7.7)	1 (25)	0	14 (7.7)
6MWD, m	407.25 ± 136.16	388.21 ± 132.1	351.67 ± 119.54	NA	413.98 ± 137.07
N	205	56	3	0	146
mPAP, mmHg	41.32 ± 14.27	40.17 ± 13.62	46.75 ± 14.2	45	41.53 ± 14.39
N	251	65	4	1	182
PCWP, mmHg	11.13 ± 3.15	10.78 ± 2.98	13.75 ± 1.09	12	11.19 ± 3.45
N	251	65	4	1	182
mRAP, mmHg	10.61 ± 19.95	8.47 ± 8.87	10.75 ± 4.6	NA	8.78 ± 4.61
N	248	60	4	1	174
PVR, wu	4.66 ± 6.43	6.78 ± 4.44	7.83 ± 5.38	5.5	7.87 ± 6.99
N	246	62	4	1	180
CO, TD	5.18 ± 1.64	5.16 ± 1.35	5.83 ± 1.87	NA	5.19 ± 1.74
N	209	54	4	0	152
CI, TD	2.74 ± 0.79	2.64 ± 0.63	2.62 ± 2.62	NA	2.78 ± 0.85
N	199	53	4	0	143

Presented as % or mean ± standard deviation

THE ART BEHIND LINES, OPACITIES, ADENOPATHY, AND EDEMA: PULMONARY VENO-OCCLUSIVE DISEASE

Adriana C. Mares, MS
Division of Cardiovascular Medicine; Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA

Jose B. Cruz, MD
Division of Cardiovascular Medicine; UC San Diego Health, San Diego, CA, USA

Anoop Ayyappan, MD
Radiology Department; Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA

Haider Alkhateeb, MD
Division of Cardiovascular Medicine; Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA

Hernando Garcia, MD
Division of Pulmonary and Critical Care Medicine; Mount Sinai Medical Center, Miami Beach, FL, USA

Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: Pulmonary veno-occlusive disease (PVOD) is a rare cause of Group 1 pulmonary hypertension (PH) and difficult to distinguish clinically and hemodynamically from idiopathic pulmonary arterial hypertension. Therefore, we must rely on the thorax high-resolution computed tomography (THRCT) diagnostic triad and clinical cues to reach a correct diagnosis.
Methods: (Case) A 74-year-old female with history of limited scleroderma presented with dyspnea New York Heart Association (NYHA) Class IV and NT-pro-BNP of 350 pg/mL. Right heart catheterization showed: right atrial pressure = 3mmHG, pulmonary artery pressure = 78/33/48mmHG, pulmonary capillary wedge pressure = 10mmHG, cardiac index = 1.59L/min/m2, SVO_2 = 65%, and pulmonary vascular resistance = 15.9 WU. Shortly after epoprostenol infusion,

chest x ray revealed pulmonary edema. THRCT showed the radiological diagnostic triad (Figure).
Results: (Decision making) Findings of pulmonary edema after epoprostenol infusion, triad THRCT features, and limited scleroderma strongly suggested diagnosis of PVOD. Therapy was initiated with low-dose up-titration of intravenous infusion epoprostenol with a target dose of 10–12 ng/kg/min in combination with endothelin receptor antagonist macitentan. After 8 months, NT-pro-BNP reduced to 57 pg/mL, and dyspnea improved to NYHA Class III, along with quality of life.
Conclusions: This case illustrates the sensitivity of radiological features, which led to the diagnosis of PVOD, the presumptive high prevalence of PVOD in limited scleroderma, and the possible treatment response with pulmonary arterial hypertension-specific therapy in patients who are not lung transplant candidates.

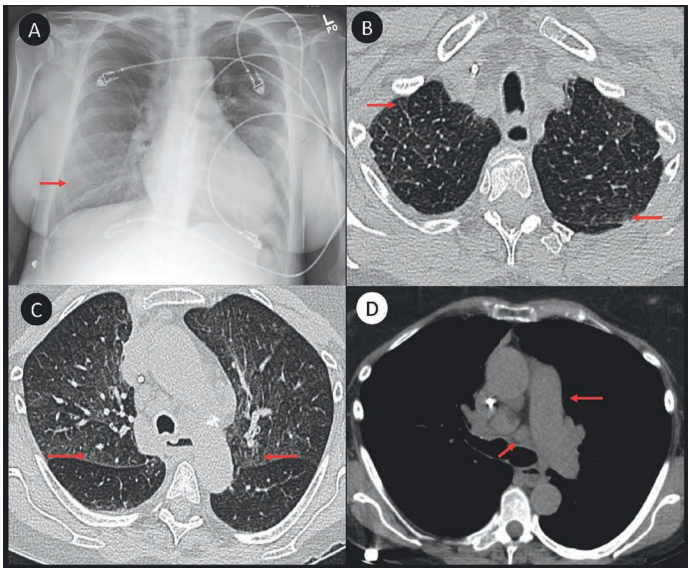


Figure 1: Radiologic diagnostic triad. (**A**) Posteroanterior chest x ray shows a prominent main pulmonary artery and Kerley B lines (arrow). (**B**) Axial high-resolution computed tomographic (CT) image of the upper lobes shows smoothly thickened interlobular septa (arrows) and geographic ground-glass opacities. (**C**) Axial high-resolution CT image shows widespread ground-glass opacities (arrows) and few septal lines. (**D**) Axial CT image (mediastinal window) shows dilated main pulmonary artery and enlarged mediastinal lymph nodes (arrows).

OUTCOMES OF EXTRACORPOREAL MEMBRANE OXYGENATOR SUPPORT IN PULMONARY HYPERTENSION PATIENT WITH COVID-19 INFECTION: MULTICENTER EXPERIENCE

Raysa Morales-Demori
Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA

Jamil Ortoleva
Tufts University School of Medicine, Boston, MA, USA

Marc Anders
Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA

Category: Clinical Science
Selected Areas: Databases and Registries

Background: Extracorporeal membrane oxygenator (ECMO) support in adult patients diagnosed with COVID-19 infection has been widely used; however, the outcomes of this procedure in chronic pulmonary hypertension remain unknown.
Methods: A retrospective cohort study of all patients over 18 years old diagnosed with COVID-19 infection reported to the Extracorporeal Life Support Organization Registry from 2020 until 2021.
Results: A total of 7253 patients diagnosed with COVID-19 who underwent ECMO support were divided into patients without pulmonary hypertension (No-PH; 96%), patients with acute PH (acute-PH; 2%), and patients with chronic PH (chronic-PH; 2%). There were no differences on median age (No-PH = 49 years versus acute-PH = 48 years versus chronic-PH = 50 years). Chronic-PH patients had more comorbidities, such as acute renal failure (45% versus No-PH 29% versus acute-PH 29%, $P < 0.001$), liver disease (27% versus No-PH 3% versus acute-PH 4%, $P < 0.001$), and heart failure (25% versus No-PH 6% versus acute-PH 15%, $P < 0.001$). Chronic-PH patients had longer median hours on ECMO support (604 hours versus No-PH 425 hours versus acute-PH 409 hours, $P < 0.001$), and higher complications (84% versus No-PH 70% versus acute-PH 81%, $P < 0.001$). Inpatient mortality was higher in chronic-PH patients (64% versus No-PH 53% versus acute-PH 51%, $P = 0.04$). When comparing mortality cases between groups, chronic-PH patients had more liver disease (No-PH 4% versus chronic-PH 33%, $P < 0.001$, odds ratio [OR] = 12.4 [7.7–20.0]), chronic lung disease (No-PH 5% versus chronic-PH 10%, OR = 2.3 [1.1–4.6]), and heart failure (No-PH 8% versus chronic-PH 26%, $P < 0.001$, OR = 4.3 [2.6–7.1]); however, liver disease was the only factor associated with increased mortality ($P = 0.03$, OR = 2.6 [1.1–6.3]).
Conclusions: Chronic-PH patients diagnosed with COVID-19 infection undergoing ECMO support have higher comorbidities and inpatient mortality than No-PH or acute-PH patients.

USE OF LIQ861 TO IMPROVE HEALTH-RELATED QUALITY OF LIFE FOR PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

Martha Kingman
University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

Savan Patel
Liquidia Technologies, Morrisville, NC, USA

Category: Clinical Science
Selected Areas: Quality of Life; Therapeutic Strategies

Background: Liquidia has developed LIQ861, a dry powder formulation of treprostinil by using PRINT Technology, designed to enhance deep-lung delivery and enable QID delivery of doses in 2 breaths per capsule via a convenient, palm-sized dry powder inhaler. PRINT Technology produces drug particles that are precise in size, shape, and composition.
Methods: The INSPIRE trial was a phase 3, open-label, multicenter trial (LTI-301) that enrolled patients with pulmonary arterial hypertension (PAH) over 18 years of age who transitioned to LIQ861 from nebulized treprostinil (Transition) or added LIQ861 to 2 nonprostacyclin oral therapies, prostacyclin naïve (Naïve). The Minnesota Living With Heart Failure Questionnaire (MLHFQ) survey was administered at baseline, 2 months, and 4 months during the trial.
Results: One hundred and twenty-one patients were enrolled in the trial, including 55 in the Transition group and 66 in the Naïve group. Most patients were female, white, and non-Hispanic, with a mean age of 54.2 years. Approximately two-thirds of the patients were New York Heart Association (NYHA) Functional Classification (FC) II, the remaining being NYHA FC III. Most patients received background PAH medications, with 71% receiving a combination of endothelin receptor antagonist and phosphodiesterase 5 inhibitor or soluble guanylate cyclase agonists.
By month 4 (N = 104), there was a clinically meaningful improvement in the total MLHFQ score for all patients from baseline. Overall, the mean score of 36.0 at baseline decreased to 25.8. At month 4, both physical and emotional dimension scores decreased from 16.2 to 11.8 and 7.8 to 5.2, respectively. Improvements were seen in both the Transition and Naïve patient groups.
Conclusions: Treatment with LIQ861 may help improve health-related quality of life, which has been shown to be impaired in PAH patients.

PULMONARY HYPERTENSION IN A LIMPING CHILD: A CASE OF URGEN-C

Alvin Rocha
Children's Hospital Los Angeles, Los Angeles, CA, USA

Reem Itani
Children's Hospital Los Angeles, Los Angeles, CA, USA

Jacqueline Szmuszkovicz
Children's Hospital Los Angeles, Los Angeles, CA, USA

Lara C. Bishay
Children's Hospital Los Angeles, Los Angeles, CA, USA

Category: Case Reports
Selected Areas: Diseases and Conditions Associated with PH; Pediatrics

Background: Scurvy is a rare and reversible cause of pulmonary hypertension in pediatrics with few case reports. Our case is unlike prior cases, as it also included hypothyroidism.
Methods: (Case) A 4-year-old male presented with 2 months of refusal to walk due to leg pain.
Results: Right femur magnetic resonance imaging (MRI) showed presumed osteomyelitis, yet oral antibiotics were ineffective, and thus, he underwent bone biopsy. Postoperatively, he developed acute respiratory distress and hypoxia. D-dimer was elevated, and computed tomography angiogram revealed possible pulmonary embolism or acute infection. Echocardiogram indicated severe pulmonary hypertension (tricuspid regurgitation gradient 119 Torr), presumably secondary to possible pulmonary embolism. Oxygen supplementation and anticoagulation started. Hypercoagulable workup was unremarkable. Whole-body MRI indicated osteopenia. Thyroid function tests revealed severe hypothyroidism without autoimmunity. Levothyroxine was started. Rheumatologic and infectious evaluations were unremarkable. Sildenafil was initiated with mild improvement in right ventricular (RV) pressures. Given history of limited diet of peanut butter sandwiches, vitamin C level was checked and returned undetectable. Intravenous vitamin C started. Within 3 days, RV pressure reduced to 32 Torr. Exome sequencing indicated a variant of uncertain significance in NKX2-1.
He was discharged on oral vitamin C, sildenafil, levothyroxine, and oxygen. Echocardiogram normalized 4 weeks after discharge, and oxygen was weaned. He resumed ambulation. Follow-up echocardiogram 4 weeks after weaning sildenafil off remained normal.
Conclusions: (Discussion) Severe pulmonary hypertension and hypothyroidism were reversed with supplemental vitamin C. We are not aware of other case reports of scurvy with hypothyroidism. Exome findings could be relevant.

ACUTE ONSET PULMONARY ARTERIAL HYPERTENSION IN THE POSTPARTUM PERIOD: A PHANTOM PHENOTYPE

Brandon Croft
UCSF Fresno, Fresno, CA, USA

Coralee Koning
UCSF Fresno, Fresno, CA, USA

Marcus Cummins
UCSF School of Medicine, San Francisco, CA, USA

Vijay Balasubramanian
UCSF Fresno, Fresno, CA, USA

Category: Case Report
Selected Areas: Diagnosis or Screening and Physiologic Studies; Diseases and Conditions Associated with PH; Quality of Life

Background: Idiopathic pulmonary arterial hypertension (IPAH) is a rare entity that leads to right ventricular (RV) overload and death. Postpartum unmasking of IPAH is rarely reported in the literature but may suggest a new phenotype. We report a case of a young previously healthy female with new onset severe IPAH that was discovered 3 weeks after delivery.
Methods: (Case) A 24-year-old young mother of 4 children presented to our facility 3 weeks after uneventful vaginal delivery with severe dyspnea and syncope found to have a brain natriuretic peptide (BNP) of 2056 pg/mL and normal troponin.
Results: Echocardiogram revealed a severely dilated RV, severe tricuspid regurgitation, and septal flattening. Right heart catheterization confirmed World Health Organization (WHO) Group 1 PAH with high-risk features. Parenteral prostacyclin therapy was initiated immediately. Endothelin receptor antagonist (ERA) and tadalafil was added later sequentially at various times. Acute onset PAH was followed by rapid improvement as well. She was switched to oral treprostinil after 17 months of parenteral therapy. Currently, she remains in a low-risk status—WHO Functional Class 1 after >72 months of prescription (Table).
Conclusions: This case illustrates a phenotype of PAH characterized by acute onset followed by rapid improvement with aggressive upfront treatment measures.

Table 1. Right Heart Cath, Labs, Functional Class, and Reveal Risk scores for the patient over time

	TIME OF PAH DIAGNOSIS	6 MONTHS AFTER DIAGNOSIS PRIOR TO TRANSITION ONTO ORAL TREPROSTINIL *	72 MONTHS AFTER DIAGNOSIS (ON TRIPLE COMBO THERAPY**)
mRAP (mmHg)	8	8	2
mPAP (mmHg)	67	45	28
PCWP (mmHg)	10	13	16
PVR (WU'S)	28	5.2	1.0
CO (L/MIN)	1.92	6.17	8.08
CI (L/MIN/M2)	1.14	3.55	4.38
BNP (pg/mL)	2,056	15	18
6MWT (METERS)		467	500
WHO FX CLASS	IV	I-II	I
REVEAL RISK (2.0)	13 (High)	1.0 (Low)	1.0 (Low)

*On subcutaneous treprostinil 46 ng/kg/min and ambrisentan 10 mg PO QD.

**On oral treprostinil 8 mg TID, tadalafil 40 mg QD, and ambrisentan 10 mg PO QD.

ACUTE CORONARY SYNDROME IN PULMONARY ARTERIAL HYPERTENSION—A PRESSING ISSUE

Brandon J. Croft, MD
UCSF Fresno, Fresno, CA, USA

Marcus Cummins, BS
UCSF School of Medicine, San Francisco, CA, USA

Siri Kunchakarra, MD
UCSF Fresno, Fresno, CA, USA

Vaikom Mahadevan, MD
UCSF Division of Cardiology, San Francisco, CA, USA

Vijay Balasubramanian, MD
UCSF Fresno, Fresno, CA, USA

Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies; Diseases and Conditions Associated with PH

Background: Atrial septal defect (ASD) with Eisenmenger's physiology (EP) is classified as World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH). Pulmonary artery (PA) dilation in this setting can cause left main coronary artery (LMCA) compression and myocardial ischemia. We report a case of a 35-year-old female with ASD who had PAH decompensation secondary to myocardial infarction (MI) from LMCA compression.
Methods: (Case) A 35-year-old woman with WHO Group 1 PAH secondary to ASD and EP presented with abdominal pain and shortness of breath and was found to have acute sepsis from pelvic inflammatory disease on initial presentation.
Results: Troponin was 61 ng/mL with anterolateral T-wave inversion on electrocardiogram. Acute coronary syndrome was diagnosed, and therapeutic heparin was started. Brain natriuretic peptide was 2287 pg/mL with echocardiogram showing

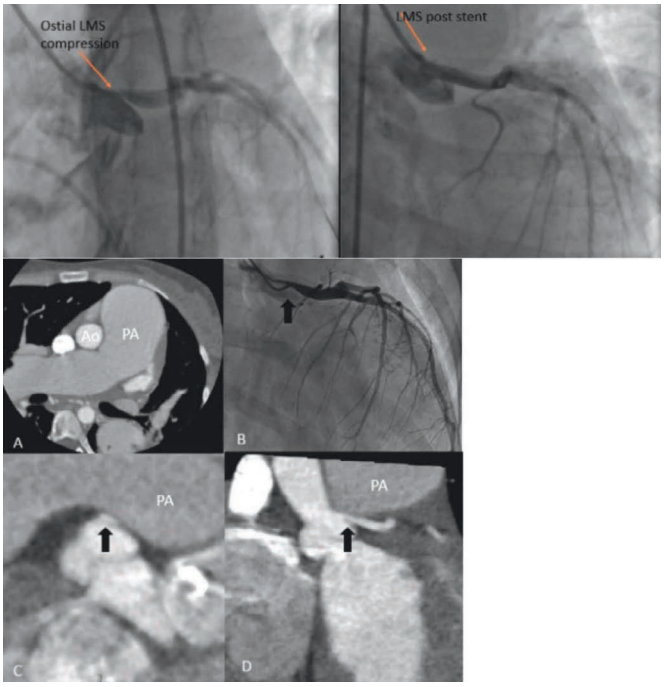


Figure 1: Cardiac imaging for (**Top left**) ostial compression of the left main stem (LMS) coronary artery by the dilated pulmonary artery (PA). (**Top right**) Image after stent placement. (**A**) Dilated PA. Ao, aorta. (**B**) Coronary angiogram showing severe LMS stenosis (arrow). (**C**) Coronary computed tomography (CT) angiogram showing severe stenosis with slitlike opening of the ostial LMS (seen in short axis, arrow). (**D**) Oblique view showing large PA compressing the ostial LMS (arrow).

preserved ejection fraction, right ventricular systolic pressure of 70 mm Hg, and septal flattening. Computed tomography pulmonary angiogram showed external LMCA compression by the PA (Figure). Coronary angiogram confirmed 95% stenosis of the LMCA without angiographic evidence of atherosclerosis. Right heart catheterization revealed mean pulmonary artery pressure of 54 mm Hg, pulmonary arterial systolic pressure of 102 mm Hg, pulmonary capillary wedge pressure of 15 mm Hg, and pulmonary vascular resistance of 4.3 Wood units. Percutaneous intervention with stent placement resulted in resolution of stenosis.

Conclusions: Sepsis can increase myocardial demand which may worsen right heart function and result in PAH decompensation. Dilatation of main PA predisposes to LMCA compression causing myocardial ischemia. Prompt recognition and intervention resulted in a positive outcome.

PLAIN LANGUAGE SUMMARY OF THE INCREASE STUDY: USING INHALED TREPROSTINIL FOR TREATING PULMONARY HYPERTENSION AND INTERSTITIAL LUNG DISEASE

Natalie W. Anderson
United Therapeutics Corp., RTP, NC, USA

Melissa Miceli
United Therapeutics Corp., RTP, NC, USA

Natalie E. Patzlaff
United Therapeutics Corp., RTP, NC, USA

Aaron B. Waxman
Brigham and Women's Hospital, Boston, MA, USA

Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH

Background: The goal of the INCREASE study was to see if inhaled treprostinil could help people with pulmonary hypertension and interstitial lung disease (PH-ILD). Before INCREASE, there was no Food and Drug Administration-approved drug for treating PH-ILD. The goal of this plain language summary is to explain the INCREASE trial so that nondoctors can understand the results.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled clinical trial that lasted 16 weeks. A total of 326 people with PH-ILD took part in the study; 163 were given inhaled treprostinil (Tyvaso), and 163 were given a placebo that does not contain any medicine. Because PH-ILD causes breathing problems and tiredness, researchers wanted to test if taking inhaled treprostinil would help people with

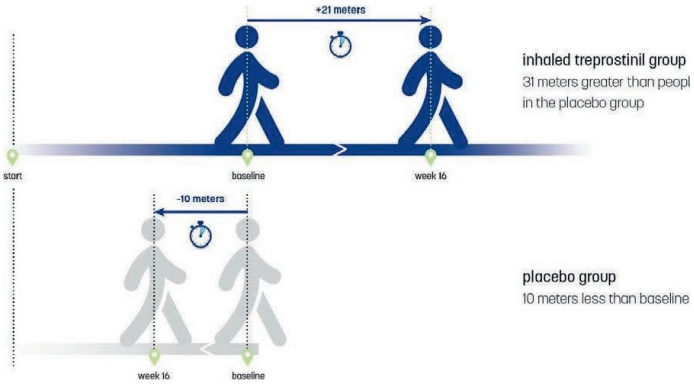


Figure 1: After 16 weeks in the study, participants taking inhaled treprostinil walked farther in 6 minutes than participants taking the placebo. At week 16, on average, participants in the inhaled treprostinil group walked 21 meters further than they did at the beginning of the study. Overall, participants in the inhaled treprostinil group had an average change from the baseline in 6-minute walk distance (6MWD) that was 31 meters (about 102 feet) greater than participants in the placebo group.

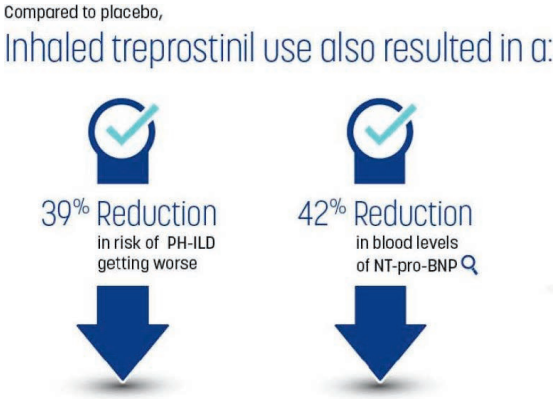


Figure 2: Study participants taking oral treprostinil showed improved clinical measurements, specifically, a reduced risk of pulmonary hypertension and interstitial lung disease (PH-ILD) getting worse and lowered NT-pro-BNP levels. Compared with participants taking the placebo, those taking inhaled treprostinil had a 39% reduced risk of their PH-ILD getting worse. NT-pro-BNP is a protein marker of heart function that can be measured with a blood test. NT-pro-BNP levels that are higher can mean that a person has heart problems. Compared with participants taking the placebo, those taking inhaled treprostinil lowered their NT-pro-BNP levels from the beginning of the study by 42%.

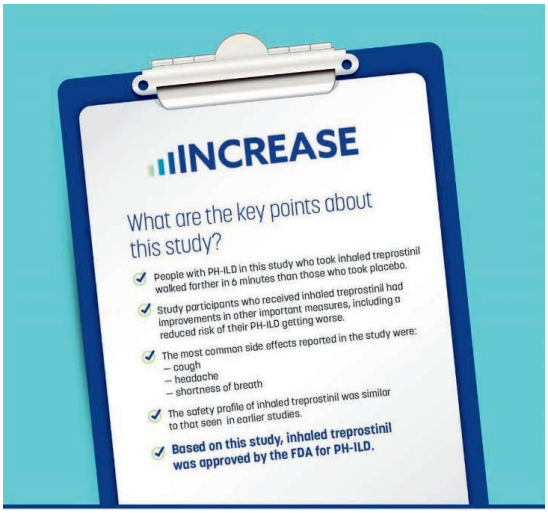


Figure 3: Summary of the INCREASE study results. For complete results, see Waxman et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Eng J Med*. 2021;384(4):325–334. doi:.10.1056/NEJMoa2008470.

Table 1. Side Effects Reported by >10% of Participants in Either Group During the Study

Side Effect	Participants receiving inhaled treprostinil number, (percentage)	Participants receiving placebo number, (percentage)
Cough	71 (43.6%)	54 (33.1%)
Headache	45 (27.6%)	32 (19.6%)
Shortness of breath (dyspnea)	41 (25.2%)	51 (31.3%)
Dizziness	30(18.4%)	23 (14.1%)
Nausea	25 (15.3%)	26 (16%)
Fatigue	23 (14.1%)	23 (14.1%)
Diarrhea	22 (13.5%)	19 (11.7%)
Throat irritation	20 (12.3%)	6 (3.7%)
Throat (oropharyngeal) pain	18 (11%)	4 (2.5%)

Cough, headache, and throat pain were reported more often by participants taking inhaled treprostinil than those taking the placebo.

PH-ILD walk farther in 6 minutes than people with PH-ILD taking placebo.

Results: On average, after 16 weeks in the study, people taking inhaled treprostinil raised their 6-minute walking distance by 31 meters (about 102 feet) more than people in the placebo group (Figure 1). NT-pro-BNP is a protein measuring heart function. Participants taking inhaled treprostinil lowered (improved) their NT-pro-BNP levels from the study start by 42% versus placebo (Figure 2). Compared with placebo, participants taking inhaled treprostinil had a 39% reduced risk of their PH-ILD getting worse. Cough, headache, and throat pain were reported more often by people taking inhaled treprostinil than by people taking placebo (Figure 3; Table).

Conclusions: People with PH-ILD in this study who took inhaled treprostinil walked farther in 6 minutes than those who took placebo. Study participants who received inhaled treprostinil improved other important measures, including a reduced risk of their PH-ILD getting worse.

Cough, headache, and throat pain were reported more often by participants taking inhaled treprostinil than those taking the placebo.

YOUNG WOMAN FIGHTING TWO DEMONS

Coralee Koning
UCSF Fresno, Fresno, CA, USA

Brandon Croft
UCSF Fresno, Fresno, CA, USA

Marcus Cummins
UCSF School of Medicine, San Francisco, CA, USA

Ibironke Adelaijaja
UCSF Fresno, Fresno, CA, USA

Vijay Balasubramanian
UCSF Fresno, Fresno, CA, USA

Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies; Diseases and Conditions Associated with PH; Quality of Life

Background: Pulmonary arterial hypertension (PAH) is a devastating disease caused by remodeling of precapillary arterioles leading to a progressive increase in pulmonary vascular resistance, right heart failure, and death. Breast cancer also is a serious diagnosis associated with an adverse prognosis. We describe the case of a young woman who was diagnosed with both conditions in a brief time span. PAH was optimized with parenteral prostacyclin therapy, and she underwent successful surgical mastectomy.
Methods: (Case) A 35-year-old female was diagnosed with World Health Organization Group 1 idiopathic PAH (IPAH) with high-risk features (Table).
Results: Treatment regimen included treprostinil (SQ) and tadalafil. Shortly after, a right breast lump was detected. Evaluation revealed stage IIIb invasive ductal carcinoma with axillary lymph node (LN) involvement. Surgical mastectomy was rendered necessary despite her heightened mortality risk due to PAH. Following multidisciplinary (Surgical Oncology, Cardiac Anesthesiology, Palliative Care, and Pulmonary Hypertension teams) discussion of risks and benefits with the patient, surgery was planned. Preoperative optimization of PAH included increase in treprostinil dose and conversion to intravenous, aggressive diuresis, and pulmonary artery catheter placement. Mastectomy with axillary LN dissection was successfully completed without complication.
Conclusions: Against all odds, this young woman is fighting two serious disease processes associated with high mortality. The above case illustrates her first success. However, the road ahead is less known. A multidisciplinary approach, patient education, and hope are essential to maximize improved outcomes.

Table 1. Right Heart Catheterization Data and Brain Natriuretic Peptide

	TIME OF DIAGNOSIS	PRE-OP* (17 MONTHS AFTER DIAGNOSIS)
mRAP (mmHg)	14	4
PAP (mmHg)	66	43
PCWP (mmHg)	6	3
PVR (WU'S)	28.7	10.36
CO (L/MIN)	2.16	3.86
CI (L/MIN/M^2)	1.2	2.4
BNP	741	29
REVEAL RISK	10 (high)	8 (intermediate)

*On intravenous treprostinil 81.9 ng/kg/min.

PULMONARY HYPERTENSION ASSOCIATED WITH PARTIAL ANOMALOUS PULMONARY VENOUS RETURN

Usha Yendrapalli
Huntsville Hospital, Huntsville, AL, USA

Muhammad Mohsin Zafar
UAB, Huntsville Hospital, Huntsville, AL, USA

Abdulwahab Hritani
Cardiology, Huntsville Hospital, Huntsville, AL, USA

Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH; Therapeutic Strategies

Background: Partial anomalous pulmonary venous return (PAPVR) is rare congenital condition that may present during late adulthood or can go undiagnosed for years. We present 3 patients with pulmonary arterial hypertension (PAH) secondary to PAPVR whose symptoms improved after treatment.
Methods: Retrospective chart review and case series.
Results: A 60-year-old male presented with dyspnea. Echocardiogram revealed ejection fraction (EF) of 45%–50% and pulmonary arterial systolic pressure (PASP) of 83 mm Hg. Right heart catheterization (RHC) revealed PAH with pulmonary arterial pressure (PAP) of 80/40 mm Hg, and pulmonary capillary wedge pressure (PCWP) of 18 mm Hg. Computed tomography (CT) angiogram of the heart showed anomalous pulmonary venous return from the right lung. Patient was initiated on PDE-5 inhibitor with improvement in his symptoms.

A 73-year-old male presented with dyspnea. Echocardiogram revealed EF of 60% and PASP of 90 mm Hg. RHC revealed severe PAH with mean PAP of 65 mm Hg and PCWP of 26 mm Hg. Serial O_2 saturation showed a significant increase in O_2 saturation, particularly at high right atrium (RA), and superior vena cava junction of 86%. CT angiogram of the heart showed anomalous return of the left upper pulmonary vein to the superior vena cava. Patient began PDE-5 inhibitor treatment with good symptomatic response.
A 75-year-old female presented with dyspnea. Echocardiogram revealed EF of 55% and PASP of 50 mm Hg. Bubble study was positive for a right to left shunt via both arm access with a shunt ratio of 4.7. CT angiogram of the heart showed anomalous drainage of the right-sided pulmonic veins into the RA. RHC revealed PAP of 76/17 mm Hg and PCWP of 18 with a pulmonary angiogram, which demonstrated right upper, middle pulmonary veins draining into RA. Patient began PDE-5 inhibitor with improvement in her symptoms.
Conclusions: Patients with unexplained PAH should have a high degree of suspicion for PAPVR. Awareness of PAPVR is important because untreated PAPVR can lead to PAH.

SAFETY AND EFFICACY OF TRANSITIONING FROM PARENTERAL PROSTACYCLIN ANALOGS TO ORAL PROSTACYCLIN AGONIST AND THE EFFECT ON QUALITY OF LIFE

Jason Peng, MD
Loyola University Medical Center, Maywood, IL, USA

Phoebe Stracener, PharmD
Loyola University Medical Center, Maywood, IL, USA

Jenny Altobelli, RN, BSN
Loyola University Medical Center, Maywood, IL, USA

James Gagermeier, MD
Loyola University Medical Center, Maywood, IL, USA

Sana Quddus, MD
Loyola University Medical Center, Maywood, IL, USA

Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH; Quality of Life; Therapeutic Strategies

Background: Parenteral prostacyclin therapy is well established for patients with World Health Organization Group 1 pulmonary arterial hypertension (PAH). However, difficulty tolerating long-term parenteral therapy due to line- and delivery-related complications is common, resulting in poor quality of life. While case series describing the transition from parenteral prostacyclin to selexipag exist, there is no standardized protocol. Furthermore, we sought to assess the change in quality of life associated with the transition.
Methods: This case series includes 3 transitions (2 inpatient and 1 outpatient) from parenteral prostacyclins to selexipag between February 2020 and November 2021. Protocols are shown in Figures 1–3. Quality of life was assessed using the emPHasis-10 score.
Results: Patient 1 is a 50-year-old female with PAH and sarcoidosis on macitentan and intravenous (IV) epoprostenol, who transitioned over 7 days as an inpatient for recurrent line infections. Patient 2 is a 22-year-old female with idiopathic PAH on macitentan, sildenafil, and IV treprostinil, who transitioned over 5 days as an inpatient for recurrent line infections. Patient 3 is a 71-year-old female with HIV-associated PAH on macitentan and SQ treprostinil who had a prolonged outpatient transition for severe site discomfort. This transition over 647 days was interrupted by the COVID-19 pandemic. Mean emPHasis-10 scores decreased from 28.3 (pretransition) to 15.3 (posttransition). Six-minute walk distance (6MWD) improved, while the New York Heart Association (NYHA) Functional Class remained stable pretransition and posttransition (Table).

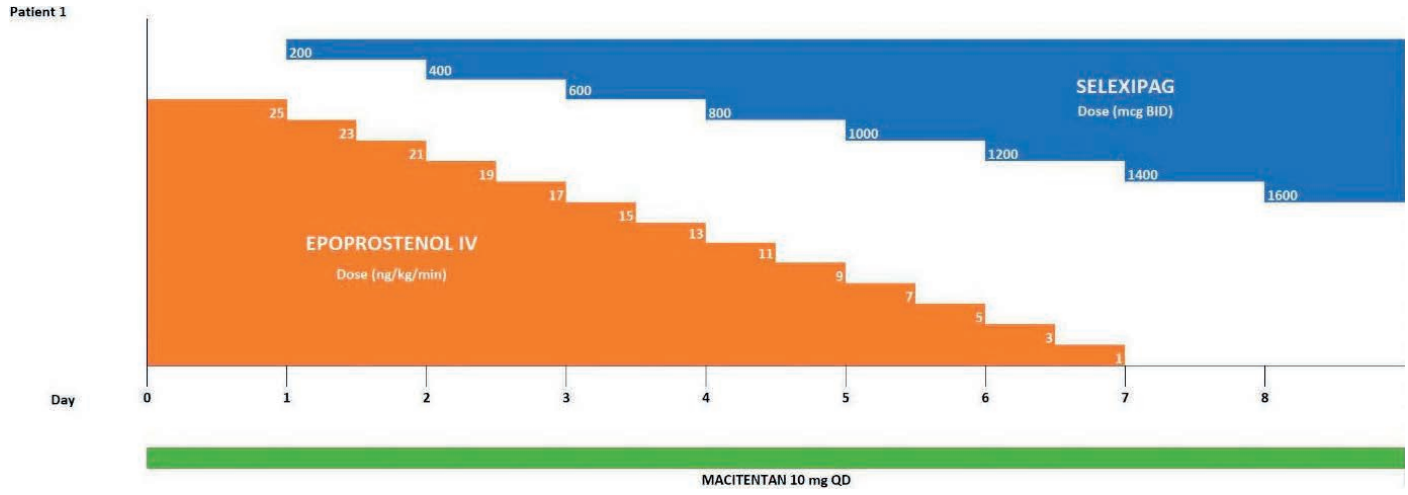


Figure 1: Protocols used for parenteral prostacyclin to selexipag transitions for Patient 1.

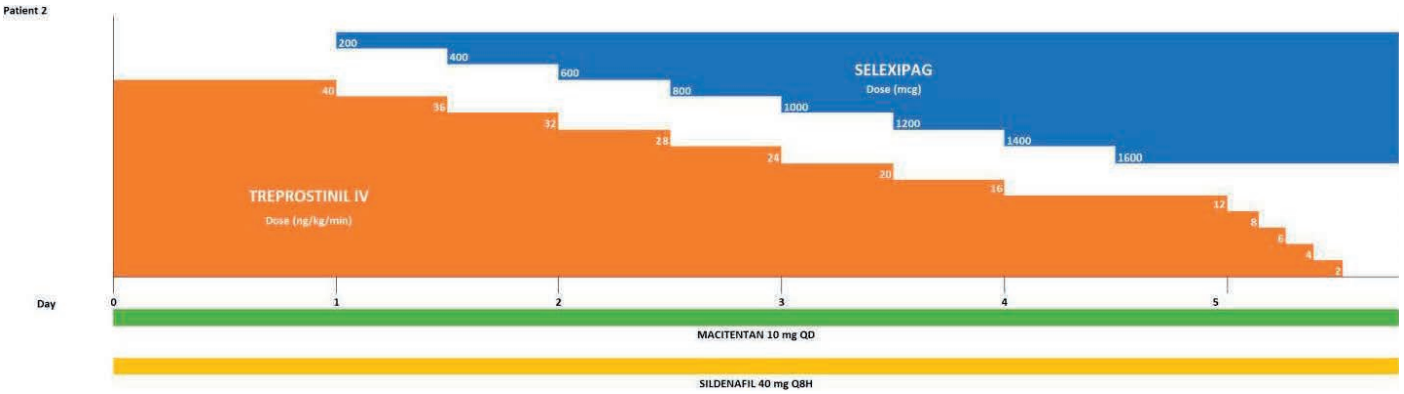


Figure 2: Protocols used for parenteral prostacyclin to selexipag transitions for Patient 2.

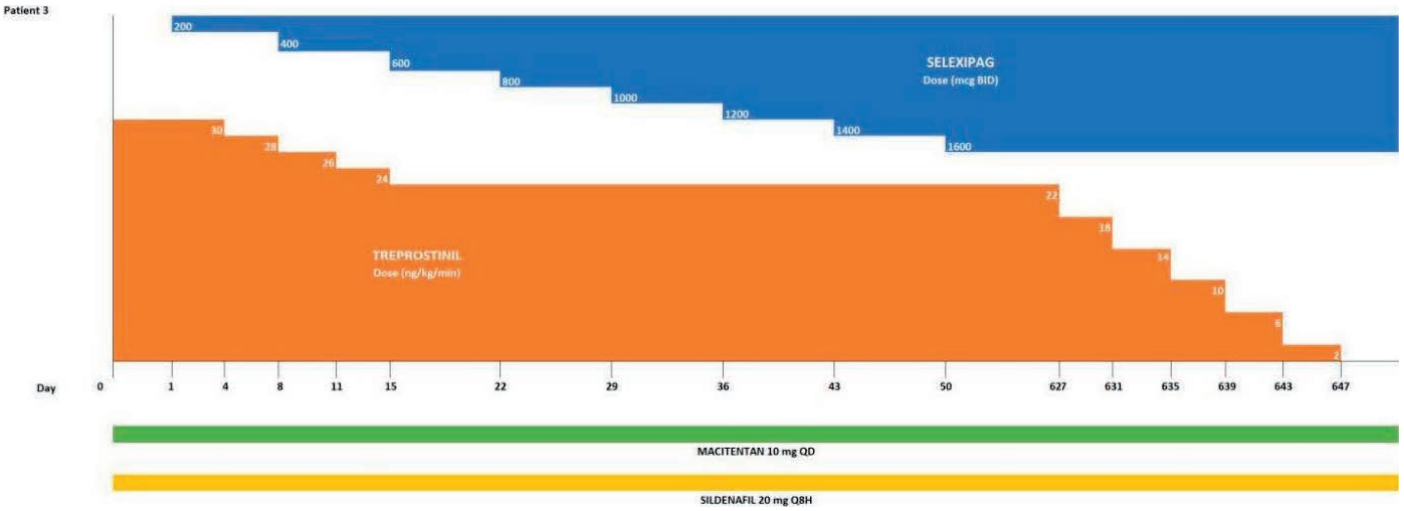


Figure 3: Protocols used for parenteral prostacyclin to selexipag transitions for Patient 3.

Table 1. Patient Demographics and Quality of Life, 6-Minute Walk Distance (6MWD), and Echocardiogram Findings

				Parenteral Prostacyclin		Selexipag		6MWD		Echocardiogram Findings		emPHasis-10 Score		NYHA Functional Class	
Patient	Age	Diagnosis	Transition	Duration on Prior to Transition	Dose at Time of Transition	Final Dose	Reason for Transition	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	50	Sarcoidosis and Group 1 PAH	IV epoprostenol to PO selexipag	36 months	23 ng/kg/min	1600 mcg BID	Line related infections	226 meters	284 meters	TAPSE: 1.8 cm RA Area: 12.2 cm^2	TAPSE: pending RA Area: pending	37	27	2	2
2	22	Idiopathic PAH	IV treprostinil to PO selexipag	19 months	36 ng/kg/min	1600 mcg BID	Line related infections, patient preference	610 meters	624 meters	TAPSE: 2.04 cm RA Area: 12.5 cm^2	TAPSE: 2.1 cm RA Area: 13 cm^2	32	8	1	1
3	71	HIV-associated PAH	SQ treprostinil to PO selexipag	13 months	30 ng/kg/min	1600 mcg BID	Severe site discomfort	190 meters	248 meters	TAPSE: 1.8 cm RA Area: 22.1 cm^2	TAPSE: 1.9 cm RA Area: 11.5 cm^2	16	11	2	2

Conclusions: Our case series provides a reference with timelines for transitioning from low-dose parenteral prostacyclins to selexipag. Patients had significant improvements in quality of life and 6MWD.

PULMONARY HYPERTENSION ASSOCIATED WITH COR TRIATRIATUM

Usha Yendrapalli
Huntsville Hospital, Huntsville, AL, USA

Muhammad Mohsin Zafar
UAB, Huntsville Hospital, Huntsville, AL, USA

Abdulwahab Hritani
Cardiology, Huntsville Hospital, Huntsville, AL, USA

James D Murphy
Cardiology, Huntsville Hospital, Huntsville, AL, USA

Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: Cor triatriatum sinister is a rare congenital heart defect in which a fibromuscular membrane subdivides the left atrium (LA) into 2 chambers. We present a case report of pulmonary arterial hypertension (PAH) secondary to cor triatriatum.
Methods: Retrospective chart review and case report.
Results: A 43-year-old male presented for dyspnea on exertion. Echocardiogram showed ejection fraction of 60%, right ventricular pressure overload, pulmonary arterial systolic pressure of 80 mm Hg, and membrane separating LA chambers concerning cor triatriatum. Computed tomography (CT) angiogram of the heart showed dilated pulmonary artery (PA; 4 cm), enlarged and septated LA with evidence for cor triatriatum. Right heart catheterization (RHC) revealed severe PAH with pulmonary arterial pressure (PAP) of 95/65 mm Hg with mean of 75 mm Hg, transpulmonary gradient of 70, cardiac output was 4.65, cardiac input of 2.4. He underwent complete repair of the cor triatriatum with surgical resection of the membranes. Post-surgery repeat echocardiogram showed improved right-sided pressures, and RHC showed PAP of 62/37 with a mean of 47 mm Hg. Symptoms improved significantly after surgery.
Conclusions: Awareness of cor triatriatum is important because untreated cor triatriatum can lead to PAH. Identification of cor triatriatum sinister is increasing due to widespread use of advanced techniques, such as CT and angiography. Cor triatriatum is amenable to surgical repair with good outcomes when diagnosed early.

PAUSE AT YOUR OWN PERIL: REBOUND PULMONARY HYPERTENSION

Sindhubarathi Murali
SUNY Upstate Medical University, Syracuse, NY, USA

Subrat Khanal
SUNY Upstate Medical University, Syracuse, NY, USA

Kartik Ramakrishna
SUNY Upstate Medical University, Syracuse, NY, USA

Category: Case Report
Selected Areas: Therapeutic Strategies

Background: After initiation of combination therapy, one must be careful about potential interruption in therapy resulting in rebound pulmonary arterial hypertension (PAH).
Methods: The first case involved a 41-year-old woman with heritable pulmonary hypertension (PH) on ambrisentan, tadalafil, and inhaled treprostinil. Given her acute cholecystitis, she was unable to tolerate her medications. The second case involved a 55-year-old woman with PAH on intravenous treprostinil and macitentan. She was without infusion for 50 minutes.
Results: Both patients experienced right heart failure and required aggressive diuresis. The first patient's echocardiogram showed a severely dilated right ventricle (RV) and right atrium (RA; 90.1 mL/m), moderate tricuspid regurgitation (TR V Max, 4.88 m/s; tricuspid annular plane systolic excursion (TAPSE), 1 cm) and RV systolic pressure of 110 mm Hg (Figure 1). The second patient's computed tomography of the thorax showed a dilated pulmonary artery (PA; Figure 2). Right heart catheterization showed RA pressure of 6 mm Hg, RV pressure of 74/10, PA pressures of 73/25, pulmonary capillary wedge pressure of 10 mm Hg, cardiac output/cardiac input of 2.4/1.6, and pulmonary vascular resistance of 15 consistent with severe precapillary PH. She was started on tadalafil.
Conclusions: Despite the vast benefits PGI2 analogues provide, careful consideration should be taken before starting them given their difficulty to discontinue. Those with poor functional class or abnormal hemodynamics have greater difficulty discontinuing from a PGI2 analogue. If discontinuation of the medication is <4–5 half-lives of the last dose taken, then the medication should be taken at the last tolerated dose. If the time between doses is >4–5 half-lives, then a lower dose with rapid up-titration based on tolerance is required (Narechania S, Torbic H, Tonelli

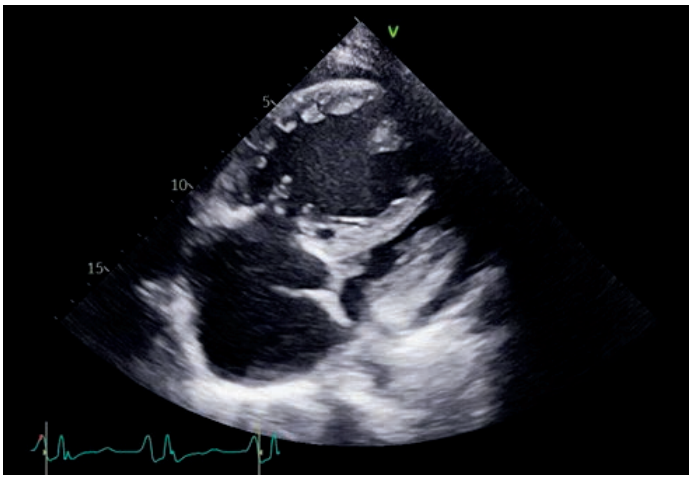


Figure 1: Echocardiogram of the first patient showing severely dilated right ventricle and right atrium.

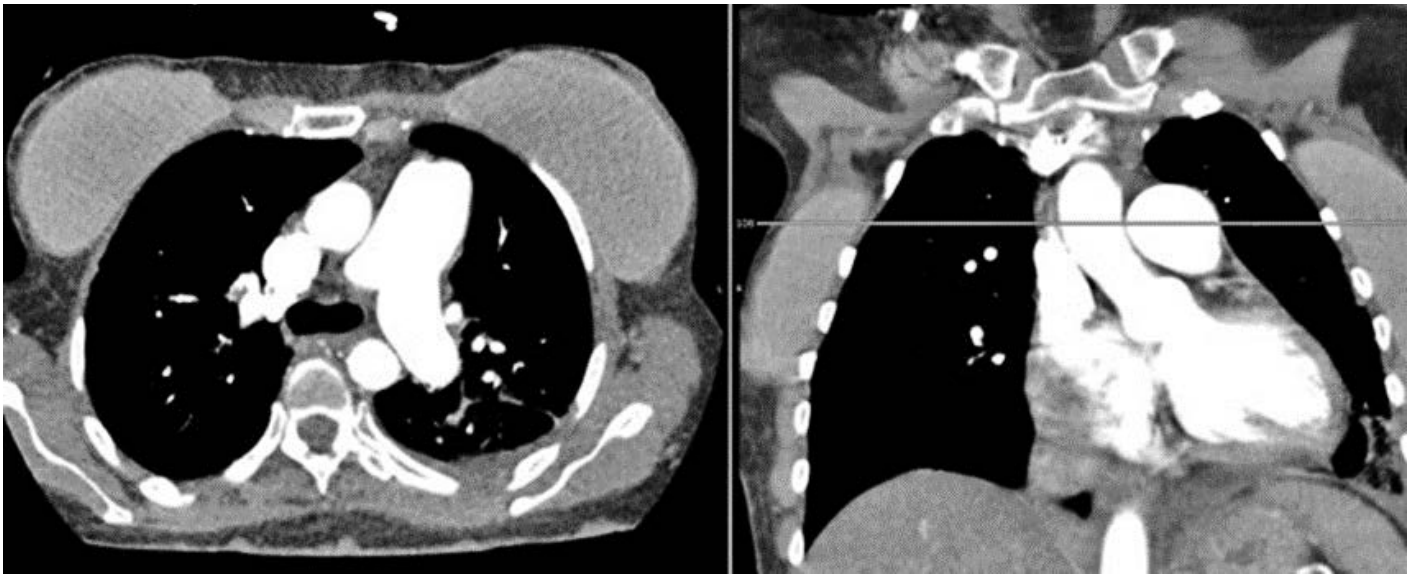


Figure 2: Computed tomography of the thorax of the second patient showing a markedly dilated pulmonary artery in comparison to the aorta.

AR. Treatment discontinuation or interruption in pulmonary arterial hypertension. *J Cardiovasc Pharmacol Ther*. 2019;25(2): 131-141. https://doi.org/10.1177/1074248419877740). These case reports highlight the importance and severity of abrupt discontinuation of PAH medication and in turn provide some guidance on how to manage such patients.

MALE SEX IS ASSOCIATED WITH DECREASED RIGHT VENTRICULAR FUNCTION AND SURVIVAL IN GROUP 1–5 PULMONARY HYPERTENSION

Nicholas Shelburne
Department of Medicine, Division of Allergy, Pulmonary and Critical Care, Vanderbilt University Medical Center, Nashville, TN, USA

Hui Nian
Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA

Chang Yu
Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA

Anna Hemnes
Department of Medicine, Division of Allergy, Pulmonary and Critical Care, Vanderbilt University Medical Center, Nashville, TN, USA

PVDOMICS Study Group

Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Sex-based differences are important factors in the development and progression of PH. We sought to use the deep phenotyping of the PVDOMICS project to test the hypothesis that males with pulmonary hypertension (PH) will have worse right ventricular (RV) function than females at similar elevations of pulmonary vascular resistance (PVR).

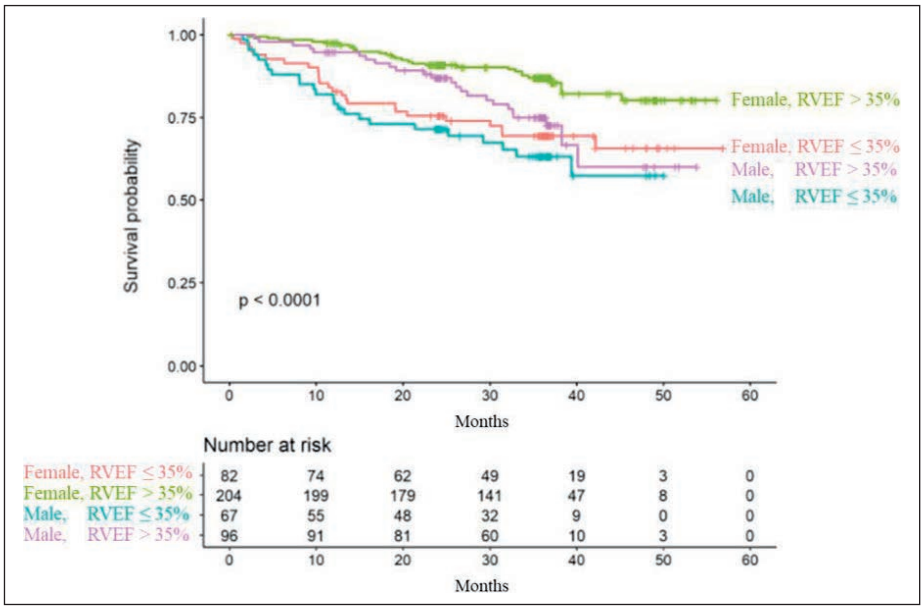


Figure 1: (**Top**) Kaplan-Meier curve for transplant-free survival by sex and (**Bottom**) number at risk based on the presence or absence of right ventricular dysfunction on cardiac magnetic resonance imaging (defined by RVEF = 35%).

Methods: Subjects enrolled in PVDOMICS with PH were included. For this analysis, subjects were grouped based on PVR: 2.4–5 and >5 Wood units (WU), and differences in RV ejection fraction (EF) on cardiac magnetic resonance imaging between men and women were assessed using the Wilcoxon rank sum test. Effects of sex and RV function on transplant-free survival were assessed using Cox Proportional Hazards Model.
Results: A total of 750 patients with PH (62.8% female) were enrolled. World Symposia on Pulmonary Hypertension Group 1 patients were most predominantly female at 73.4%. Among the 349 PH patients (61.8% female) with measurements of both RVEF and PVR, RVEF was significantly lower in men (38.3 ± 10.2% versus 42.4 ± 11.8%, $P < 0.001$), while there was no significant difference in PVR (5.4 ± 3.4 versus 5.9 ± 3.8 WU, $P = 0.3$). In PH patients with mild elevation in PVR (2.4–5 WU; n = 148, 58.8% female), RVEF was reduced in men (41.0 ± 9.3% versus 46.8 ± 10.3%, $P < 0.001$); however, in patients with PVR >5 WU (n = 157, 64.3% female), the trend toward worsened RVEF in men was not significant (34.3 ± 9.8% versus 37.3 ± 11.5%, $P = 0.09$). In PH patients, female sex was associated with improved survival (heart rate = 0.61, 95% confidence interval = 0.46–0.82), and this difference was partially mediated by differences in RVEF (natural indirect effect: -0.14, $P = 0.01$; Figure).
Conclusions: Among PH patients with mild elevations in PVR, RV function is significantly worse in men. Women with PH have improved survival compared with men, and this difference is partially explained by differences in RV function.

FEASIBILITY OF INTRAVENOUS TO ORAL HOME TRANSITIONS WITH PROSTACYCLIN THERAPY IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION DURING THE COVID-19 ERA

Meghan Morrisette PharmD
Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC, USA

Kristine Ritenour RN
Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC, USA

Denise Sese MD
Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC, USA

Rahul G. Argula MBBS, MPH
Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC, USA

Category: Case Report
Selected Areas: Effect of COVID and Telemedicine on PH Management; Quality of Life; Therapeutic Strategies

Background: During the COVID-19 pandemic, there was a need for providers to continue providing quality care for pulmonary arterial hypertension (PAH) patients despite limitations in access to care. Safe transitions of PAH patients from intravenous (IV) prostacyclin therapy to PO selexipag therapy in the inpatient setting have previously been described in several case series with mixed results, but there is a dearth of experience with the outpatient setting.

Methods: In this case series, we describe the successful transition of 4 patients with World Health Organization (WHO) Group 1 PAH and WHO Functional Class (FC) 1 or 2 symptoms who were transitioned at home under supervision of the PAH team. We compared the differences in their baseline and follow-up functional class, 6-minute walk distance, echocardiograms, right heart catheterizations, and reported quality of life.
Results: Patients were all female (2 Caucasian, 2 African American) with an age range of 26–54 years. The primary reasons for transitioning patients to PO therapy were to improve quality of life and unmanageable IV prostacyclin side effects. The length of IV therapy prior to PO transition ranged from 3 to 100 months with an epoprostenol maintenance dose range of 9–29.5 ng/kg/min. Three out of the 4 patients were on triple PAH therapy. Patients were transitioned with an average decrement of epoprostenol of 0.62 ng/kg/min/day and an average weekly increase of selexipag of 172 mcg twice daily over a range of 17–57 days. There were no significant changes in FC nor significant complications related to PAH in the first 3 months following transition. All patients reported an improvement in their quality of life.
Conclusions: Home IV to PO therapy transitions can be done successfully in carefully selected patients with guidance from a multidisciplinary team.

RODATRISTAT ETHYL, A TRYPTOPHAN HYDROXYLASE INHIBITOR IN PHASE 2B FOR PAH DEMONSTRATES LOW POTENTIAL FOR AFFECTING BRAIN SEROTONIN BIOSYNTHESIS

Michelle Palacios
Altavanty Sciences Inc, Cary, NC, USA

Howard Lazarus
Altavanty Sciences Inc, Cary, NC, USA

Jill Denning
Altavanty Sciences Inc, Cary, NC, USA

Stephen Wring
Altavanty Sciences Inc, Cary, NC, USA

Category: Basic Science
Selected Areas: Diseases and Conditions Associated with PH

Background: Rodatristat (R), as rodatristat ethyl (RE) prodrug, inhibits tryptophan hydroxylase (TPH) the rate-limiting enzyme in serotonin (5-HT) biosynthesis. In pulmonary arterial hypertension (PAH), elevated 5-HT in pulmonary endothelial cells drives vascular remodeling. Key to TPH therapy is avoiding reductions in brain 5-HT. Here, we leverage nonclinical disposition data, with mood and Columbia-Suicide Severity Rating Scale (C-SSRS) assessments in healthy subjects, to assess potential for central nervous system effects.
Methods: Potency for TPH inhibition, protein binding, and blood-brain barrier passage were measured in vitro. Tissue disposition was by quantitative whole-body autoradiography in rats receiving 14C-RE at the dose efficacious in rat PAH models. Rat brain 5-HT was measured after 21 days RE at 2× the efficacious dose. In healthy subjects, C-SSRS data were collected at baseline and after 14 days of either: 400 mg BID, 800 mg BID, 500 mg QD, or 800 mg QD RE.
Results: In vitro R potently inhibits nonneuronal TPH1 (IC50, 52 nM) and neuronal TPH2 (9 nM); however, exposure was barely detectable in rat brain consistent with in vitro data (>99% protein bound; permeability <25 nm/s). Brain 5-HT was unaffected in monocarboxylate transporter (MCT) + vehicle and MCT + RE animals. Free R levels in lung were ~3× the TPH1 IC50, yielding robust reductions in tissue 5-HT in MCT rats. Plasma concentration (Cmax) for R was ~2560 ng/mL. In healthy subjects, steady-state Cmax was 1370 ng/mL (800 mg BID RE) and 1260 ng/mL (600 mg BID, highest phase 2b dose). Plasma concentrations in humans are ~50% of rat where no changes in brain 5-HT were observed. In humans, there were no changes in mood or suicidal ideation in any subject across all dose groups (n = 36).
Conclusions: RE should not affect brain 5-HT nor mood in humans.

GROWTH DIFFERENTIATION FACTOR 15 IS ASSOCIATED WITH INCREASED PULMONARY ARTERIAL HYPERTENSION SEVERITY AND DECREASED SURVIVAL

Kate Schole, MD
Division of Pediatric Cardiology, Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA

Guillermo Torres, MD
Division of Pediatric Cardiology, Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA

Jun Yang, PhD
Division of Pediatric Cardiology, Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA

Stephanie Brandal
Division of Pediatric Cardiology, Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA

Megan Griffiths, MD
Division of Pediatric Cardiology, Department of Pediatrics, Columbia University Medical Center, New York, NY, USA

Rachel Damico, MD, PhD
Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA

Dhananjay Vaidya, MD, PhD
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
Division of General Internal Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

Catherine E. Simpson, MD, PhD
Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA

Michael W. Pauciulo, PhD
Division of Human Genetics, Cincinnati Children's Hospital Medical Center; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

William C. Nichols, PhD
Division of Human Genetics, Cincinnati Children's Hospital Medical Center; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

David D. Ivy, MD
Department of Pediatric Cardiology, Children's Hospital Colorado, Denver, CO, USA

Eric D. Austin, MD
Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA

Paul M. Hassoun, MD
Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA

Allen D. Everett, MD
Division of Pediatric Cardiology, Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA

Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Pulmonary arterial hypertension (PAH) is a progressive disease characterized by vascular remodeling resulting in right ventricular pressure overload and right heart failure. Growth differentiation factor 15 (GDF-15), a member of the transforming growth factor-B cytokine superfamily, is a

left heart failure biomarker with pilot evidence of elevation in patients with PAH.
Rationale: Determine diagnostic and prognostic utility of GDF-15 levels in PAH patients via correlation with deteriorating clinical severity and mortality rates.
Methods: Serum GDF-15 levels from the National Heart, Lung, and Blood Institute PAH Biobank were evaluated by enzyme-linked immunosorbent assay (ELISA). A total of 1932 subjects and 50 healthy controls was evaluated. Association of GDF-15 levels with PAH clinical variables were assessed via Spearman's rank correlation test and Kruskal-Wallis test. Cox multivariable and Kaplan-Meier analyses were used to examine survival associations with GDF-15.
Results: Receiver operating characteristic (ROC) analysis evaluated GDF-15's ability to distinguish between PAH and controls with area under the curve = 0.85. By PAH classification, connective tissue participants had highest overall GDF-15 levels (3.07 ± 2.5 ng/mL). Higher GDF-15 correlated with higher New York Heart Association Classification. Adjusted GDF-15 levels were associated with a 20 m decrease in 6-minute walk distance (95% confidence interval [CI] = −29.2 to −11.3, $P < 0.001$), and a 0.58 mm Hg increase in right atrial pressure (95% CI = 0.29–0.86, $P < 0.001$). Kaplan-Meier analyses showed a significant difference in survival curves and adjusted Cox proportional hazards showed a 1.88 greater risk of death (95% CI = 1.59–2.23, $P < 0.001$; Figure).
Conclusions: Measuring GDF-15 levels may offer additional prognostic value in the clinical evaluation of PAH.

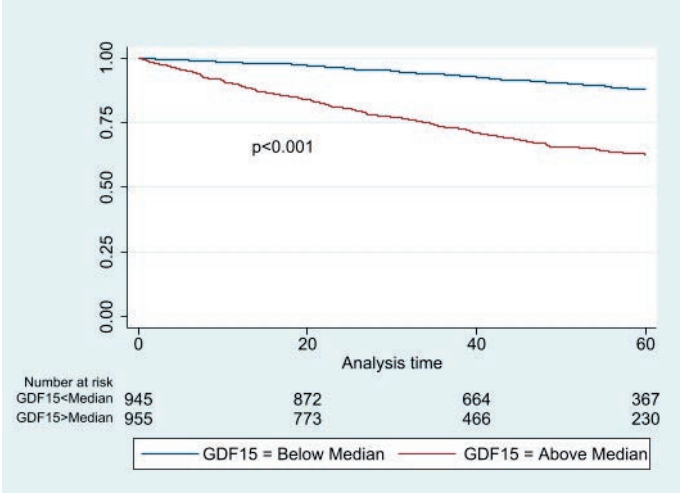


Figure 1: GDF-15 Kaplan-Meier survival estimates.

MULTIDISCIPLINARY CARE TEAM INTEGRATION: THE BASIS OF A SUCCESSFUL PEDIATRIC PULMONARY HYPERTENSION CARE CENTER

Elise Whalen
Department of Pulmonary Medicine, Texas Children's Hospital, Houston, TX, USA

Myra Baker
Department of Pulmonary Medicine, Texas Children's Hospital, Houston, TX, USA

Amy Alonzo
Department of Pharmacy, Texas Children's Hospital, Houston, TX, USA

Rozmeen Fombin
Department of Pulmonary Medicine, Texas Children's Hospital, Houston, TX, USA

Erin Ely
Department of Pulmonary Medicine, Texas Children's Hospital, Houston, TX, USA

Neelam Bhatt
Department of Pharmacy, Texas Children's Hospital, Houston, TX, USA

Nidhy Varghese
Department of Pediatric Pulmonology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

Category: Clinical Science
Selected Areas: Pediatrics

Background: Multidisciplinary care teams (MDTs) work jointly to implement patient care interventions to meet the complex needs of individuals with chronic illnesses. Pediatric pulmonary hypertension (PH) is specifically associated with significant morbidity and mortality, putting children at high risk of clinical deterioration.
Methods: A MDT care team model was adapted to meet the needs of our large pediatric PH population of >300 patients, infants to 21 years of age. This care team model was separated into 2 major clinical care settings of the PH patient: outpatient and inpatient. To target specific care concerns within these 2 clinical care settings, MDT activities were established. To improve outpatient MDT involvement, an outpatient huddle was structured and preanesthesia recommendation documentation was created. Weekly team inpatient rounds, multidisciplinary rounds, and integration of a discharge checklist were targeted at improving inpatient MDT care team involvement.
Results: There are many strengths associated with the MDT care model in the PH population. These strengths include improved collaboration among various specialties to work jointly to meet the needs of the patient and family, reduction of patient safety errors, and increased team member satisfaction. Weaknesses include a need for clearly defined roles in the team and frequent collaboration via meetings.
Conclusions: The complexities of the pediatric PH population are best matched with the expertise of an experienced MDT team. Adapting a MDT care team model that integrates various activities to optimize the care of the pediatric PH patient in the inpatient and outpatient settings ensures time for collaboration.

COMPREHENSIVE CARDIAC SCREENING CAMPS IN RESOURCE-LIMITED SETTINGS CAN BREAK THE ICEBERG PHENOMENA IN PULMONARY HYPERTENSION

Chooda M. Khanal, PhD
Miami Dade College, Miami, FL, USA
Pulmonary Hypertension Association Nepal, Miami, FL, USA

Roshan Khatiwada
Himal Hospital, Kathmandu, Nepal
Pulmonary Hypertension Association Nepal, Urlabari, Province No. 1, Nepal

George B. J. Katwal
Annapurna Neurological Institute & Allied Sciences, Kathmandu, Nepal
Pulmonary Hypertension Association Nepal, Urlabari, Province No. 1, Nepal

Chandeshwar P. Yadav
Sanjeevani Heart Hospital, Birtamode, Nepal
Pulmonary Hypertension Association Nepal, Urlabari, Province No. 1, Nepal

Shankar P. Adhikari
Hamro Aspatal, Biratnagar, Nepal
Pulmonary Hypertension Association Nepal, Urlabari, Province No. 1, Nepal

Keshav P. Gadtaula, PhD
Tribhuvan University, Department of Management, Biratnagar, Nepal
Pulmonary Hypertension Association Nepal, Urlabari, Province No. 1, Nepal

Suman Karmacharya
Tamakoshi Hospital, Manthali, Nepal
Pulmonary Hypertension Association Nepal, Urlabari, Province No. 1, Nepal

Prasansha Thapa
Manmohan Cardiothoracic Vascular & Transplant Center, Kathmandu, Nepal
Pulmonary Hypertension Association Nepal, Urlabari, Province No. 1, Nepal

Anam Pyakurel
Civil Service Hospital, Kathmandu, Nepal
Pulmonary Hypertension Association Nepal, Urlabari, Province No. 1, Nepal

Sahadev Bidari
Green City Hospital, Kathmandu, Nepal
Pulmonary Hypertension Association Nepal, Urlabari, Province No. 1, Nepal

Lava R. Timsina, PhD
Indiana University, School of Medicine, Department of Surgery, Indianapolis, IN
Pulmonary Hypertension Association Nepal, Miami, Florida, USA

Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Pulmonary hypertension (PH), defined by mean pulmonary arterial pressure = 25 mm Hg at rest, that is related with congenital heart disease is usually known as congenital heart disease associated with pulmonary arterial hypertension (CHD-APAH). Undiagnosed congenital heart defects such as septal defect, subaortic stenosis, and mitral valve prolapse are rare. However, in a resource-limited rural setting with a lack of diagnostic awareness and services like echocardiograms or cardiac catheterization, they are likely to go unnoticed or be diagnosed late and with complications. Hence, we proposed implementing comprehensive cardiac screening camps in these settings to diagnose CHD-APAH, which would otherwise have gone unnoticed.
Methods: Pulmonary Hypertension Association Nepal, together with local health officials and cardiac specialists, implemented health screening camps at several elementary and middle schools in 4 rural villages in Nepal. We did comprehensive cardiac screening of 1383 children (mean age = 11 ± 3 years) by conducting interviews on cardiac-related clinical features and risk factors as well as doing 4–6-minute walk tests, detailed physical examinations of heart and lung conditions.
Results: Here, 21% of those evaluated had an abnormal heart sound. Thirty-two suspected cases were referred and evaluated in tertiary centers using echocardiogram and catheterization. Of these, 18 were suffering from mild to moderate CHD, and 8 were diagnosed to be suffering from CHD-APAH.
Conclusions: Comprehensive screening in a resource-limited setting via an outreach camp is a novel method to break the iceberg phenomenon in PH and may prevent PH-associated disability and early mortality.

EFFECT OF PEDIATRIC COVID-19 VACCINATION IMPLEMENTATION ON INFLUENZA VACCINATION RATES AMONG CHILDREN WITH PULMONARY HYPERTENSION

Nidhy Varghese
Department of Pediatrics, Pulmonology, Baylor College of Medicine. Texas Children's Hospital Pulmonary Hypertension Center, Houston, TX, USA

Fadel Ruiz
Department of Pediatrics, Pulmonology, Baylor College of Medicine. Texas Children's Hospital Pulmonary Hypertension Center, Houston, TX, USA

Raysa Morales
Department of Pediatrics, Critical Care Medicine, Baylor College of Medicine. Texas Children's Hospital Pulmonary Hypertension Center, Houston, TX, USA

Elise Whalen
Department of Pediatrics, Pulmonology, Baylor College of Medicine. Texas Children's Hospital Pulmonary Hypertension Center, Houston, TX, USA

Corey Chartan
Department of Pediatrics, Critical Care Medicine, Baylor College of Medicine. Texas Children's Hospital Pulmonary Hypertension Center, Houston, TX, USA

Ivan Markley
Information Services, Texas Children's Hospital, Houston, TX, USA

Category: Clinical Science
Selected Areas: Databases and Registries; Effect of COVID and Telemedicine on PH Management; Pediatrics

Background: Over the past several decades, caregivers have expressed increasing concern over the safety and efficacy of pediatric vaccinations. In 2021, the US Food and Drug Administration (FDA) authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine (CV) for the prevention of COVID-19 in children 5–18 years of age. However, the administration of the CV in the pediatric population triggered considerable controversy that exposed and created significant parental hesitation over vaccinations in general. Immunization reluctance was of particular concern in the pediatric pulmonary hypertension (PH) population due to high risk for negative sequelae from infections such as influenza. We hypothesized that caregiver concerns regarding CVs would decrease vaccination rates for influenza vaccine in the pediatric PH population.
Methods: This was a single-center, retrospective study of vaccination rates for COVID-19 and seasonal influenza in children with PH, ages 5–18 years. Vaccination rates were tracked from August 2021 to March 2022 (2021 flu season, during the pandemic; Figures 1 and 2) and compared with August 2019 to March 2021 (2019 flu season, prepandemic). Data were obtained from the hospital's electronic medical record, Epic (Wiscon-

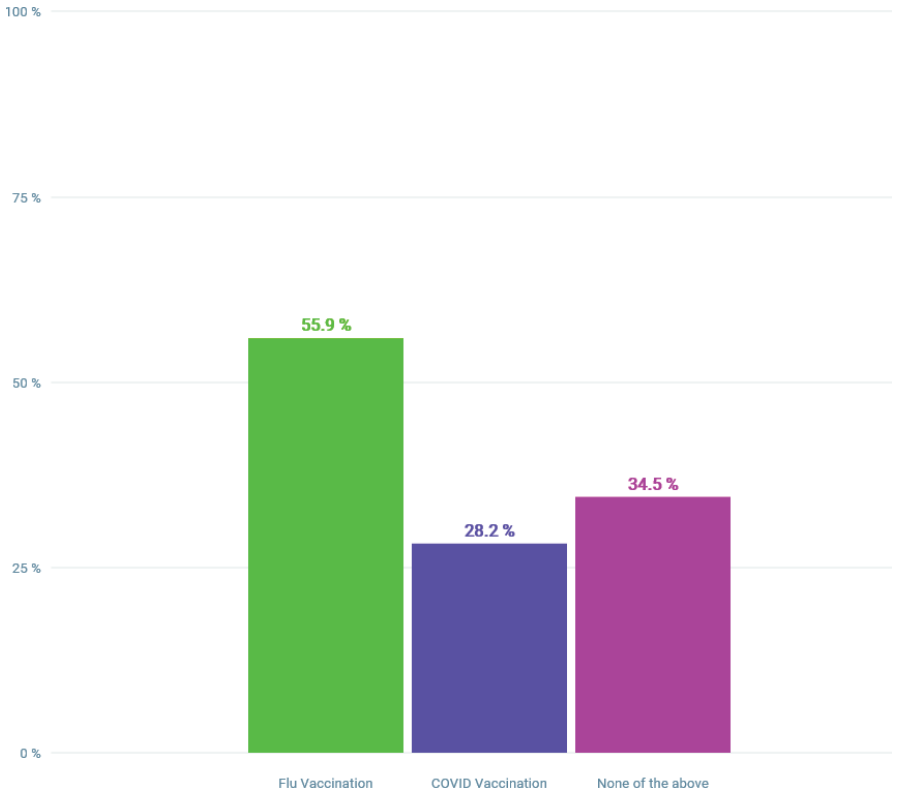


Figure 1: Percentage of population by immunizations (between August 1, 2021, and March 1, 2022).

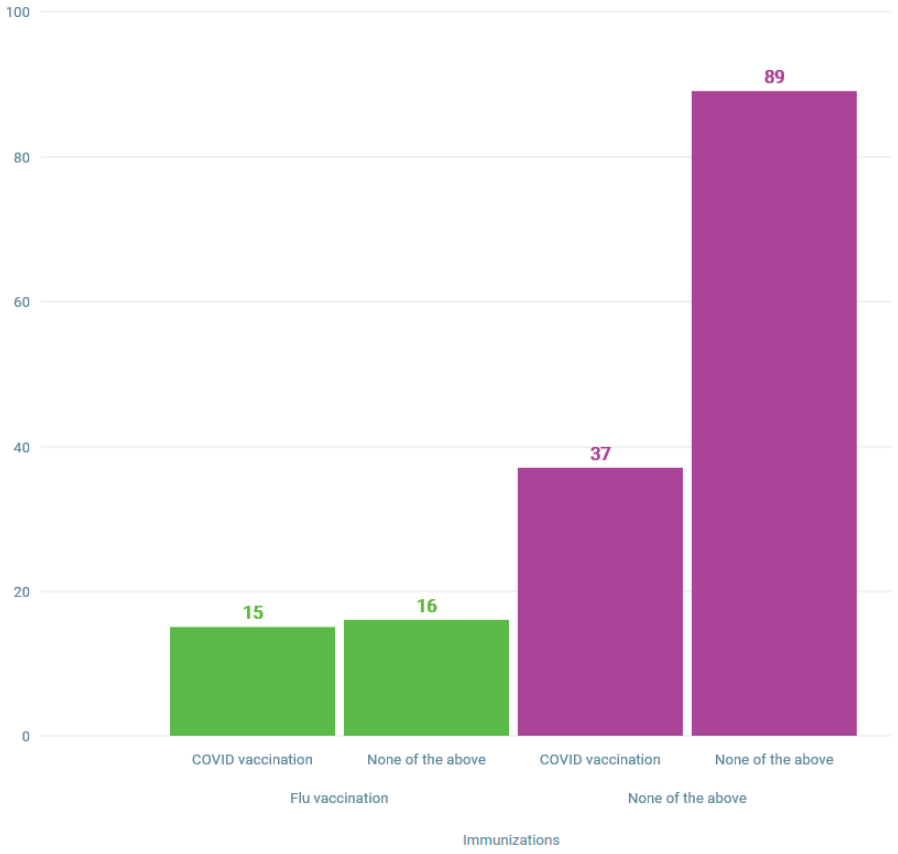


Figure 2: Number of patients by immunizations and immunization types (between August 1, 2021, and March 1, 2022).

sin, May 2021). Institutional review board approval was obtained.

Results: During the study period, 295 children actively received care at our PH Center. One hundred fifty-seven patients were between the ages of 5 and 18 year. During the 2021 influenza season, 31 children received the flu vaccine (20%), 37 children received the CV (24%), and 15 children received both flu vaccine and CV (10%). In comparison, during the 2019 influenza season, 37 children received the flu vaccine (24%; Figure 3). Community burden of influenza infection in the 5–18-year-old age group during these periods was 3% in the 2019 season and <1% in the 2021 season.

Conclusions: In this single-center study, rates of influenza vaccination did not vary greatly between prepandemic and pandemic periods. Controversies around CV for children did not seem to affect rates of influenza vaccination among our patients. Overall, the influenza vaccination rates in our pediatric PH population were low, suggesting opportunity for a dedicated quality improvement project to address vaccination rates in our clinic.

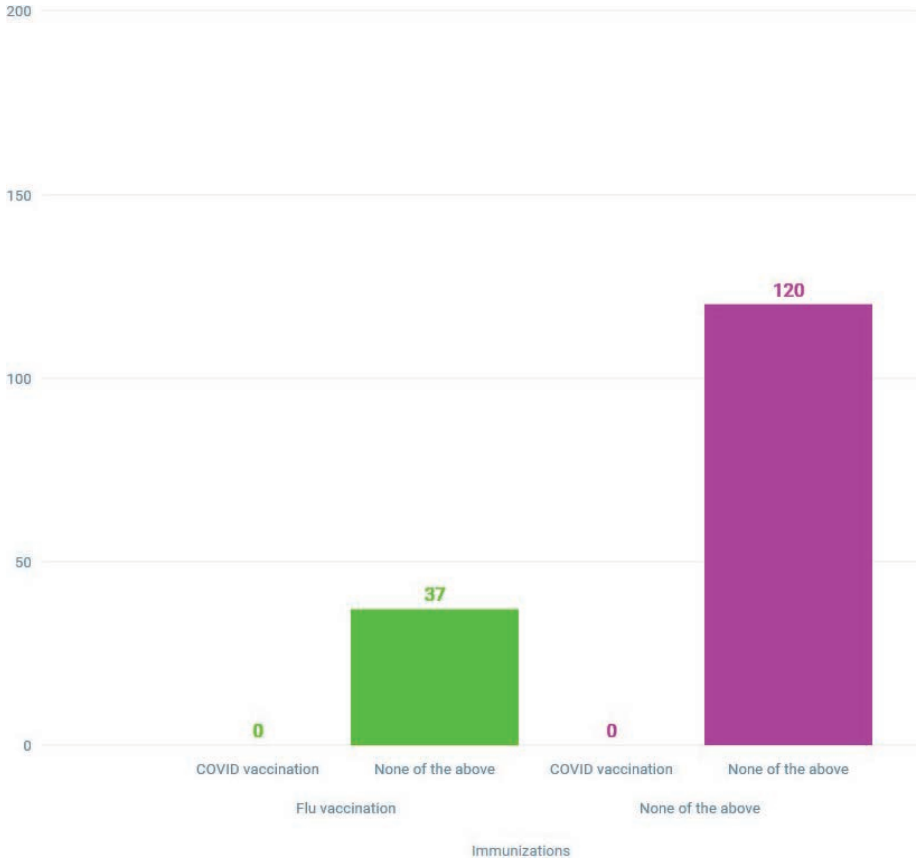


Figure 3: Number of patients by immunizations and immunization types (between August 1, 2019, and March 1, 2020).

REGULAR ARTICLE

The Future of PAH Treatment

Jennifer L. Keen, MD
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA

Nadine Al-Naamani, MD, MS
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA

Corey E. Ventetuolo, MD, MS
Division of Pulmonary, Critical Care & Sleep Medicine
Brown University
Providence, RI

Pulmonary arterial hypertension (PAH) is a devastating disease mediated by vasoconstriction and vascular remodeling of the pulmonary vasculature. Current therapies target the imbalance of vasoconstrictors and vasorelaxants in 3 pathways: nitric oxide, prostacyclin, and endothelin. While these have extended lifespans for PAH patients, significant morbidity and mortality remains. Notably, the progress in PAH therapy for over a decade has utilized these same 3 pathways. Fortunately, several new treatment options utilizing different mechanisms are emerging and will be reviewed here.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a result of complex pathologic processes culminating in a progressive, incurable disease characterized by elevated pulmonary vascular resistance and right ventricular (RV) dysfunction. Elevated pulmonary afterload derives from both increased vasoconstrictive tone and deranged vascular remodeling that has been likened to a pseudomalignant phenotype. Significant efforts have been made to understand the underlying pathophysiologic processes in the quest for treatment options. Currently approved therapies target 3 pathways—nitric oxide, prostacyclin, and endothelin—as patients with PAH have chronic upregulation of vasoconstrictors such as endothelin and chronic deficiency in vasodilators such as nitric oxide and prostacyclins. However, significant pulmonary vascular disease remains, reflected clinically with an improved but persistently high mortality, particularly in those with high-risk disease.[1] Fortunately, additional pathways involved in the disease have been elucidated and are now candidates for targeted intervention. Many emerging pharmaceuticals target pulmonary vascular fixed remodeling mediated by imbalanced pro-proliferative and antiapoptotic pathways (Figure 1). These potential treatments, together with current therapies, may provide synergistic effects to improve outcomes for our PAH patients. At the same time, ideally we will continue to advance our understanding of precision-based treatments in PAH and move toward the "right drug(s)" for

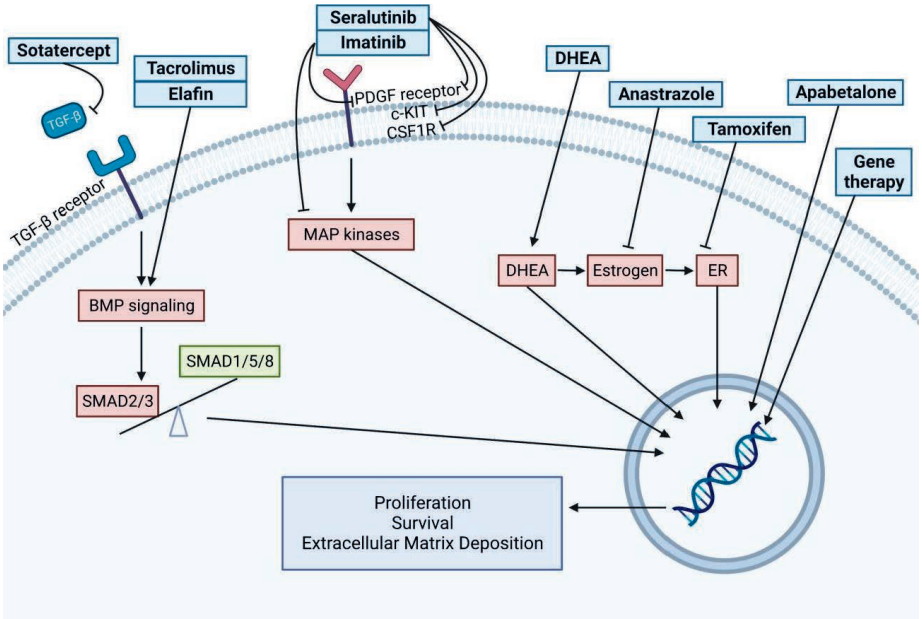


Figure 1: Mechanisms of action of emerging PAH therapies.

Key Words—pulmonary arterial hypertension, novel therapy, drug therapy, clinical trials, growth factors
Correspondence: jennifer.keen@pennmedicine.upenn.edu

Table 1. Summary of Selected New Potential Drugs in the Treatment of PAH

Drug	Mechanism	Trial	Phase	Primary Outcome	Status
Sotatercept	TGF-β ligand trap, BMP signal potentiation	STELLAR	Phase III	Change in 6MWD at 24 weeks	Completed
		SOTERIA	Phase III	Adverse events, detectable anti-drug antibodies, abnormal hematology or chemistry laboratory results, abnormal weight, abnormal blood pressure, ECG, abnormal urinalysis up to 200 weeks	Recruiting
		ZENITH	Phase III	Time to first confirmed morbidity or mortality up to 46 months	Recruiting
		HYPERION	Phase III	Time to clinical worsening	Recruiting
Elafin	Elastase inhibitor, BMP signaling potentiation	*Planned*			
Tacrolimus (FK506)	Calcineurin inhibitor, BMP signaling potentiation	*Planned*			
Imatinib	Tyrosine kinase inhibitor	PIPAH (NCT04416750)	Phase II	Change in PVR at 24 weeks	Recruiting
		IMPAHCT (NCT05036135)	Phase IIb/III	2b: Change in PVR at 24 weeks 3: Change in 6MWD at 24 weeks	Recruiting
Seralutinib (GB002)	Tyrosine kinase inhibitor BMP signaling potentiation	TORREY (NCT04456998)	Phase II	Change in PVR at 24 weeks	Completed
Apabetalone	BET protein inhibitor	APPROACH-2 (NCT04915300)	Phase II	Change in PVR at 24 weeks	Not yet recruiting
Tamoxifen	Estrogen receptor	T3PAH	Phase II	Change in TAPSE at 24 weeks	Recruiting
	inhibitor	(NCT03528902)			
Anastrazole	Aromatase inhibitor	PHANTOM (NCT03229499)	Phase II	Change in 6MWD at 6 months	Completed
DHEA	Steroid hormone precursor	EDIPHY (NCT03648385)	Phase II	Change in RV longitudinal strain on CMRI at 18, 40 weeks	Recruiting
Gene therapy		*Preclinical stage*			
eNOS enhanced progenitor cell transplant	eNOS enhancement	SAPPHIRE (NCT03001414)	Phase II/III	Change in 6MWD at 6 months	Recruiting
Microbiome transfer	Modulating systemic inflammation	NCT04884971	Phase I	Adverse effects and compliance	Recruiting

Abbreviations: TGF indicates transforming growth factor; BMP, bone morphogenetic protein; 6MWD, 6-minute walk distance; ECG, electrocardiogram; PVR, pulmonary vascular resistance; BET, bromodomain and extraterminal motif; TAPSE, tricuspid annular plane systolic excursion; DHEA, dehydroepiandrosterone, RV, right ventricle; CMRI, cardiac magnetic resonance imaging; eNOS, endothelial nitric oxide synthase.

the "right patients" to minimize costly and burdensome regimens and maximize outcomes and quality of life for our patients. It is equally important to validate surrogate endpoints that reflect patient-centered outcomes in PAH trials alongside the discovery of novel mechanistic targets. Readily available PAH risk scores have been suggested as surrogate outcomes in randomized controlled trials of PAH but further validation is required (data unpublished). Identification of alternative validated surrogates is warranted as the efficacy of these emerging potential therapeutics is studied. We will review some of the most promising novel pharmaceuticals currently on the horizon and in clinical trials (Table 1).

BONE MORPHOGENETIC PROTEIN SIGNALING MODULATORS

Disruptions in signaling of the transforming growth factor–β (TGF-β) superfamily contributes significantly to the dysregulated vascular proliferation of PAH. Germline mutations specifically in the TGF receptor of bone morphogenetic protein receptor type 2 (*BMPR2*) and its downstream signalers are the most common genetic cause of heritable PAH,[2] with BMPR2 itself playing a critical gatekeeping role.[3] Bone morphogenetic protein signaling and function is also decreased in nonheritable PAH.[4,5] Downstream of BMPR2, evidence

suggests an imbalance of SMAD signaling with underactive antiproliferative SMAD 1/5/8 signaling and overactive pro-proliferative SMAD 2/3.[6]

Sotatercept

The recombinant fusion protein sotatercept targets this deranged signaling by preferentially inhibiting the pro-proliferative SMAD2/3 pathway. Sotatercept has been previously studied in conditions characterized by TGF-β signaling dysregulation, including multiple myeloma and myelodysplastic syndrome.[7,8] The recent phase II PULSAR trial evaluated sotatercept's efficacy in PAH patients on stable background therapy, at doses of 0.3 mg/kg and 0.7 mg/kg for 24 weeks.[9] The least-squares mean difference of change in pulmonary vascular resistance (PVR) in the sotatercept 0.3-mg/kg group as compared with the placebo group was −145.8 dyn·sec·cm^{-5} (95% confidence interval [CI]: −241.0 to −50.6 dyn·sec·cm^{-5}, $P = .003$), while that for the sotatercept 0.7-mg/kg group compared with placebo group was −239.5 dyn·sec·cm^{-5} (95% CI: −329.3 to 149.7 dyn·sec·cm^{-5}; $P < .001$). Secondary endpoints included improved 6-minute walk distance (6MWD) with least-squares mean difference for the 0.3-mg/kg sotatercept participants compared to placebo participants of 29.4 m (95% CI: 3.8 to 55.0 m) and that of the 0.7-mg/kg group compared to placebo at 21.4 m (95% CI: −2.8 to 45.7 m). Additionally, N-terminal pro-B-type natriuretic peptide (NT-proBNP) decreased with least-squares mean difference between the sotatercept 0.3-mg/kg group and placebo group of −931.5 pg/mL (95% CI: −1353.2 to −509.7 pg/mL) and of the sotatercept 0.7-mg/kg group, −651.0 pg/mL (95% CI: −1043.3 to −258.7 pg/mL).

Multiple phase 3 trials of sotatercept in patients with PAH with varying disease duration and risk profiles are currently ongoing. Early results from STELLAR, a randomized, multi-center study of sotatercept in patients with PAH with World Health Organization (WHO) functional class (FC) II or III on background PAH therapies, were recently reported as meeting the study's primary endpoint of improvement in 6MWD, along with 8 of 9 secondary endpoints including time to clinical worsening, a multicomponent improvement from baseline, maintenance or improvement in WHO FC, change from baseline PVR, change from baseline in NT-proBNP, maintenance or improvement to low risk score, change from baseline in physical impacts, and change from baseline cardiopulmonary symptoms.[10,11] Additional active phase III trials of sotatercept include SOTERIA (NCT04796337),[12] evaluating long-term efficacy and safety; ZENITH (NCT04896008),[13] investigating efficacy in advanced WHO FC III or IV patients on maximally tolerated background therapy; and HYPERION (NCT04896008)[14], studying the drug's efficacy in incident PAH patients.

Elafin

Increased elastase activity has been demonstrated in the pulmonary arteries of experimental PAH models with degradation of elastin, a structural protein that contributes to pulmonary vascular integrity and elastance. Elastin degradation is associated with pulmonary artery smooth muscle cell (PASMC) proliferation.[15] Elafin is a naturally occurring elastase inhibitor with additional antimicrobial and anti-inflammatory properties. Treating pulmonary artery endothelial cells from PAH patients with elafin led to an increase in BMP signaling and a reduction in neointimal formation in cultured pulmonary artery endothelial cells.[16] In the Sugen-hypoxia rat model of PAH, elafin reversed pulmonary vascular occlusive changes and normalized RV pressure.[16,17] These data suggest that elafin may augment BMPR2 signaling in PAH as well as increase expression of apelin, a target of BMPR2 signaling. A small phase I trial (NCT03522935) in healthy patients treated with elafin is complete with plans for a phase 2 proof-of-concept study[18].

Tacrolimus

Tacrolimus, a calcineurin inhibitor used routinely for immunosuppression in transplant patients, also activates BMPR2 signaling.[19] In animal models, low-dose tacrolimus increased BMPR2 signaling in pulmonary artery endothelial cells and reversed pulmonary vascular remodeling in a murine BMPR2 knockout.[19] A small phase 2a trial of tacrolimus at 3 different target levels in PAH patients on background therapy showed no improvement in 6MWD or RV function, but may be efficacious in select patients.[20] Nonetheless, a larger phase II study is being planned to determine the efficacy of tacrolimus more definitively in PAH.

TYROSINE KINASE PATHWAY

Aberrant proliferation of pulmonary vascular smooth muscle cells has been in part attributed to growth factors such as platelet-derived growth factor (PDGF), a potent PASMC mitogen[21] that is increased in PAH patients.[22] PDGF receptors (PDGFRs) belong to a family of tyrosine kinase receptors, and preclinical data have demonstrated that tyrosine kinase inhibitors both attenuate pulmonary vascular remodeling through PDGFR inhibition but also directly relax the pulmonary vasculature.[23] As such, several tyrosine kinase inhibitors are now under clinical investigation for PAH.

Imatinib

Imatinib, a Bcr-Abl inhibitor originally developed to treat chronic myeloid leukemia, also inhibits PDGF. Imatinib potently inhibited PDGF-dependent PASMC proliferation, with near full reversal of pulmonary hypertension in the monocrotaline and hypoxic rat model.[24] Further in vitro data demonstrated that imatinib exerted proapoptotic effects in PDGF-stimulated PASMCs from idiopathic PAH patients.[25] A phase II study of imatinib versus placebo found improvements in PVR and cardiac output specifically in patients with more significant hemodynamic impairment (PVR ≥ 1000 dyn·sec·cm^{-5}), suggesting a role as add-on therapy for a subset of advanced PAH patients.[26] The compelling preclinical data and phase II trial ultimately led to evaluation of imatinib in the IMPRES trial, which enrolled subjects on at least dual background PAH therapies. At 24 weeks, the mean placebo-corrected treatment effect on 6MWD was 32 m (95% CI: 12 to 52 m; $P = .002$) and PVR decreased by 379

dyn·sec·cm^{-5} (95% CI: −502 to −255 dyn·sec·cm^{-5}; P < .001, between-group difference); however, WHO FC, time to clinical worsening, and mortality did not differ between the groups.[27] Serious adverse effects were noted in the imatinib group compared to placebo (44% versus 30%), particularly subdural hematomas, which in addition to significant dropout due to intolerances tempered enthusiasm for imatinib. At present, the ongoing phase II PIPAH trial (NCT04416750)[28] aims to identify the highest tolerated dose of oral imatinib, assess efficacy as measured by PVR reduction, and identify the patients most likely to respond via analyses of plasma proteins and genes, particularly those encoding PDGF. A phase III study of an additional oral formulation of imatinib with enteric coating meant to mitigate gastrointestinal side effects is also planned.[29] Concurrently, IMPAHCT (NCT05036135) is a phase IIb/III trial of dry powder inhaled form of imatinib, which will identify the optimal dose and examine effects of inhaled imatinib on 6MWD and PVR at 24 weeks.[30]

Seralutinib

Seralutinib, which was specifically developed to target several tyrosine kinase inhibitors implicated in PAH pathogenesis including PDGFRα/β, colony stimulating factor 1 receptor, and c-KIT while also increasing BMPR2, has reversed pulmonary vascular remodeling and improved hemodynamics in 2 preclinical pulmonary hypertension models.[31] The phase II TORREY trial of seralutinib delivered by dry powder inhaler was recently completed with early reports of modest improvements in the primary endpoint of PVR at 24 weeks (14.3% placebo-corrected improvement; P = .03) with the secondary endpoint of 6MWD favoring seralutinib as well.[32,33] Findings were more striking in subgroup analyses of more symptomatic WHO FC III patients for the seralutinib arm versus placebo (21% reduction in PVR, P = .04; 37-m improvement in 6MWD, P = .048), and in patients with intermediate- or high-risk REVEAL 2.0 scores (23% reduction in PVR, P = .01; 22-m increase in 6MWD, P = .25) for the seralutinib arm versus placebo.

BROMODOMAIN PROTEINS

Bromodomains (BRDs) are epigenetic drivers of the BRD and extraterminal motif protein family that regulate gene transcription. BRD and extraterminal motif inhibitors may also exert favorable effects on the myocardium and decreased hospitalizations in patients with left heart disease following acute coronary syndrome.[34] BRD4 specifically can inhibit apoptosis, promote hyperproliferation, and stimulate a switch into a proinflammatory phenotype and as such has been implicated in cancer.[35-37] BRD inhibitors have thus been identified as treatment options for cancers.[38] Given the cancer-like proliferation of PASMCs in PAH, it is not surprising that BRD4 has also been identified as a contributor to the proliferation in PAH, with significant upregulation detected in human pulmonary artery tissue.[35]. Accordingly, inhibition of BRD4 reverses pulmonary vascular remodeling and improves hemodynamics in preclinical pulmonary hypertension models.[35] Similar findings were observed in the Phase I APPROACH-p trial of the BRD4 inhibitor apabetalone, with decreased PVR (−140 dyn·s·cm^{-5}; 95% CI: −200 to −79 dyn·sec·cm^{-5}) noted in 7 PAH patients treated for 16 weeks.[39] Improvements in cardiac output (+0.73 L/min; 95% CI: −0.22 to +1.68 L/min) and stroke volume (+8 mL; 95% CI: −4 to +20 mL) were also noted with apabetalone. The larger phase II APPROACH-2 trial (NCT04915300) will confirm or refute these findings.[40]

SEX HORMONES

Estrogen

Despite early identification of female sex as a major risk factor for PAH[41,42] and subsequent intense investigation into sex hormones and their contribution to PAH pathobiology, the exact role of estrogen remains incompletely defined as reviewed more thoroughly in other works.[43–46] Briefly, it is clear that despite female predominance, once PAH is established estrogen provides protective effects on RV function,[47,48] allowing female patients better prognoses.[33,34,41,42,47,49] However, the role of estrogen signaling and metabolism in the pulmonary vasculature itself is complex. Beneficial effects including vasodilation and angiogenesis are noted in some animal studies,[50,51] but other studies report that estrogen promoted destructive vascular remodeling.[52,53] Clinical evidence supports a deleterious relationship with higher circulating estrogen noted in PAH patients, including men.[54] Furthermore, in animal models of PAH, inhibiting estrogen receptors with tamoxifen or inhibiting conversion of androgens to estrogen with anastrazole reversed PAH[55,56] A small phase II clinical trial showed that anastrazole decreased circulating estrogen by 40% and increased 6MWD.[57] This launched the PHANTOM trial (NCT03229499) now underway examining the effects of anastrazole in postmenopausal women and men with PAH.[58] Whether inhibition of estrogen receptors with tamoxifen may benefit PAH patients is also being evaluated with the single-center Phase II T3PAH trial (NCT03528902).[59]

Dehydroepiandrosterone

The precursor to both estrogen and androgens, dehydroepiandrosterone (DHEA) prevented and treated PAH and RV dysfunction in animal models.[60] Clinically, lower DHEA is associated with higher risk of PAH in men[46] and increased risk and severity in women.[61] The consistent data suggesting benefit of DHEA in PAH may be explained by DHEA-mediated enhanced endothelial nitric oxide synthesis or through direct cardioprotective effects. The single-center crossover trial EDIPHY (NCT03648385) is currently testing DHEA efficacy in PAH patients by measuring RV longitudinal strain.[62]

EXPLORATORY THERAPIES

Beyond typical pharmacologic options, other novel approaches are currently under investigation for this complex and morbid disease. As specific gene mutations are implicated in heritable PAH and account for 6% to 10% of all PAH, gene therapy provides an attractive approach to directly correct aberrant genes and restore balance between proliferation and apoptosis. Preclinical pulmonary hypertension models have proven amenable with improvements in

pulmonary vascular remodeling via viral transfection endotracheally and intravenously.[63–65] Work in experimental models is ongoing to determine ideal and effective gene therapy delivery methods.

Stem or progenitor cell therapy may offer similar direct restoration of pulmonary vasculature homeostasis. With the abnormal endothelial dysfunction and hyperproliferation of PASMCs, regenerative cell treatment could interfere and restore vasculature architecture. Endothelial progenitor cells (EPCs) appear protective in PH animal models, including specifically with BMPR2-augmented EPCs, which improved mean pulmonary artery pressures and RV hypertrophy in monocrotaline-induced models.[66] Small pilot randomized controlled trials have demonstrated safety and efficacy of stem cell therapy in humans and a 2019 meta-analysis of 16 small clinical trials with stem cell therapy in PAH patients revealed that despite heterogeneity in findings, weighted-means differences indicated improvements in RV systolic pressure, mean pulmonary artery pressure, and mean RV pressure with P values all $< .001$ in patients treated with stem cells.[67] The PHACeT study in 2015 reported that when treated with 3 doses of enhanced endothelial nitric oxide synthase EPCs, PAH patient demonstrated improved hemodynamics in the short term with good tolerance; however, findings were not sustained at 3 and 6 months,[68] despite prior EPC data showing sustained hemodynamic and exertional effects at 3 months.[69] A recent landmark report described the use of human umbilical cord mesenchymal stems cells to treat a child with heritable PAH and hereditary hemorrhagic telangiectasia which improved clinical parameters at 6 months.[70] Currently the phase II SAPPHIRE study (NCT03001414) is recruiting and aims to assess safety and efficacy of monthly administration of autologous EPCs transfected with human endothelial nitric oxide synthase in severe PAH patients.[71]

Finally, investigation into the microbiome may elucidate novel mechanisms and therapeutic targets in PAH. Compared to controls, PAH patient microbiomes demonstrated decreased alpha diversity with distinct signatures even from unaffected family members, and enrichment of bacteria associated with the proinflammatory metabolite trimethylamine oxide.[72,73] Species associated with trimethylamine oxide were increased as was serum trimethylamine oxide in high-risk PAH patients, whereas species associated with anti-inflammatory metabolites were reduced. Guided by this data, a Phase I trial (NCT04884971) is currently evaluating the safety of microbiome transplant in PAH patients.[74]

CONCLUSION

Despite significant progress in PAH therapeutics over the last 2 decades, innovative treatments are needed to ameliorate morbidity and mortality in this progressive deadly disease. Beyond our current arsenal of treatments, BMP signaling, tyrosine kinase signaling, BRD proteins, sex hormones, and other more novel approaches such as gene therapy targeting pulmonary vascular remodeling are in varied stages of development. With continued scientific rigor used to explore new signaling pathways and mechanisms, we are one step closer to halting, if not reversing, this devastating disease.

References

1. Chang KY, Duval S, Badesch DB, et al. Mortality in pulmonary arterial hypertension in the modern era: early insights from the Pulmonary Hypertension Association Registry. *J Am Heart Assoc*. 2022;11(9):e024969. doi:10.1161/JAHA.121.024969
2. Deng Z, Morse JH, S.L. C, et al. Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. *Am J Hum Genet*. 2000;67(3):737-744. doi:10.1086/303059
3. Hiepen C, Jatzlau J, Hildebrandt S, et al. BMPR2 acts as a gatekeeper to protect endothelial cells from increased TGFβ responses and altered cell mechanics. *PLoS Biol*. 2019;17(12):e3000557. doi:10.1371/journal.pbio.3000557
4. Dewachter L, Adnot S, Guignabert C, et al. Bone morphogenetic protein signalling in heritable versus idiopathic pulmonary hypertension. *Eur Respir J*. 2009;34(5):1100-1110. doi:10.1183/09031936.00183008
5. Atkinson C, Stewart S, Upton PD, et al. Primary pulmonary hypertension is associated with reduced pulmonary vascular expression of type II bone morphogenetic protein receptor. *Circulation*. 2002;105(14):1672-1678. doi:10.1161/01.cir.0000012754.72951.3d
6. Sanada TJ, Sun X, Happe C, et al. Altered TGFβ/SMAD signaling in human and rat models of pulmonary hypertension: an old target needs attention. *Cells*. 2021;10(1) :84. doi:10.3390/cells10010084
7. Abdulkadryov KM, Salogub GN, Khuazheva NK, et al. Sotatercept in patients with osteolytic lesions of multiple myeloma. *Br J Haematol*. 2014;165(8):814-823. doi:10.1111/bjh.12835
8. Komrokji R, Garcia-Manero G, Ades L, et al. Sotatercept with long-term extension for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes: a phase 2, dose-ranging trial. *Lancet Haematol*. 2016;5(2):e63-e72. doi:10.1016/S2352-3026(18)30002-4
9. Humbert M, McLaughlin V, Gibbs JSR, et al. Sotatercept for the treatment of pulmonary arterial hypertension. research-article. *New Eng J Med*.2021;385:1204-1215. doi:10.1056/NEJMoa2024277
10. A Study of Sotatercept for the Treatment of Pulmonary Arterial Hypertension (MK-7962-003/A011-11)(STELLAR): NCT04576988. Updated January 26, 2023. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT04576988.
11. Merck. Merck announces positive top-line results from pivotal phase 3 STELLAR trial evaluating sotatercept for the treatment of adults with pulmonary arterial hypertension (PAH). https://www.merck.com/news/merck-announces-positive-top-line-results-from-pivotal-phase-3-stellar-trial-evaluating-sotatercept-for-the-treatment-of-adults-with-pulmonary-arterial-hypertension-pah/. Accessed January 6, 2023.
12. A Long-term Follow-up Study of Sotatercept for PAH Treatmnet (MK-7962-004) (SOTERIA): NCT04796337. Updated February 10, 2023. Accessed March 8. 2023. https://clinicaltrials.gov/ct2/show/NCT04796337.
13. A Study of Sotatercept in Participants With PAH WHO FC III or FC IV at High Risk of Mortality (MK-7962-006/ZENITH) (ZENITH): NCT04896008. Updated March 7, 2023. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT04896008.
14. Study of Sotatercept in Newly Diagnosed Intermediate- and High-Risk PAH Participants: NCT04811092. Updated March 7, 2023. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT04811092
15. Thompson K, Rabinovitvh M. Exogenous leukocyte and endogenous elastases can mediate mitogenic activity in pulmonary artery smooth muscle cells by release of extracellular-matric bound basic fibroblast growth factor. *J Cell Physiol*. 1996;166(3):495-505. doi:10.1002/

(SICI)1097-4652(199603)166:3<495::AID-JCP4>3.0.CO;2-K.
16. Nickel NP, Spiekerkoetter E, Gu M, et al. Elafin reverses pulmonary hypertension via caveolin-1-dependent bone morphogenic protein signaling. *Am J Respir Crit Care Med*. 2015;191(11):1273-1286. doi:10.1164/rccm.201412-2291OC
17. Zaidi SHE, You X, Ciura S, Husain M, Rabinovitch M. Overexpression of the serine elastase inhibitor elafin protects transgenic mice from hypoxic pulmonary hypertension. *Circulation*. 2002;105(4):516-521. doi:10.1161/hc0402.102866
18. Subcutaneous Elafin in Healthy Subjects: NCT03522935. Updated April 28, 2021. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT03522935
19. Spiekerkoetter E, Tian X, Cai J, et al. FK506 activates BMPR2, rescues endothelial dysfunction, and reverses pulmonary hypertension. *J Clin Invest*. 2013;123(8):3600-3613. doi:10.1172/JCI65592
20. Spiekerkoetter E, Sung YK, Sudheendra D, et al. Randomized placebo-controlled safety and tolerability trial of FK506 (tacrolimus) for pulmonary arterial hypertension. *Eur Respir J*. 2017;50(3):1602449. doi:10.1183/13993003.02449-2016
21. Perros F, Montani D, Dorfmuller P, et al. Platelet-derived growth factor expression and function in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2008;178(1):81-88. doi:10.1164/rccm.200707-1037OC
22. Yu Y, Sweeney M, Zhang S, et al. DGF stimulates pulmonary vascular smooth muscle cell proliferation by upregulating TRPC6 expression. *Am J Physiol Cell Physiol*. 2003;284(2):C316-30. doi:10.1152/ajpcell.00125.2002
23. Rieg AD, Bünting NA, Cranen C, et al. Tyrosine kinase inhibitors relax pulmonary arteries in human and murine precision-cut lung slices. *Respir Res*. 2019;20(1):1-14. doi:10.1186/s12931-019-1074-2
24. Schermuly RT, Dony E, Ghofrani HA, et al. Reversal of experimental pulmonary hypertension by PDGF inhibition. *J Clin Invest*. 2005;115(10):2811-2821. doi:10.1172/JCI24838
25. Nakamura K, Akagi S, Ogawa A, et al. Pro-apoptotic effects of imatinib on PDGF-stimulated pulmonary artery smooth muscle cells from patients with idiopathic pulmonary arterial hypertension. *Int J Cardiol*. 2012;159(2):100-106. doi:10.1016/j.ijcard.2011.02.024
26. Ghofrani H, Morrell N, Hoeper M, et al. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. *AmJ Respir Crit Care Med*. 2010;182(9):1171-1177. doi:10.1164/rccm.201001-0123OC
27. Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension. research-article. *Circulation*. 2013;127(10):1128-38. doi:10.1161/CIRCULATIONAHA.112.000765
28. Positioning Imatinib for Pulmonary Arterial Hypertension (PIPAH): NCT04416750. Updated March 1, 2023. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT04416750
29. Tenax Therapeutics. Clinical Development—The impres trial of imatinib as a treatment of PAH. https://tenaxthera.com/products/imatinib/clinical-development/. Accessed January 15, 2023.
30. A Study of AV-101 (Dry Powder Inhaled Imatinib) in Patients With Pulmonary Arterial Hypertension (PAH) (IMPAHCT). Updated February 17. 2023. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT05036135.
31. Galkin A, Sitapara R, Clemons B, et al. Inhaled seralutinib exhibits potent efficacy in models of pulmonary arterial hypertension. *Eur Respir J*. 2022;60(6):2102356. doi:10.1183/13993003.02356-2021
32. GB002 in Adult Subjects with Pulmonary Arterial Hypertension: NCT04456998. Updated February 9, 2023. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT04456998.
33. Businesswire. Gossamer Bio Announces seralutinib meets primary endpoint in phase 2 TORREY study in PAH. /. Accessed January 3, 2023.
34. Nicholls SJ, Schwartz GG, Bur KA, et al. Apabetalone and hospitalizations for heart failure in patients following an acute coronary syndrome: a prespecified analysis of the BETonMACE study. *Cardiovasc Diabetol*. 2021;20(1):13. doi:10.1186/s12933-020-01199-x
35. Meloche J, Potus F, Vaillancourt M, et al. Bromodomain-containing protein 4. *Circulation Research*. 2015;117(6):525-535. doi:10.1161/CIRCRESAHA.115.307004
36. Zhang J, Dulak AM, Hattersley MM, et al. BRD4 facilitates replication stress-induced DNA damage response. *Oncogene*. 2019;37(28):3763-3777. doi:10.1038/s41388-018-0194-3
37. Tasdemir N, Banito A, Roe JS, et al. RD4 connects ENhancer remodeling to senescence immune surveillance. *Cancer Discov*. 2016;6(6):612-629. doi:10.1158/2159-8290.CD-16-0217
38. Shorstova T, Foulkes WD, Witcher M. Achieving clinical success with BET inhibitors as anti-cancer agents. *Br J Cancer*. 2021;124(9):1478-1490. doi:10.1038/s41416-021-01321-0
39. Provencher S, Potus F, Blais-Lecours P, et al. BET protein inhibition for pulmonary arterial hypertension: a pilot clinical trial. *J Respir Crit Care Med*. 2022;205(11):1357-1360. doi:10.1164/rccm.202109-2182LE
40. Apabetalone for Pulmonary Arterial Hypertension (APPROACH-2): NCT04915300. Updated April 25, 2022. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT04915300
41. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation*. 2010;122(2):64-172. doi:10.1161/CIRCULATIONAHA.109.898122
42. Hoeper MM, Huscher D, Ghofrani HA, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol*. 2013;168(2):871-880. doi:10.1016/j.ijcard.2012.10.026
43. Hester J, Ventetuolo C, Lahm T. Sex, gender, and sex hormones in pulmonary hypertension and right ventricular failure. *Compr Physiol*. 2019;10(1):125-170. doi:10.1002/cphy.c190011
44. Volkmann ER, Siegfried J, Lahm T, et al. Impact of sex and gender on autoimmune lung disease: opportunities for future research: NHLBI working group report. *Am J Respir Crit Crae Med*. 2022;206(7):817-823. doi:10.1164/rccm.202112-2746PP
45. Ventetuolo CE, Ouyang P, Bluemke DA, et al. Sex hormones are associated with right ventricular structure and function: the MESA right ventricle study. *Am J Respir Crit Care Med*. 2011;183(5):659-667. doi:10.1164/rccm.201007-1027OC
46. Baird GL, Walsh T, Aliotta J, et al. Insights from the menstrual cycle in pulmonary arterial hypertension. *Ann Am Thorac Soc*. 2021;18(2):218-228. doi:10.1513/AnnalsATS.202006-671OC
47. Kawut SM, Al-Naamani N, Agerstrand C, et al. Determinants of right ventricular ejection fraction in pulmonary arterial hypertension. *Chest*. 2009;135(3):752-759. doi:10.1378/chest.08-1758
48. Ventetuolo CE, Praestgaard A, Palvesky HI, Klinger JR, Halpern SD, Kawut SM. Sex and haemodynamics in pulmonary arterial hypertension. *Eur Respir J*. 2014;43(2):523-530. doi:10.1183/09031936.00027613
49. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation*. 2010;122(2):156-163.
50. Umar S, Iorga A, Matori H, et al. Estrogen rescues preexisting severe pulmonary hypertension in rats. *Am J Respir Crit Care Med*. 2011;184(6):712-723. doi:10.1164/rccm.201101-0078OC
51. Chen Z, Yuhanna IS, Galcheva-Gargova Z, Karas RH, Mendelsohn ME, Shaul PW. Estrogen receptor alpha mediates the nongenomic activation of endothelial nitric oxide synthase by estrogen. *J Clin Invest*. 1999;103(3):401-406. doi:10.1172/JCI5347
52. White K, Dempsie Y, Nilsen M, Wright AF, Loughlin L, MacLean MR. The serotonin transporter, gender, and 17β oestradiol

in the development of pulmonary arterial hypertension. *Cardiovasc Res*. 2011;90(2):373-382. doi:10.1093/cvr/cvq408
53. Dempsie Y, Nilsen M, White K, et al. Development of pulmonary arterial hypertension in mice over-expressing S100A4/Mts1 is specific to females. *Respir Res*. 2011;12(1):159. doi:10.1186/1465-9921-12-159
54. Ventetuolo CE, Baird GL, Barr RG, et al. Higher estradiol and lower dehydroepiandrosterone-sulfate levels are associated with pulmonary arterial hypertension in men. *Am J Respir Crit Care Med*. 2016;193(10):168-175. doi:10.1164/rccm.201509-1785OC
55. Chen X, Austin ED, Talati M, et al. Oestrogen inhibition reverses pulmonary arterial hypertension and associated metabolic defects. *Eur Respir J*. 2017;50(2):1602337. doi:10.1183/13993003.02337-2016
56. Mair KM, Wright AF, Duggan N, et al. Sex-dependent influence of endogenous estrogen in pulmonary hypertension. *Am J Respir Crit Care Med*. 2014;190(4):456-467. doi:10.1164/rccm.201403-0483OC
57. Kawut SM, Archer-Chicko CL, DeMichele A, et al. Anastrozole in pulmonary arterial hypertension. A randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med*. 2017;195(3):360-368. doi:10.1164/rccm.201605-1024OC
58. Pulmonary Hypertension and Anastrozole Trial (PHANTOM): NCT03229499. Updated October 21, 2022. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT03229499.
59. Tamoxifen Therapy to Treat Pulmonary Arterial Hypertensin (T3PAH): NCT03528902. Updated August 23, 2022. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT03528902.
60. Lahm, Tuder RM, Petrache I. Progress in solving the sex hormone paradox in pulmonary hypertension. *AmJ Physiol Lung Cell Mol Physiol*. 2014;307(1):L7-26. doi:10.1152/ajplung.00337.2013
61. Baird GL, Archer-Chicko C, Barr RG, et al. Lower DHEA-S levels predict disease and worse outcomes in post-menopausal women with idiopathic, connective tissue disease- and congenital heart disease-associated pulmonary arterial hypertension. *Eur Respir J*. 2018;51(6):1800467. doi:10.1183/13993003.00467-2018
62. Effects of DHEA in Pulmonary Hypertension: NCT03648385. Updated February 21, 2023. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT03648385.
63. Ozaki M, Kawashima S, Yamashita T, et al. Reduced hypoxic pulmonary vascular remodeling by nitric oxide from the endothelium. *Hypertension*. 2001;37(2):322-327. doi:10.1161/01.hyp.37.2.322
64. Champion HC, Bivalacqua TJ, Greenberg SS, Giles TD, Hyman AL, Kadowitz PJ. Adenoviral gene transfer of endothelial nitric-oxide synthase (eNOS) partially restores normal pulmonary arterial pressure in eNOS-deficient mice. *Proc Natl Acad Sci USA*. 2002;99(20):13248-13253. doi:10.1073/pnas.182225899
65. Song YK, Liu F, Liu D. Enhanced gene expression in mouse lung by prolonging the retention time of intravenously injected plasmid DNA. *Gene Ther*. 1998;5(11):1531-1537. doi:10.1038/sj.gt.3300770
66. Harper RL, Maiolo S, Ward RJ, et al. BMPR2-expressing bone marrow-derived endothelial-like progenitor cells alleviate pulmonary arterial hypertension in vivo. *Respirology*. 2019;24(11):1095-1103. doi:10.1111/resp.13552
67. Ding XF, Liang HY, Yuan B, et al. Efficacy of stem cell therapy for pulmonary arterial hypertension: a systematic review and meta-analysis of preclinical studies. *Stem Cell Res Ther*. 2019;10(1):55. doi:10.1186/s13287-019-1162-8
68. Granton J, Langleben D, Kutryk MB, et al. Endothelial NO-synthase gene-enhanced progenitor cell therapy for pulmonary arterial hypertension: the PHACeT trial. *Circ Res*. 2015;117(7):645-654. doi:10.1161/CIRCRESAHA.114.305951
69. Wang XX, Zhang FR, Shang YP, et al. Transplantation of autologous endothelial progenitor cells may be beneficial in patients with idiopathic pulmonary arterial hypertension: a pilot randomized controlled trial. *J Am Coll Cardiol*. 2007;49(14):1566-1571. doi:10.1016/j.jacc.2006.12.037
70. Hansmann G, Chouvarine P, Diekmann F, et al. Human umbilical cord mesenchymal stem cell-derived treatment of severe pulmonary arterial hypertension. *Nat Cardiovasc Res*. 2022;1:568-576. doi:10.1038/s44161-022-00083-z
71. Study of Angiogenic Cell Therapy for Progressive Pulmonary Hypertensin: Intervention With Repeat Dosing of eNOS-enhanced EPCs: NCT03001414. Updated January 11, 2023. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT03001414.
72. Kim S, Rigatto K, Gazzana MB, et al. Altered gut microbiome profile in patients with pulmonary arterial hypertension. *Hypertension*. 2020;75(4):1063-1071. doi:10.1161/HYPERTENSIONAHA.119.14294
73. Moutsoglou DM, Tateh J, Prisco SZ, et al. Pulmonary arterial hypertension patients have a proinflammatory gut microbiome and altered circulating microbial metabolites. *Am J Resp Crit Care Med*. 2022. doi:10.1164/rccm.202203-0490OC [online ahead of print].
74. Microbiota Transplant Therapy for Pulmonary Arterial Hypertension: Early Safety and Feasibility Study: NCT04884971. Updated January 10, 2023. Accessed March 8, 2023. https://clinicaltrials.gov/ct2/show/NCT04884971.

REGULAR ARTICLE

POINT: Is It Time to Lower the Cut-off for Increased Pulmonary Vascular Resistance? Yes

Georgios A. Triantafyllou, MD
Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

Bradley A. Maron, MD
Division of Cardiovascular Medicine
Brigham and Women's Hospital
Harvard Medical School and Departments of Cardiology and Pulmonary and Critical Care Medicine
VA Boston Healthcare System
Boston, MA

Background: For decades, pulmonary hypertension (PH) used to be defined by a mean pulmonary artery pressure (mPAP) ≥25 mm Hg; however, this criterion was not based on data that were systematically collected. With the availability of contemporary datasets however, it was evident that the upper limit of normal mPAP was ~20 mm Hg, which is also the level of mPAP above which adverse outcomes increase. In addition, it is now evident that the specificity of mPAP >20 mm Hg to denote precapillary pulmonary vascular disease could be enhanced by adding pulmonary vascular resistance (PVR) to the precapillary PH definition. Finally, after characterizing large groups of normal individuals, akin to observations for mPAP, it was recently demonstrated that a PVR of ~2.0 Wood units (WU) is the upper limit of normal, and the lower level associated with all-cause mortality in at-risk patients.
Clinical Implications: The current hemodynamic criteria for PH are positioned to capture more patients compared to the classical definition, with particular implications for earlier diagnosis. Importantly, pulmonary vasodilator therapies have not been tested adequately in patients with mPAP <25 mm Hg or PVR between 2 to 3 WU and, thus, should not be administered in these patients. Mild PH is an active focus of clinical trial design; at present, these patients should be referred to expert PH centers earlier for individualized therapeutic planning.
Conclusions: The revised definition of precapillary PH uses a PVR threshold of >2 WU. This value is evidence-based, and exceeding this threshold is associated with adverse clinical outcomes. This revision places focus on early diagnosis, close monitoring, and consideration for certain treatments. Further studies are needed that test the efficacy and safety of pulmonary arterial hypertension-specific therapy in precapillary PH patients with PVR 2 to 3 WU.

INTRODUCTION: SETTING THE STAGE FOR DEFINING PRECAPILLARY PH USING PULMONARY VASCULAR RESISTANCE 2.0 WU

In 1973, a small group of clinicians relied on personal experience and consensus opinion to determine that mean pulmonary artery pressure (mPAP) >25 mm Hg alone should be used to diagnose pulmonary hypertension (PH). This determination was made without 2 pieces of information that are crucial for defining diseases characterized by a continuous variable: normative values and data associated with clinical events.[1-4] Despite this shortcoming, the definition of PH that was used in clinical practice remained unchanged for over 4 decades, which was due, in part, to the fact that virtually all patients in that era were initially diagnosed with advanced stage disease, often in the setting of a mPAP that was substantially greater than 25 mm Hg.

Then, Kovacs and colleagues reported on data from >1000 healthy individuals whose mean mPAP was 14±3.3 mm Hg. Thus, they determined that the upper limit of normal mPAP was 20 mm Hg, based on a conventional biostatical calculation that considers 2 standard deviations (SD) above the mean to be abnormal.[5] Supporting the 20 mm Hg upper limit are large cohort studies involving unselected referral populations, where a continuous relationship between mPAP and mortality was observed when the mPAP of approximately 20 mm Hg was exceeded.[6,7] The relationship between mPAP was affirmed for PH-relevant endpoints by studies focusing on well-phenotyped but smaller cohorts of patients with various cardiopulmonary diseases.[8,9] These observations led the scientific community to revise the mPAP threshold for diagnosing PH from ≥25 to >20 mm Hg in 2019.[10]

Generically, lowering the mPAP threshold from 25 to 20 mm Hg

Key Words—pulmonary vascular disease, pulmonary hypertension, pulmonary vascular resistance, PVR, guidelines
Correspondence: bmaron@bwh.harvard.edu
Disclosure: B.A.M.: Actelion Pharmaceuticals (Steering committee; outside the scope of the current work), Deerfield Company (investigator sponsored research; outside the scope of the current work), Tenax Therapeutics (Scientific advisory board; outside the scope of the current work), Regeneron (Consultant; outside the scope of the current work)

increases the pool of patients with a diagnosis of PH; however, immediately reversible and nonpathogenic conditions that increase pulmonary blood flow can elevate pulmonary artery pressure without indicating pulmonary vascular pathology. In order to maintain adequate specificity for classifying a patient with pulmonary vascular disease, the hemodynamic classification system of PH was expanded to include pulmonary vascular resistance (PVR) threshold. In 2019, PVR of ≥3.0 WU was used to delineate patients with a component of precapillary PH in all PH groups. However, this PVR threshold was not based on normative or outcome data collected systematically. Rather, this threshold was repurposed using deductive reasoning from pulmonary arterial hypertension clinical trials that used this threshold, and because poorer outcomes in patients with congenital heart lesions and PH had been reported when shunt closure was performed with PVR exceeding 3.0 WU.[10] Until relatively recently, data to inform of an outcomes-derived PVR threshold were lacking.

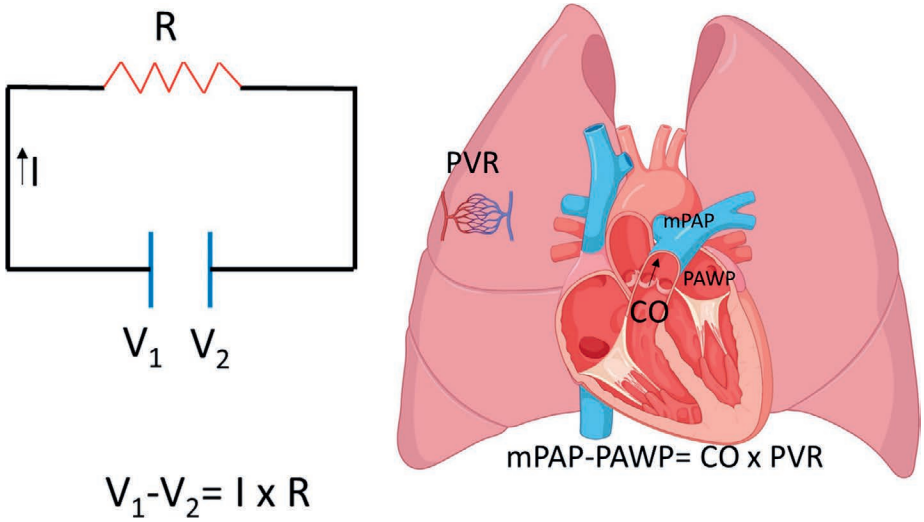


Figure 1: Analogy of the pulmonary circulation to an electrical circuit for purposes of application of Ohm's law in the calculation of pulmonary vascular resistance. CO indicates cardiac output; I, current; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure (to approximate left atrial pressure); PVR, pulmonary vascular resistance; R, resistance; V, voltage.

PVR AND THE DEFINITION OF PH

The Biophysics of Blood Flow in the Pulmonary Circulation

Under normal conditions, the pulmonary vasculature is a high-flow, low-resistance circuit oriented in parallel. PVR is the resistance against blood flow from the pulmonary artery to the left atrium (LA). It is estimated by applying Ohm's law on the pulmonary circulation (Figure 1). According to Ohm's law, the difference in potential (V) across a resistor is proportional to the electrical current (I) times the resistance (R) or V = IR. In the pulmonary circulation, the pressure gradient that drives the flow of blood from the right ventricle to the left atrium is the difference between the mPAP and the pulmonary artery wedge pressure (PAWP). By applying Ohm's law we get mPAP – PAWP = cardiac output (CO) × PVR.[11] Therefore, PVR helps distinguish increased mPAP owing to states of increased flow (such as obesity, anemia, and others) from increased mPAP when due to pulmonary vascular remodeling.[12,13] PVR is measured in mm Hg × min/L or in dynes/sec/cm^5. The units of mm Hg × min/L are referred to as Wood units (WU), the namesake of cardiologist Paul Wood, who was one of the pioneers of hemodynamic interpretation.[10,14,15] One WU equals 80 dynes/sec/cm^5.[15]

The Historical Basis of PVR in Defining PH. (Figure 2)

A normal PVR has been reported to be between 150 to 300 dynes/sec/cm^5 (1.9-3.8 WU), although the number of subjects that were assessed for this value in this study was not povided.[4] In 1998, the 3rd World Symposium on Pulmonary Hypertension (WSPH) formally included PVR into the definition of pulmonary *arterial* hypertension (denoted as primary pulmonary hypertension then). The task force set the cut-off at >3 WU but did not provide rationale to support this decision.[16] In 2008 the 4th WSPH committee acknowledged that a normal PVR was likely <2 (or 3) WU, indicating that the exact threshold was not known.[17]

Normative Values for PVR

In 2012, Kovacs and colleagues published a meta-analysis summarizing PVR data from studies on normal volunteers. They analyzed 88 subjects and found that the PVR in their cohort was 69±28 dynes/sec/cm^5 in individuals younger than 50 years old versus 88±28 dynes/sec/cm^5 in older volunteers.[18] Considering the statistical definition of normality, the upper limit of normal for PVR in that study was 135 dynes/sec/cm^5 (~1.7 WU), which was later supported by the 5th WSPH that acknowledged the upper level of normal PVR is likely ~2 WU.[10]

Using Outcomes Data to Calibrate the Definition of PH

The first study to reconsider the association between PVR and outcome that also incorporated the mPAP threshold of 20 mm Hg to define PH was by Xanthouli and colleagues[19] involving 208 patients with systemic sclerosis. The authors found that patients with mPAP 21 to 24 mm Hg and PVR ≥2 WU (selected based on the findings by Kovacs et al[18]) had reduced tricuspid annular planar systolic excursion (21±6 vs 24±4 mm, P = .004), decreased 6-minute walk distance (6MWD) (414±100 vs 488±101 m, P < .001) and decreased pulmonary artery compliance (4±1.3 vs 6.2±2.8 mL/mm Hg, P < .001) compared to patients with mPAP <21mm Hg. These findings show that right ventricle and functional impairment is prevalent even in patients with mild PH and PVR 2 to 3 WU, which was internally consistent with findings on survival. Compared to patients with mPAP >20

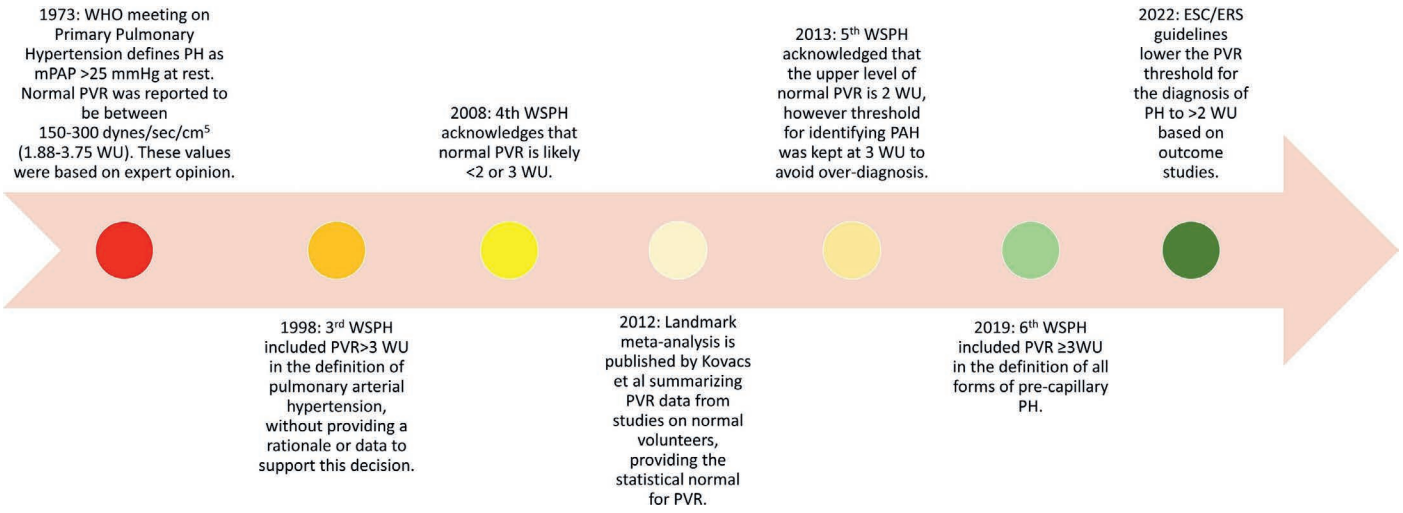


Figure 2: Timeline of pulmonary vascular resistance in the definition of pulmonary hypertension. ESC indicates European Society of Cardiology; ERS, European Respiratory Society; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WSPH: World Symposium on Pulmonary Hypertension; WU, Wood units; WHO: World Health Organization.

mm Hg and PVR <2.0 WU, patients with mPAP >20 mm Hg and PVR ≥2.0 WU had lower survival at 1 year (97.7% vs 100%), 3 years (90.7% vs 94.2%), 5 years (79.4% vs 91%) and 7 years (54.3% vs 84.2%) (age-adjusted Cox regression $P = .028$). Interestingly 25% of the mortality in the PVR <2 WU was reported to be due to pulmonary vascular disease vs 50% in the PVR ≥2 WU group.[19]

Our group[7] investigated the relationship between PVR and hard clinical events in patients referred for right heart catheterization in the Veterans Affairs Clinical Assessment, Reporting, and Tracking (VA-CART) Program, which included a total of 32 725 individuals with mPAP ≥19 mm Hg who underwent right heart catheterization between October 2008 and September 2016. This study found that all-cause mortality increases continuously beginning at PVR 2.0 to 2.2 WU (Figure 3). When PVR was dichotomized at 2.2 WU, patients with PVR ≥2.2 WU had higher 1-year (20.5% vs 11.3%) and 5-year (43.5% vs 28.5%) mortality rates, and higher 1-year (15.6% vs 10.1%) and 5-year (22.6% vs 16.1%) all-cause hospitalization rates. The association between PVR and mortality was maintained when restricting the analysis to patients with mPAP 19-24 mm Hg alone. Importantly, these data were validated in a second cohort of patients from Vanderbilt University Medical Center. This cohort included a similar number of female and male patients, which is important to consider since the VA-CART cohort is mostly comprised from male patients. These collective findings provide clinical endpoint data that support lowering the PVR cut-off for defining PH to 2 WU (Table).

Increasing Sensitivity in PH Diagnosis

"It is better to prevent than to cure" is a traditional adage attributed to Hippocrates with implications to pulmonary vascular disease: most patients are diagnosed at an advanced stage, as evidenced by the AMBITION trial, in which the mean mPAP at time of PAH diagnosis was ~48 mm Hg corresponding to World Health Organization functional class III in most patients.[20] Early diagnosis of PH and referral to expert centers for evaluation and treatment could lead to prevention of right ventricular failure and increased survival. It has been shown that the risk of adverse outcomes in association with PH increases from mPAP >20 mm Hg, and PVR >2 WU. Nevertheless, lowering of PH threshold to 20 mm Hg has a small effect on capturing more patients with PH when maintaining a PVR threshold of 3.0 WU.[21]

In the study by Xanthouli et al,[19] 50 patients with Group I PH had mPAP between 21 to 24 mm Hg. Of those, 48% had PVR between 2 to 3 WU. Additionally, of the 54 Group I PH patients with mPAP ≥25 mm Hg in that study, 35.2% had PVR between 2 to 3 WU. In 2018, Coghlan et al[22] reported outcomes of a 3-year follow-up of patients with systemic sclerosis and mPAP <25 mm Hg. Notably, patients with mPAP between 21 to 24 mm Hg had nigher incidence of "frank" PH (defined by mPAP >25mm Hg at that time) in the 3-year follow-up period

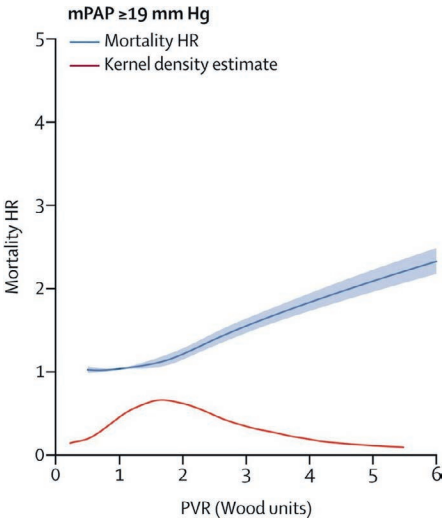


Figure 3: Hazard ratio (95% confidence interval) for all-cause mortality is plotted for PVR 1-6 WU relative to a reference value of 1.0 WU in patients with mean pulmonary artery pressure ≥19 mm Hg. All-cause mortality increases form PVR ~ 2 WU. mPAP indicates mean pulmonary artery pressure; PVR, pulmonary vascular resistance; WU, Wood units. Reproduced with permission from Elsevier.[7]

Table. Studies evaluating the significance of PVR>2 WU in patients with PH.

Study	PH group	Duration of follow-up	Outcomes	Comments/interpretation
Coghlan et al[22] 2018	Scleroderma patients (WHO Groups I, II, & III)	3 years	Patients with mPAP 21-24 had mean PVR of 2.35, which progressed to >3 WU within 3 years	Most patients with mild PH have PVR 2-3 WU, and these patients progress to more severe PH that warrants treatment
Xanthouli et al[19] 2020	Scleroderma patients with Group I	3.5 years	48% of patients with mPAP 21-24 mm Hg had PVR 2-3 WU. Patients with PVR ≥2 WU had decreased TAPSE (21 ± 6 vs 24 ± 4 mm, $P = .004$), 6MWD (414 ± 100 vs 488 ± 101 m, $P < .001$) and PAC (4 ± 1.3 vs 6.2 ± 2.8 mL/mm Hg, $P < .001$) compared to patients without PH. PVR was independently associated with survival.	Lowering PVR threshold for diagnosing PH captures more patients. Patients with mild PH and PVR ≥2 WU have impaired functional and cardiac status compared to patients without PH
Maron et al[7] 2020	Any group (I-V)	~2 years	Mortality increases progressively over a PVR ≥2 WU when PVR is plotted as a continuous variable	Identified the PVR cut-off above which the risk of adverse outcomes increases. Outcomes-based method of identifying "abnormal"

Abbreviations: 6MWD, 6-minute walk distance; mPAP, mean pulmonary artery pressure; PAC, pulmonary artery compliance; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular place systolic excursion; WHO, World Health Organization; WU, Wood units

of that study compared to those with mPAP <21 mm Hg (33.3% vs 22%, respectively). Finally, in the larger study conducted by Maron and colleagues[7] lowering the PVR threshold to 2.2 WU would capture an additional 55.9% of patients with PH. From the above it is evident that lowering PVR to 2 WU helps diagnose PH in a significantly larger percentage of patients, compared to lowering of the mPAP threshold to 20 mm Hg alone.

PERSPECTIVES ON THE NEW PH DEFINITION

Despite the above, lowering the PVR cut-off used to define PH to >2 WU should not equate to treating patients with PVR 2 to 3 WU with PAH-specific therapies, as the safety and efficacy of our current medical treatment of PH has not been established for individuals with PVR <3 WU.[23] The EDITA study is the only randomized controlled trial to evaluate the safety and efficacy of PAH-specific therapies in those with mPAP 21 to 24 mm Hg.[24] In this study, 38 patients received either placebo or ambrisentan for 6 months. Treatment with ambrisentan decreased progression to mPAP ≥25 mm Hg (3 vs 0 patients) and improved cardiac index (CI) and PVR (CI 0.36 ± 0.66 l/min/m^2 vs −0.31 ± 0.71 l/min/m^2, $P = .010$; PVR −0.70 ± 0.78 WU vs 0.01 ± 0.71 WU, $P = .012$). The adverse events reported were among those already known for ambrisentan (edema, diarrhea, epistaxis).

Ratwatte and colleagues report data from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) Registry on treatment of patients with Group I PH with mPAP ≥25mm Hg and PVR <3 WU. The study included 82 patients with a median PVR or 2.2 WU. Patients were initially treated with monotherapy with either an endothelin receptor antagonist or a phosphodiesterase type-5 inhibitor (PDE5i). Patients were followed on average for 5.5 years. During the follow-up period, 14% of patients needed to be escalated to combination therapy. The mediations were well tolerated and there were no treatment interruptions. The patients' functional capacity improved (+46 m median increase in 6-minute walk distance, 35% of patients improved New York Heart Association functional class). In addition, PAH therapy increased the patients that would fall under the low-risk REVEAL 2.0 category from 61% to 72%.[25]

The results of these studies should be viewed as exploratory but somewhat encouraging given the improvement in functional capacity of the patients. Larger studies are needed to determine whether treating patients with mPAP >20 mm Hg and PVR >2 WU with PAH-specific therapies would be safe and effective.

CONCLUSIONS

The new definition of precapillary PH uses a PVR cutoff of >2 WU, which is based on data from healthy populations determining the normal cut-off as mean ± 2 SD, as well as from data associated with clinical outcomes. This approach facilitates earlier stage diagnosis, which is positioned to test strategies that delay or prevent clinical worsening, including the development of right ventricular failure and death. In this regard, patients with mPAP 20 to 25 mm Hg and PVR 2 to 3 WU should be monitored closely, referred to expert centers, and considered for clinical trials that are designed to assess the safety and efficacy of multidimensional care plans, perhaps inclusive of PAH-specific therapies.

Acknowledgments: Part of Figure 1 was created with BioRender.com (illustration software, Toronto, Canada).

References

1. Ceriotti F, Henny J. "Are my Laboratory Results Normal?" Considerations to be made

concerning reference intervals and decision limits. *EJIFCC*. Oct 2008;19(2):106-114
2. Ceriotti F, Hinzmann R, Panteghini M. Reference intervals: the way forward. *Ann Clin Biochem*. 2009;46(1):8-17. doi:10.1258/acb.2008.008170
3. Ozarda Y, Sikaris K, Streichert T, Macri J. Distinguishing reference intervals and clinical decision limits - A review by the IFCC Committee on reference intervals and decision limits. *Crit Rev Clin Lab Sci*. Sep 2018;55(6):420-431. doi:10.1080/10408363.2018.1482256
4. Hatano S, Strasser T, World Health Organization. *Primary Pulmonary Hypertension: Report on a WHO Meeting, Geneva, 15-17 October 1973*. Geneva:World Health Organization; 1975. Accessed March 21, 2023. https://apps.who.int/iris/handle/10665/39094
5. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J*. 2009;34(4):888-894. doi:10.1183/09031936.00145608
6. Assad TR, Maron BA, Robbins IM, et al. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. *JAMA Cardiol*. Dec 1 2017;2(12):1361-1368. doi:10.1001/jamacardio.2017.3882
7. Maron BA, Brittain EL, Hess E, et al. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. *Lancet Respir Med*. Sep 2020;8(9):873-884. doi:10.1016/s2213-2600(20)30317-9
8. Douschan P, Kovacs G, Avian A, et al. Mild elevation of pulmonary arterial pressure as a predictor of mortality. *Am J Respir Crit Care Med*. Feb 15 2018;197(4):509-516. doi:10.1164/rccm.201706-1215OC
9. Kolte D, Lakshmanan S, Jankowich MD, Brittain EL, Maron BA, Choudhary G. Mild pulmonary hypertension is associated with increased mortality: a systematic review and meta-analysis. *J Am Heart Assoc*. Sep 18 2018;7(18):e009729. doi:10.1161/jaha.118.009729
10. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. Jan 2019;53(1):1801913. doi:10.1183/13993003.01913-2018
11. Lai YC, Potoka KC, Champion HC, Mora AL, Gladwin MT. Pulmonary arterial hypertension: the clinical syndrome. *Circ Res*. Jun 20 2014;115(1):115-130. doi:10.1161/circresaha.115.301146
12. Deng J. Clinical application of pulmonary vascular resistance in patients with pulmonary arterial hypertension. *J Cardiothorac Surg*. 2021/10/20 2021;16(1):311. doi:10.1186/s13019-021-01696-4
13. Maron BA, Kleiner DE, Arons E, et al. Evidence of advanced pulmonary vascular remodeling in obstructive hypertrophic cardiomyopathy with pulmonary hypertension. *Chest*. Oct 13 2022;S0012-3692(22)03912-5. doi:10.1016/j.chest.2022.09.040
14. Camm J. The contributions of Paul Wood to clinical cardiology. *Heart Lung Circ*. 2003;12 Suppl 1:S10-4. doi:10.1046/j.1444-2892.12.s1.1.x
15. Kwan WC, Shavelle DM, Laughrun DR. Pulmonary vascular resistance index: getting the units right and why it matters. *Clin Cardiol*. Mar 2019;42(3):334-338. doi:10.1002/clc.23151
16. Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. Jun 16 2004;43(12 Suppl S):40s-47s. doi:10.1016/j.jacc.2004.02.032
17. Badesch DB, Champion HC, Gomez Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. Jun 30 2009;54(1 Suppl):S55-S66. doi:10.1016/j.jacc.2009.04.011
18. Kovacs G, Olschewski A, Berghold A, Olschewski H. Pulmonary vascular resistances during exercise in normal subjects: a systematic review. *Eu Respir J*. 2012;39(2):319-328. doi:10.1183/09031936.00008611
19. Xanthouli P, Jordan S, Milde N, et al. Haemodynamic phenotypes and survival in patients with systemic sclerosis: the impact of the new definition of pulmonary arterial hypertension. *Ann Rheum Dis*. Mar 2020;79(3):370-378. doi:10.1136/annrheumdis-2019-216476
20. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373(9):834-844. doi:10.1056/NEJMoa1413687
21. Jaafar S, Visovatti S, Young A, et al. Impact of the revised haemodynamic definition on the diagnosis of pulmonary hypertension in patients with systemic sclerosis. *Eur Respir J*. 2019;54(2):1900586. doi:10.1183/13993003.00586-2019
22. Coghlan JG, Wolf M, Distler O, et al. Incidence of pulmonary hypertension and determining factors in patients with systemic sclerosis. *Eur Respir J*. Apr 2018;51(4):1701197. doi:10.1183/13993003.01197-2017
23. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol*. 2018;71(19):e127-e248. doi:10.1016/j.jacc.2017.11.006
24. Pan Z, Marra AM, Benjamin N, et al. Early treatment with ambrisentan of mildly elevated mean pulmonary arterial pressure associated with systemic sclerosis: a randomized, controlled, double-blind, parallel group study (EDITA study). *Arthritis Res Ther*. 2019/10/26 2019;21(1):217. doi:10.1186/s13075-019-1981-0
25. Ratwatte S, Anderson J, Strange G, et al. Pulmonary arterial hypertension with below threshold pulmonary vascular resistance. *Eur Respir J*. 2020;56(1):1901654. doi:10.1183/13993003.01654-2019

REGULAR ARTICLE

COUNTERPOINT: Pulmonary Vascular Resistance 2.0—Shedding Light or Casting Shadows?

Robert P. Frantz, MD
Mayo Clinic
Department of Cardiovascular Medicine
200 First St SW
Rochester, MN 55905

The recent revision of the European Society of Cardiology/European Respiratory Society pulmonary hypertension (PH) guidelines, which lower the threshold for pulmonary vascular resistance (PVR) deemed to be abnormal to >2 Wood units (160 dynes·cm^{-5}), is based on sound evidence.[1] This includes expanding knowledge about the range of pulmonary artery pressure and PVR at rest and with exercise in healthy adults.[2,3] Although the PVR in healthy adults drifts up with age, it is consistently 2 Wood units or less. Additional information derives from analysis of a large database of subjects undergoing right heart catheterization, with the finding that PVR ≥2.2 was associated with worse outcome than lower PVR values.[4] This value was derived from a large cohort, and the findings were validated in a separate cohort. However, the derivation cohort is from the US Veterans Affairs Health Care System and reflects the nature of that population. On closer inspection it is quite remarkable to realize that the derivation cohort was 97% male, 88% had systemic hypertension, and 58% had coronary heart disease. In the validation cohort, about half were male and around 80% had systemic hypertension while over half had coronary heart disease. Precapillary PH, of particular interest to readers of *Advances in Pulmonary Hypertension*, carried greater risk than postcapillary PH, perhaps reflecting relatively robust treatment approaches for left heart disease. Of those with precapillary PH, 42% had chronic obstructive pulmonary disease (COPD), while less than 1% had interstitial lung disease. Presence of PH in patients with COPD is known to be associated with increased risk, but no PH-directed therapy has been found that has positive impact on outcome in PH due to COPD. Whether the PH in such patients mediates outcome or is just a marker of more advanced disease is also unknown. The only actions based on knowledge of mild PH in COPD are to redouble efforts to prevent hypoxemia (which should be done anyway) and to consider timing of lung transplant referral (which should be done anyway based on other COPD prognostic information and patient eligibility). Accordingly, there does not seem to be any point in chasing down presence of mild PH in COPD unless relevant to lung allocation score calculation in patients being considered for lung transplantation.

To be diagnosed with mildly elevated PVR, it is necessary to have undergone a right heart catheterization. Presumably the majority of the patients who underwent right heart catheterization in the cohorts described above and were found to have mildly elevated PVR were having the right heart catheterization not with a goal of detecting that condition, but for some other purpose likely associated with adverse prognosis (eg, severe COPD undergoing lung transplant evaluation, evaluation of left heart failure or valvular heart disease). Therefore, it is not known whether patients with undiagnosed mildly elevated PVR have as adverse a prognosis as those who have undergone right heart catheterization and had the diagnosis established. Furthermore, since we remain uncertain of the role for treatment of mildly elevated PVR, perhaps there is no great role for finding it. This may be part of the reason that there was not a decision in the latest PH guidelines to change the echo tricuspid regurgitation velocity worthy of further pursuing for PH. Another reason may reflect concern about reducing the specificity of echocardiographically suspected PH for presence of PH worth pursuing with right heart catheterization.

THE CONUNDRUM OF MILD PRECAPILLARY PH: MEAN PULMONARY ARTERY PRESSURE 19 TO 24, PULMONARY CAPILLARY WEDGE <15, AND PVR 2.2 TO 2.9

Recently this writer cared for a patient with a mean pulmonary artery pressure (mPAP) of 19 to 24, pulmonary capillary wedge pressure <15, and PVR of 2.2 to 2.9, thus meeting the criteria for mild precapillary PH. She had googled "pulmonary hypertension" and came to the visit following her right heart catheterization extremely worried about her condition. She had great questions for me. When I told her that we were not going to treat her PH with vasodilators, she became even more concerned. This is the ugly underbelly of the concept

Key Words—mild pulmonary hypertension, guidelines, right heart catheterization, exercise, prognosis
Correspondence: Frantz.robert@mayo.edu
Disclosure: Dr. Frantz reports consulting relationships with Aerovate, Acceleron, Altavant Sciences, Bayer, Gossamer Bio, Insmed, Janssen, Shouti, Tenax Pharmaceuticals, and UptoDate and stock ownership of Tenax pharmaceuticals.

of mild PH, and is where harm can be done. "Doctor, you mean you are just going to watch it get worse and do nothing? How does that make any sense? Tell me I have a condition that worsens my prognosis and do nothing but get me more worried? Can you even tell me why I have pulmonary hypertension? How quickly is it going to get worse? What should we do to keep track of it? *What can I do to improve my outcome?*" For the busy practitioner with the clock ticking until the next patient is ready, navigating this discussion in a compassionate fashion that provides clear information, when even the experienced practitioner may not be sure of what is driving the mild PH, requires a lexicon and approach that is in its infancy. No matter the debate about the pros and cons of the concept of mild PH, it is here to stay. In the spirit of providing an approach to the patient with mild PH that has been detected on right heart catheterization, consider the following:

- Consider the context of why the patient underwent a right heart catheterization.
- Strongly consider referral to a PH expert center.
- Strive to be a master clinician.
    - Take a thorough history, considering all possible causes of PH.
    - Follow the clues in the history, exam, labs, electrocardiogram, echocardiogram, and lung function tests.
    - Collate patient risk factors for heart failure with preserved ejection fraction.[5]
    - Always do overnight oximetry, and consider a formal polysomnogram.
    - If pulmonary function tests are abnormal and/or diffusing capacity of the lungs for carbon monoxide (DLCO) is low, always do thin-section chest computed tomography.
    - Always do an exercise test (6-minute walk, also cardiopulmonary exercise test if available).
    - Strongly consider ventilation/perfusion lung scan.
    - Strongly consider invasive exercise hemodynamics if the patient is symptomatic.
- Maximize information obtained at time of right heart catheterization.
    - Examine nitric oxide vasodilator challenge for those with wedge pressure ≤15 mm Hg.
    - Obtain exercise hemodynamics if available.
    - Perform 500-mL saline fluid challenge if wedge values are 12 to 18 mm Hg and exercise is not feasible.

Nitric Oxide Vasodilator Challenge: Rationale

Some patients with precapillary PH and PVR values of 2.2 to <3 Wood units will normalize PVR with inhaled nitric oxide (R.P.F., unpublished data). The prognostic implications of this finding are unknown, but may suggest less pulmonary vascular remodeling, may provide some rationale for using calcium channel blockers if the patient requires antihypertensive therapy anyway, and careful collection of this information may in the future be analyzed to better understand implications of such a finding.

Exercise Hemodynamics or Fluid Challenge: Rationale

Patients with PVR values of 2.2 to 3 Wood units and wedge values <15 mm Hg, or even up to 18 mm Hg, may have exercise hemodynamic or volume challenge tests that are very informative.

Scenario 1: Occult Heart Failure With Preserved Ejection Fraction

- Patients with occult heart failure with preserved ejection fraction (HFpEF) may already be on diuretics so may have a wedge pressure <15 mm Hg, which may rise with exercise or fluid challenge in a fashion that is diagnostic of exercise-induced HFpEF.
- Patients with wedge pressure of up to 18 mm Hg but with elevated PVR of 2.2 to <3 form a group of diagnostic uncertainty. Fluid challenge or exercise hemodynamics may be clarifying. This scenario, particularly when combined with other clinical features to support the diagnosis, can allow the practitioner to consider HFpEF treatment options and/or referral for clinical trials for HFpEF. This approach may be considered in patients with wedge pressure of up to 18 mm Hg, to help further define extent of pre- and postcapillary disease. If the wedge pressure does not rise much further but there is major rise in pulmonary arterial (PA) pressure, this may identify a phenotype where the precapillary PH is not merely secondary to the left heart disease. An example could be an elderly patient with scleroderma and history of systemic hypertension who has precapillary pulmonary vascular disease related to their scleroderma, but also has a comorbidity of mild left heart disease.

Scenario 2: Mild Precapillary PH That Worsens With Exercise, With Wedge Staying Normal

- Patients with mild precapillary PH may have significant pulmonary vascular remodeling and be unable to recruit sufficient additional pulmonary vasculature during exercise to avoid further substantial rise in PA pressure with exercise.
- Mean PA pressure to cardiac output slope >3 mm Hg/L/min is abnormal.[6]
- Pulmonary artery wedge pressure to cardiac output slope of <2 mm Hg/L/min suggests precapillary PH, while values >2 mm Hg/L/min suggest postcapillary PH.[6]

Exercising such patients may reveal limitation in exercise capacity that in turn may explain symptoms of dyspnea based upon limited cardiac output response, abnormal rise in PA pressure and occasionally right atrial pressure, and further confirm abnormalities of the precapillary pulmonary vasculature. This may be particularly informative in patients with risk factors for PAH, such as connective tissue disease, methamphetamine use, family history of PAH, HIV infection. Measurement of gas exchange parameters with a metabolic cart can allow assessment of ventilatory inefficiency (eg, the ratio of minute ventilation to carbon dioxide; VE/VCO_2 slope and na-

dir), detect exercise-related desaturation, and assess adequacy of cardiac output response.

Doctor, What Are We Going to Do? Context Is Everything

With these thoughts in mind, it is worth stepping back and putting the patient at the center of the conversation. Why are they being seen? If the patient is being seen for unexplained dyspnea, the following approach can be taken.

- Exclude chronic thromboembolic PH with nuclear medicine ventilation/perfusion lung scan, and additional evaluation if needed. Chronic thromboembolic PH or chronic thromboembolic pulmonary disease can cause significant exertional dyspnea, sometimes in the absence of PVR of >3 Wood units.[7] It can be treated with surgical thromboendarterectomy, balloon pulmonary angioplasty, or vasodilators such as riociguat. The best approach requires evaluation at a comprehensive chronic thromboembolic PH center.
- When mildly elevated PVR is found in a patient with unexplained dyspnea, invasive cardiopulmonary exercise testing at the time of diagnostic right heart catheterization is recommended if available.
- If only resting right heart catheterization was performed, then additional noninvasive testing in an effort to establish a clinical phenotype that explains the dyspnea is warranted.
- If the noninvasive testing fails to establish sufficient phenotypic information, then referral to a center that can perform invasive hemodynamic exercise testing is suggested.

Risk Factors for PAH Sufficient to Screen for PAH

Connective Tissue Disease

- Patients with scleroderma should be screened for PAH. In scleroderma, the DETECT algorithm can be utilized to guide utilization of echocardiography and right heart catheterization.[8] An approach to mild PH in scleroderma is shown in Figure 1.

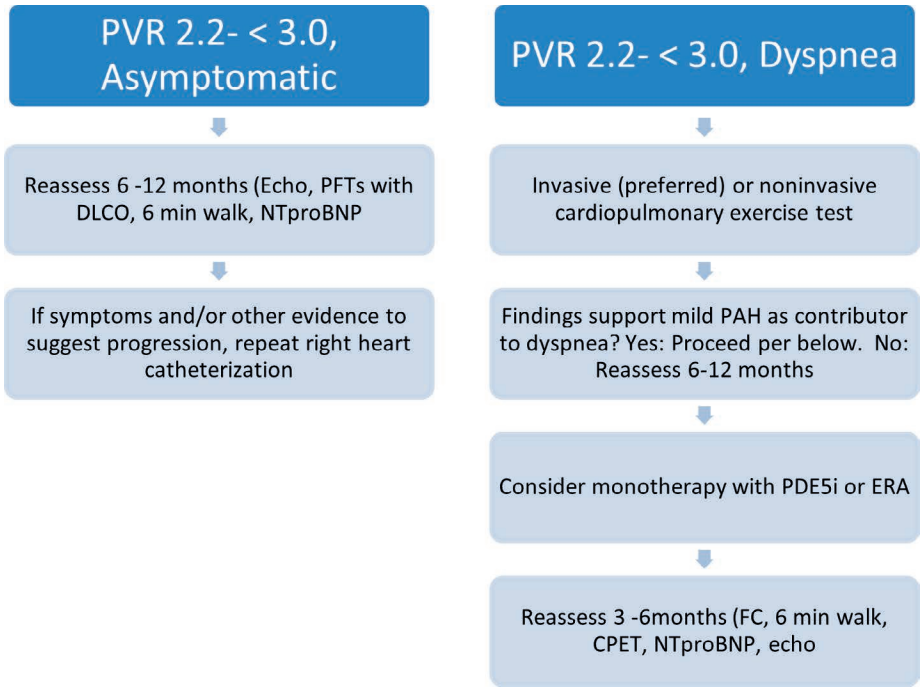


Figure 1: Approach to mild pulmonary hypertension in scleroderma.

If mild precapillary PH (mPAP 21 to 24, or >25 but PVR 2 to <3) is present, what is known? For those with DLCO <60% predicted and mPAP 21 to 24, there is about a 25% 5-year risk of developing mPAP >25 mm Hg.[9] These patients with scleroderma and PVR of 2 to < 3.0 fall into 3 categories: (1) asymptomatic; (2) asymptomatic but with objective exercise testing limitations; (3) symptomatic (eg, exertional dyspnea). If they are asymptomatic, then the presence of the mild PH needs to be explained to the patient. The following steps form a reasonable approach to this discussion:

1. The PH is mild and knowledge about role of treatment is limited.
2. Reassessment in 6 months to 1 year with repeat echocardiography, 6-minute walk test, pulmonary function tests with DLCO, and NTproBNP or BNP is appropriate.
3. If at reassessment there is concern for progression of PH, a repeat right heart catheterization should be performed.
4. Subsequent reassessment at 6- to 12-month intervals should be performed, or sooner if symptoms of dyspnea develop.
5. Those patients who are asymptomatic but with objective exercise limitation should be followed at 6-month intervals.
6. For symptomatic patients with PVR of 2.0 to <3 Wood units, there are some data to support treatment but the evidence base remains limited.[10 11]

Family History of PAH

For patients with a family history of PAH, a finding of PVR 2.2 to <3.0 raises concern that the patient may have an early stage of heritable PAH. Recommendations in this situation include the following:

1. Discuss genetic testing if it has not already been done.
2. Determine whether affected family members have genotyping results available; if so test specifically for that gene. If not, do full-panel testing.
3. If positive and asymptomatic, reassess in 6 months.
4. If positive and symptomatic, consider monotherapy (phosphodies-

terase type 5 inhibitors or endothelin receptor antagonist); reassess in 6 months.
5. If negative but other affected family members have not been genotyped or were negative, there may be an unrecognized mutation. Reassess in 6 months; if symptomatic consider monotherapy.

Idiopathic PH

1. Take a careful history (including drug use, especially methamphetamine).
2. Perform a perfusion lung scan to look for chronic thromboembolic disease.
3. If asymptomatic, recheck in 6 to 12 months.
4. If symptomatic with objective exercise limitation, Consider monotherapy with PDE5i or ERA.
5. Assess treatment response in 3 months.

Liver Disease

1. If asymptomatic, reassess in 6 months.
2. If symptomatic, it can be difficult to separate symptoms possibly attributable to PAH from those related to the liver disease such as due to anemia.
3. Perform exercise testing.
4. Reassess in 6 months.

HIV With Dyspnea

1. Perform exercise testing.
2. If there is an objective limitation, consider monotherapy but always consult with HIV pharmacist about drug interactions, which can be major.

SUMMARY

Proper diagnosis of PH is challenging even in situations where the PVR is >3 Wood units. Understanding the pathophysiology and causes of PH with PVR 2.0 to <3.0 Wood units is even more challenging, but noting these challenges is not going to make them go away. There is significant risk of creating confusion and psychological distress for the patient. There is significant financial cost for the patient as well, related to testing, time away from work, and travel to the medical center. In the worst-case scenario, an incorrect diagnosis is made, useless or harmful and expensive therapies are prescribed, and there is significant disruption of the patient's wellbeing. Providers who are evaluating and caring for patients with mild PH must be thorough, expert, compassionate, and able to acknowledge potential for misdiagnosis. Provisional diagnosis demands careful follow-up and a willingness to modify an approach based upon subsequent developments in patient symptoms and findings. In the best-case scenario, identification of mild PH allows detection of associated conditions for which appropriate treatment may be available, results in earlier diagnosis of disease that could lead to improved outcomes, and provides an opportunity for participation in research.

FUTURE DIRECTIONS

It is incumbent upon the PH community to facilitate research pertinent to mild PH. This includes funding, as well as careful design and conduct of prospective longitudinal registries to further our understanding of the natural history of mild PH. To be meaningful, such registries will require highly detailed patient characterization. Innovative study design regarding treatment of mild PH is also warranted. This is particularly challenging since the phenotypic variation in the mild PH population raises potential for differing and poorly understood pathophysiologies to be inadvertently lumped together. In addition, demonstration of an impact of a therapeutic approach in mild disease will demand very long-term follow-up, innovative study endpoints, or both. When patients with mild PH are identified, they should be offered the opportunity to participate in research pertinent to advancing understanding of the significance, natural history, and possible treatment of mild PH and, accordingly, referral to a PH center of excellence that is conducting such research is recommended. In this fashion, in the future we will hopefully not need to debate the pros and cons of identifying mild PH, because we will have developed better understanding of approaches to its evaluation and management.

References

1. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731.
2. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J*. 2009;34(4):888-894.
3. Kovacs G, Olschewski A, Berghold A, Olschewski H. Pulmonary vascular resistances during exercise in normal subjects: a systematic review. *Eur Respir J*. 2012;39(2):319-328.
4. Maron BA, Brittain EL, Hess E, et al. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. *Lancet Respir Med*. 2020;8(9):873-884.
5. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018;138(9):861-870.
6. Zeder K, Banfi C, Steinrisser-Allex G, et al. Diagnostic, prognostic and differential-diagnostic relevance of pulmonary haemodynamic parameters during exercise: a systematic review. *Eur Respir J*. 2022;60(4):2103181.
7. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2021;57(6):2002828.
8. Coghlan JG, Denton CP, Grünig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis*. 2014;73(7):1340-1349.
9. Visovatti SH, Distler O, Coghlan JG, et al. Borderline pulmonary arterial pressure in systemic sclerosis patients: a post-hoc analysis of the DETECT study. *Arthritis Res Ther*. 2014;16(6):493.
10. Pan Z, Marra AM, Benjamin N, et al. Early treatment with ambrisentan of mildly elevated mean pulmonary arterial pressure associated with systemic sclerosis: a randomized, controlled, double-blind, parallel group study (EDITA study). *Arthritis Res Ther*. 2019;21(1):217.
11. Ratwatte S, Anderson J, Strange G, et al. Pulmonary arterial hypertension with below threshold pulmonary vascular resistance. *Eur Respir J*. 2020;56(1):1901654.

Pros and Cons of the 2022 ERS/ESC Guidelines: Practicality vs Real World View

This spring, Dr Thenappan Thenappan, University of Minnesota, Minneapolis; Dr Marc Humbert, Université Paris-Saclay, Paris; Dr Vallerie McLaughlin, University of Michigan, Ann Arbor; Dr Hilary DuBrock, Mayo Clinic, Rochester; and Dr Charles D. Burger, Mayo Clinic, Jacksonville, Florida, gathered to discuss the 2022 ERS/ESC guidelines.

Dr Thenappan Thenappan: Welcome to our roundtable discussion, pros and cons of the 2022 ERS/ESC guidelines, practicality versus real world view. As you know, the ESC and ERS published new guidelines for the diagnosis and management of pulmonary hypertension in August of 2022, with an intent to improve care for patients with pulmonary hypertension. First, I want to congratulate our European colleagues on this monumental task.

The new guidelines have made several important changes, including a revised definition of precapillary pulmonary hypertension with the lower PVR threshold of 2 Wood units, has provided pathways and guidance for early diagnosis of pulmonary hypertension, a different risk stratification approach for patients with PAH at the time of diagnosis and during follow up, a modified treatment algorithm for patients with PAH with a focus on comorbidities, which I think is very important, multimodality treatment approach for CTEPH, and finally, and not least, is the recognition of severe forms of PH associated with left heart disease and chronic lung disease to better understand them and develop novel therapies.

Undoubtedly, these new guidelines have shed light on many areas in the diagnosis and management of pulmonary hypertension. However, it has also created potential disagreements in some areas. Thus, to discuss the pros and cons of these new guidelines, we have assembled an amazing group of panelists and friends here today. These are world-renowned experts in the field of pulmonary hypertension, and we are really delighted to have them. We have Dr Vallerie McLaughlin, who is a Kim Eagle endowed professor of cardiovascular medicine and director of the pulmonary hypertension program at University of Michigan in Ann Arbor. We have Dr Marc Humbert, who's a professor of respiratory medicine at the South Paris University in Paris. He's also the director of the French National Reference Center for Pulmonary Hypertension and more importantly, he was one of the members of the guidelines writing committee. We have Dr Charles Burger, who is a professor of pulmonary and critical care medicine at the Mayo Clinic in Jacksonville, Florida. Dr Burger was our past editor-in-chief for *Advances in Pulmonary Hypertension* journal. Finally, but not least, we have Dr Hilary DuBrock, a rising star and associate professor of pulmonary medicine at Mayo Clinic in Rochester.

With that, I'll start our discussion with the first question. Probably I'll start with Dr Marc Humbert. Realizing you have a potential conflict of interest since you are on the committee, what is your overall impression of the new guidelines?

Dr Marc Humbert: Well, thank you very much for the kind invitation. I am really happy to be with you today. I would like to add just one thing on top of your introduction, which was excellent. There is a very important thing in the guidelines. We included patients in the guideline taskforce, and they are authors of the guidelines. I think that's something really important for the discussion today. That being said, producing guidelines, it's an exercise, which is very strict. When you use the word disagreements, I would contest that a little bit.

I mean, the facts are the facts, but they are either very strong evidence, and we write the evidence and the higher rating is 1A.

They are less robust evidence and you can go down to 2BC and even less sometimes when we are less sure of something we consider as important for future development. I would like to say that the guidelines are interesting, of course, and that it's a real challenge to produce those guidelines with a diverse group of people. Finally, is the way we develop it is systematic review, systematic analysis, and usually we end up with good quality data we can rate in terms of evidence, so I would pose here.

Dr Thenappan: Anybody else? Dr McLaughlin, your thoughts on the guidelines?

Dr Vallerie McLaughlin: First of all, I want to congratulate Marc and the whole committee. They did such a wonderful job on this document, this very thorough, very thoughtful document, so kudos to you. I would also say that there are always going to be areas that are open to interpretation of how you translate evidence into clinical practice and areas that might even have new evidence since the guideline decisions were made. I mean, it takes a very long time to create those guidelines, so I feel like there might be some areas where further discussion might lead to a better next set of guidelines when they're available. I think we all need to collaboratively discuss those areas to progress our field forward.

Dr Thenappan: Dr Dubrock or Dr Burger, your thoughts on the guidelines?

Dr Charles Burger: Yes, thank you. I couldn't agree more with Vallerie in congratulations to Dr Humbert and his colleagues on the guidelines. I real-

ly have enjoyed delving into them. It definitely represents a lot of work. How you pulled it off, I don't know. I think it would be almost impossible for us to support a similar endeavor in the US. There is some tension that is generated at times by these guidelines in the US. For example, it's difficult, I think, for all the patients to get to the centers despite our recommendation to do so. The diagnosis and the delivery of care for pulmonary hypertension is quite a diverse practice across the 330 million in the US in the 50 different states.

Practice has evolved, in my experience, with general clinicians, who don't have subject matter expertise in every rare disease that they see, relying on a quick review of the guidelines on their phone and almost mindlessly following them in a rote way. That, of course, may not necessarily involve careful consideration of the individual patient's circumstances, what's the difference between a diagnostic threshold and a treatment threshold.

There can also be some controversy that's created just in the translation of guidelines to clinical practice. Not really around the rating of evidence as it would currently exist, and certainly not around the effort to try to provide earlier detection in the subgroups that you emphasized in the document, connective tissue disease and CTEPH, for which there's lots of interest, but rather understanding whether or not the efficacy of these medications that are approved when the threshold is 25 or higher for the mean PA pressure, might also translate into earlier diagnostic thresholds for that pressure.

Then, of course, now around an even earlier threshold with the pulmonary vascular resistance. While some tension exists in the application of guidelines to practice due to the differences in the practices in the US versus Europe, I enjoy the controversy around that, quite frankly, because I think it then generates interest, further conversation, and as Vallerie said, maybe some opportunities for refinement going forward. Again, congratulations.

Dr Hilary DuBrock: I'd like to echo the comment that it's really important that patients were included in these guidelines, and I think it's a good standard to set moving forward of incorporating patients and patient-reported outcomes in both guideline development and clinical decision making. Also, I liked how this set of guidelines acknowledged that pulmonary hypertension is really heterogeneous. Many of the patients that we see in clinical practice don't necessarily fit our textbook definitions and were underrepresented in clinical trials, and thus require a more individualized approach to treatment.

I think that this individualized approach to patients was an important emphasis in these guidelines and also validated what we see in clinical practice where patients don't always fit neatly into one category. Certainly, I am also hopeful that these new definitions will lead to meaningful improvements in diagnostic delays, which I think is one of the major things we still need to improve upon within our field.

Dr Thenappan: That's a very nice way to start our next conversation. Maybe we could start with the new definition. What do you think the strengths of the new definition of PVR less than 2 Wood units for the precapillary pulmonary hypertension and what are all the things we should be careful about?

Dr Humbert: If I may start, first, thank you very much for the very nice start. I think we did not want to make a revolution, but we just wanted to identify the upper limit of normal of mean PAP and pulmonary vascular resistance. We made a systematic review with Gabor Kovacs and the committee. What we did is setting the upper limit of normal and any value above it defines pulmonary hypertension, which is a hemodynamic state, not a disease.

Then it's our job together in PH centers, not in any place and that's something we need to discuss maybe later. Defining the 2upper limit of normal establishes a limit above which you can have a wide landscape of different conditions ranging from group 1 PAH, group 4 CTEPH, and the very, very common group 2 and group 3 PH. Then, Charlie said something very important about it's not an indication to treat immediately, of course. It's just the start of the process.

Dr McLaughlin: Marc, I would be very curious to have a little glimpse of what the committee discussed when talking about the hemodynamics with respect to wedge pressure because we lowered the mean PA pressure at the last world symposium and now you also lowered the PVR and you're talking about really the upper limits of normal when really 15 isn't a normal wedge. In my view, there's a little inconsistency there. Tell me what the conversation was around leaving the wedge cut off at 15 versus moving it to 12.

Dr Humbert: Honestly, I think we kept it for the next round of revision because the consequences of lowering capillary wedge pressure are quite important in terms of excluding a group of patients who currently are treated with approved drugs and who might become more challenged if we lower the mean pulmonary capillary wedge pressure from 15 to 12, but you know me. I was really in favor of considering the wedge pressure as early as 2022 guidelines. We decided that first there will be a world symposium next year and this world symposium should really take care of the unmet portions of the guidelines and the capillary wedge pressure is very important to reconsider.

We should be cautious because if we lower the mean wedge pressure to 12, there will be a large group, I would say, of patients who may be in difficulty.

Dr McLaughlin: You're right. It's a very delicate area. All these patients are different and so I get that the 55-year-old with heritable PAH, who has a mean PA pressure of 50, if she has a wedge of 13, she's still PAH. With lowering it to 12, there may be some patients with other comorbidities who have a mean PA pressure of 24, and a wedge pressure of 15, and a PVR of 2.1 and that's a little bit of a different patient. I think it's a very complex issue.

Dr Humbert: I fully agree with that. Clearly, later in our discussion, you will see that we are very, very cautious when we discuss treatment of people with

cardiopulmonary comorbidities and that many people are difficult to categorize, and that's a very important point. That's the reason why what we said in the introduction is so important, being treated in expert center or at least PH centers with multidisciplinary teams and a lot of discussion around each case.

Dr Burger: I think it also creates a dynamic around using these thresholds in a very strict sense, as you articulated, Val, for purposes of research and discovery and better understanding high-risk groups, as opposed to clinical practice. There's always that challenge for strict recommendations based on evidence to identify those phenotypes of special high interest, certainly following clinically, and perhaps intervening earlier than we otherwise would, if there is drug approved for that hemodynamic definition. That is in contrast to having a standard recommendation for everyday clinical practice that's juxtaposed to a guideline that's very comprehensive in its science-based, research-based, evidence-based approach.

Dr Thenappan: The one advantage of lowering the PVR in my mind is identifying the other groups like left heart disease and lung disease. We could probably identify these patients early and aggressively treat their left heart disease and lung disease, which I think would be very important in this patient population.

Dr DuBrock: One challenge I have with the lower PVR threshold is how do you discuss it with patients who have a diagnosis of pulmonary hypertension by the new criteria but don't necessarily qualify for PAH therapy? This happened to me just last week. The patient I saw had a mean PA pressure of 23 with a PVR of 2.2 Wood units. I find it difficult to tell them that they have pulmonary hypertension but to not have any therapeutic options. It's a challenging situation and I'm curious how other people approach and discuss this scenario with patients.

Dr Humbert: I can start briefly. The patient should be characterized more completely in terms of phenotype. An elderly multimorbid patient is not the same than a BMPR2 mutation carriers. As you know, we follow very aggressively BMPR2 mutation carriers before having any symptom. Somebody would carry a BMPR2 mutation with that presentation would be followed very carefully every 6 months and would certainly be treated as early as possible if we can, but we can't treat these people at this stage. Sometimes okay, but at this stage, no. An elderly lady or gentleman with multiple morbidities, I think I would be quite reassuring.

I would say what Thenappan said. These patients have to be optimized in terms of cardiopulmonary comorbidities and followed up by cardiologists and pulmonologists. Every single patient is a story.

Dr Burger: Yes. I would agree with that. That's the stance I've taken. I don't know if it" absolutely the right stance but that we do want to pick this up earlier. We don't know that our therapies have efficacy because it hasn't been studied in a thorough way to know that. Nonetheless, increased attention to monitoring those patients. Close monitoring seems advisable in those groups in whom we think that this is likely to progress. Usually that helps but doesn't mitigate their anxiety. Certainly. I think you have to take extra steps to do that in some cases, but it does present a bit of a challenge, like you said, Hilary, that we're not necessarily used to.

Dr Thenappan: All of us would like to have a clinical trial that shows the safety and efficacy of pulmonary vasodilator therapies in PAH patients with a PVR of 2 to 3 WU. However, I would argue that it will be hard to find these patients. As you all know, still patients present to us at a later stage of the disease with PVR ~ 10 WU. I am worried that we are not going to have enough patients, and it will be difficult to find endpoints as these patients are not very sick. Do we think it's realistic to plan a trial for patients with PVR 2 to 3 WU only?

Dr McLaughlin: I don't think so for the exact reasons you said. For specifically a trial in patients with a PVR of 2 to 3, they're few and far between, and what do you use for the endpoint? They're probably functioning pretty well. I do think that it's quite possible that future trials will change their hemodynamic entry criteria to a PVR of greater than 2 and very likely there'll be so few patients with a PVR between 2 to 3 in those trials but probably drugs will get labeled for that if the entry criteria change.

Dr Thenappan: Thank you.

Dr Humbert: Yes. Maybe you can enrich the information with registry data. There are many good quality registries worldwide and I always insist that the entry criteria in the registry should be enlarged in order to have populations monitored with these very early levels.

Dr Thenappan: That's a great point. I wanted to bring the next topic. The guidelines have recommended risk-stratifying these patients differently at baseline and then at follow-up. At baseline, patients are categorized into low risk, intermediate risk, and high risk categories, but at follow-up, patients are stratified into low risk, low-intermediate risk, high-intermediate risk, and high risk for escalation of therapy. Curious to know your thoughts on this and how we should apply them in practice?

Dr Humbert: Once again, I may start and then the people can debate. We have been pragmatic. Why don't we need for strata baseline? It's because the initial treatment decision is rather simple. It's either 1, 2, or 3 drugs and for people without comorbidities, we strongly advocate for initial oral double combination therapy, or initial triple combination therapy, depending on the presence or absence of high risk. That's pragmatic for the initial presentation, and we advocate for quite aggressive treatment for these people. Then at follow-up, it's more delicate. Having 70% of the patients in the intermediate risk category with traditional risk stratification approaches was not acceptable.

We decided to try to separate those intermediate with the lowest risk of pro-

gression and mortality versus the ones with the highest risk of mortality in order to offer the people with intermediate-high risk a more aggressive approach in terms of treatments. Of course, at baseline, and I know that Vallerie is going to advocate for that and we do it sometimes in France, at baseline, you have some intermediate risk who have a lot of, let's say, borderline high-risk characteristics, and these people may be considered with a more aggressive approach, but I let Vallerie comment.

Dr McLaughlin: Marc knows me so well and I would say that I would gently challenge what he said that it's simple at baseline. It's actually French literature that showed a benefit in some of these intermediate patients who get upfront triple therapy that includes a parenteral prostanoid. I am a strong advocate of perhaps looking a little bit more closely at that intermediate risk group at baseline, and while it does not appear this way in the figure, it's certainly commented upon in the text in the ERS/ESC guidelines that some intermediate risk patients who have high-risk hemodynamics might be considered for more aggressive therapy that includes a parenteral prostacyclin.

It's in there. It's just not in the figure. We do not disagree so much, Marc, but I do gracefully challenge that.

I do think the 4 strata at follow-up is really, really critical. I think both the COMPERA registry and the French registry did a nice job of putting those papers out right before the guidelines and was able to be incorporated there, which I think is very important. I do also want to comment that our risk stratification tools are imperfect and there are other things that should be considered as well. I will have to tell you that my very favorite figure from the guidelines is Figure 4, where it goes into all of the echo images that are so critical to assess the RV. Marc, I tell you, I want to laminate that figure and hang it in every single echo lab in the world because we just don't do that as well. I just would put in a plug for thinking about RV function as a complement to the objective risk assessment tools that we have.

Dr Thenappan: Anybody else?

Dr Burger: Yes. I would agree that incorporation of the echo and the explanations that accompany it, cardiac imaging if it's available, additional ways to distinguish those folks on the high end of that intermediate risk in whom you might want to consider more aggressive therapy at the offset, is very important. It's hard to do because some of these values may be disparate, what you might see on echo versus the hemodynamics versus cardiac MR at times, but when they're consistently bad, I would push for aggressive therapy including an infusion prostanoid upfront.

I really like the 4 stratas. Very simple, very point-based, easy. My only concern is that as advanced therapies hopefully continue to be improved and we're on 3, 4, maybe more, what exactly is low risk? Is up to a 5% mortality at 1 year really low-risk, and are there additional ways to be discriminatory in that group? Maybe REVEAL Lite gives you a little extra discrimination just because each point value has a linear Kaplan-Meier curve that's a little bit different from the one less than that and the one higher than that. I don't know that. It's just speculative, but I think is where if sotatercept gets approved or rodatristat or seralutinib and we're adding that on sequentially for patients in that low risk strata. How do we further tease out lower risk going forward?

Dr Thenappan: I think that's the great thing about the new guidelines. So far, none of the risk stratifications really accounted for RV imaging. The new guidelines have to be congratulated. They have included echocardiographic surrogates of RV-PA coupling and also included extensive cardiac MRI parameters, which I think is important.

Dr Humbert: Yes. Excellent discussion. I must say that I did challenge a lot of my colleagues who do imaging of the heart, and thanks to that, they generated data because to make guidelines you need data. That's something very simple but sometimes people forget, [chuckles] and they don't publish their good quality data, which it may be a single center retrospective but if it's good it will not be 1A. It will be 2BC or 2BD.

We can generate information and Vallerie very kindly mentioned our work in France on 16 patients in 2014 which influenced the guidelines, not with the highest level of evidence, but with good quality information. Of course, guidelines are a work in progress, and there are always questions. When you spot a question, for example, a question about the 4 strata, adding more information, et cetera, we have to generate data. I mean, that's always the big thing. You have to identify the question and try to make a study or at least an analysis which will enrich the guidelines.

Dr Thenappan: Anybody else have any other thoughts on risk stratification?

Dr DuBrock: I like the 4 strata at follow-up since I find it very practical. The parameters are simple, modifiable test results that you generally have available when you're seeing patients. It's helpful to discriminate intermediate-low risk from intermediate-high risk since we all know these are very different patients with different treatment approaches. For my intermediate-low risk patient, I'm probably going to add an oral prostacyclin if they're on dual therapy or change their PDE5 inhibitor to riociguat versus for my intermediate-high risk patients, I'm certainly thinking now about adding parenteral prostacyclin therapy. Although we are always incorporating other information into our clinical decision-making, such as RV function or patient preferences. I think this is a simple but also very practical way to outline specific treatment recommendations.

Dr Burger: I was just going to say I think the other advantage, and Marc has always been very gracious about this, is just emphasizing doing that risk assessment regardless of the tool that you favor, which also emphasizes follow-up that should be regular and then impact treatment decisions. I think that's what everybody agrees on, I hope. Then what tools serve you and are most appropriate for your demographic. Obviously, the choice would be up to you to know

which tool is best as the subject matter expert in your center.

Dr Thenappan: One of the things that I have struggled with is the simplified, noninvasive, risk stratification tools. Expert centers just don't go by the risk stratification alone. They look at the patient as a whole. I'm just worried about how this will be handled outside of the expert centers. For discussion, let's take the noninvasive 3-variable risk stratification model based on 6-minute walk test, BNP, and functional class. When we use this in a relatively older patient with PAH, there are multiple reasons other than PAH that could lead to higher serum BNP levels. For example, atrial fibrillation, left heart failure, and renal dysfunction can make your BNP go up. Likewise, the 6-minute walk distance can be influenced by multiple other factors. Could that lead to overtreatment?

Dr McLaughlin: Thenappan, I think that's one of the reasons why incorporating the echo is so important as well because you have all those comorbidities and other circumstances and they may be high or intermediate-high risk, but if you do the echo and the RV function is normal, then that's always my rationale to say they're not low risk, but their symptoms are not from pulmonary vascular disease. It's more likely related to those comorbidities. Those two really go hand in hand for me.

Dr Burger: That's not an uncommon scenario quite frankly, and we heavily rely on echo as well. To have a high BNP and a suboptimal 6-minute walk, but a cold normal RV is very illustrative and does influence treatment decisions.

Dr DuBrock: I also felt the statement that "low risk is not always achievable, particularly in patients with comorbidities" is really helpful because our patients often have comorbidities and it's hard to achieve low risk in these patients where their functional class and exercise capacity may be driven by cardiac comorbidities. It's good to acknowledge that additional pulmonary hypertension therapy may not help in these scenarios where symptoms are multifactorial. I think that was a helpful comment to include.

Dr McLaughlin: It also works the other way too. Especially in the younger patients who may walk 450 meters, but their predicted is 700 and they can do what they want. Then sometimes they have these big blown out right ventricles. These are the people that keep me up at night because they seem low risk, but the right ventricle is living on the edge. That's why, as Marc said earlier, every patient is an individual. We have broad generalizations that help us, but there are many individualities that need to be considered.

Dr Humbert: Yes. Thanks to all of you for this very rich discussion. In fact, I think as always, when we generate a simple tool, it attracts a lot of attention and people think that the simple tool summarizes the guidelines while it's an addition. It's here to help the clinicians and the relationship with the patients, but if you look at Table 17 in the guidelines, we don't say you have to do only the 3 noninvasive follow-up parameters. Of course, walk distance, functional class, and blood tests, BNP or NT-proBNP have to be done at each visit and as Charlie says, we have to repeat the visit even if the patient is doing well. We have to see them regularly but of course, we also do echo.

In my center, we do quite a lot of [unintelligible 00:34:47] and it's valuable sometimes to refine in young patients with no comorbidities sometimes. They look quite nice with noninvasive tools, but they still have low cardiac index, like at baseline, as Vallerie said, and PROs. I mean, we have to learn to use more PROs. I work in Europe, and we have European reference networks, and we are going to advocate for systematic inclusion of PROs at each follow-up in the patients. For the moment, it is good to have, according to the guidelines, but we may push more, and we need to have good-quality PROs.

Dr Thenappan: We have several new therapies on the horizon for PAH. How might the treatment algorithm change if and when new targeted therapies are approved?

Dr Humbert: Always work in progress. Always work in progress. That's a beautiful image of our field to see that we generate so much new evidence. We should be happy, proud of that. My dream would be that these guidelines become history as soon as possible. We have new data, new information. Clearly with Val right now, we work quite a lot on an invitation to think outside the box and have a look to the future. Of course, guidelines cannot do that at all. Very soon, we will be able to maybe use our current thinking on a look to the future and try to incorporate in a revision of the guidelines. I will let my colleague speak. We want these guidelines to be history as soon as possible.

Dr McLaughlin: Thenappan, I think what we know is that there's one agent, [unintelligible 00:37:28], sotatercept that has a positive phase 2 trial, and more recently, positive phase 3 trial. In the phase 3 trial, that therapy was used in addition to standard of care. Certainly, at the very least, you think it will likely be incorporated on top of standard of care when sotatercept is commercially available.

As you also know, there are other clinical trials with sotatercept looking earlier in the disease state and later in the disease state. Hopefully, that will complement our evidence base and give us more information about how that agent might be used along the continuum of our patients with pulmonary hypertension.

Dr Burger: Yes. I would say you'll have to fall back on the cohort that was studied, the subgroups included versus excluded. What was their functional class? What was the range of hemodynamics, 6-minute walk? Then what were the breakpoints perhaps as it was layered on top of standard background therapy to help guide, I think, future recommendations around when would you recommend using a newly approved agent in your patient? It's not going to be perfect, but I think you would come back to the efficacy trials and try to stick as closely

as possible to the inclusion and exclusion criteria that were used.

Dr DuBrock: I think it's exciting to think about studying novel agents in different phases of the disease. For example, if antiproliferative agents can alter the disease process and vascular remodeling, maybe they are more beneficial earlier in the course of the disease? I think it's a really exciting area but agree that these therapies will be primarily approved for use in those types of patients that were included in the clinical trials, but certainly, I think a lot more is to come hopefully.

Dr Thenappan: The other question I want to bring to you all and get your thoughts on is the comorbidities. The new guidelines nicely differentiate this patient population rather than one-size-fits-all. It recommends monotherapy for PAH patients with cardiovascular comorbidities. At least in the US, the majority of the PAH patients we see have at least 1 cardiovascular comorbidity. How do we address this? If we follow the guidelines, the majority of the patients in our practice would be monotherapy to begin with. Is that what we should do?

Dr Burger: I would say I've heard Marc talk on this, so I've really appreciated his explanation. Despite that, I do struggle clinically with this because as I would approach a patient, if I'm convinced in my professional opinion that they have group 1 PAH, I'm really not paying too much attention to those comorbidities and would treat them with dual oral combination therapy. Now, on a practical note, with drug authorization and tolerance, this often plays out into sequential over a fairly short period of time, which was AMBITION in essence. It took 8 weeks to get a maximal dose of the ambrisentan and the tadalafil in that trial, so it's not too much different than the main trial that showed the efficacy. TRITON's design provided for more rapid upfront therapy in terms of the dosing. I think when I feel like they have it, I want to treat it aggressively, but that's just a practice bias. I can't give you data on that.

Dr Humbert: No, I appreciate that and I agree, in fact. When I see a patient with, to the best of my knowledge, a true group 1 PAH patient, I can of course start with initial combination therapy in those patients. In fact, the guidelines will have to be improved in that section because it can be misunderstood. It doesn't state that you should not. It says that you should be aware that there is an enrichment in patients with poor tolerability of initial combination therapy and with even some risks sometimes when you start with initial double oral combination therapy because of marked comorbidities mostly in elderly people.

At this level, I think that's where the personalized approach is so important and where sometimes a multidisciplinary approach is so important. If you look at the French registry, half of the patients are on monotherapy at first site. We are one of the most aggressive countries in terms of treatments, so it's interesting. In other countries, it's even more. I mean, we all know the registry data, so it means that it's maybe a mistake or maybe something people care about. They think it's better to start with 1 and then sequentially combine. We need to work on that.

We try to put together a randomized control trial in France on that very question, but it will take time and we need to find government funding because no company will fund that. We are currently discussing with the French Ministry of Health to have a support for that.

Dr McLaughlin: I think the issue is that the figure is really an oversimplification when we think about all these issues that we're talking about and individual patients. While both of what you said is correct, it doesn't come through in the figure. When you think about comorbidities, you also think about the duration and severity of those comorbidities, and you think about the severity of the pulmonary vascular disease.

Charlie, that 50-year-old patient with a PVR of 10, who just happens to have systemic hypertension that you're convinced is group 1 PAH, and you treat them along the left side of the algorithm. But it's the 75-year-old woman with hypertension, diabetes, obesity, and a PVR of 3.2 that is on the right side where we would all treat with just one thing, if at all. I think some of those details just aren't as apparent in the algorithm.

Dr Burger: In full transparency because I've been around a while, I have a ton of those patients that are on monotherapy that fit where you were trying to direct the thought process up front in the figure, so I get the nuances. You've explained it. They're on single drug therapy and they're doing fine, and I don't really know what their disease is, to be honest with you.

They seem to be doing well. The RV is remodeled to an extent. Their functional capacity is better. The other markers that we've used have improved and they tolerate the single drug, and I haven't been inclined to escalate therapy.

Dr DuBrock: Rather than defining these patients by the presence of 1 comorbidity, particularly in the United States where these comorbidities are common, I think it's important to consider the whole phenotype of the patient and whether they have multiple comorbidities. Age is also an important factor, and I think that's reflected in these example cases we're describing of varied treatment approaches. I think looking beyond just the presence or absence of 1 comorbidity such as obesity to determine if an individual has that left heart phenotype with multiple cardiac comorbidities is perhaps a better way to characterize the patients where our treatment approach might be different from someone who just has obesity with a BMI of 32.

Dr Thenappan: Moving on, do the new guidelines apply to non-European patients? Should they be adapted worldwide, or should they be modified? If not, what are all the considerations for diagnosis and management outside of the Western world? How should the guideline be adopted?

Dr Humbert: I can maybe start with my feeling. When we made the guide-

lines, the idea was global. We are now treating close in the borders of Europe. It's a global guideline. Of course, we know very well that there are countries where the drugs we propose are not available, not affordable. That's certainly the biggest challenge because I think US, Europe it can be a debate, but it's a rich-people discussion.

There are many countries and the vast majority of countries have no access to all the treatments we have. We want it to be global, and that's the reason why we are very, let's say, educational and that people should not focus only on the table and figures but read the text. When the text says you have to read the supplement, read the supplement, and read the reference. It's not a very simple guide, you open it on your mobile phone and you know how to treat them. That's important.

Then, of course, it's improvable and we need to improve it. What I love in our field is that we have the straight guidelines and we have the world symposium and other occasions to think outside the box and go a little bit quicker. The last thing I wanted to say was about the way we work in these guidelines. We are really strict in terms of evidence, and that's something we need to know. If we have a conviction, we are convinced that something is wrong, we have to do a study. I am myself trying to address some points, but it takes time.

Dr Burger: I would say that from my perspective, that more standardization around our approach to these patients as the basis for careful consideration and application to the individualized situation the better. It shouldn't be restricted to a certain part of the world, certainly. Having said that, there's wild disparities, as Marc just pointed out, in availability of drugs and clinical practice, and we just have to be mindful of that.

I think you go from the guidelines to a diagnosis and a recommendation for management in an individual. It's that translation and the expertise that's involved in order to make that translation is the most important aspect of it. We all hope that patients get to experts who have some experience and expertise to be able to make wise decisions. We know that isn't always the case, but that's a limitation that we face particularly in the US.

Dr Thenappan: Thank you, all. That's great. The next topic I would like to get your thoughts on is the individualized care for patients with PH due to left heart disease and lung disease with the PVR greater than 5 WU.

I will start with Dr Humbert, curious about why the PVR of 5 WU? How should we approach these patients? We know that there is no indication for pulmonary vasodilator therapy in these patients except for those with PH due to interstitial lung disease.

Dr Humbert: Yes. It was once again based on data which are not as strong as a randomized control trial but registry data. Because of the guidelines, we advocated for publication of registry data in group 2 and group 3 PH. Group 2 did not produce that many, but group 3 clearly identified both in COPD and interstitial lung disease that the PVR above 5 identifies a very high risk group.

Once again, you have to individualize the approach. If you have very advanced lung disease, it's not the same story than minimal shadows on both lungs. The devil is in the details, but it's a starting point. We don't advocate for treating mild PH in group 2 and group 3. We think you have to optimize the treatment of the comorbidity, but if you have significant elevation in PVR, you may consider, on a case-per-case approach, a treatment decision which has to be very careful and followed up very, very systematically.

My own approach is to do a randomized control trial, and that's something we try to do. In the US, you have approved drugs also for some patients with group 3 PH. You have to follow your own local possibilities.

Dr McLaughlin: Yes, I would agree. These are very challenging patients. I think it's always important to put in context the severity of their underlying disease. As Marc said, someone with horrible COPD and a PVR of 5, they may not benefit. They may actually get worse with some of these therapies. I think we have to have very long conversations with patients about the potential risks and potential benefits when we consider using these therapies on an off-label basis and watch them very closely.

Dr Burger: Yes. I think emphasizing the PVR particularly in the PHILD, that's born out in the increased data where PVR over 4 identified the group that had the best response and it was no great shakes at that, 21 meters in the treatment cohort at 16 weeks. It was the 10 meter deterioration in the placebo group that drove the statistical significance.

I don't know about COPD. I've been less impressed just on an individual basis. Obviously, the PERFECT trial was stopped with some safety concerns. I worry that in group 2 about obviously increasing upstream pulmonary flow when the cause of the PH is downstream in the left heart.

Even with a higher PVR, I do look carefully at the wedge and the v-wave with an acute vasodilator trial just to get some sense of what's happening acutely. The hemodynamic response does influence my decision, but that's just my experience.

Dr DuBrock: I think it's important to highlight these definitions and thresholds for PH from left heart disease. I don't typically treat them with pulmonary vasodilator therapy, but there are those combined precapillary, postcapillary pulmonary hypertension patients with a PVR greater than 5 who have disproportionate PH, and I think those patients really need further study. It's not uncommon that we're seeing those patients in clinic, and it's really hard to know what to do with them. Defining that PVR threshold, I think, is helpful just to guide further study of these patients.

My approach generally in PH ILD is to use inhaled treprostinil since it is an approved therapy in the United States and it is nice to have something to offer these patients without a lot of treatment options.

Dr Burger: I rely a great deal on chest imaging. If there is a great deal of

parenchymal scarring, then I think there is end-stage lung disease. We look at these patients and we know the lung is largely dead; therefore, it's a mechanical problem that requires a mechanical fix. If they're eligible for a transplant, you direct them that way. If they're not, it's difficult.

Dr Humbert: Yes. It's very important, Charlie, what you just said. We should never forget the transplantation in some of these patients because it's really a life-saving approach and for the most advanced patients, it should be considered.

Dr Thenappan: This is great. We are at the top of the hour. Maybe we can just end with closing remarks from everyone on the guidelines.

Dr Humbert: If you want, I start. Guidelines are really a work in progress, and at the end of the guidelines we have a section, Gaps in Evidence. That's really what you have to focus on. We need to have our field move forward. Maybe the next guidelines will be less comprehensive because we don't have to repeat the entire story. As a member of the European Respiratory Society, we more and more recommend to select a few questions and use a grade approach and we have a question, [unintelligible 00:56:46], what we call [unintelligible 00:56:47], and a grade approach.

It allows us to focus on the gaps in evidence, so maybe that's what we will do one day. Thank you for the invitation.

Dr McLaughlin: Marc, I just want to congratulate you and the whole team. It was really quite a tour de force, and we've learned so much from the guidelines. It's also raised some questions and some discussions and some opportunities to discuss at the world symposium and the next guidelines. That's actually good, right? If it was all cut and dry, it would be very boring. I think it's raised some important questions, but I just also want to emphasize, some of those figures are so beautiful, I want your artist, right? The echo figures, I love. The symptoms figures, I love. I think it's a really wonderful teaching tool.

Dr Burger: I would agree completely, Val. It's a wonderful starting point for conversations like the one we just had today, right? You can't begin to discuss what the definition should be or what the treatment indications are unless you have that starting point. It's a wonderful job by you and your committee, Marc. It's really been a pleasure participating today.

Dr DuBrock: I agree. It is a tour de force that was fascinating to read as it highlighted both the current evidence and also the gaps in evidence and areas for future research, which is inspirational in a way. I think this is an excellent framework that'll help guide us moving forward with advancing the field, which is really important. Congratulations and excellent work and thank you for the opportunity to discuss with everyone here today. It was an honor and was really informative and enlightening, so thanks.

Dr Thenappan: Thank you all again. It was a very enriching, thoughtful, and thorough discussion. I really appreciate everyone's time, knowledge and effort.

Real-World Implementation: Nursing Role in Balancing the Art and Science of PAH Risk Assessment

Susanne McDevitt, DNP, ACNP-BC
University of Michigan
Ann Arbor, MI

Melisa Wilson, DNP, ACNP-BC
AdventHealth Orlando
Orlando, FL

Comprehensive serial risk assessment in pulmonary arterial hypertension has shown to determine prognosis, monitor disease progression, and guide treatment decisions. The treatment goal is to achieve a low-risk status, which is associated with lower mortality rate. However, use of formal risk assessment in clinical practice has been inconsistent due to numerous barriers related to the multivariable nature of the scores. This publication reviews strategies to increase risk evaluation in daily clinical practice, while emphasizing the role of the RN and APRN in implementing risk assessment calculation and skillful communication to the patient-family dyad to promote open dialogue with shared decision making and improved patient outcomes.

INTRODUCTION

Pulmonary arterial hypertension (PAH), World Health Organization Group 1, is a rare, progressive disease of the pulmonary vasculature leading to right ventricular failure. While no curative therapy is available for PAH, options for medical therapy are increasing. Despite advances in treatment options, morbidity and mortality remain high, reaching median survival for idiopathic PAH of merely 7 years.[1]

Persistent suboptimal outcomes have led to novel care approaches.[2-4] Specifically, comprehensive PAH risk assessment has been developed to determine prognosis, monitor disease progression, and guide treatment decisions based on therapeutic response.[2] Numerous risk stratification tools have been validated to stratify patients into low, intermediate, and high risk categories,[4] including REVEAL 1.0, REVEAL 2.0, REVEAL Lite 2, COMPERA method, SPAHR method, FPHR method, the Bologna strategy, and the Four Strata methodology.[4,5] The overall treatment goal is to achieve a low-risk stratification by escalating medical therapy, which is associated with a lower mortality rate.[6] Routine, comprehensive evaluation of risk status is included in the most recent clinical care guidelines for PAH and is considered current evidence-based practice.[6,7] Early and serial risk assessment is recommended, with escalation of medical treatment until a low-risk status is achieved.[6] Low-risk status is associated with a mortality risk of <5% at year 1 in comparison to >20% for a high-risk patient.[2,7] Regular, multifactorial risk assessment may lead to favorable outcomes for each patient.[8]

Even with this state-of-the-art approach, formal risk assessment in pulmonary hypertension (PH) clinical practice is inconsistent or absent.[3,4] Per recent survey data, merely 59% of clinicians in the United States use risk assessment tools in PAH management.[4] Researchers have identified numerous barriers to risk assessment, including complexity of the tool, number of diagnostic parameters required, need for invasive testing, time constraints, lack of integration into the electronic medical record, inadequate administrative support, and lack of education, training, and awareness.[4,9] While validated risk assessment tools may improve patient outcomes, novel strategies are warranted to increase feasibility of incorporating risk assessment tools into routine practice.[2,3,10]

Current tools use 3 to 13 variables to stratify patient risk, employing modifiable and nonmodifiable parameters, as well as invasive and noninvasive measures.[3,11] However, the literature fails to indicate the most appropriate risk tool for clinical practice nor frequency of use. Given this limitation, the clinician is left to choose the most feasible tool for individual clinical practice, usual diagnostic testing and treatment practices, and overall knowledge of this construct. While clinical testing practices may vary among PH centers, specific parameters may not be readily available for complete risk assessment scoring.

Though several modalities exist to evaluate a patient's risk stratification, it was noted that most patients did not meet the low-risk criteria even after being medically treated for PAH.[5] The majority of patients were deemed to remain in the intermediate-risk category, and that a more granular risk evaluation is required to differentiate the large cohort of *intermediate* patients.[12] This recent refined risk methodology stratifies into 4 strata including low, intermediate-low, intermediate-high, and high risk.[5,11] Boucly and colleagues noted the 4-strata method was more sensitive in measuring changes in risk after treatment and demonstrated better discrimination of short-term and long-term mortality.[11] The hope is that patients and PAH clinicians may make better informed treatment decisions based on this more refined approach. Future studies with the newer 4 strata methodology are needed to determine if a greater number of PAH patients will achieve low risk status.

Correspondence: smcd@med.umich.edu

Furthermore, previous data have shown that clinician subjective gestalt is inferior to formal, objective risk stratification.[13] Clinical judgment, which can underestimate or overestimate risk, may include subjective interpretation of patient history, exercise tests, hemodynamics, and imaging. Inaccurate risk stratification is suboptimal, as intermediate-risk and high-risk patients face worse outcomes. Sahay and colleagues found that patients with moderate or high activity levels were more likely to have discrepant subjective and objective risk stratification.[13]

The evidence suggests inconsistent use and multiple barriers to risk assessment.[1,4,9] Wilson and colleagues cited the most frequent rationale for inconsistent use as lack of time and lack of technology or electronic health record integration.[1,4,9] Undoubtedly, the evidence supports developing a simple method to calculate a risk score during routine medical visits. A more streamlined tool such as REVEAL Lite 2 or Four Strata methodology may increase the use and sustainability of risk assessment in PAH. The aim of this publication is to share expert PAH allied health clinician experience to mitigate barriers to incorporating risk assessment and effective communication regarding risk into clinical practice, to fully inform patients, enhance shared decision making, and improve outcomes.

RISK ASSESSMENT IMPLEMENTATION

Numerous strategies to ensure timely, accurate, and evidence-based risk assessment may be employed by the PH Care Team and specifically PH nurse clinicians. Due to the growing number of risk assessment tools available, the PH center should build consensus on which tools to use and at which time intervals in a patient's disease trajectory. In our experience, we recommend use of a comprehensive risk tool such as REVEAL 2.0 at index diagnosis and then more streamlined tools at each follow up visit such as REVEAL Lite 2 and Four Strata methodology. Consistent tools allow for longitudinal tracking for individual patients. With certainty, each PH care team member who is responsible for assessing or discussing risk with a patient should be fully educated on routine risk tools and methods for scoring. Nursing PH care team members should have autonomy to complete risk assessment, similar to other PH colleagues such as physicians and advanced practice providers.

Risk score implementation may be completed in multiple formats by the PH clinician. In our experience with formal quality improvement projects, automation of risk scoring tools into the electronic health record (EHR) has the greatest effect on consistent use and tracking of patient risk status.[14,15] In PH centers with access to Epic or Cerner, EHR technical support teams can assist with how to create and implement automated risk scoring. We recommend use of *flowsheets* and *smartphrases* to adeptly include a point of care risk score into medical documentation. This allows longitudinal tracking of scores over time in a streamlined format. Alternatives to use of automated EHR methods include use of web-based calculators such as the PH Outcomes Risk Assessment website,[16] use of risk assessment tear pads, and calculation sheets. PH programs may use support staff to assist with gathering risk assessment parameter results prior to or at the time of clinic visits, as a mechanism to improve documentation.[17]

With the increase in telemedicine in recent years, formal risk assessment may present more challenges. Personal health devices such as smartphones, smartwatches/bands, and various health-monitoring apps provide an increasing amount of information that allow for remote PAH risk assessment in some situations. However, the digital divide and lack of technological access remains a tremendous limitation for a large percentage of patients and areas in the United States. In our experience, the greatest challenge in remote risk assessment is obtaining an accurate 6-minute hallwalk distance from a home setting. Mobile-based 6-minute walk testing is an area of recent study.[18]

NURSES' ROLE IN RISK ASSESSMENT PATIENT ENGAGEMENT

PH nurse clinicians, because of their frequency of contact and close nature of therapeutic relationship, are well poised to assist PH patients and their families throughout the disease trajectory. PAH risk assessment should be included in patient and family education in addition to disease state, medications, self-care management, and goals of treatment. Just as all of nursing care is based, communication regarding risk status should be grounded in principles of ethics, individual care, and shared decision making.[19] In our experience, using compassionate and patient-centered communication techniques, an individual's risk status can be used as a tool to fully inform a patient regarding disease severity, treatment recommendations, and mutual hopes for their future therapeutic response. Patients and their families coping with a serious illness such as PAH require adequate information to make informed decisions about treatment options.[19]

Nurses are positioned to effectively balance the art and the science of discussing a PH patient's individual risk profile. While PH patients are afforded the benefits of a multidisciplinary team from initial diagnosis to treatment, nurses play a vital role in communication, and communication is a powerful therapeutic tool in PH care. At the time of diagnosis or during turning points in the PH journey, communication has the potential to empower a patient with a sense of control while reducing uncertainty, stress, and anxiety.[19] Similar to cancer or other life-threatening illnesses, PH nurses are able to provide information across the illness trajectory related to prognosis and quality of life issues. PH nurses provide a safe place for patients to disclose complex feelings about their diagnosis, receive information to help them maintain a sense of control, and continue to have a sense of hope. Thoughtful discussions regarding PH risk status can improve conversation of values, goals, and preferences and facilitate collaboration with the PH team. Nurses offer emotional support in coping, illness information, and understanding of risk stratification. Similar to oncology nursing, by the nature of the PH illness trajectory, PH nursing demands more attention to palliative care communication as it involves both

patient and family.[20] Wittenberg and colleagues offer communication strategies based on the COMFORT Communication curriculum, created for the field of oncology but with relevance in the PH disease course (Table 1).[20,21] This provides tangible communication techniques that may enhance patient and family trust and lead to meaningful discussions about PH illness status, care, and treatment decisions.

In addition, patients in the current era are provided with their own medical documentation and deserve a thoughtful and skilled explanation of risk evaluation included in their office visit notes. Specifically, we recommend an open discussion at index diagnosis of risk status, informing the patient with verbiage including a risk category is a tool for the clinician to know "how well a patient may do in the next 1 year." Including risk status in the discussion of PH therapy recommendations has been useful to support the need for more aggressive treatment such as triple and parenteral prostacyclin therapy, as well as refer for lung transplant evaluation sooner. Per previous studies, an informed patient may be more likely to take an active part in their care.[17]

Skillful communication to engage patients with serious PAH findings can be a powerful tool in shared decision making, which is a key component of patient-centered health care. Shared decision making makes patients feel they are listened to and their needs are prioritized, which may have a positive effect on outcome.[22] We find patients and families find comfort in hearing that while they may have evidence of an initial high-risk status, the team of expert PH clinicians will strive to improve the risk profile with close and compassionate care and follow up. We share with the patient-family dyad our hopes for their future, including potential benefits derived from escalation of PH therapy. On the other hand, when we are unable to improve a patient's risk status because of end-stage disease trajectory, use of risk status may also be useful to frame delicate discussions about goals of care and end-of-life decisions. The REMAP framework (REframe, Map, Align, Plan) by Ismail and colleagues provides a tool to enhance a shared treatment plan that is based on patient values and goals (Table 2).[23] These conversations help a patient take an active role in their overall disease management. In various PH illness trajectory scenarios, risk status information allows for patients to make fully informed treatment decisions.

Table 1. Overview of the COMFORT Communication Curriculum[21]

Module	Communication processes
Communication	Understanding the patient's story
	Recognizing task and relationship practices
Orientation and options	Gauging health-literacy levels
	Understanding cultural humility
Mindful communication	Engaging in active listening
	Understanding nonverbal communication
	Being aware of self-care needs
Family	Observing family communication patterns
	Recognizing caregiver communication patterns
	Responding to the varying needs of family caregivers
Openings	Identifying pivotal points in patient/family care
	Finding common ground with patients/families
Relating	Realizing the multiple goals of patients/families
	Linking care to quality-of-life domains
Team	Developing team processes
	Cultivating team structures
	Distinguishing successful collaboration from group cohesion

Table 2. REMAP Model of Communication[23]

Step	Action
REframe	Assess patient's understanding of illness trajectory
Map	Map patient values
Align	Align with patient stated values
Plan	Propose a plan

DISCUSSION

In our experience, building PH clinical team consensus on risk assessment tool timing and use in addition to EHR risk score integration are feasible and effective methods of increasing risk status documentation. Provider barriers may be greatly reduced, and evidence-based clinical care is enhanced. Formal risk stratification is superior to clinician gestalt and should be employed for all Group 1 PAH patients at every visit. Risk stratification is an integral step in the management of PAH patients, and achieving and maintaining a low-risk profile is the goal of treatment.[6]

PH nurse clinicians including RNs and APRNs play a crucial role in balancing the art and science of understanding and communicating risk assessment. Use of formal communication tools and strategies such as the COMFORT Communication curriculum and REMAP model may provide a strong foundation for nurse-patient discussion of risk status. Further evaluation of the effect of patient risk status education on patient treatment decisions and outcomes is warranted.

References

1. Kanwar M, Raina A, Lohmueller L, Kraisangka J, Benza R. The use of risk assessment tools and prognostic scores in managing patients with pulmonary arterial hypertension. *Curr Hypertens Rep*. 2019;21(6):45. doi:10.1007/s11906-019-0950-y.
2. Benza RL, Gomberg-Maitland M, Elliott CG, et al. Predicting survival in patients with pulmonary arterial hypertension: the

REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest*. 2019;156(2):323-337. doi:10.1016/j.chest.2019.02.004.
3. Benza RL, Kanwar MK, Raina A, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. *Chest*. 2021 Jan;159(1):337-346. doi:10.1016/j.chest.2020.08.2069.
4. Wilson M, Keeley J, Kingman M, Wang J, Rogers F. Current clinical utilization of risk assessment tools in pulmonary arterial hypertension: a descriptive survey of facilitation strategies, patterns, and barriers to use in the United States. *Pulm Circ*. 2020;10(3):1-10. doi:10.1177/2045894020950186.
5. Hoeper MM, Pausch C, Olsson KM, et al. COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension. *Eur Respir J*. 2022;60(1):2102311. doi:10.1183/13993003.02311-2021.
6. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119. doi:10.1093/eurheartj/ehv317.
7. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731. doi:10.1093/eurheartj/ehac237.
8. McLaughlin VV, Hoeper MM, Channick RN, et al. Pulmonary arterial hypertension-related morbidity is prognostic for mortality. *J Am Coll Cardiol*. 2018;71(7):752-763. doi:10.1016/j.jacc.2017.12.010.
9. Raina A, Humbert M. Risk assessment in pulmonary arterial hypertension. *Eur Respir Rev*. 2016;25(142):390-398. doi:10.1183/16000617.0077-2016.
10. Sitbon O, Benza RL, Badesch DB, et al. Validation of two predictive models for survival in pulmonary arterial hypertension. *Eur Respir J*. 2015;46(1):152-164. doi:10.1183/09031936.00004414.
11. Boucly A, Weatherald J, Savale L, et al. External validation of a refined 4-strata risk assessment score from the French pulmonary hypertension registry. *Eur Respir J*. Published online November 4, 2021:2102419. doi:10.1183/13993003.02419-2021
12. Hoeper MM, Pausch C, Olsson KM, et al. COMPERA 2.0: A refined 4-strata risk assessment model for pulmonary arterial hypertension [published online ahead of print November 4, 2021]. *Eur Respir J*. 2022 Jun 30;59(6):2102419. doi:10.1183/13993003.02311-2021.
13. Sahay S, Tonelli AR, Selej M, Watson Z, Benza RL. Risk assessment in patients with functional class II pulmonary arterial hypertension: comparison of physician gestalt with ESC/ERS and the REVEAL 2.0 risk score. *PLoS One*. 2020;15(11):e0241504. doi:10.1371/journal.pone.0241504.
14. Wilson MA, Benza R, Bowers M, Tarver J, Dawson K. Standardized approach to guideline adherence through a single mortality risk assessment tool in pulmonary arterial hypertension by quality improvement methods. *Am Coll Cardiol*. 2021 May;77(18 Suppl 1):1976. doi:10.1016/S0735-1097(21)03332-5.
15. McDevitt S, Bowers M, McLaughlin VV, Moles V. Increasing documentation of REVEAL Lite 2 risk assessment in management of pulmonary arterial hypertension [published online ahead of print May 2022]. *Mich Med RN Poster Day*.
16. Ohio State University. PHORA – Pulmonary Hypertension Outcome Risks Assessment. http://myphora.org. Accessed January 26, 2023.
17. Wilson M, Keeley J, Kingman M, et al. Clinical application of risk assessment in PAH: expert center APRN recommendations. *Pulm Circ*. 2022;12(3):e12106. doi:10.1002/pul2.12106.
18. Salvi D, Poffley E, Tarassenko L, Orchard E. App-based versus standard six-minute walk test in pulmonary hypertension: mixed methods study. *JMIR mHealth uHealth*. 2021;9(6):e22748. doi:10.2196/22748.
19. Dahlin C, Coyne P. End of life: reflecting on things that matter. *Semin Oncol Nurs*. 2017;33(5):483-488. doi:10.1016/j.soncn.2017.09.006.
20. Wittenberg E, Reb A, Kanter E. Communicating with patients and families around difficult topics in cancer care using the COMFORT communication curriculum. *Semin Oncol Nurs*. 2018;34(3):264-273. doi:10.1016/j.soncn.2018.06.007.
21. Wittenberg E, Ferrell B, Goldsmith J, Ragan SL, Paice J. Assessment of a statewide palliative care team training course: COMFORT communication for palliative care teams. *J Palliat Med*. 2016;19(7):746-752. doi:10.1089/jpm.2015.0552.
22. Faiman B, Tariman JD. Shared decision making: improving patient outcomes by understanding the benefits of and barriers to effective communication. *Clin J Oncol Nurs*. 2019;23(5):540-542. doi:10.1188/19.CJON.540-542.
23. Ismail R, Hegab S, Kelly B, et al. Serious illness conversations in pulmonary hypertension. *Pulm Circ*. 2021;11(4):20458940211037530. doi:10.1177/20458940211037529.

Advances in
Pulmonary Hypertension
Pulmonary Hypertension Association
801 Roeder Road, Suite 1000
Silver Spring, MD 20910-4496