Scientific Sessions and Education
for Medical Professionals
Thursday, June 16 – Sunday, June 19, 2016

PH Around the World
Dear Friends,

Welcome to PHA’s 2016 International PH Conference and Scientific Sessions, 25 Years of Progress: Changing the History of PH. Since the founding of PHA in 1991 and the first Conference in 1994, together we have come a long way in our collective fight against pulmonary hypertension.

This 25th anniversary year for PHA is a chance to reflect on our many accomplishments. Every day, PH treatment and research is continuing to advance. We now have 14 FDA-approved therapies for PH. Many Conference attendees arriving here today have been significantly impacted by these advancements, yet we still have much to accomplish.

The 25th anniversary also gives us a chance to peer into the future where the most effective early diagnosis is made and treatments improve and lengthen the lives of those affected by PH.

The Scientific Sessions are designed for researchers and medical professionals to hear the latest in scientific advances and exchange ideas for future research. This year’s theme, “PH Around the World,” will be explored by internationally recognized experts in PH and related fields all coming together to exchange ideas as we look for more effective treatments for PH. This year’s theme will additionally focus on the differences in the diagnosis, epidemiology, pathophysiology, and medical management of PH and PAH between developed and developing regions in order to facilitate the development and dissemination of novel treatment strategies for these conditions.

The Scientific Sessions begin Thursday evening with viewing of research posters submitted for Conference. At this poster session, researchers and attendees of the Scientific Sessions will have an opportunity to discuss the findings, generate future ideas, and identify collaborators for future work. The posters will be available throughout Conference for review.

Friday’s sessions feature major leaders in PH with a focus on the etiology of PH around the world and the challenges faced in accessing appropriate diagnostic and treatment options.

While you’re here, we also invite you to take part in the PH Fundamentals: Continuing Education Sessions for Medical Professionals. These sessions target medical professionals interested in learning more about the basics of PH, and will take place Friday through Sunday.

There is also an opportunity for PH specialists that are considering applying for designation as a PHCC or RCP to get advice and assistance with understanding the complex application and review process.

Conference is an incredible opportunity for us to see how far we’ve come as a community of patients, family members, medical professionals and friends. On this 25th anniversary year we are positioned to look back at where we started, celebrate where we are, and plot a course for the future.

Allow yourself to get swept up in the magic of us all coming together as a community at Conference and I am sure you will be invigorated with new energy and purpose. Don’t forget to take in all that the Conference has that is not on the schedule – a chance to network, connect and reconnect, reflect, celebrate, and have fun!

Thank you for joining us for this amazing event.

Karen A. Fagan, MD
Chair, Scientific Leadership Council
Professor of Medicine and Pharmacology Chief
Division of Pulmonary and Critical Care Medicine
University of South Alabama
Mobile, Ala.

Thank you for attending the Scientific Sessions and PH Fundamentals: Continuing Education Sessions! Unlike the Medically Led Sessions during Conference, the Scientific Sessions and PH Fundamentals: Continuing Education Sessions are dedicated to the exchange of information among medical professionals who work in the field of pulmonary hypertension. If you are not a medical professional, we ask that you refrain from asking questions during the presentations.
Welcome

Dear Colleagues and Friends,

Welcome to PHA’s 2016 International PH Conference and Scientific Sessions! As in years past, this Conference is sure to be energizing, inspiring and motivating. As the only PH-specific Conference that brings together health care providers, patients and caregivers under one roof, this meeting provides a unique and exciting opportunity to reflect on the progress we made, identify knowledge gaps and areas of need, and develop new ideas for the path forward. We are looking forward to four days of learning, exchanging ideas and fun.

This year’s Conference marks two milestones. First, we celebrate PHA’s 25th anniversary. And second, with epoprostenol just having had its 20th anniversary since approval by the Food and Drug Administration, we can now look back on more than two decades of availability of PAH-specific therapies. Acknowledging and celebrating these achievements, we also realize that PH is a disease that still affects millions of people throughout the world. We therefore elected to have “PH Around the World” as the theme of this year’s Scientific Sessions. We believe that this provides a unique platform to celebrate our successes and to identify pathways for progress in reaching our ultimate goal of understanding and curing PH in all parts of the world.

The Scientific Sessions program will take you on a journey around the world that will review what we have learned from treating PH patients in the last 25 years, discuss the hallmarks of common PH types in both the western and the developing world, identify strategies on making PAH treatments available to everyone with PAH, and reflect on new and emerging treatment modalities. The plenary session will be complemented by an abstract poster session, where new and established investigators will present their work. With the last 25 years of PAH treatment being such a success story, and with the understanding that we all live and breathe in a global environment, we hope that the presentations and discussions at the Scientific Sessions will generate new ideas and foster new collaborations to advance the care of PH patients worldwide.

Being a member of the Scientific Sessions Committee allowed me the privilege of working with a large number of inspiring and energetic individuals who contributed to the 2016 International PH Conference and Scientific Sessions. In particular, I would like to thank my fellow committee members, our program faculty, the PHA staff and the many volunteers, medical professionals, patients, and caregivers at this Conference. It is through their motivation, dedication and efforts that we can continue to change the history of PH. I wish everyone an educational and fun-filled weekend as we enter the next 25 years of progress.

Thanks for attending and welcome!

Tim Lahm, MD
Chair, SLC Scientific Sessions Committee
Associate Professor of Medicine and Cellular & Integrative Physiology
Division of Pulmonary, Critical Care, Sleep and Occupational Medicine
Indiana University School of Medicine
Indianapolis, Ind.
# Full Medical Education Agenda

## Thursday, June 16

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:00 p.m. – 6:00 p.m.</td>
<td>PH Care Centers (PHCC) Workshop</td>
<td>Trinity 5, Omni</td>
</tr>
<tr>
<td>5:30 p.m. – 7:30 p.m.</td>
<td>Scientific Sessions &amp; PH Clinicians and Researchers Poster Hall Reception&lt;br&gt;&lt;i&gt;Sponsored by Actelion Pharmaceuticals&lt;/i&gt;</td>
<td>Arts District Foyer, Omni</td>
</tr>
<tr>
<td>6:30 p.m. – 9:30 p.m.</td>
<td>PH Professional Network Dinner&lt;br&gt;&lt;i&gt;(See page 4)&lt;/i&gt;&lt;br&gt;&lt;i&gt;Sponsored by Accredo Health Group and Steady Med Ltd.&lt;/i&gt;</td>
<td>Dallas D/H, Omni</td>
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## Friday, June 17

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Location</th>
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<tbody>
<tr>
<td>7:00 a.m. – 8:00 a.m.</td>
<td>Scientific Sessions Continental Breakfast</td>
<td>D Ballroom Foyer, Convention Center</td>
</tr>
<tr>
<td>8:00 a.m. – 12:55 p.m.</td>
<td>Scientific Sessions: Part I&lt;br&gt;&lt;i&gt;(See pages 11–18)&lt;/i&gt;</td>
<td>D2/D3, Convention Center</td>
</tr>
<tr>
<td>1:00 p.m. – 2:30 p.m.</td>
<td>Conference Opening: Celebrating 25 Years of PHA&lt;br&gt;&lt;i&gt;(See General Conference Program Book)&lt;/i&gt;&lt;br&gt;&lt;i&gt;Sponsored by Bayer Healthcare&lt;/i&gt;</td>
<td>Dallas A, B, C, D &amp; H, Omni</td>
</tr>
<tr>
<td>2:30 p.m. – 5:30 p.m.</td>
<td>Scientific Sessions: Part II&lt;br&gt;&lt;i&gt;(See pages 19–21)&lt;/i&gt;</td>
<td>D2/D3, Convention Center</td>
</tr>
<tr>
<td>2:30 p.m. – 3:30 p.m.</td>
<td>PH Fundamentals: Continuing Education for Medical Professionals&lt;br&gt;&lt;i&gt;(See pages 22–23)&lt;/i&gt;</td>
<td>D1/D4, Convention Center</td>
</tr>
<tr>
<td>5:30 p.m. – 6:45 p.m.</td>
<td>Unopposed Poster Viewing</td>
<td>Arts District Foyer, Omni</td>
</tr>
<tr>
<td>8:30 p.m. – 10:00 p.m.</td>
<td>Fellow and Junior Faculty Reception</td>
<td>Katy Trail, Omni</td>
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## Saturday, June 18

<table>
<thead>
<tr>
<th>Time</th>
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<th>Location</th>
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<tbody>
<tr>
<td>9:30 a.m. – 10:30 a.m.</td>
<td>PH Fundamentals: Continuing Education for Medical Professionals&lt;br&gt;&lt;i&gt;(See pages 24–25)&lt;/i&gt;</td>
<td>D1/D4, Convention Center</td>
</tr>
<tr>
<td>11:00 a.m. – 12:00 p.m.</td>
<td>PH Fundamentals: Continuing Education for Medical Professionals&lt;br&gt;&lt;i&gt;(See pages 26–27)&lt;/i&gt;</td>
<td>D1/D4, Convention Center</td>
</tr>
<tr>
<td>1:30 p.m. – 2:30 p.m.</td>
<td>PH Fundamentals: Continuing Education for Medical Professionals&lt;br&gt;&lt;i&gt;(See pages 28–29)&lt;/i&gt;</td>
<td>D1/D4, Convention Center</td>
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## Sunday, June 19

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<thead>
<tr>
<th>Time</th>
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<tr>
<td>8:00 a.m. – 9:00 a.m.</td>
<td>PH Fundamentals: Continuing Education for Medical Professionals&lt;br&gt;&lt;i&gt;(See pages 30–31)&lt;/i&gt;</td>
<td>D1/D4, Convention Center</td>
</tr>
<tr>
<td>11:00 a.m. – 12:00 p.m.</td>
<td>PH Fundamentals: Continuing Education for Medical Professionals&lt;br&gt;&lt;i&gt;(See pages 32–33)&lt;/i&gt;</td>
<td>D1/D4, Convention Center</td>
</tr>
</tbody>
</table>
Scientific Sessions Agenda
Friday, June 17
Scientific Sessions will take place in D2/D3, Convention Center, unless otherwise noted below.

<table>
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<tr>
<th>Time</th>
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</table>
| 7:00 a.m. – 8:00 a.m. | Scientific Sessions Continental Breakfast  
(D Ballroom Foyer, Convention Center)                                                                                           |
| 8:00 a.m. – 8:15 a.m. | Welcome and Introduction                                                                                                                                                                                                                                                                                                           |
| 8:15 a.m. – 9:05 a.m. | What Has Happened in the Last 25 Years: Global Perspectives/20 Years of Prostacyclins  
See page 11                                                                                                             |
| 9:05 a.m. – 9:20 a.m. | Oral Abstract Presentation: PHD2 Deficiency in Endothelial Cells and Hematopoietic Cells  
Induces Obliterative Vascular Remodeling and Severe Pulmonary Arterial Hypertension  
Recapitulating Clinical PAH  
See page 12                                                                                                                          |
| 9:20 a.m. – 10:10 a.m. | What Have We Learned from Modern Worldwide Registries?  
See page 13                                                                                                                                         |
| 10:10 a.m. – 10:25 a.m. | Oral Abstract Presentation: A Selective TGFβ Ligand Trap Attenuates Pulmonary Arterial Hypertension  
See page 14                                                                                                                                         |
| 10:25 a.m. – 10:35 a.m. | Coffee Break (D Ballroom Foyer, Convention Center)  
Sponsored by Actelion Pharmaceuticals and Accredo Health Group                                                                                   |
| 10:35 a.m. – 11:35 a.m. | Etiologies of PH Across the World  
See page 15                                                                                                                                         |
| 11:35 a.m. – 11:50 a.m. | Oral Abstract Presentation: Evidence of Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension  
See page 16                                                                                                                                         |
| 11:50 a.m. – 12:40 p.m. | Panel Discussion: Enhancing Access to Drugs in Developing Countries, Challenges of Making Generic Drugs Available in Developing Countries  
See page 17                                                                                                                                         |
| 12:40 p.m. – 12:55 p.m. | Oral Abstract Presentation: A Computer Simulation Model for Atrial Fenestration Sizing in Pulmonary Arterial Hypertension with Right Ventricular Failure  
See page 18                                                                                                                                         |
| 1:00 p.m. – 2:30 p.m. | General Conference Opening: Celebrating 25 Years of PHA (Dallas A, B, C, D & H, Omni)  
Sponsored by Bayer Healthcare                                                                                                               |
| 2:30 p.m. – 3:20 p.m. | Salvage Therapies in the U.S. and Europe Versus Elsewhere  
See page 19                                                                                                                                         |
| 3:20 p.m. – 4:10 p.m. | Rethinking Pediatric PH – International Aspects  
See page 20                                                                                                                                         |
| 4:10 p.m. – 4:25 p.m. | Coffee Break (D Ballroom Foyer, Convention Center)  
Sponsored by Actelion Pharmaceuticals and Accredo Health Group                                                                                   |
| 4:25 p.m. – 5:15 p.m. | From Bench to Bedside: Which Novel Pathways are Most Likely to be Harnessed Therapeutically in the Next 25 Years?  
See page 21                                                                                                                                         |
| 5:15 p.m. – 5:30 p.m. | Closing Remarks                                                                                                                                                                                                                                                                                                                  |
Allied Health Professional Educational Opportunities*

PH Professional Network Dinner (PH Professional Network Members Only)
Sponsored by Accredo Health Group and Steady Med Ltd.
Thursday, June 16 | 6:30 p.m. – 9:30 p.m.

Presenters:
Laura Duvall, PharmD, BCPS
*The Ohio State University, Columbus, Ohio
Rebekah Hanson, PharmD, BCPS, BCACP
University of Illinois Hospital and Health Sciences System, Chicago, Ill.
Traci Stewart, RN, MSN, CHFN
University of Iowa Hospitals and Clinics, Iowa City, Iowa
Melisa Wilson, ARNP, ACNP-BC
Florida Hospital, Orlando, Fla.

The PH Professional Network (PHPN) Dinner is an exclusive event for members of the network to honor the contributions of allied health professionals working to help PH patients. This year, the dinner will feature three captivating case presentations, all presented by your fellow PHPN members. We will honor Glenna Traiger, recipient of the Outstanding Allied Health Professional Award, as well as the work of PHPN’s four committees. This dinner is an excellent opportunity to reconnect with your colleagues from around the world and welcome new PHPN members.

PH Fundamentals: Continuing Education for Medical Professionals

Therapies for PAH: Transitions and Case Examples
Saturday, June 18 | 1:30 p.m. – 2:00 p.m.

Presenter:
Martha Kingman, FNP-C, DNP
UT Southwestern Medical Center, Dallas, Texas
See page 28

*These sessions are designed specifically for allied health professionals.
Hotel Floorplan

Omni Dallas Level Three

Omni Dallas Level Two
Accreditation and Credit Designation

Physicians and Physician Assistants
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the Joint Providership of Professional Education Services Group and the Pulmonary Hypertension Association. Professional Education Services Group is accredited by the ACCME to provide continuing medical education for physicians. The Planning Committee is developing a program that will provide approximately 13 AMA Category 1 Credits™.

Nurses
Professional Education Services Group is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation. The Planning Committee is developing a program that will provide approximately 13 contact hours.

Respiratory Therapists
Application will be made to the American Association for Respiratory Care (AARC) for continuing education contact hours for respiratory therapists. The Planning Committee is developing a program that will provide approximately 13 contact hours.

Pharmacists and Pharmacy Technicians
Professional Education Services Group is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The Planning Committee is developing a program that will provide approximately 13 hours.

Social Workers
Application will be made to the National Association of Social Workers for Social Work continuing education credit. The Planning Committee is developing a program that will provide approximately 6 contact hours.

Other Professionals
Other professionals participating in this activity may obtain a General Participation Certificate indicating their participation and the number of hours of continuing education credit.

All participants seeking continuing education credit must record their attendance and complete an activity evaluation at http://pha.cds.pesgce.com. Please complete this process and print your CE certificate no later than August 16, 2016.
Faculty Disclosures

William Auger, MD, discloses the following financial or non-financial relationships: Bayer HealthCare – Co-Investigator, US CTEPH Registry – Grant provided by Bayer, Uncompensated member Advisory Board, CTEPH.com; and has indicated the following discussion of unapproved drug or product uses: the unknowns about PH targeted medical therapies in the treatment of operable CTEPH.

Eric Austin, MD, MSCI, has no financial or non-financial arrangements or affiliations to disclose; but has indicated the following discussion of unapproved drug or product uses: there are no medications approved by the FDA for chronic therapy for pulmonary hypertension in children (short term use of iNO is approved for PPHN).

David Badesch, MD, FACP, discloses the following financial or non-financial relationships: Actelion Pharmaceuticals US, Inc. – Advisory Board Member, Steering Committee Member, Grant Recipient; Gilead Sciences, Inc. – Advisory Board Member, Grant Recipient; Bayer HealthCare – Advisory Board Member, Grant Recipient; United Therapeutics Corporation – Advisory Board Member, Grant Recipient; Lung LLC – Advisory Board Member, Grant Recipient; Arena – Grant Recipient; Reatta – Grant Recipient; Bellerophon – Advisory Board Member, Steering Committee Member, Grant Recipient; NIH – Grant Recipient; and has indicated no discussion of unapproved drug or product uses.

Christopher Barnett, MD, MPH, has not provided a disclosure.

Ghazwan Butrous, MB, ChB, PhD, FESC, FRSA, has no financial or non-financial arrangements or affiliations to disclose; and has indicated no discussion of unapproved drug or product uses.

Vinicio de Jesus Perez, MD, has no financial or non-financial arrangements or affiliations to disclose; and has indicated no discussion of unapproved drug or product uses.

Gregory Elliott, MD, discloses the following financial or non-financial relationships: Actelion Pharmaceuticals US, Inc. – Chair of the United States Pulmonary Hypertension Scientific Registry Steering Committee; Bellerophon – Chairman of the iNO Steering Committee; Bayer HealthCare – Member of the CTEPH Registry Steering Committee; and has indicated no discussion of unapproved drug or product uses.

Harrison Farber, MD, has not provided a disclosure.

Mardi Gomberg-Maitland, MD, MSc, discloses the following financial or non-financial relationships: Gilead Sciences, Inc. – Consultant, U of Chicago Research Grant; Actelion Pharmaceuticals US, Inc. – Consultant, U of Chicago Research Grant; Medtronic – Consultant, U of Chicago Research Grant; Lung Biotechnology – U of Chicago Research Grant; Novartis – U of Chicago Received Research Grant; Reata – Consultant, U of Chicago Research Grant; Bayer HealthCare – Consultant, U of Chicago Research Grant; Bellerophon – Consultant; United Therapeutics Corporation – Consultant; GeNO – Consultant; PCORI Rare Disease Advisory Panel – Member; and has indicated no discussion of unapproved drug or product uses.

Steven M. Kawut, MD, MS, has no financial or non-financial arrangements or affiliations to disclose; and has indicated no discussion of unapproved drug or product uses.

Martha Kingman, FNP-C, DNP, discloses the following financial or non-financial relationships: Actelion Pharmaceuticals US, Inc. – Speaker Bureau and Advisory Board member; Bayer HealthCare – Speaker Bureau and Advisory Board member; Gilead Sciences, Inc. – Speaker Bureau and Advisory Board member; United Therapeutics Corporation and Lung LLC – Speaker Bureau and Advisory Board member; and has indicated no discussion of unapproved drug or product uses.

Vallerie McLaughlin, MD, discloses the following financial or non-financial relationships: Actelion Pharmaceuticals US, Inc. – Consultant, Research Support; Bayer HealthCare – Consultant, Research Support; Gilead Sciences, Inc. – Research Support; Arena – Research Support; and has indicated no discussion of unapproved drug or product uses.

Myung Park, MD, has not provided a disclosure.
Ioana Preston, MD, discloses the following financial or non-financial relationships: Actelion Pharmaceuticals US, Inc. – Research grants (to Tufts Medical Center), consultancies to (Tufts Medical Center and personal); Bayer HealthCare – Research grants (to Tufts Medical Center), consultancies to (Tufts Medical Center and personal); Gilead Sciences, Inc. – Research grants (to Tufts Medical Center), consultancies to (Tufts Medical Center and personal); United Therapeutics Corporation – Research grants (to Tufts Medical Center), consultancies to (Tufts Medical Center and personal); and has indicated the following discussion of unapproved drug or product uses: will discuss drugs under development.

Tomas Pulido, MD, has not provided a disclosure.

Erika Berman Rosenzweig, MD, discloses the following financial or non-financial relationships: Actelion Pharmaceuticals US, Inc. – Honoraria; Gilead Sciences, Inc. – Honoraria; and has indicated the following discussion of unapproved drug or product uses: may discuss use of medications for PAH in children which is all off-label use.

John Ryan, MD, FACC, FAHA, has no financial or non-financial arrangements or affiliations to disclose; and has indicated no discussion of unapproved drug or product uses.

Mona Selej, MD, MS, discloses the following financial or non-financial relationships: Actelion Pharmaceuticals US, Inc. – Employer; and has indicated no discussion of unapproved drug or product uses.

Oksana Shlobin, MD, FCCP, has no financial or non-financial arrangements or affiliations to disclose; and has indicated the following discussion of unapproved drug or product uses: PDE-5 inhibitors, ERAs, prostanoids.

Talant M. Sooronbaev, MD, has no financial or non-financial arrangements or affiliations to disclose; and has indicated no discussion of unapproved drug or product uses.

Erik R. Swenson, MD, has no financial or non-financial arrangements or affiliations to disclose; and has indicated the following discussion of unapproved drug or product uses: nifedipine, dexamethasone, acetazolamide, sildenafil, tadalafil.

Yon Sung, MD, has no financial or non-financial arrangements or affiliations to disclose; and has indicated no discussion of unapproved drug or product uses.

Fernando Torres, MD, discloses the following financial or non-financial relationships: Actelion Pharmaceuticals US, Inc. – Speaker and consultant; Gilead Sciences, Inc. – Research consultant; United Therapeutics Corporation – Research; Medtronic – Research; Bayer HealthCare – Speaker and consultant; Steady Med – Consultant; Arena – Research; Eiges Pharmaceutical – Research; GENO – Research; Reata – Consultant; and has indicated no discussion of unapproved drug or product uses.

Corey E. Ventetuolo, MD, MS, discloses the following financial or non-financial relationships: Maquet Cardiovascular – Consultant; Bayer HealthCare – Consultant/Advisory Panel; Actelion Pharmaceuticals US, Inc. – Advisory Panel; and has indicated the following discussion of unapproved drug or product uses: extracorporeal life support devices are FDA-approved for use for up to six hours outside of the operating room.

Prof. Martin Wilkins discloses the following financial or non-financial relationships: Bayer HealthCare – Member of Advisory Board; and has indicated the following discussion of unapproved drug or product uses: may refer to drugs in development or licensed for other diseases if these shed light on candidate pathways.

Disclaimer
The information presented in this activity reflects the view of the faculty only and not necessarily those of the Pulmonary Hypertension Association (PHA), the sponsors or the educational grant providers. All participants should verify information and data presented before treating patients or utilizing any therapies noted in these materials. No portion of this activity may be reproduced without the expressed written consent of PHA.
Workshop

PH Care Centers (PHCC) Workshop
Thursday, June 16 | 3:00 p.m. – 6:00 p.m.

Presenters:
Traci Housten, RN, MS (PHCC Review Committee member)
Johns Hopkins University
Baltimore, Md.

Melisa Wilson, ARNP, ACNP-BC (PHCC Oversight Committee member)
Florida Hospital
Orlando, Fla.

Joel Wirth, MD (PHCC Review Committee Chair-Elect)
Maine Medical Center
Portland, Maine

Learning Objectives:
• Review recent developments and structural changes to PHCC.
• Discuss application and site visit preparation process.
• Describe how to present your center PAH/CTEPH Roster for review.
• Prepare for coordinator/director interviews through mock site interview.

The final step in the process of accreditation is a one-day site visit conducted by trained PHCC physician and coordinator reviewers. This workshop will bring awareness to key PHCC criteria, help identify ways to organize the site visit day, and provide a basis to coordinate meetings with key facility staff and patient care area tours. Careful attention will be given on how to develop and present your center PAH/CTEPH roster for review and how to prepare for the coordinator and director interviews through staging of a mock site visit interview.

Notes:

All participants seeking continuing education credit must record their attendance and complete an activity evaluation at http://pha.cds.pesgce.com. Please complete this process and print your CE certificate no later than August 16, 2016.
Scientific Sessions Presentation

What Has Happened in the Last 25 Years: Global Perspectives/20 Years of Prostacyclins
Friday, June 17 l 8:15 a.m. – 9:05 a.m.

Presenter:
Vallerie McLaughlin, MD
University of Michigan
Ann Arbor, Mich.

Learning Objectives:
• Review the scope of PAH and the evolution of PAH therapy over the past 25 years.
• Highlight the progress of prostacyclins over the past two decades.
• Discuss the impact of therapy on outcomes in PAH.

When the PHA was founded 25 years ago, there were no specific therapies approved for PAH. While a small percentage of patients were candidates for calcium channel blockers, therapy for the overwhelming majority of patients consisted of nothing more than diuretics, digoxin and warfarin. Two decades ago, IV epoprostenol was approved based on a 12-week, 81 patient trial. Since then, an additional dozen therapies have been approved. Current therapies address the three pathologic pathways that have been well characterized, although investigational studies are reaching to new pathways. Clinical trial design has progressed over the past two decades as well. This session will give a perspective on the past 25 years in PAH.

Notes:

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Oral Abstract Presentation

1002: PHD2 Deficiency in Endothelial Cells and Hematopoietic Cells Induces Obliterative Vascular Remodeling and Severe Pulmonary Arterial Hypertension Recapitulating Clinical PAH

Friday, June 17 | 9:05 a.m. – 9:20 a.m.

Presenter:
Zhiyu Dai, PhD
University of Illinois College of Medicine
Chicago, Ill.

Notes:
Scientific Sessions Presentation

What Have We Learned from Modern Worldwide Registries?
Friday, June 17 | 9:20 a.m. – 10:10 a.m.

Presenter:
David Badesch, MD, FACP
University of Colorado Anschutz Medical Campus
Denver, Colo.

Learning Objectives:

• Enhance knowledge and understanding of recently conducted pulmonary hypertension registries.
• Review how knowledge of pulmonary hypertension has evolved over time as a result of registries conducted in differing time periods and areas of the world.
• Discuss how knowledge gained from registry studies is impacting future studies of pulmonary hypertension.
• Discuss how knowledge acquired from registries might impact clinical care of patients with pulmonary hypertension.
• Discuss the limitations of data obtained from registries.

A number of registry studies of patients with pulmonary hypertension have been conducted in various regions of the world over the past decade. These registries have made valuable contributions to our understanding of the demographics, epidemiology, and outcomes of pulmonary hypertension and its various diagnostic subgroups, and lead to the development of improved predictors of prognosis. While the information gained from registry studies clearly has limitations, knowledge acquired from these important studies is impacting disease awareness, diagnosis, clinical care, and the design of clinical trials.

Notes:

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Oral Abstract Presentation

1010: A Selective TGFβ Ligand Trap Attenuates Pulmonary Arterial Hypertension
Friday, June 17 | 10:10 a.m. – 10:25 a.m.

Presenter:
Lai-Ming Yung, MD
Brigham and Women’s Hospital
Boston, Mass.

Notes:

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Scientific Sessions Presentation

Etiologies of PH Across the World
Friday, June 17 | 10:35 a.m. – 11:35 a.m.

Presenters:

Schistosomiasis
Ghazwan Butrous, MB, ChB, PhD, FESC, FRSA
University of Kent
Canterbury, U.K.

Drug and Toxins
Vinicio de Jesus Perez, MD
Stanford University
Stanford, Calif.

HIV
Christopher Barnett, MD, MPH
Medstar Washington Hospital Center
Washington, D.C.

High Altitude
Erik R. Swenson, MD
University of Washington, Seattle
Seattle, Wash.

Learning Objectives:

• Understand the pathology of PH associated with schistosomiasis, HIV, drugs and toxins, and high altitude.
• Learn about the current research activities on schistosomiasis-associated PH and its impact on understanding the role of information on pulmonary vascular diseases.
• Discuss treatment options for HIV-associated PAH.
• Review the global impact and discuss recent genetic insights concerning the pathogenesis of drug and toxin PAH.
• Understand how acute excessive hypoxic pulmonary vasoconstriction (HPV) and other factors can lead to high altitude pulmonary edema (HAPE).

This session will focus on four common causes of PAH around the world. Schistosomiasis is one of the most common causes of PH worldwide. Similarly, HIV and chronic high altitude exposure are major causes for PH development on a global level. Drugs and toxins, on the other hand, represent a specific problem in the western world. This session will focus on key features of these specific types of PH/PAH, review established and emerging paradigms, and discuss their implications for both the western and the developing world.

Notes:

All participants seeking continuing education credit must record their attendance and complete an activity evaluation at http://pha.cds.pesgce.com. Please complete this process and print your CE certificate no later than August 16, 2016.
Oral Abstract Presentation

1051: Evidence of Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension
Friday, June 17 | 11:35 a.m. – 11:50 a.m.

Presenter:
Evan L. Brittain, MD, MSCI
Vanderbilt University
Nashville, Tenn.

Notes:
Scientific Sessions Presentation

Panel Discussion: Enhancing Access to Drugs in Developing Countries, Challenges of Making Generic Drugs Available in Developing Countries
Friday, June 17 | 11:50 a.m. – 12:40 p.m.

Presenters:
Steven M. Kawut, MD, MS
Perelman School of Medicine at the University of Pennsylvania

Mona Selej, MD, MS
Stanford University
Stanford, Calif.

Ghazwan Butrous, MB, ChB, PhD, FESC, FRSA
University of Kent
Canterbury, U.K.

Talant M. Sooronbaev, MD
Central Asia Pulmonary Hypertension (CAPH) PVRI Task Force
Bishkek, Kyrgyzstan

Learning Objectives:
• Get new knowledge for the management of patients with pulmonary hypertension.
• Understand important information about the experience for the management and providing of essential drugs to patients with PH in other countries.
• Discuss ways we can improve the management and treatment of patients with PH in developing countries.

This session will focus on the challenges facing physicians caring for PH patients in developing countries. It will also discuss alternative clinical approaches and research ideas that can be implemented to advance PH care in the developing world.

Notes:

All participants seeking continuing education credit must record their attendance and complete an activity evaluation at http://pha.cds.pesgce.com. Please complete this process and print your CE certificate no later than August 16, 2016.
Oral Abstract Presentation

1042: A Computer Simulation Model for Atrial Fenestration Sizing in Pulmonary Arterial Hypertension with Right Ventricular Failure
Friday, June 17 | 12:40 p.m. – 12:55 p.m.

Presenter:
Joseph Kuruvilla, DO
Helen DeVos Children’s Hospital of Spectrum Health
Grand Rapids, Mich.

Notes:

All participants seeking continuing education credit must record their attendance and complete an activity evaluation at http://pha.cds.pesgce.com. Please complete this process and print your CE certificate no later than August 16, 2016.
Scientific Sessions Presentation

Salvage Therapies in the U.S. and Europe Versus Elsewhere
Friday, June 17 | 2:30 p.m. – 3:20 p.m.

Presenters:
Tomas Pulido, MD
Instituto Nacional de Cardiología
Ignacio Chavez, Mexico

Corey E. Ventetuolo, MD, MS
Alpert Medical School of Brown University
Providence, R.I.

Learning Objectives:

• Understand the rationale for shunt creation and extracorporeal life support (ECLS) in advanced pulmonary arterial hypertension (PAH).

• Learn methods for shunt creation in PAH and review ECLS configurations utilized in PAH.

• Learn the clinical indications for shunt creation and ECLS in PAH.

The session will focus on the definition and indications for interventional (surgical, non-surgical, and extracorporeal devices) strategies in patients with advanced PAH. Atrial septostomy, Pott’s shunt, and current ECLS technologies as a bridging strategy to recovery or transplant will be discussed in the context of global resources and restrictions and limitations of organ donation.

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Scientific Sessions Presentation

Rethinking Pediatric PH – International Aspects
Friday, June 17 | 3:20 p.m. – 4:10 p.m.

Presenter:
Eric Austin, MD, MSCI
Vanderbilt University School of Medicine
Nashville, Tenn.

Learning Objectives:
• Review why it is important to consider the similarities and differences between pediatric and adult forms of pulmonary hypertensive vascular disease (PHVD), including pulmonary hypertension (PH).
• Understand the consensus approach to the international classification of PHVD, now known as the Panama Classification of Pediatric PHVD.
• Review the current approaches to pediatric PH care, including traditional PH-directed therapeutic approaches as well as additional aspects such as procedural planning, preventive care approaches, genetics, and family-centered care issues particularly relevant to pediatrics.

Tremendous advances in the understanding of pulmonary hypertensive vascular disease, including pulmonary hypertension (PH), have occurred the past 30 years. The resultant improvements in quality of life and survival hold great promise for current and future patients of all ages, and their families. In concert with that progress, there has been a renewed international effort amongst pediatric-focused clinicians to highlight the areas of diagnosis and care that are similar to adults versus those that are unique the pediatric patient. In this session, we will discuss the similarities and differences between adult and pediatric conditions, with particular emphasis on the Panama Classification of Pediatric Pulmonary Hypertensive Vascular Disease, as well as additional features of particular relevance to the care of the pediatric patient.

Notes:

All participants seeking continuing education credit must record their attendance and complete an activity evaluation at http://pha.cds.pesgce.com. Please complete this process and print your CE certificate no later than August 16, 2016.
Scientific Sessions Presentation

From Bench to Bedside: Which Novel Pathways are Most Likely to be Harnessed Therapeutically in the Next 25 Years?
Friday, June 17 | 4:25 p.m. – 5:15 p.m.

Presenter:
Prof. Martin Wilkins
Imperial College London
London, U.K.

Learning Objectives:
• Discuss the challenges facing new drug development for pulmonary arterial hypertension.
• Discuss the value of genetics and genomics in drug target validation.
• Review the novel pathways emerging and supported by patient-orientated research.

The current treatments for pulmonary arterial hypertension (PAH) offer some relief but do not provide a cure. This requires a better understanding of the underlying pathology and in particular the molecular drivers of the disease. There is no shortage of new drug targets. The challenge is in prioritizing the most promising; that is, getting consensus on targets in which we have the highest confidence of likely success. Direct evidence that a new target causes the disease, usually, but not always, comes from genetic evidence. Family studies have identified mutations in BMPR2 and a few other genes. These provide an important opportunity for new drug development. An alternative to family studies is to use Mendelian randomization, which utilizes the random allocation of alleles at conception. Here, potential confounding factors are distributed equally between different genotype groups for a given variant. Observed phenotype associations with the variant can be interpreted as direct consequences of that mutation. This approach requires studies in large, well-characterized patient groups. The UK Pulmonary Hypertension Consortium is studying over 650 patients with idiopathic PAH and early data point to the importance of pathways mediating inflammation and cell metabolism as well a proliferation. As we learn more about the molecular drivers of PAH, it is likely that we will need to target not one novel pathway but several novel pathways therapeutically as we seek to arrest and reverse the course of PAH over the next 25 years.

Notes:
PH Fundamentals: Continuing Education for Medical Professionals

Update on Classification, Screening, and Diagnosis of PH
Friday, June 17 | 2:30 p.m. – 3:00 p.m.

Presenter:
Gregory Elliott, MD
University of Utah School of Medicine
Salt Lake City, Utah

Learning Objectives:

• Understand and be able to use the ESC/ERS Comprehensive Clinical Classification (Updated from 2013).
• Understand evidence based criteria and recommendations for screening individuals for PAH.
• Understand criteria for the diagnosis of pulmonary hypertension.
• Understand the importance of the differential diagnosis of pulmonary hypertension i.e. distinguishing between different diagnostic possibilities and identifying the correct diagnosis or diagnoses.

This session will provide an update on the classification of pulmonary hypertension based upon the most recent guideline statement(s) with emphasis given to the key revisions of the 5th World Symposium on Pulmonary Hypertension Classification. The presenter will also describe evidence based criteria and recommendations for screening individuals for PH; and will identify criteria for the diagnosis of pulmonary hypertension, as well as discuss and illustrate the importance of the differential diagnosis of pulmonary hypertension.

Notes:

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PH Fundamentals: Continuing Education for Medical Professionals

Is It PAH or Not: Diagnostic Challenges
Friday, June 17 | 3:00 p.m. – 3:30 p.m.

Presenter:
Ioana Preston, MD
Tufts Medical Center
Boston, Mass.

Learning Objectives:
• Differentiate between the five groups of PH.
• Integrate various tests to improve accuracy in PH diagnosis.
• Determine the right therapeutic approach depending on the type of PH.

While idiopathic pulmonary arterial hypertension (IPAH) is a rare disease, pulmonary hypertension (PH) often complicates various pulmonary and cardiovascular diseases and is a very common entity. There are significant differences between the five types of pulmonary hypertension, as described by the five groups defined by the World Health Organization. For example, Group II PH due to left heart disease has a clear distinction in its hemodynamic presentation. Nevertheless, pulmonary hemodynamics without the clinical context and noninvasive tests are not sufficient to make the correct diagnosis. For example, pulmonary hemodynamics are very similar among groups I, III, IV, and V, and clinicians need to incorporate and integrate several tests in addition to pulmonary hemodynamics in order to achieve an accurate diagnosis. This step is crucial in determining the outcome, evaluating the severity of the disease, and, most importantly, in choosing the best treatment for our PH patients.

Notes:
PH Fundamentals: Continuing Education for Medical Professionals

Imaging in PH: What Can a Picture Tell You?
Saturday, June 18 | 9:30 a.m. – 10:00 a.m.

Presenter:
John Ryan, MD, FACC, FAHA
University of Utah Department of Internal Medicine
Salt Lake City, Utah

Learning Objectives:
- Describe the role of echocardiograms in PAH in diagnosis and management.
- Discuss the role of cardiac MRI in PAH.
- Explain the need for extensive imaging at the time of diagnosis of PH in order to determine the group of PH.

Patients are often first diagnosed with pulmonary hypertension (PH) on echocardiogram. In order to define the cause of pulmonary hypertension and in turn, determine the treatment, a vast array of imaging tests are often ordered. These can include CT, MRI, PET scans, and in some cases lung biopsy. In this talk, we will discuss the role of imaging in the diagnosis and management of PH and in particular how it pertains to pulmonary arterial hypertension (PAH). Imaging of the heart with echocardiogram and MRI can provide additional information in terms of prognosis and in some cases help guide therapeutic decisions.

Notes:
PH Fundamentals: Continuing Education for Medical Professionals

Updated Algorithm of PAH Treatment: PHrontline News
Saturday, June 18 | 10:00 a.m. – 10:30 a.m.

Presenter:
Mardi Gomberg-Maitland, MD, MSc
University of Chicago Medical Center
Chicago, Ill.

Learning Objectives:
- Review both general therapeutic and health maintenance measures of care.
- Understand the evidence based data of current therapeutics for PAH.
- Understand the gaps in clinical care knowledge pertaining to these guidelines.

This session will discuss the current treatment algorithm based on guideline consensus. The new guidelines include the recently reported Phase 3 studies of macitentan, riociguat, and selexipag. The session will cover general measures of care, and discuss monotherapy and combination therapy evidence based data. The session will conclude with a discussion of remaining gaps in clinical care that need further evidence.

Notes:

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PH Fundamentals: Continuing Education for Medical Professionals

PH Group II: Cases and Challenges
Saturday, June 18 | 11:00 a.m. – 11:30 a.m.

Presenter:
Myung Park, MD
Houston Methodist Hospital
Houston, Texas

Notes:
PH Fundamentals: Continuing Education for Medical Professionals

PH Group III: Cases and Challenges
Saturday, June 18 | 11:30 a.m. – 12:00 p.m.

Presenter:
Oksana Shlobin, MD, FCCP
*Inova Fairfax Medical Campus*
*Falls Church, Va.*

Learning Objectives:
- Discuss the pathophysiology of PH in chronic fibrotic lung diseases.
- Discuss the impact of PH in chronic fibrotic lung diseases.
- Review the existing data in chronic fibrotic lung diseases.

This session will provide a case-centered update on pathogenesis and epidemiology and significance of pulmonary hypertension in parenchymal lung disease. The currently available treatment data and ongoing clinical trials will be discussed.

Notes:
PH Fundamentals: Continuing Education for Medical Professionals

Therapies for PAH: Transitions and Case Examples
Saturday, June 18 | 1:30 p.m. – 2:00 p.m.

Presenter:
Martha Kingman, FNP-C, DNP
UT Southwestern Medical Center
Dallas, Texas

Learning Objectives:

- Understand basic principles for transitioning between PAH therapies.
- Describe some published transition methods.
- Discuss several transition cases that occurred at University of Texas Southwestern Medical Center, Dallas.

This session will cover the basic principles for transitioning between PAH therapies. Several published transition methods will be presented. The session will conclude with case studies describing transition methods used at University of Texas Southwestern Medical Center at Dallas. Helpful tips for managing side effects during transitions will be discussed as well.

Notes:
PH Fundamentals: Continuing Education for Medical Professionals

Management of PH in the ICU
Saturday, June 18 | 2:00 p.m. – 2:30 p.m.

Presenter:
Yon Sung, MD
Stanford Hospital and Clinics
Stanford, Calif.

Learning Objectives:

- Recognize the unique features of PH patients with critical illness.
- Discuss considerations for the use of invasive hemodynamic monitoring in PH patients in the ICU.
- Review therapies for the management of acute right ventricular failure in patients with PH.
- Understand the indications for initiation and/or continuation of pulmonary vasodilators in critical illness.

The management of critically ill patients with pulmonary hypertension can be particularly challenging as many of the treatments used in the ICU setting can exacerbate PH and right heart failure. In the session, we will review the unique aspects of the physiology of critically ill PH patients, which will then inform our approach to management. Specifically, we will discuss the role of invasive hemodynamic monitoring, the advantages and disadvantages of specific vasoactive medications, and the indications for pulmonary vasodilators in the acute setting.

Notes:
PH Fundamentals: Continuing Education for Medical Professionals

CTEPH: Surgical Versus Medical Patient
Sunday, June 19 | 8:00 a.m. – 8:30 a.m.

Presenter:
William Auger, MD
University of California, San Diego Medical Center
La Jolla, Calif.

Learning Objectives:
- Understand the rationale for screening all patients with pulmonary hypertension for CTEPH.
- Describe the difference between those patients with operable versus inoperable chronic thromboembolic disease.
- Understand the benefits of a pulmonary thromboendarterectomy.
- Know the therapeutic options for those patients with inoperable or nonsurgical CTEPH, including PH-targeted medical therapy and/or balloon pulmonary angioplasty.

The identification of patients with chronic thromboembolic pulmonary hypertension (CTEPH) is essential as this is a potentially curable form of pulmonary hypertension. This session will highlight the rationale and recommendation for screening all pulmonary hypertensive patients for CTEPH, and will outline the evaluation algorithm for establishing the diagnosis. Working with an experienced PTE surgery center to ascertain whether or not the chronic thromboembolic disease is operable will be emphasized. For those patients with nonsurgical disease, the treatment options of balloon pulmonary angioplasty and pulmonary hypertension targeted medical therapy will be reviewed.

Notes:
PH Fundamentals: Continuing Education for Medical Professionals

Interesting and Challenging Cases in PH
Sunday, June 19 | 8:30 a.m. – 9:00 a.m.

Presenter:
Harrison Farber, MD
Boston University School of Medicine
Boston, Mass.

Notes:
PH Fundamentals: Continuing Education for Medical Professionals

Pediatric PAH Patients: How to Manage, How to Treat
Sunday, June 19 | 11:00 a.m. – 11:30 a.m.

Presenter:
Erika Berman Rosenzweig, MD
Columbia Presbyterian Medical Center
New York, N.Y.

Learning Objectives:
• Understand the general management strategies for children with PAH.
• Understand the currently available targeted treatments and their role in the management of pediatric PAH.
• Understand risk factors for rapidly progressive disease and how to best manage.

Notes:
Transplanting in the PAH Patient: Screening and Evaluation for Lung Transplant
Sunday, June 19 | 11:30 a.m. – 12:00 p.m.

Presenter:
Fernando Torres, MD
UT Southwestern Medical Center
Dallas, Texas

Learning Objectives:
- Understand relative and absolute contraindications for lung transplantation.
- Understand the difference between bilateral lung transplant and single lung transplant.
- Understand the need for a heart lung block vs bilateral lung transplantation.
- Understand survival after lung transplantation.

The lung transplantation of a patient with PAH is very challenging. These patients carry the highest perioperative mortality of all lung transplant patients, but once the patients make it to one year, they tend to have one of the best long term survivals. Thus, the selection of patients with PAH is critical for a successful transplant. In this section, we will concentrate on the screening and evaluation of patients with PAH to undergo lung transplantation.
Oral Abstract Presentations

The following abstracts will be presented during the Scientific Sessions. PHA congratulates the winners of the awards for best abstracts in basic and clinical science.

**BASIC SCIENCE**

1002 WINNER!
**PHD2 Deficiency in Endothelial Cells and Hematopoietic Cells Induces Obliterative Vascular Remodeling and Severe Pulmonary Arterial Hypertension Recapitulating Clinical PAH**

*Presenter:* Zhiyu Dai, PhD
*University of Illinois College of Medicine*  
*Chicago, Ill.*

1010
**A Selective TGFβ Ligand Trap Attenuates Pulmonary Arterial Hypertension**

*Presenter:* Lai-Ming Yung, MD
*Brigham and Women’s Hospital*  
*Boston, Mass.*

**CLINICAL SCIENCE**

1051 WINNER!
**Evidence of Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension**

*Presenter:* Evan L. Brittain, MD, MSCI
*Vanderbilt University*  
*Nashville, Tenn.*

1042
**A Computer Simulation Model for Atrial Fenestration Sizing in Pulmonary Arterial Hypertension with Right Ventricular Failure**

*Presenter:* Joseph Kuruvilla, DO
*Helen DeVos Children’s Hospital of Spectrum Health*  
*Grand Rapids, Mich.*
Basic Science Abstracts

MECHANISTIC STUDIES

1001 Extra-Cellular Superoxide Dismutase Protects Against the Development and Progression of Chronic Pulmonary Arterial Hypertension
Ahmed M, Lopez Da Re JM, Patel H, Ayyasola K, Zaghloul N, Kanta Ochani K, Manssor N, Miller E

1002 PHD2 Deficiency in Endothelial Cells and Hematopoietic Cells Induces Obliterative Vascular Remodeling and Severe Pulmonary Arterial Hypertension Recapitulating Clinical PAH
Dai Z, Li M, Zhu MM, Zhao YY

1003 A Cardioprotective Estrogen Receptor α-Apelin Axis Mediates Salutary Effects of 17β-Estradiol (E2) on Right Ventricular Function in Pulmonary Hypertension
Frump AL, Albrecht M, Breuils-Bonnet S, Provencher S, Bonnet S, Brown MB, Lahm T

1004 Loss of Caveolin-1 Induces an Invasive, Proliferative, and Inflammatory Phenotype in Pulmonary Arterial Endothelial Cells
Gairhe S, Elinoff JM, Danner RL

1005 Postnatal Hyperoxia Exposure Durably Impairs Right Ventricular Function in Aged Male Rats

1006 Inhibition of miR-130a in the Lungs Prevents Monocrotaline Induced Pulmonary Arterial Hypertension in Mice
Gupta LL, Gupta S

1007 NF-κB Mediated miRNAs Modulation in Pulmonary Arterial Hypertension Induced Right Ventricular Hypertrophy
Gupta S, Kim I, Wei C, Jones WK

1008 Inhibition of Macrophage Leukotriene B4 Synthesis Attenuates and Reverses Pulmonary Hypertension in Animal Models
Nicolls M, Peters-Golden M, Quan J, Tian W, Voelkel NF, Zamanian RT

1009 Endothelial CXCL12 Contribution to Obliterative Vascular Remodeling and Severe Pulmonary Arterial Hypertension
Tarjus A, Dai Z, Zhao Y

1010 A Selective TGFβ Ligand Trap Attenuates Pulmonary Arterial Hypertension
Yung LM, Nikolic I, Paskin-Flerlage SD, Pearsall RS, Kumar R, Yu PB
## Case Studies

### ASSOCIATED DISEASES AND CONDITIONS

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<td>Krishnan S, Lahm T</td>
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<td>Pulmonary Arterial Hypertension (PAH) Associated with Interferon Beta 1B: A Case Report</td>
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### THERAPEUTIC STRATEGIES

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<td>Combination Therapy with Riociguat and Inhaled Treprostinil in Inoperable and Progressive Chronic Thromboembolic Pulmonary Hypertension</td>
<td>Byrd H, Elliott D, Overton-Barnes R, Swisher J</td>
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<td>Troubleshooting Inpatient IV Infusion of Prostacyclin: Backflow and Boluses</td>
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Successful Rescue Therapy for Digital Ischemia with Sildenafil and Epoprostenol
Lee C, Elwing J

Treat and Repair Strategy for Pulmonary Arterial Hypertension Associated with Atrial Septal Defect and Heterotaxy Syndrome
Shibata A, Fukushima H, Maeda J, Yamagishi H

Gastric Bypass Surgery is Safe and Effective in a Patient with Pulmonary Arterial Hypertension
Worden NE, Lovig A, Stewart T, Gerke AK, Cadaret LM

Rescue Therapy with Oral Prostacyclin (Orenitram) in an Octogenarian Female with Refractory Pulmonary Arterial Hypertension
Zaman H, Roberts D, Khanal C, Jimenez J

Compassionate Use of Inhaled Prostacyclin in the Management of PAH with Concomitant Cancer: A Case Series
Balasubramanian V, Gresham P

Right Heart Catheterization Data in End Stage Renal Disease: A Retrospective, Descriptive Analysis
Bensimhon H, Caughey M, Ford HJ, Hinderliter A, Rose-Jones L

Identification of Plasma Biomarkers Associated with the Development of Scleroderma-Associated Pulmonary Arterial Hypertension

Pulmonary Arterial Hypertension (PAH) Associated with Interferon (IFN) Therapy: A Population Based Study
Papani R, Duarte A, Lin Y, Sharma G

Targeting the Prostacyclin Pathway in the Treatment of Connective Tissue Disease Associated Pulmonary Arterial Hypertension (PAH): Insights from the Randomized Controlled GRIPHON Trial with Selexipag

Pulmonary Arterial Hypertension Patients’ Treatment Patterns After Initial Therapy in the United States

Predicting Outcomes in Pulmonary Arterial Hypertension Based on Estimated Glomerular Filtration Rate in the REVEAL Registry
Chakinala M, Coyne DW, Benza RL, Frost AE, McGoon MD, Hartline BK, Frantz RP, Selej M, Mink DR, Farber HW
1034  **The Patterns of Healthcare Utilization and Prevalence of Pulmonary Arterial Hypertension Patients on Prostacyclin Therapy in the United States**  
Drake W, Lickert C, Janis Pruett, Rotella P, Schneider G

1035  **Characterization of Centers Accredited by the Pulmonary Hypertension Association (PHA) in the Pulmonary Hypertension Care Centers (PHCC) Initiative during Programmatic Year One**  

1036  **Evaluation of Quality of Care and Quality of Life of Pulmonary Hypertension Patients Seen in PH Care Centers: PHA Registry Study Design**  

**DIAGNOSIS, SCREENING AND ASSESSMENT**

1037  **Factors Affecting Accuracy of Transthoracic Echocardiography in the Evaluation of Pulmonary Hypertension**  
Allen L, Collins C, Heidel RE, Swisher J

1038  **Right Heart Catheterization in Patients Initiated on Pulmonary Arterial Hypertension Therapies: A Population Based Study**  
Duarte AG, Lin Y, Sharma G

1039  **What is the Prognostic Value of the Baseline Serum Sodium Level in PAH?**  
Fares WH, Tonelli AR, Adonteng-Boateng P, Bazan IS, Kholdani CA, Rao Y, Dweik RA

1040  **Right-to-Left Ventricular End Diastolic Diameter Ratio in Severe Sepsis and Septic Shock**  

1041  **Risk Factors for Chronic Thromboembolic Disease in Patients with Newly Diagnosed Pulmonary Hypertension: A Community Based Study**  
Kanwar M, Raina A, Gladowski P, Benza R

1042  **A Computer Simulation Model for Atrial Fenestration Sizing in Pulmonary Arterial Hypertension with Right Ventricular Failure**  
Kurup HKN, Broomé M, Vettukattil JJ, Kuruvilla J

1043  **Slope of 6MWD as a Predictor of Clinical Outcome in PAH**  
Risbano MG, Rao Y

1044  **Circulating Aldosterone Levels and Disease Severity in Pulmonary Arterial Hypertension**  
Safdar Z, Thakur A, Singh S, Ji Y, Guffey D, Minard CG, Entman ML

1045  **Microfluidic Chip-Based Quantification of Circulating Endothelial Cells in Patients with Pulmonary Arterial Hypertension**  
Sallmon H, Hatch A, Plouffe BD, Murthy SK, Hansmann G

1046  **Pulmonary Artery Pulsatility: Potential Prognostic Marker in Pulmonary Hypertension due to Left Heart Failure**  
Supine Exercise Stress Echocardiography (ESE) Assessment of Right Ventricular (RV) Structure and Function in Normal Individuals
Stokem K, Rancourt D, Atherton D, Lucas L, Wirth JA

End Tidal CO2 as a Predictor of Outcomes in Patients with Pulmonary Arterial Hypertension
Welch CE, Robbins IM, Brittain EL, Newman JH, Hemnes AR

Recognition and Clinical Importance of a Newly Identified Interatrial Shunt (Tunneled Atrial Septal Defect) in Patients With Pulmonary Hypertension
Zwicke D, Paulus S, Pinninti M, Khandheria B, Bajwa T, Kramer C, Thohan V

MECHANISTIC STUDIES

Evidence of Shared Genetic Architecture Between Combined Pulmonary Hypertension and Pulmonary Arterial Hypertension
Assad TR, Hemnes AR, Larkin EK, Glazer AM, Wells QS, Farber-Eger EH, Xu M, Brittain EL

Evidence of Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension

Heritability in Chronic Thromboembolic Pulmonary Hypertension: Pedigree Analysis Suggests a High Prevalence of Venous Thromboembolism in Family Members of CTEPH Patients, But a Low Prevalence of CTEPH
Dodson MW, Desmarais J, Best DH, Knight S, Cannon-Albright L, Brown L, Elliott CG

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Extra-Cellular Superoxide Dismutase Protects Against the Development and Progression of Chronic Pulmonary Arterial Hypertension

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Purpose: To establish the chronic PAH model in adult mice and examine the role of EC-SOD overexpression on the progression of PAH induced by hypoxia and Sugen 516 (HySu).

Background: Pulmonary arterial hypertension (PAH) is characterized by vascular cell growth and proliferation leading to increased pulmonary vascular resistance, increased pulmonary arterial pressure, right ventricular failure, and death. In our previous work, we showed that extracellular superoxide dismutase overexpression (EC-SOD) can attenuate, prevent, and reverse hypoxia-induced pulmonary hypertension in adult mice. In this study, we wished to assess the efficacy of the EC-SOD strategy in the Hypoxia/Sugen model, which induces a more severe, late stage PAH.

Methods: Chronic PAH was established in adult male C57BL6 mice (9–10 week old). Mice were injected with VGEF receptor blocker (Sugen 5416) 20 mg/kg, once per week for 3 weeks and exposed to hypoxia (FiO2 of 10%). The animals were divided into 6 groups: wild-type mice (WT) housed in room air (RA), WT mice housed in hypoxia, WT mice administered Sugen and housed in hypoxia, and 3 groups of transgenic (TG) mice expressing a copy of human EC-SOD and treated in a similar manner to the WT groups. After exposures, Right ventricular systolic pressures (RVP) and right sided hypertrophy (as measured by Right Ventricle /Septum + Left Ventricle weight ratio) was estimated at 3, 7 and 11 weeks. Histopathological sections of all groups at different intervals were studied and immunostained for VGEF and αSMA.

Results: In this chronic form of PAH, TG mice expressing an extra copy of the human EC-SOD gene had less evidence of PAH (RVP and right sided hypertrophy) when housed in hypoxia and treated with Sugen. Histopathologically, WT mice, housed in hypoxia and treated with Sugen, showed a marked and significant evidence of progression of pulmonary vascular wall thickening and hypertrophy. In addition, there were various degrees of concentric neointimal thickness of pulmonary arterioles which peaked at 11 weeks of hypoxic exposure. In TG-hypoxia group treated with Sugen, vascular remodeling showed significant regression after hypoxic exposure. Immuno-staining for both VEGF and αSMA, was consistent with the above findings.

Conclusions: We have used a chronic model of PAH in adult mice which was consistant with the pathology found in previous studies in adult rats. Using this model, we showed that EC-SOD has a marked and a significant role in ameliorating and attenuating the progression of chronic PAH. The data suggest that the use of EC-SOD may be useful to alter the progression of PAH. Further studies are needed to examine the possible therapeutic administration of EC-SOD to reverse PAH pathology.
**PHD2 Deficiency in Endothelial Cells and Hematopoietic Cells Induces Obliterative Vascular Remodeling and Severe Pulmonary Arterial Hypertension Recapitulating Clinical PAH**

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**Purpose:** The aim of this study is to determine the fundamental role of prolyl-4 hydroxylase 2 (PHD2) in regulating pulmonary vascular remodeling and the pathogenesis of severe pulmonary arterial hypertension (PAH).

**Background:** Vascular occlusion and complex plexiform lesions are hallmarks of the pathology of severe pulmonary arterial hypertension (PAH) in patients. However, mechanisms of obliterative vascular remodeling remain elusive and hence current therapies have not targeted the fundamental disease modifying mechanisms and result in only modest improvement in morbidity and mortality.

**Methods:** To gain insights into the role of PHD2 in the pathogenesis of PAH, Egln1 (encoding prolyl-4 hydroxylase 2, PHD2) floxed mice were bred with Tie2 promoter/enhancer-driven Cre transgenic mice to generate Egln1Tie2 mice. Egln1Tie2/Hif1aTie2 and Egln1Tie2/Hif2aTie2 double knockout mice were also generated. Right ventricular (RV) hemodynamic measurement and echocardiography were performed to evaluate the RV systolic pressure (RVSP), and cardiac size and function. RV/LV+S ratio were also determined as an indicator of RV hypertrophy. Bone marrow cell transplantation was employed to determine the contribution of PHD2-deficient hematopoietic cells in PAH. Histology was used to quantify vascular remodeling. RNA-sequencing, bioinformatics and molecular analysis were carried out to define the molecular mechanisms of PAH in Egln1Tie2 mice.

**Results:** Mice with Tie2Cre-mediated disruption of (Egln1Tie2) in endothelial cells and hematopoietic cells exhibited spontaneous severe PAH (RVSP ranging from 60 to 90 mmHg) with extensive pulmonary vascular remodeling including vascular occlusion and plexiform-like lesions resembling the hallmarks of the pathology of clinical PAH. As seen in idiopathic PAH patients, Egln1Tie2 mice exhibited unprecedented severe RV hypertrophy (RV/LV+S, 0.9±0.15) and failure and progressive mortality. Consistently, PHD2 expression was diminished in lung endothelial cells of obliterated pulmonary vessels in idiopathic PAH patients. Genetic deletions of both Egln1 and Hif1a or Egln1 and Hif2a identified hypoxia-inducible factor-2α (HIF-2α) as the critical mediator of severe PAH seen in Egln1Tie2 mice. We also observed altered expression of many PH-causing genes in Egln1Tie2 lungs which were normalized in Egln1Tie2/Hif2aTie2 lungs. Additionally, reconstitution of WT bone marrow cells in Egln1Tie2 chimeric mice attenuated PAH whereas PHD2 deficient bone marrow cells failed to induce PAH in WT chimeric mice, demonstrating the essential role of PHD2 deficiency in endothelial cells in the development of PAH and PHD2 deficiency in bone marrow cells as an important contributor of the severity of the pathogenesis.

**Conclusions:** These studies defined an unexpected role of PHD2 deficiency in the mechanisms of severe PAH and identified the first genetically modified mouse model with irreversible obliterative vascular remodeling and pathophysiology recapitulating clinical PAH. Thus, targeting PHD2/HIF-2α signaling is a promising strategy to reverse vascular remodeling for treatment of severe PAH and promote survival.
Research Abstracts and Case Studies

**Fig 1.** Figure 1. Spontaneous severe PAH and RV hypertrophy in Egltn1tm2 mice. (A) Tie2Cre-mediated disruption of Egltn in lung ECs. A diagram showing the strategy for generation of Egltn1tm2 mice. Representative micrographs of immunostaining showing EC-specific disruption of PHD2 in Egltn1tm2 mouse lungs. (B) Dramatic increase of RVSP in Egltn1tm2 mice. (C-D) Representative echocardiography showing an enlarged RV chamber and thickened RV wall (hypertrophy, C), and increased RV wall thickness diastole (RVWTD, D) in 3.5 mo old Egltn1tm2 mice. (E) Marked RV hypertrophy in Egltn1tm2 mice. *, $P < 0.05$; ***, $P < 0.001$ (Student’s t test. D: ANOVA followed by Games-Howell post hoc analysis: B and E).

**Fig 2.** Occlusive pulmonary vascular remodeling in Egltn1tm2 mice. (A-C) Representative micrographs of Russel-Movat pentachrome staining demonstrating thickening of the intima, medial, and adventitial, occlusion of the large and small vessels (black arrowheads) in 3.5 mo old Egltn1tm2 mice (B, C) and WT mice (A). (D) Anti-CD31 immunohistochemistry showing multiple-channel lesions positive for the endothelial marker CD31 (arrows) in Egltn1tm2 mice.
Fig 3. Diminished PHD2 expression in occlusive pulmonary vessels of IPAH patients. (A) Immunostaining demonstrating diminished PHD2 expression (red) in the lumen of occlusive vessels (arrowheads) of IPAH lungs. Nuclei were counterstained with DAPI (blue). Lung sections exhibited strong autofluorescence (AutoF) which helped to show the morphology. Arrows point to non-occlusive vessels; asterisk indicates blood cells. Scale bar, 50 µm.

Fig 4. Role of HIF-2α activation in Egln1−/− mice in mediating severe PAH. (A) Western blot showing stabilized HIF-1α and HIF-2α expression in Egln1−/− mouse lungs. (B-D) Genetic deletion of NIf2α but not HIF1α in Egln1−/− mice completely normalized RVSP (C) and inhibited RV hypertrophy (D) as evident by normalized RV/LV+S ratio at 2 months. (E) Representative heat map of RNA-seq analysis in WT, Egln1−/− (CKO) and EH2 mouse lungs (n=3 mice/group). (F-G) RNA-seq analysis PH-causing genes in mouse lungs. *** P < 0.001. ANOVA followed by Games-Howell post hoc analysis was used for statistical analysis.
A Cardioprotective Estrogen Receptor α-apelin Axis Mediates Salutary Effects of 17β-Estradiol (E2) on Right Ventricular Function in Pulmonary Hypertension

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Purpose: To elucidate novel therapeutically targetable mechanisms by which E2 exerts RV-protective effects in PAH.

Background: Women with pulmonary arterial hypertension (PAH) exhibit superior RV function and survival compared to men; this protection is attributed to cardioprotective effects of E2. We previously demonstrated that E2 increases the cardioprotective peptide apelin; however, the underlying mechanisms remain unknown. We hypothesized that E2, via estrogen receptor (ER)α-dependent signaling, increases apelin in RV cardiomyocytes, and that apelin is necessary for E2 to exert anti-apoptotic and cytoprotective effects in RV failure.

Methods: Apelin expression (western blot [WB], RT-PCR) was evaluated in RV homogenates from male or female Sprague-Dawley rats with sugen/hypoxia (SuHx)-, monocrotaline (MCT)- or hypoxia-induced PH. For relevance, we also evaluated apelin and ERα expression (WB, RT-PCR) in RVs from patients with PAH-induced RV failure. Complementary mechanistic studies were performed in cultured H9c2 rat cardiomyoblasts stressed with TNF-α (10 ng/ml) or staurosporine (50–100 nM) and treated with E2 (10–100 nM). ER-dependence of E2’s effects was evaluated with ER antagonist fulvestrant (100 nM) or ERα siRNA (conc); apelin-dependence was tested with apelin siRNA (conc). Stress responses (p38MAPK activation) and pro-survival (bcl2, p-ERK1/2), pro-apoptotic (bax, cleaved caspase-3), as well as pro-contractile and pro-angiogenic signaling (apelin) were evaluated by WB. p<0.05 by ANOVA was considered significant.

Results: Apelin expression was decreased in RVs from rats with maladaptive (SuHx-PH and MCT-PH) but not adaptive RV remodeling (hypoxic PH), suggesting protective effects of apelin on RV failure development. Both apelin and ERα localized to cardiomyocytes. ERα abundance correlated positively with apelin expression in SuHx-RVs and in human RVs. In vitro, TNF-α and staurosporine induced H9c2 dysfunction (evidenced by decreased bcl2/bax ratio, decreased apelin and increased p38; all p<0.05 vs untreated control); however, these effects were not observed in cells pretreated (24h) with E2 (p<0.05 for all endpoints). Of note, E2 protection was abolished in presence of fulvestrant, ERα siRNA, or apelin siRNA (p<0.05). Important to our hypothesis, apelin was decreased in E2-treated H9c2 cells after ERα knockdown and in E2-treated hypoxic ERα knockout mice (p<0.05), but not in E2-treated hypoxic ERα knockout mice.

Conclusions: Our studies suggest a cardioprotective E2-ERα-apelin axis in stressed rat cardiomyoblasts and in the failing RV. Apelin represents a novel target of E2 and ERαs and is required for E2 to exert cytoprotective effects. ERα is necessary for E2-mediated increases in apelin. This E2-ERα-apelin axis may be harnessed therapeutically in order to develop novel, targeted, and non-hormonal therapies for PAH patients of either sex.
Loss of Caveolin-1 Induces an Invasive, Proliferative, and Inflammatory Phenotype in Pulmonary Arterial Endothelial Cells

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Purpose: Pulmonary arterial hypertension (PAH) is a rare disease characterized by a pro-proliferative endothelial cell phenotype, vascular inflammation and pulmonary vessel remodeling culminating in right ventricular failure and ultimately death. With the advent of selective pulmonary vasodilator therapy, outcomes for PAH patients have improved, but current therapy is not curative and mortality remains unacceptably high. Therefore, it is important to develop in vitro model to study the molecular determinant of PAH pathogenesis.

Background: Caveolin-1 (CAV-1) is an endothelial scaffolding protein located in flask-shaped invaginations present in the plasma membrane. CAV-1 interacts with several key molecules relevant to pulmonary arterial hypertension (PAH) via its scaffolding domain. Recently, a heterozygous single nucleotide deletion resulting in CAV-1 loss-of-function has been linked to the development of PAH. However, the relationship between CAV-1 loss-of-function and the development of the dysfunctional pulmonary endothelial phenotype associated with PAH pathogenesis is unknown. Here, we hypothesized that CAV-1 loss-of-function in the pulmonary artery endothelium leads to a hyperproliferative, invasive and pro-inflammatory phenotype that contributes to the pathogenic pulmonary vascular remodeling seen in patients with PAH.

Methods: In primary, human pulmonary artery endothelial cells (PAECs), CAV-1 was knocked down using an siRNA approach. Cells were then examined for proliferation using an MTS and ATP production assay. Migration assay was performed using Oris™ Pr, Platypus Technologies. RT-PCR and western blot analysis was performed to measure the mRNA and protein expression of ICAM1 and VCAM1 adhesion molecules.

Results: CAV-1 knocked down using an siRNA resulted in an efficient ≥80% knockdown of CAV-1 protein. Using an MTS assay and ATP production, we found increased cell proliferation in Cav-1-silenced compared to control PAECs. Loss of CAV-1 function also increased PAECs migration. Similarly, the mRNA and protein expression of ICAM1 and VCAM1 increased after CAV-1 knockdown.

Conclusions: These findings demonstrate that CAV-1 loss-of-function in PAECs leads to a proliferative, hypermigratory and pro-inflammatory phenotype. Thus, CAV-1 gene silencing may be a useful in vitro model to study molecular mechanisms important to PAH pathogenesis.
Postnatal Hyperoxia Exposure Durably Impairs Right Ventricular Function in Aged Male Rats

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Purpose: To determine the long term effects of postnatal hyperoxia exposure with respect to right ventricular (RV) function and ventriculo-vascular coupling.

Background: Prematurity complicates 12% of births nationwide. Recent human studies demonstrate RV hypertrophy (RVH) and impairment persisting into adulthood. However, long term abnormalities in pulmonary hypertension (PH) and ventricular-vascular coupling following prematurity and prematurity-related lung disease remain poorly defined.

Methods: Male and female pups from timed-pregnant Sprague Dawley rats were randomized to normoxia or hyperoxia (FIO2 0.85) exposure for the first 14 days of life, a commonly used model of chronic lung disease of prematurity. Animals were then aged out to 1 year in standard normoxic conditions, at which point they underwent echocardiographic assessment of RV and left ventricular (LV) function followed by invasive measurement of RV pressure volume loops by admittance catheter.

Results: Aged hyperoxia-exposed animals (n=6 male, 7 female) demonstrated significantly greater RVH than aged normoxia-exposed animals (n=3 male, 5 female; p=0.007). Echocardiography demonstrated no significant differences in LV ejection fraction, fractional shortening, stroke volume, cardiac output, or tricuspid annular plane systolic excursion in aged hyperoxic animals compared to aged normoxic controls. However, invasive measures demonstrated significantly higher systolic pulmonary artery pressures (PAP) in males exposed to postnatal hyperoxia (PAP 34.3 ± 3.4 versus 20.3 ± 3.7 mmHg for hyperoxic versus control males, p=0.05). PAP in aged hyperoxic females were not significantly different than aged normoxic females (PAP 27.5 ± 2.9 versus 21.6 ± 1.5 mmHg for hyperoxic versus control females, p=0.5). In males, there was an increase in arterial elastance (Ea) and decrease in the end systolic pressure volume relationship (Ees), resulting in a marked decrease in the ventriculo-vascular coupling ratio, Ees/Ea, consistent with impaired ventriculo-vascular coupling efficiency (Ees/Ea 0.72 ± 0.15 versus 3.36 ± 0.61 in hyperoxic versus normoxic males, p=0.001). Aged hyperoxic females demonstrated a less significant decline in Ees/Ea (1.32 ± 0.31 versus 2.40 ± 0.43 in hyperoxic versus normoxic females, p=0.13)

Conclusions: Males with a history of prematurity and prematurity-related lung disease may be at increased risk for RV dysfunction and ventriculo-vascular uncoupling with age.
Inhibition of miR-130a in the Lungs Prevents Monocrotaline Induced Pulmonary Arterial Hypertension in Mice

Gupta LL, Gupta S

**Purpose:** Current therapies are limited to reverse the vascular remodeling. Investigating a key molecule is required for development of new therapeutic intervention. The purpose of this study is to determine the underlying molecular mechanism of development of pulmonary hypertension that eventually culminating in right ventricular hypertrophy.

**Background:** Pulmonary arterial hypertension (PAH) is characterized by multicellular vascular lesions which obstruct and obliterate pulmonary arteries. The occluded vessels impede blood flow and increase right ventricular afterload leading to right ventricular hypertrophy (RVH) and RV failure. The pathology of PAH involves vascular cell remodeling including pulmonary arterial endothelial cell (PAEC) dysfunction and pulmonary arterial smooth muscle cell (PASMC) proliferation. Recently, microRNAs (miRNAs) have emerged as a new class of post-transcriptional regulator capable of repressing gene expression by base pairing to the 3’ UTR of mRNA targets; and are involved in diverse cardiovascular diseases; but, the role of miRNA(s) in miRNAs’ role in PAEC dysfunction, a critical phenomenon during the development of PAH is unknown.

**Methods:** We have performed miRNA array in the RV and lungs of monocrotaline (MCT) treated mice. We discovered miR-130a is critical for the development of PAH. We confirmed the role of miR-130a using in vitro using pulmonary arterial endothelial cells and in vivo using MCT treated mouse model.

**Results:** We identified a panel of novel dysregulated miRNAs by miRNA array in the RV and lungs of monocrotaline treated mice and among them; we discovered miR-130a is critical for the development of PAH. We confirmed our finding using MCT and hypoxia-induced mouse models and observed significant upregulation of miR-130a in the RV and lungs. To screen the potential target genes for miR-130a in an unbiased fashion, we transfected mouse PAEC with miR-130a mimic and inhibitor and followed by the stimulation with TGFβ1, separately and confirmed BMPRII is the bona-fide target for miR-130a. The in vitro studies showed that both miR-130a overexpression and TGFβ1 stimulation significantly enhanced the expression of mature miR-130a, promotes apoptosis and endothelial-to-mesenchymal transition (EndMT) and reduced BMPRII level in rodent PAEC. Inhibition of miR-130a in PAEC reversed the above process. The in vivo inhibition of miR-130a using locked nucleic acid of anti-miR-130a showed a promise in attenuating PAH by restoring the BMPR II level, reduction of endothelial cell apoptosis and EndMT.

**Conclusions:** Our study indicates that miR-130a could be a triggering factor in regulating PAH and providing new mechanistic information for therapeutic benefit. We envision an innovative treatment paradigm that alleviates progressive RVH due to PAH.
**NF-kB Mediated miRNAs Modulation in Pulmonary Arterial Hypertension Induced Right Ventricular Hypertrophy**

**Gupta S, Kim I, Wei C, Jones WK**

**Purpose:** Pulmonary arterial hypertension (PAH) is a proliferative vascular remodeling disease with a poor prognosis and limited treatment regimen resulting in right ventricular dysfunction and failure. The purpose of the study is to develop new experimental tools and approaches which will delineate the fundamental mechanism of PAH induced RVH. This study may reveal novel regulatory circuitry that functions adversely in RV and lung remodeling, will pave the way to develop new therapeutic modalities in PAH induced RVH.

**Background:** PAH is a progressive pulmonary vascular disease with high morbidity and mortality. PAH is associated with pulmonary arterial endothelial cell (PAEC) dysfunction; pulmonary arterial smooth muscle cells proliferation, leading to right ventricular hypertrophy (RVH) and RV failure. Endothelial cell dysfunction is thought to be regulated by Rac1 and Rho A-GTPase activity, actin cytoskeleton remodeling and reduced expression of endothelial NO synthase and VE-cadherin. Using cardiac specific I\(\beta\)B triple mutant mice (3M, prevent NF-kB activation), we recently showed that PAH induced RVH was prevented in monocrotaline (MCT) treated 3M mice (3M-MCT), compared to the wild type (WT) mice. We identified bone morphogenic protein (BMP), BMP receptor, inhibitory of differentiation (Id), Smad and Notch signaling axis (BMP-Smad-Id-Notch) required for the development of RVH. Recently, microRNAs (miRNAs) have emerged as a new class of post-transcriptional regulators of genes having a key role in cardiac remodeling; but, the role of miRNA(s) in PAH induced RVH remains elusive. We will test the hypothesis that NF-kB regulates a set of miRNAs responsible for PAH induced vascular remodeling leading to RVH and fibrosis; and inhibition of NF-kB mitigates the vascular damage and abrogates RVH and fibrosis by NF-kB regulated miRNAs.

**Methods:** We have performed miRNA array analysis in MCT treated RV and lungs of wild-type and 3M mice. The in vitro studies were performed using pulmonary arterial endothelial cells treated with TGF\(\beta\)1. The in vivo studies were performed using WT and 3M mice treated with MCT. All western blotting and qRT-PCR were performed using specific antibodies and gene specific primers.

**Results:** we identified and validated several dysregulated NF-kB dependent miRNAs (miR-1,-21,-23b,-26a,-130a and-669f) targeting BMP-Smad-Id-Notch axis in MCT treated WT mice and, were restored in 3M-MCT mice in miRNA array analysis, indicated a potential role in PAH induced RVH. In vitro analysis using mouse PAEC showed that inhibition of NF-kB prevented MCT and TGF\(\beta\)1 stimulated BMP-Smad-Id-Notch gene expressions, restored VE-cadherin level along with NF-kB-dependent miRNA alteration, suggested a link between NF-kB-dependent miRNA regulation and vascular cell remodeling. To define a specific role of miRNA in Endothelial-to-mesenchymal transition (EndoMT), a critical phenomenon in endothelial dysfunction, our data indicated a potential role of miR-1 targeting Notch-3 gene that restored the loss of VE-cadherin triggered by MCT and TGF\(\beta\)1.

**Conclusions:** Our data highlight a new role of miR-1 in EndoMT. We conclude that NF-kB-dependent miRNA modulation targeting BMP-Smad-Id-Notch axes play a critical role in PAH induced RVH. MCT and TGF\(\beta\)1 mediated EndoMT may be regulated in part by miR-1 via Notch signaling that provide new therapeutic modalities in PAH induced RVH.
Fig 7. Expression of miR-130a in the RV and lungs of WT and 3M mice treated with MCT. The analysis was performed using a kit from SA Bioscience (n=3).
Inhibition of Macrophage Leukotriene B4 Synthesis Attenuates and Reverses Pulmonary Hypertension in Animal Models

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Purpose: Despite multiple approved drugs for treatment of PAH, disease remains progressive, suggesting that novel approaches should target unique pathways.

Background: Pulmonary arterial hypertension (PAH) is a progressive and potentially fatal disease characterized by increased pulmonary resistance due to pulmonary arterial remodeling. Despite multiple approved drugs for treatment of PAH, disease remains progressive, suggesting that novel approaches should target unique pathways. Data from animal models of pulmonary hypertension (PH) and supporting data from human PAH samples suggest that leukotriene B4 may play a critical role in the progression of PAH.

Methods: Rat models of PAH were generated by treating athymic (T-cell deficient) rats with a vascular endothelial cell growth factor receptor 2 inhibitor (SU5416), or treating wild-type Sprague-Dawley rats with monocrotaline. Healthy human lung tissue and lung tissue from PAH patients were obtained from the Pulmonary Hypertension Tissue Bank at Stanford University.

Results: Lung lesions generated in the SU/athymic rat model of PH and those from human PAH tissue show prominent accumulation of macrophages with increased expression of leukotriene A4 hydrolase (LTA4H), the biosynthetic enzyme for LTB4. Macrophage-derived LTB4 directly induced apoptosis in pulmonary artery endothelial cells (PAEC), promoted proliferation and hypertrophy of pulmonary artery smooth muscle cells and enhanced proliferation, migration and differentiation of pulmonary artery adventitial fibroblasts (PAAF). LTB4, acting through the BLT1 receptor, induced PAEC apoptosis by inhibition of the sphingosine kinase 1 (Sphk1)-endothelial nitric oxide synthase (eNOS) pathway. LTB4 activates PAAF by upregulating p38 mitogen activated protein kinase (MAPK) associated ROS (reactive oxygen species) signaling. Inhibiting LTA4H or antagonizing BLT1 restored nitric oxide signaling, improved cardiac function and reversed fulminant PH in the SU/athymic rat model. This effect was also seen in the monocrotaline model of PH. Patients with connective-tissue associated-PAH showed higher levels of circulating LTB4 compared to healthy controls. These data suggest that LTB4 may have effects through multiple signaling pathways on multiple cell types to promote the pathogenesis of PH in animal models.

Conclusions: These findings indicate that macrophage-derived LTB4 may play a critical role in the pathogenesis of PH in animal models. These data suggest that inhibition of LTB4 is a potential therapeutic target for the treatment of PAH.
Endothelial CXCL12 Contribution to Obliterative Vascular Remodeling and Severe Pulmonary Arterial Hypertension

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Purpose: The aim of this study is to identify potential molecules/signaling pathways contributing to obliterative vascular remodeling in PAH.

Background: Pulmonary hypertension (PH) is an unremitting disease with increased pulmonary vascular resistance and progressive vascular remodeling that result in right heart failure and death. Vascular occlusion and complex plexiform lesions are hallmarks of the pathology of severe pulmonary arterial hypertension (PAH) in patients.

Methods: Lung CXCL12 mRNA expression was measured by QRT-PCR in IPAH patients and in mice with Tie2Cre-mediated disruption of Egln1 (encoding HIF prolyl hydroxylase 2, PHD2). Egln1Tie2, a novel mouse model with obliterative vascular remodeling and severe PAH recapitulating clinical PAH. To gain insight into the role of Cxcl12 in the pathogenesis of PAH, Cxcl12 floxed mice were bred with Egln1Tie2 mice to generate double knockout mice Egln1Tie2/Cxcl12Tie2. Right ventricular (RV) hemodynamic measurement were carried out to evaluate the RV systolic pressure (RVSP). Echocardiography and determination of right/left ventricle plus septum (RV/LV+S) ratio were used to determine RV hypertrophy. Histology were used to quantify vascular remodeling including muscularization of distal pulmonary arterials. QRT-PCR and Western Blot analysis were carried out to identify the molecular mechanism of PAH in Egln1Tie2/Cxcl12Tie2 mice. In vitro Transwell co-culture of human lung microvascular endothelial cells (HLMEC) and pulmonary arterial smooth muscle cells (HPASMCs) was employed to analyze the effects of PHD2-deficient endothelial cells-derived CXCL12 on SMC proliferation. CXCR4 antagonist AMD3100 was administrated to Egln1Tie2 mice to determine the role of Cxcl12/CXCR4 signaling in mediating severe PAH.

Results: CXCL12 expression was increased in lungs of idiopathic PAH patients and Egln1Tie2 mice. Egln1Tie2/Cxcl12Tie2 mice exhibited significantly decreased RVSP and RV/LV+S ratio compared to Egln1Tie2 mice. Histological examination showed Egln1Tie2/Cxcl12Tie2 mice had mild pulmonary vascular remodeling and decreased RV hypertrophy. Consistently, Egln1Tie2/Cxcl12Tie2 mice had decreased pulmonary vascular SMC proliferation and resulting decreased medial thickening compared to Egln1Tie2 mice. All Egln1Tie2/Cxcl12Tie2 mice survived for at least 6 months whereas 75% of Egln1Tie2 mice died during the same period. We also observed a marked increase of CXCL12 expression in PHD2-deficient HLMECs in a HIF-2a-dependent manner. In vitro co-culture of HLMECs and HPASMCs demonstrated that PHD2-deficient lung EC-released CXCL12 induced SMC proliferation responsible for vascular remodeling. Furthermore, AMD3100 inhibition of CXCR4 signaling in Egln1Tie2 mice attenuated RVSP and RV hypertrophy.

Conclusions: These studies defined the critical role of lung vascular endothelial CXCL12 in mediating severe pulmonary vascular remodeling and resultant severe PAH. Thus, targeting CXCL12/CXCR4 signaling may be a novel therapeutic approach to reverse pulmonary vascular remodeling for treatment of severe PAH.
Fig 2. Endothelial CXCL12 in lung ECs induced SMC proliferation. Representative micrographs showing PHD2-deficient ECs induced SMC proliferation employing the Transwell co-culture system. Proliferating SMCs were immunostained with anti-BrdU antibody (green). Scale bar, 50 μm.

Fig 3. Endothelial Cxcl12 contributed to severe PAH in Eglnf1<sup>TM2</sup> mice. (A) Generation of a mouse model with genetic deletions of both Eglnf1 and Cxcl12 (ECx) by breeding Cxcl12<sup>flxed</sup> mice into the genetic background of Eglnf1<sup>TM2</sup> mice. (B) ECx mice exhibited markedly decreased RVSP compared to CKO mice (3.5 mo old). (C) RV hypertrophy was also partially inhibited in ECx mice. ***, P < 0.001. Student’s t test was used for statistical analysis.
A Selective TGFβ Ligand Trap Attenuates Pulmonary Arterial Hypertension

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Purpose: We aim to test the impact of TGFBRII-Fc, a selective TGFβ1/3 ligand trap, upon experimental PAH and pulmonary vascular remodeling.

Background: Transforming Growth Factor-β (TGFβ) ligands serve as critical regulators of development and tissue homeostasis, signaling via type I and type II serine-threonine kinase receptors to regulate broad transcriptional programs. Excessive TGFβ-mediated signaling is implicated in the pathogenesis of pulmonary arterial hypertension (PAH), based in part on the ability of broad inhibitors of TGFβ/Activin/GDF/Nodal receptors ALK4/5/7 to attenuate experimental PAH. While these inhibitors are effective and promising, their clinical application is limited by cardiovascular and systemic toxicity. Also, these broad inhibition strategies do not delineate the specific contribution of TGFβ vs. a multitude of other ligands. We tested the impact of TGFBRII-Fc, a selective TGFβ1/3 ligand trap, upon experimental PAH and pulmonary vascular remodeling.

Methods: Signaling studies utilized cultured human pulmonary artery smooth muscle cells. PAH was studied in monocrotaline-treated Sprague-Dawley rats, SUGEN/hypoxia-treated Sprague-Dawley rats and SUGEN/hypoxia-treated C57BL/6 mice. PAH, cardiac function, remodeling, and valve structure were assessed by ultrasound, invasive hemodynamic measurements, and histomorphometry.

Results: TGFBRII-Fc is an inhibitor of TGFβ1 and TGFβ3 but not TGFβ2 signaling. In vivo, treatment with TGFBRII-Fc attenuated SMAD2 phosphorylation, normalized expression of PAI-1, and mitigated PAH and pulmonary vascular remodeling in monocrotaline-treated rats, SUGEN/hypoxia-treated rats and SUGEN/hypoxia-treated mice. Administration of TGFBRII-Fc to monocrotaline-treated or SUGEN/hypoxia-treated rats with established PAH improved right ventricular systolic pressures, right ventricular function, and survival. Importantly, no cardiac structural or valvular abnormalities were observed following treatment with TGFBRII-Fc.

Conclusions: Our findings directly implicate TGFβ1/3 in the pathogenesis of PAH while demonstrating the efficacy and tolerability of selective TGFβ ligand blockade for improving hemodynamics, remodeling, and survival in PAH.
An Intriguing Case of Rapid Onset PAH Along with Chronic Hypersensitivity Pneumonitis

Balasubramanian V, Gresham P

**Purpose:** We describe an intriguing case of Avian Chronic Hypersensitivity Pneumonitis (CHP) who subsequently developed rapid onset severe PAH.

**Background:** The association between PH and ILD is well-described (WHO Group III) but poorly understood. In practice, it is not uncommon to see patients with “WHO Group-I” type hemodynamics with a background of ILD particularly in Scleroderma and related Connective tissue diseases (CTD’s). We describe an intriguing case of Avian Chronic Hypersensitivity Pneumonitis (CHP) who subsequently developed rapid onset severe PAH.

**Methods:** Case Report

**Results:** Description: A 72-year-old Hispanic female presented with chronic progressive dyspnea & intermittent dry cough at 2008. She had multiple birds at home. Chest imaging revealed ILD highly suggestive of CHP confirmed by thorascopic lung biopsy. Echocardiography at the time of diagnosis of ILD revealed no features of PH. Treatment with Corticosteroids and Mycophenolate resulted in improvement of symptoms & stabilization of Forced Vital capacity (FVC) over a 3-year period. In 2012, patient presented with “acute right heart failure”. Evaluation revealed severe PAH (Table 1). Pulmonary embolism was ruled out. She was stabilized on Parenteral Prostacyclin therapy (Sub cutaneous treprostinil - PPT-SQT). Her functional and clinical status gradually improved over the next 2 years. Serial RHC’s revealed steady lowering of pulmonary pressures and family requested discontinuation of PPT-SQT. Patient presented with recurrent right heart failure (Table 2) yet again after approximately 1 year of discontinuation of PPT-SQT. PPT-SQT was reinitiated and clinical and functional status stabilized yet again. Table 1 – Serial hemodynamics

**Conclusions:** This case illustrates the complexity and heterogeneity of PAH alongside ILD. These unique phenotypes need improved recognition & better understanding with regards to their pathogenesis, treatment and outcomes.
Pulmonary Tumor Emboli – An Uncommon Cause of Fatal Pulmonary Hypertension in the Young

Balasubramanian V, Gresham P

Purpose: We present a case series of Fatal PH secondary to pulmonary tumor thrombo-embolism (PTTE) in young adults, which is rather unusual.

Background: Acute Pulmonary Hypertension (PH) and Right heart failure can ensue following occlusion of pulmonary arteries secondary to thrombo-emboli. However, thrombo-emboli secondary to microvascular tumor metastases is an unusual cause for PH. We present a case series of Fatal PH secondary to pulmonary tumor thrombo-embolism (PTTE) in young adults, which is rather unusual.

Methods: A case series

Results: Case I – 47-year-old Hispanic female with pleural & metastatic adenocarcinoma of unknown primary presented with progressive dyspnea and severe hypoxemia. Echocardiography revealed signs severe Right ventricular (RV) pressure and volume overload signs. Acute Right heart failure culminated in sudden cardiac death during initiation of right heart catheterization (RHC). Autopsy revealed RV dilatation & Hypertrophy. Pathology showed widespread occlusive “tumor” thrombo-emboli – Pulmonary tumor thrombotic microangiopathy (PTTM) – (Figs 1&2)

Case II – 25-year-old Hispanic male with recent pancreatitis history presented with acute onset dyspnea, Hip pain, diaphoresis and Hypotension. Imaging revealed bilateral subsegmental pulmonary emboli, extensive bony lytic lesions and pelvic and mesenteric adenopathy. Echocardiography revealed features of pulmonary hypertension with right atrial and ventricular enlargement and septal deviation. Patient was deemed as not a candidate for thrombolysis. He was anticoagulated with Heparin. Acute worsening of hypoxemia and hypotension ensued a few days later that rapidly culminated in a cardio-respiratory arrest and death. Autopsy revealed extensive metastatic adenocarcinoma. Pulmonary emboli were admixed with fibrin and tumor cells consistent with tumor thromboemboli and related PTTM.

Conclusions: PTTE is a rare cause of pulmonary hypertension, often fatal and highly uncommon presentation in the young.
Pulmonary Tumor Thrombotic Microangiopathy (PTTM): Additional PAH Group 1 Member?

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Purpose: Suggestion to include PTTM in the WHO classification under group 1.

Background: Pulmonary tumor thrombotic microangiopathy (PTTM), described by Von Herbay et al in 1990, occurs when adenocarcinoma embolic cells induce local activation of coagulation and fibrocellular intimal proliferation in the pulmonary small arteries and arterioles. Activation of tissue factor (TF), vascular endothelial growth factor (VEGF), and osteopontin (OPN) amongst others leads to luminal narrowing, development of plexiform-like lesions and severe, rapidly fatal pulmonary hypertension and right heart failure.

Methods: We evaluated a 51-year-old healthy non-smoker Caucasian female with 3 weeks of progressive dyspnea and dry cough. On exam she had tachypnea (RR 22), tachycardia (HR 129) and hypoxia (SpO2 85% on RA) with bibasilar inspiratory crackles, accentuated S2, no JVD or edema.

Results: CXR showed diffuse nodular opacities with preserved lung volumes and chest CT showed interstitial and peribronchial thickening, large lymph nodes and bilateral patchy infiltrate. Figure 1: CXR left panel and CT lung and mediastinal windows center and right panels respectively.

2-D echocardiogram found EF of 55–60%, flattened septum, severely dilated RV, and an estimated RVSP >90 mmHg. FEV1 was 2.02 L (69% predicted), FVC (unreliable). RHC confirmed severe pre-capillary pulmonary hypertension: RA: 13 mmHg, RV: 74/39, RVEDP: 20 mmHg, PA: 73/39, Mean 54 mmHg, PW: Mean 9 mmHg. Fick CO: 2.21 L/min, Fick CI: 1.32 L/min/m2, AO Sat 100 %, PA Sat: 49 %. Post cardiac catheterization the patient had PEA arrest and succumbed despite resuscitative efforts. The lungs at autopsy had complex plexiform-like vascular lesions with widespread microscopic tumor deposits, tumor cell embolism with local thrombosis and fibrocellular intimal proliferation. Positive CK7 and TTF-1 suggest a lung adenocarcinoma. Figure 2: Left panel: plexiform-like lesion. CK7 and TTF-1 center and right panels.

Conclusions: PTTM is a rapidly progressive and fatal complication of malignancy, usually adenocarcinoma manifest clinically as subacute respiratory failure with pulmonary hypertension, rapidly progressive right heart failure, and sudden death. Antemortem diagnosis of PTTM associated pulmonary hypertension is extremely challenging. We suggest the inclusion of PTTM in the WHO classification under group 1. This will increase the physician’s awareness of this disease when evaluating patients for pulmonary hypertension.

Figure 1:

Figure 2:
Just Another Case of Pulmonary Hypertension due to Pulmonary Embolism?

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Methods: A 74 y/o woman with no significant past medical history presented to her PCP with a 1 month history of dyspnea and decreased exercise tolerance. Echocardiography demonstrated a severely dilated and dysfunctional right ventricle (RV), RV systolic pressure 75 mmHg and pulmonic valve gradient 26 mmHg. Contrast chest CT demonstrated a mass in the RVOT which extended into the main pulmonary artery (PA). Tissue characterization of the mass on cardiac MRI was consistent with thrombus. She was treated with anticoagulation for pulmonary embolism (PE). Her symptoms did not improve and she was hospitalized 2 months later in severe right heart failure. Echo showed no change in the RVOT obstruction. PET scan demonstrated slightly increased metabolic activity in the mass suggestive of neoplasm and V/Q scan was low probability for chronic PE, making CTEPH unlikely. Surgical resection was felt to be too high risk due to concern for hemodynamic instability, lack of myocardial support for a valve prosthesis and bleeding related to neoplastic myocardial infiltration. In an attempt to relieve the RVOT obstruction, we proceeded with successful deployment of a 20 mm Melody transcatheter pulmonary valve. (Figures 1&2). Initial hemodynamics: RAP 22 mmHg, RVP 59/26 mmHg, MPAP 8 mmHg, PAOP 13 mmHg, CI 1.0 L/min/m². Post-procedure hemodynamics: RVP 58/15 mmHg, PAP 58/28(37) mmHg, CI 1.6 L/min/m². Unfortunately, the patient’s post-procedure course was complicated by pulmonary reperfusion injury, hemorrhagic pericardial effusion, stress cardiomyopathy, shock and sepsis. She was transitioned to comfort care and expired 4 days later. An autopsy showed that a paucicellular fibrotic mass was present in the RVOT extending into the PA with features consistent with a small (0.8cm) cardiac fibroma (Figure 3) combined with a larger (2.2cm) organized thrombus wedged in the stenotic space. The Melody valve remained intact in proper position.

Conclusions: To our knowledge this is the first report of a fibroma causing symptomatic severe RVOT obstruction and RV failure in an adult, and its association with thrombus is unusual. This diagnosis requires a high index of suspicion as it can mimic PV stenosis or “pulmonary hypertension” from thromboembolism.
Hepatopulmonary Syndrome in Hereditary Hemorrhagic Telangiectasia (HHT): Not all Right-to-Left Shunting in HHT is due to Pulmonary Arteriovenous Malformations

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Purpose: The purpose of this report is to highlight other etiologies of right to left shunting in patients with HHT to prevent misdiagnosis.

Background: Up to 30% of patients with HHT exhibit pulmonary arteriovenous malformations (PAVMs), clinically manifesting as right-to-left shunting (RLS) and hypoxemia. We report the case of a HHT patient that presented with RLS and hypoxemia due to hepatopulmonary syndrome (HPS) from HHT-induced portal hypertension (PoH) rather than AVM.

Methods: Chart review

Results: A 60-year-old male with a history of colon cancer and Crohn’s ileitis presented with persistent abdominal pain and fevers post-chemotherapy. Workup included an upper endoscopy, which demonstrated esophageal varices. In order to further evaluate the etiology, an abdominal MRI was performed; this revealed large abnormal hepatic artery to portal venous shunting and atrophy of the right lobe of the liver. A transjugular liver biopsy confirmed the presence of non-cirrhotic PoH. Viewed in context of a history of recurrent epistaxis and physical examination findings of facial telangiectasias, a diagnosis of HHT was made. Genetic testing was negative. An echocardiogram with bubble study was performed to evaluate for PAVMs and revealed a small non-cardiac RLS. Lung perfusion scanning was normal. Further testing with multiple contrasted chest computer tomograms did not reveal any PAVMs. Due to known PoH and oximetry of 93% on room air, an arterial blood gas was ordered. This revealed an elevated A-a gradient of 18 mmHg. Given the triad of PoH, RLS and increased A-a gradient, a diagnosis of HPS was made.

Conclusions: Patients with HHT can have AVMs in the pulmonary, cerebral and hepatic vasculature. The urgency in identifying PAVMs relates to the potential for detrimental events resulting from direct communication of venous blood into the systemic circulation; these include cerebrovascular accidents from paradoxical emboli, septic emboli, and brain abscesses. While the presence of PAVMs requires an aggressive management approach with embolization, other pulmonary pathology should be pursued when appropriate. Hepatic AVMs, if draining into the portal vein, can cause significant non-cirrhotic PoH, putting patients at risk for diseases associated with this condition, such as HPS (as noted in our patient and explaining the RLS noted on echocardiogram). While HHT patients are also at risk for the development of pulmonary arterial hypertension (PAH), this was ruled out in our patient by echocardiography and B-type natriuretic peptide testing. In addition, PAH would be unlikely to cause non-cardiac RLS. This case emphasizes that while suspicion for PAVMs should be high in HHT patients with RLS and hypoxemia, HPS from PoH should be considered in the differential diagnosis.
Pulmonary hypertension caused by amyloid infiltration of pulmonary vasculature

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Purpose: To describe a case of pulmonary hypertension due to pulmonary amyloid infiltration and to discuss the difference in diagnosis and treatment of this disease, as compared to pulmonary hypertension due to amyloid cardiomyopathy.

Background: Amyloidosis is a complex spectrum of diseases resulting in end-organ damage from abnormal protein deposition. One of the rarer complications of amyloidosis is pulmonary hypertension, consequent most frequently to restrictive cardiomyopathy induced by amyloid infiltration of the myocardium. A much less common entity, pulmonary arterial hypertension (PAH) due to infiltration of the pulmonary vasculature, is an important consideration given the potential differences in therapeutic approach.

Methods: A single patient presenting with pulmonary hypertension and amyloid cardiomyopathy with pulmonary amyloid underwent a full workup for characterization of the etiology of her pulmonary hypertension in an effort to guide further therapy. A literature review was done to further describe this disease and optimal therapeutic approaches.

Results: A 69-year-old Caucasian nonsmoker female with a history of biopsy-proven amyloid cardiomyopathy with consequent systolic heart failure, since recovered with amyloid therapy, presented with progressively worsening dyspnea of 2 months’ duration, now oxygen-dependent. A bronchoscopy during the preceding months with transbronchial biopsy revealed pulmonary involvement with amyloid demonstrated by positive Congo red stains (Fig 1,2). She was admitted for progressive hypoxia with an oxygen saturation of 70% on room air and bilateral infiltrates on chest radiograph. The physical examination revealed mild respiratory distress, clear breath sounds bilaterally, no jugular venous distention, regular rate and rhythm with a prominent P2 component of S2, 3/6 holosystolic murmur at the left parasternal border, and cyanosis and clubbing of the extremities. Vital signs were notable for mild tachypnea. B-type natriuretic peptide level was 322 pg/ml. A workup for HIV, connective tissue disease, and liver disease was negative. A CT of the chest showed upper lobe mosaic perfusion abnormalities and enlarged pulmonary arteries, which had not been present on a CT several months earlier (Fig 3,4). A repeat transthoracic echocardiogram showed right heart enlargement and new right ventricular systolic pressure of 70 mmHg by tricuspid regurgitation velocity. Right heart catheterization which documented a right atrial pressure of 4, pulmonary artery pressure 77/29, mean pulmonary artery pressure of 47 mmHg, a pulmonary capillary wedge pressure (PCWP) of 9 mmHg, cardiac output and index 3.25 and 1.98 L/min, respectively. The calculated pulmonary vascular resistance was 1016 dynes/second. She had a negative vasodilator response to epoprostenol with no change in PCWP. The patient was started on a phosphodiesterase-5 inhibitor and an endothelin receptor antagonist and discharged with outpatient follow-up.

Conclusions: The patient was found to have PAH due to pulmonary amyloid, rather than a consequence of amyloid cardiomyopathy. This is a remarkably rare condition, with fewer than 10 cases ever reported, and is likely due to the dysfunction of pulmonary vascular tone induced by amyloid infiltration or direct vascular obstruction. Though this previously conferred a poor prognosis, the use of novel targeted PAH medications may improve these patients’ survival and quality of life. Thus, it is important in patients with amyloid and evidence of pulmonary hypertension to evaluate for the exact etiology, as it may change the therapeutic approach and outcome.
Pulmonary Arterial Hypertension (PAH) Associated with Interferon Beta 1B: A Case Report

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Purpose: Describe development of pulmonary arterial hypertension (PAH) in an individual with multiple sclerosis treated with interferon therapy for 5 years.

Background: Interferon β-1b (IFN beta-1b) is a disease modifying agent commonly used in the treatment of multiple sclerosis, that is associated with development of pulmonary arterial hypertension (PAH).

Methods: Case study: A 54-year-old female with history of multiple sclerosis presented with exertional dyspnea and progressive fatigue of 8 months duration that was attributed to multiple sclerosis. She had received IFN beta-1b for 5 years. She denied chronic liver disease or HIV risk factors and was a 40 pack-year smoker. Assessment of dyspnea was initiated with an echocardiogram that revealed right ventricular (RV) dilatation, RV systolic pressure of 50 mm of Hg, mild mitral regurgitation and preserved left ventricular function. Pulmonary function tests revealed moderate airflow obstruction with preserved gas exchange. Computerized tomography of the chest with contrast and ventilation-perfusion scan excluded pulmonary embolism. Serology for connective tissue disorders, hepatitis and HIV were negative. A right heart catheterization was performed that revealed pre-capillary pulmonary hypertension (Table 1), IFN beta-1b was suspected as a cause of PAH and was replaced with dimethyl fumarate for treatment of multiple sclerosis. She was started on sildenafil and ambrisentan for PAH. Follow-up over a period of six months demonstrated significantly less fatigue and increased exercise tolerance. Six minute walk distance improved from 274 meters to 347 meters. A right heart catheterization revealed was performed six months later with an improvement in hemodynamic profile (Table 1).

Results: PAH is increasingly reported with interferon therapy. Overall, 14 cases have been reported- two associated with interferon alpha and ten with interferon beta. A case series (Savale et al. European Respiratory Journal 2014) reported a development of PAH associated with interferon-α in 48 patients and interferon-β in 5 patients. The five patients receiving interferon-β were all female between 39 to 57 years of age with a variable time of onset (59 to 117 months) from initiation of interferon therapy to PAH diagnosis. Our current level of knowledge indicates that drugs and toxins can act as modifiers in a genetically predisposed individual and result in PAH. The mechanism is unknown but suspected to be due to altered growth factor biology. Discontinuation of interferon therapy is recommended.

Conclusions: PAH associated with interferon β therapy improved after discontinuation of interferon therapy and initiation of combination PAH-specific therapy; ambrisentan and sildenafil.

Table 1. Comparison of right heart catheterization measurements at initial encounter and six month follow-up.

<table>
<thead>
<tr>
<th>Date</th>
<th>RA (mmHg)</th>
<th>RV (mmHg)</th>
<th>PAP (mean)</th>
<th>PCWP (mmHg)</th>
<th>CO (L/min)</th>
<th>PVR (Wood units)</th>
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<td>10/1/2014</td>
<td>12</td>
<td>103/4</td>
<td>104/47 (73)</td>
<td>13</td>
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<td>22</td>
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<td>13</td>
<td>68/7</td>
<td>65/26 (43)</td>
<td>15</td>
<td>3.73</td>
<td>8</td>
</tr>
</tbody>
</table>

RA - right atrium; RV - right ventricle; PAP - pulmonary artery pressure; PCWP - pulmonary capillary wedge pressure; CO - cardiac output; PVR - pulmonary vascular resistance
A Rare Cause of Pulmonary Hypertension and Right Heart Failure in Sarcoidosis

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Purpose: To describe an uncommon cause of pulmonary hypertension in a patient with active sarcoidosis.

Background: Post-capillary pulmonary hypertension is well-described in patients with sarcoidosis and is usually related to pulmonary veno-occlusive disease or left heart dysfunction. Here we describe an unusual case of post-capillary pulmonary hypertension secondary to extrinsic compression of the pulmonary veins by bulky hilar lymphadenopathy in a patient with sarcoidosis who presented with acute pulmonary edema, hemoptysis and respiratory failure.

Methods: Our patient was a 40-year-old woman with a history of tobacco abuse and biopsy-proven sarcoidosis with skin and pulmonary involvement, which had been refractory to treatment with prednisone and methotrexate. She presented with acute onset of dyspnea and hemoptysis and after intubation underwent bronchoscopy which showed bleeding localized to the lingula without a clear site for intervention. Attempted embolization with interventional radiology showed no brisk bleeding but was significant for a very elevated pulmonary artery pressure in the 80s. Chest CT scan demonstrated evidence of pulmonary edema as well as bulky hilar lymphadenopathy compressing all pulmonary veins and resulting in significant stenosis. She underwent urgent right heart catheterization which revealed a pulmonary artery systolic pressure of 99mmHg, wedge pressure of 30mmHg and normal LVEDP of 11mmHg, confirming post-capillary obstruction from venous stenosis. Balloon angioplasty of the left lower and lingular pulmonary veins resulted in minimal improvement in her pressures. Nonetheless, she improved and was extubated and discharged from the hospital.

Results: In the several years since, her lymphadenopathy has persisted despite treatment with infliximab. She has had some improvement with nifedipine but has required two additional catheterizations for stenting and dilation of her left upper, left lower, and right lower pulmonary veins and continues to have severe pulmonary hypertension.

Conclusions: This case demonstrates an atypical cause of post-capillary pulmonary hypertension from extrinsic compression of all pulmonary veins by sarcoid adenopathy which has not previously been reported in the literature.
Carfilzomib-induced Right Heart Failure and Severe Pulmonary Hypertension in a 58-year-old Woman with Refractory Multiple Myeloma

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Purpose: Few case reports have demonstrated association of carfilzomib with adverse cardiac and pulmonary events.

Background: Carfilzomib (Kyprolis), a selective proteasome inhibitor, has helped increase the median survival time in patients with refractory and/or relapsing multiple myeloma (MM). We report a case study of a patient with refractory MM currently on treatment with carfilzomib who exhibited right heart failure secondary to severe pulmonary hypertension.

Methods: This is a 58-year-old female with past medical history of Type 2 diabetes mellitus on oral medications, hypertension, hyperlipidemia, mitral valve prolapse, atrial fibrillation on anticoagulation, normal coronaries per coronary angiogram performed one year prior, and kappa light chain multiple myeloma diagnosed in 2013. She already had advanced disease (Durie-Salmon Stage IIIA) with spine involvement, status post radiation therapy. She was on her fourth cycle of carfilzomib, pomalinomide (an immunomodulator), cyclophosphamide and dexamethasone when she presented acutely with shortness of breath and chest tightness. Upon hospital admission, she was hypotensive with a blood pressure of 80/60, cold extremities with elevated jugular venous distention, and pitting lower extremity edema.

Results: The electrocardiogram (EKG) demonstrated right ventricle (RV) hypertrophy, prolonged QTc (507 ms), and nonspecific T wave changes in the anterior leads. Labs notable for peak troponin of 0.03 mg/dL, lactic acid of 6.4 mg/dL, and a white blood cell count of 13 mg/dL. Transthoracic echocardiogram (TTE) revealed a hyperdynamic left ventricle (LV) with ejection fraction (EF) of 70%, severely dilated RV with severely reduced RV systolic function, severely dilated right atrium (RA) with PA systolic pressure of 63 mmHg. A computed tomography angiogram and nuclear ventilation/perfusion scan of the chest was negative for pulmonary embolus and parenchymal lung disease. Patient was placed on low dose norepinephrine for hemodynamic support. Right heart catheterization demonstrated severe pulmonary hypertension with PA pressures of 85/20 mmHg (mean PA 38 mmHg), PCWP of 28 mmHg, RA 12 mmHg, PA saturation of 56%, and cardiac output and cardiac index of 2.86 L/min and 1.86 L/min/m2 respectively. Patient was initiated on furosemide and low dose milrinone infusions in addition to the norepinephrine infusion. PA pressures increased to 103/33 mmHg (mean PA 53 mmHg). Nitric oxide administered at 80 ppm and patient’s hemodynamic changes included a decrease in PA systolic pressure to 85/24 mmHg (mean PA 40 mmHg). Based upon vasodilator study, patient was continued on nitric oxide, milrinone, furosemide, and norepinephrine, and started on iloprost. Patient was also initiated on oral sildenafil while nitric oxide was weaned off. Patient’s clinical condition improved, as she was weaned off of norepinephrine, iloprost, and milrinone. Patient was discharged home on oral sildenafil.

Conclusions: Serial echocardiograms, troponin levels, and brain natriuretic peptide (BNP) levels may be followed in patients at risk for pulmonary and cardiac complications associated with carfilzomib therapy. This case highlights the need for stringent surveillance of pulmonary and cardiac function with carfilzomib, a widely used chemotherapeutic agent for refractory/relapsing MM.
Severe Pulmonary Arterial Hypertension in a Pediatric Patient With Hemitruncus Arteriosus

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Purpose: We describe a unique case of an infant with isolated right-sided hemitruncus presenting with severe PAH exacerbated by extrinsic left bronchial compression by a dilated and hypertensive left pulmonary artery (LPA).

Background: Anomalous origin of one pulmonary artery from the aorta, also known as hemitruncus arteriosus, is an uncommon anomaly that accounts for less than 0.1% of all congenital heart disease. In hemitruncus physiology, one lung is exposed to unrestricted systemic blood flow from the anomalous aorto-pulmonary connection, while the contralateral lung receives the entire right ventricular (RV) output. Thus, many patients experience early pulmonary vascular disease (PVD) leading to the development of pulmonary arterial hypertension (PAH).

Methods: A 1-month-old full-term girl presented with severe PAH. Echocardiogram revealed a dilated right atrium, moderately depressed RV function with evidence of suprasystemic RV pressures. The right pulmonary artery (RPA) arose anomalously from the ascending aorta and the LPA (arising from the RV) was moderately dilated. Cardiac catheterization confirmed twice-systemic RV pressures. By chest radiograph, the left lung field appeared hypoplastic, and follow-up chest CT revealed severe atelectasis of the left lung. A bronchoscopy was performed which demonstrated left bronchomalacia with pulsatile compression anteriorly and inferiorly. Despite the substantial risk for perioperative mortality, the decision was ultimately made to re-implant the RPA to the main pulmonary artery. The PA was also translocated anterior to the aorta (LeCompte) to relieve compression on the left bronchus.

Results: The patient recovered without complication, and has continued to demonstrate improvement of PAH on sildenafil and supplemental oxygen. Her atelectasis has improved without additional therapies, and an echocardiogram performed one week later revealed normalized RV function with less than half-systemic RV pressures.

Conclusions: For patients with PVD in association with hemitruncus, evaluation of exacerbating factors of PAH is essential for surgical prognostication. Prolonged extrinsic airway compression may greatly increase morbidity and mortality by causing bronchomalacia, atelectasis, respiratory infections, and respiratory insufficiency. Thus, a multidisciplinary approach to the management of these patients is essential.
Combination Therapy With Riociguat and Inhaled Treprostinil in Inoperable and Progressive Chronic Thromboembolic Pulmonary Hypertension.

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2South College School of Pharmacy

Purpose: Case report describing the favorable outcome of a 77-year-old female with inoperable CTEPH treated with riociguat in combination with inhaled treprostinil after failing sequential combination therapy with inhaled treprostinil added to sildenafil.

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by the formation of chronic, organized clot in the pulmonary arterial circulation resulting in flow limitation and development of precapillary pulmonary hypertension. While surgical thromboendarterectomy is an effective treatment for this condition, many patients are either inoperable or have persistent pulmonary arterial hypertension (PAH) following endarterectomy. We describe the favorable outcome of a 77-year-old female with inoperable CTEPH treated with riociguat in combination with inhaled treprostinil after failing sequential combination therapy with inhaled treprostinil added to sildenafil.

Methods: A review of patient history, pertinent data and outcome is presented in case report format.

Results: The patient initially presented with chest pain, was diagnosed with bilateral pulmonary emboli, and was anticoagulated with warfarin. At presentation the pulmonary artery pressure (PAP) was estimated at 50–60 mmHg by echocardiography. She was anticoagulated for 6 months. One year following the initial diagnosis, the patient presented with progressive dyspnea. Multiple bilateral pulmonary emboli were again identified in peripheral vessels. Pulmonary arterial pressure was estimated at 91 mmHg. Treatment with warfarin was reininitiated. Three months later there were no improvements in activity tolerance, echocardiogram findings or flow disruption on imaging. Sildenafil 20 mg TID was initiated. After 18 months on warfarin plus sildenafil the PAP was estimated at 106 mmHg with significant right ventricular enlargement. The patient was referred to our center for pulmonary hypertension consultation. Functional class III activity tolerance with a 6 minute walk distance of 405m were recorded. Right heart catheterization confirmed pulmonary artery pressure 102/34/58 mmHg, cardiac output 6.5 L/min by thermodilution and cardiac index 3.2 L/min/m2. The patient was not considered a candidate for thromboendarterectomy due to the peripheral nature of her disease. She declined systemic prostacyclin therapy. Inhaled treprostinil was added to sildenafil. The patient maintained good performance status for 2 years, but then developed severe functional impairment, hypoxemia and a decrease in cardiac output to 4.07 L/min with cardiac index 2.04 L/min/m2. The patient again declined systemic prostacyclin therapy. Sildenafil was replaced with riociguat, and 1 year later the patient achieved functional class II activity tolerance, a 400 m 6 minute walk and improvement in hemodynamics with cardiac output 4.5 L/min and cardiac index 2.28 L/min/m2.

Conclusions: This report describes significant treatment benefit for a patient with inoperable, progressive CTEPH treated with riociguat and inhaled treprostinil. The observed improvement in functional capacity and hemodynamics with the riociguat-treprostinil combination after failing sildenafil-treprostinil may relate to riociguat’s ability to directly stimulate production of cyclic GMP independent of nitric oxide levels in pulmonary artery smooth muscle. There may also be a unique interaction between riociguat and treprostinil that enhanced treatment outcome. Further investigation of this combination of agents may be warranted.
Troubleshooting Inpatient IV Infusion of Prostacyclin: Backflow and Boluses
Farraj M, Gray C, Jones S, Mattison K, Seckel M, Stewart J
Christiana Care Health Services

Purpose: To describe an analysis of a series of IV infusion failures to prevent new patient issues with backflow and inadvertent IV prostacyclin bolus.

Background: Christiana Care Health System (CCHS) converted to new inpatient IV pumps in January 2015. A series of pulmonary arterial patients (PAH) patients experienced blood back up in their IV lines with subsequent bolus of their prostacyclin infusion (epoprostenol and treprostinil). Symptoms included transient hypotension, lightheadedness, and nausea. Per the CCHS PAH Clinical Managed Guideline, all IV prostacyclin patients cohort to one unit and patients are changed to a hospital inpatient pump after admission.

Methods: Research was done regarding possible failure modes. This included the new IV infusion pump with a focus on specifications, its ability to deliver low infusion rates accurately and safely, and the tubing and filter used. Nursing practice was reviewed along with observations by the PAH team, and specific patient experiences. Comprehensive chart reviews were done and included patients prior to and after the new IV pump implementation. Multiple departments were involved in the investigation, including the PAH team, nurses from the PAH cohort unit, clinical engineering, pharmacy, vascular access nurses, medication safety, and patient safety. The manufacturers of the IV infusion pump, tubing, micron filter, as well as the specialty pharmacy nurse specialist were contacted.

Results: All patient backflow incidents with 1 exception occurred with epoprostenol initiation. There is nothing reported in the literature specifically regarding backflow with either epoprostenol or treprostinil. Multiple failure modes were investigated and included:

1. The current portless IV pump tubing with 0.2 micron filter extension tubing total 156.18 cm. The length may have contributed to pulling and catching on patient equipment.

2. Per manufacturer, the 0.2 micron filter should be primed without inverting and secured at the level of the infusion site. When polled, nurses reported priming was done with the filter inverted and not secured. Failure mode could be related to incorrect priming and lack of securement, causing it to act as a siphon.

3. Current inpatient practice had been to insert the IV infusion directly into the line, without the use of a neutral displacement connector. The specialty pharmacy nurse specialist recommended using the connector to prevent backflow in the event of a patient disconnect and used in approximately 50% of home patients.

4. Low infusion rates did not appear to be the concern. These infusions run at low rates via patient home CADD® pumps or hospital pumps. Queries and research show that hospitals either use CADD® pumps or change over to hospital pumps when patients are admitted. There is no national guideline for preferred pump use for in hospital use for PAH patients.

5. The new IV pump was set at the manufacturer default pressure to alarm. The manufacturer suggested changing pressure settings to increase alarm sensitivity. Instructions were sent out during the investigation. Several additional events with backflow occurred after this change.

6. An anti-siphon valve was recommended to prevent backflow with an additional 14 cm length. The valve was added to the system August 2015 with no backflow reports after use.

Conclusions: The current tubing for any patient receiving IV prostacyclin infusion at CCHS now includes portless tubing, a 0.2 micron filter, and an anti-siphon valve. Due to the length of the tubing from the 3 components (167.18 cm), we are working with the manufacturer to develop tubing with reduced length and therefore decrease risk of disconnect.
Successful Rescue Therapy for Digital Ischemia with Sildenafil and Epoprostenol

Lee C, Elwing J
University of Cincinnati, Cincinnati, Ohio, U.S.A.

**Purpose:** To present a case study describing treatment options in cases of critical digital ischemia in systemic sclerosis patients.

**Background:** Systemic sclerosis (SSc) is a rare autoimmune disorder with a wide spectrum of clinical manifestations. Pulmonary Arterial Hypertension (PAH) is one of the leading causes of mortality and morbidity in these patients. Beyond PAH, more than 95% of these patients suffer from Raynaud’s phenomenon (RP) which in severe cases, leads to digital ulceration and critical ischemia. We describe a successful case of salvage therapy for critical digital ischemia in a patient with severe PAH and SSc sine scleroderma using epoprostenol and sildenafil.

A 59-year-old African American woman with World Health Organization (WHO) group 1 PAH and severe RP was initially seen in PAH clinic for a new patient evaluation. She was diagnosed with severe PAH one month prior to the visit and started on sildenafil by another provider. Despite this, she had worsening WHO functional class III symptoms and digital ischemia with necrosis of her digits (Figure 1−2). Based on this, the decision was made to admit the patient for initiation of epoprostenol. On admission, she was continued on her home sildenafil, 40mg three times daily and started on epoprostenol 2 ng kg−1 min−1 with a goal of 7 ng kg−1 min−1. Her initial Raynaud’s Condition Score (RCS) was 10. By day 6, the patient had noted significant improvement in her symptoms. By discharge (Day 16) her RCS was 5 and her exam showed no further ulceration with improvement in overall function. She had no further progression of ischemia, salvage of her remaining digits, and also began to show signs of healing (Figure 3−4).

**Methods:** Single patient followed throughout hospital stay with photos taken before and after treatment with epoprostenol and sildenafil.

**Results:** The case results were salvage of the patients remaining digits, improvement in function, and healing of existing ulcers. Pictures included in figures 1−4.

**Conclusions:** The patient presented for discussion shows a dramatic case of severe digital ischemia in an SSc patient and the effect that epoprostenol in combination with sildenafil can have. Intravenous prostacyclins such as iloprost, have been shown to aid in digital ischemia and ulceration. However, epoprostenol has not been particularly well studied in larger trials in terms of digital ischemia in SSc. While initial studies on epoprostenol did not appear to show great effects on healing of pre-existing lesions, they did show prevention of new ulcers. Furthermore, in the recent SEDUCE study, promising results were shown with sildenafil in healing of digital ulcers. Interestingly, faster rates of healing were demonstrated in a small subgroup receiving both bosentan and sildenafil as well. This is noteworthy as bosentan has not been shown to improve healing of existing ulcers when used alone, but the combined effect with sildenafil allowed both improvement in healing rates and prevention of new ulcers. And given that prostacyclins have been shown to prevent and heal ulcers unlike bosentan, prostacyclins in combination with sildenafil could potentially be used in severe cases of digital ischemia in SSc, as seen in our patient. However, more studies would have to be done on a larger scale looking at this.
Figure 1: Left hand admission

Figure 2: Right hand admission

Figure 3: Left hand day 39

Figure 4: Right hand day 39
Treat and Repair Strategy for Pulmonary Arterial Hypertension Associated with Atrial Septal Defect and Heterotaxy Syndrome

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Purpose: A Case Report

Background: In patients with heterotaxy, especially polysplenia, syndrome and atrial septal defect (ASD), we often experience the early progression of pulmonary arterial hypertension (PAH) during their childhood. Although a “treat and repair” strategy would be considered for PAH associated with ASD, it has not been reported about this strategy for child with PAH associated with polysplenia and ASD.

Methods: We report on a 9-year-old boy with polysplenia, large ASD and PAH who has been well treated in our hospital.

Results: The patient had presented cyanosis from the birth and the echocardiogram had detected a large ASD. Cardiac catheterization (CC) at age of 8 months revealed PAH and interruption of the inferior vena cava with azygous continuation in addition to ASD. His mean PA pressure (mPAP) was 50 mmHg, Qp/Qs was 1.3, and PVRI was 6.8 Wood units (WU) m2. An additional abdominal echography showed left-sided polysplenia and right umbilical portion of the portal vein without portosystemic shunt. The early progression of PAH was noted by CC at age of 3 years (mPAP, 61mmHg; Qp/Qs, 0.84; PVRI, 14.1WU m2), and beraprost, sildenafil and bosentan were administered step by step. After continuous treatment with a combination of three kinds of PAH-targeted drugs, his PAH was getting improved and the CC at age of 7 years showed mPAP, 38mmHg; Qp/Qs, 1.54; PVRI, 5.0 WU m2, suggesting that surgical repair of ASD closure could be indicated. At age of 7 years, he successfully underwent surgical repair of ASD using a fenestrated patch. The postoperative course was uneventful and the follow-up CC at age of 9 years showed further improvement of PAH (mPAP, 25mmHg; Qp/Qs, 1.0; PVRI, 3.9 WU m2) and functional capacity.

Conclusions: Because our patient developed PAH earlier than commonly expected as a patient with large ASD, we speculate that ASD associated with polysplenia syndrome may be a risk factor for early progression of PAH. A “treat and repair” strategy during childhood may be a favorable management option for patients with PAH associated with polysplenia and ASD.
Gastric Bypass Surgery is Safe and Effective in a Patient with Pulmonary Arterial Hypertension

Worden NE, Lovig A, Stewart T, Gerke AK, Cadaret LM
University of Iowa Hospitals and Clinics, Iowa City, IA, U.S.A.

Background: Bariatric surgery among morbidly obese patients with pulmonary arterial hypertension (PAH) is relatively rare but has been reported.

Methods: In this case report, we present a morbidly obese patient who lost a significant amount of weight with bariatric surgery. TS is a 47-year-old female diagnosed with WHO group 1 PAH. On presentation, she complained of several months’ history of dyspnea on exertion. Echocardiogram revealed right-sided heart failure and pulmonary hypertension. A right heart catheterization was performed (Table 1). CT chest suggested right heart failure and pulmonary hypertension. She was diagnosed with mild sleep apnea. Work up for other etiologies of pulmonary hypertension was negative. Initial therapeutics consisted of intravenous epoprostenol, sildenafil, digoxin, furosemide, and lisinopril. Eventually, to simplify her regimen, she was transitioned to intravenous treprostinil, tadalafil, torsemide, and macitentan. Despite significant effort, she was largely unsuccessful at weight loss. The patient was referred for gastric bypass surgery. Her six minute walk distance was 955 feet on two liters per minute of supplemental oxygen. She did experience some chest pain; thus, a myocardial perfusion study was ordered which showed normal perfusion and normal left ventricular ejection fraction. A pre-operative RHC was done (Table 1). At the time of surgery, three years after initial diagnosis, echocardiogram showed improved right ventricular systolic function from previous (although still not normal).

Results: She tolerated general anesthesia for Roux-en-Y gastric bypass surgery. Her treprostinil was continued peri-operatively. Tadalafil and macitentan were restarted post-operatively. She was able to be discharged on post-operative day three. In follow up, the patient’s diuretic dosage was decreased due to pre-renal azotemia. The patient began exercising and lost 50 pounds within two months, and her BMI decreased from 52 to 42 kg/m2. Her six-minute walk distance increased to 1115 feet within two months after the procedure, and she no longer required supplemental oxygen. Shortly thereafter, her treprostinil dose was decreased from 56 ng/kg/min to 50 ng/kg/min due to weight loss.

Conclusions: Morbid obesity is a common problem in Group I PAH patients and bariatric surgery is a viable option in select patients who are hemodynamically optimized.
Rescue Therapy with Oral Prostacyclin (Orenitram) in an Octogenarian Female with Refractory Pulmonary Arterial Hypertension

Zaman H, Roberts D, Khanal C, Jimenez J
MCVI-Baptist Health South

Purpose: To demonstrate that oral prostacyclin rapid uptitration can be used in certain cases of pulmonary hypertension with advanced or refractory symptoms when intravenous prostacyclins are not indicated or refused by a patient.

Background: Care of extreme elderly patients with pulmonary arterial hypertension does not follow standard recommendation. This is due to multiple factors including perception that life is limited in the very elderly, that side effects may be more frequent and intense and that the burden of advanced therapies such as parenteral prostacyclins may be excessive for this patient group.

Methods: Case Study – chart review

Results: An 87 y.o. female with past medical history of diabetes, hypertension was diagnosed with idiopathic pulmonary hypertension in 2012. Initially the patient was placed on a diltiazem and sildenafil and remained functional until 2015 when she presented to the hospital with marked shortness of breath (NYHA class IV), lower extremity edema and hypotension. Initial echocardiogram revealed marked right ventricular dilatation and dysfunction. Right heart catheterization showed the following pressures (mm Hg): RA=15, PA=95/35 55, CO=2.46, PVR=1200. The patient and family declined parenteral prostacyclins. The patient was started on a rapid uptitration of ORENITRAM starting at 0.125 mg twice daily up to 1 mg three times daily within 7 days. Over the following month the dose was increased to 1.5 mg three times daily. At three months follow up, repeat hemodynamics revealed: RA=3, PA+85/30 45, CO=3.16, PVR=938. 6 min walk test was 60 meters, NYHA class=3.

Conclusions: Rapid oral prostacyclin uptitration with orenitram may be an alternative to intravenous prostacyclins in certain populations where intravenous prostacyclins are traditionally indicated. This case represents a successful rescue therapy in a patient with refractory symptoms of pulmonary hypertension where few options were available.
Compassionate Use of Inhaled Prostacyclin in the Management of PAH with Concomitant Cancer: A Case Series

Balasubramanian V, Gresham P

Purpose: Successful use of inhaled prostacyclin therapy on a compassionate basis for patients with PAH and cancer

Background: Pulmonary arterial hypertension (PAH) is a devastating illness which carries serious morbidity and mortality if left undiagnosed or untreated, and so does cancer. The unfortunate clinical situation of coexistence of both these conditions can pose unique challenges to the patient and in their management. We present two such scenarios where Pulmonary vasodilator therapy was used successfully on a “compassionate basis” which resulted in significant improvement in functional status and quality of Life.

Methods: A case series

Results: Case 1: 58-year-old Hispanic woman with longstanding Scleroderma was diagnosed with Stage IIIb Non-small cell Lung Cancer. She was severely functionally impaired by dyspnea. Echocardiogram revealed PH. She was initially treated with Cyberknife for her Lung Cancer. RHC confirmed severe PAH (Table 1). She also had evidence of minimal ILD on CT Chest. She was commenced on Inhaled Treprostinil which resulted remarkable improvement in her functional status and normalization of BNP (Table 2).

Case 2: 52-year-old Hispanic female presented with progressive dyspnea. PH was observed on echocardiography. She had Bilateral pleural effusions and underwent a thorascopic pleural biopsy that confirmed metastatic adenocarcinoma of unknown origin. RHC confirmed severe PAH (Table 1). Pulmonary angiography was negative for CTEPH. Pulmonary vasodilator therapy with Inhaled treprostinil was initiated followed by remarkable improvement in functional status and BNP (Table 2).

Conclusions: Both these cases illustrate the successful use of Inhaled Treprostinil on a “compassionate basis” in patients with co-existent cancer.

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<tr>
<th>Hemodynamic parameters</th>
<th>Case 1</th>
<th>Case 2</th>
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<tr>
<td>mRAP mmhg</td>
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<tr>
<td>PAP mmhg</td>
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<tr>
<td>PCWP mmhg</td>
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<td>CO L/min/Cl</td>
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<td>PVR woods units</td>
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<th>Prognostic parameters</th>
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<tr>
<td>BNP @ FU (pg/ml)</td>
<td>90 (@9 months)</td>
<td>15 (3months)</td>
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<tr>
<td>Change in 6MWD (m)</td>
<td>180 (4 months)</td>
<td>90 (3 months)</td>
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Right Heart Catheterization Data in End Stage Renal Disease: A Retrospective, Descriptive Analysis

Bensimhon H, Caughey M, Ford HJ, Hinderliter A, Rose-Jones L
University of North Carolina, Chapel Hill

Purpose: To describe the cardiopulmonary hemodynamics in patients with pulmonary hypertension and end stage renal disease.

Background: Pulmonary hypertension (PH), defined as mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg, is a recognized complication of chronic kidney disease (CKD) and is an independent predictor of mortality in patients on dialysis and in those receiving a kidney transplant. PH within this population is usually complex and multifactorial. Increased cardiac output due to arteriovenous fistula (AV fistula) in patients on hemodialysis (HD), left ventricular dysfunction (which shares many comorbidities with CKD including hypertension and diabetes), and alterations in vascular endothelium possibly resulting from dialysate and elevations in circulating vasoactive molecules are all thought to be key players. Despite the fact that right heart catheterization (RHC) allows for precise characterization of the cardiopulmonary hemodynamics that result in PH, echocardiography has remained the primary modality for evaluation in this clinical setting. Furthermore, the majority of studies evaluating pulmonary hypertension in patients with CKD have relied on echocardiography data.

In this analysis, we describe the cardiopulmonary hemodynamics of 16 patients with end stage renal disease that underwent RHC in response to echocardiographic or clinical suspicion for PH. We also describe the echocardiographic and left heart catheterization data to better understand how they relate to the RHC findings in this cohort. The overall aim is to help better clinically phenotype this population.

Methods: Our patients were all referred for evaluation of PH in the setting of work up for kidney transplant. Cardiac catheterization and echocardiographic data were gathered through retrospective chart review.

Results: Of the 16 patients studied, 14 had PH, with an average MPAP of 42 mmHg. Of those with PH, 79% demonstrated left ventricular dysfunction with elevated pulmonary capillary wedge pressures (PCWP) ≥ 15 mmHg. The mean PCWP was 24 ± 10 which correlated with a mean left ventricular end diastolic pressure of 25 ± 14. Elevated pulmonary vascular resistance (PVR) (> 3 Wood units) was seen in 43% of the patients. Elevated cardiac index was seen in 15% of patients (defined in this study as a cardiac index (CI) > 4.2 L/min/m2). Only one of our patients met criteria for true pulmonary arterial hypertension, defined as mean PAP > 25mmg, PCWP < 15, and Pulmonary Vascular Resistance > 3 Wood units. 42% of these patients demonstrated reduced right ventricular ejection fraction on echocardiography.

Conclusions: This study could not assess the prevalence of PH in this population due to selection bias: all of these patients were referred for RHC due to clinical or echocardiographic evidence of PH. The PAP observed in this study is similar to the estimated PAP (derived from echocardiography) which has been reported in many prior studies, suggesting our population is somewhat representative of other populations of patients with ESRD and PH.

We are able to demonstrate a pattern of underlying pathophysiology in these patients which is similar to that which has been reported before: the vast majority of patients with end-stage Renal disease and PH (79%) have left ventricular dysfunction. We also showed that 15% demonstrated elevation in cardiac index, which might be lower than expected in this group of patients, all of whom have an AV fistula. Only 7% showed hemodynamics consistent with Group 1 PAH.

The high percentage (42%) of these patients with right ventricular dysfunction speaks to the morbidity associated with increased RV afterload, regardless of the etiology of PH. Larger, prospective studies are needed to more definitively characterize this population.
Identification of Plasma Biomarkers Associated with the Development of Scleroderma-associated Pulmonary Arterial Hypertension

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¹University of Colorado Pulmonary Vascular Disease Center
²University of Colorado Division of Rheumatology
³Cardiovascular Pulmonary Research and Developmental Lung Biology Laboratories, University of Colorado School of Medicine

Purpose: The purpose of this project is to identify candidate protein biomarkers associated with the development of Scleroderma-associated Pulmonary Arterial Hypertension from a longitudinally followed cohort of patients with known scleroderma.

Background: Pulmonary Arterial Hypertension (PAH) is a significant cause of morbidity and mortality in patients with scleroderma (SSc). Even in the era of PAH specific therapies, the 3-year survival remains 40–50% for SSc patients with PAH, compared with greater than 90% survival for those without pulmonary vascular disease. Despite intensive monitoring of this patient population, identification of patients who develop SSc-PAH remains difficult, often resulting in delayed diagnosis. We hypothesize that by utilizing a unique cohort of SSc patients with banked plasma samples both before and after the development of SSc-PAH that we will be able to identify protein targets and pathways implicated in the development of SSc-PAH.

Methods: We conducted a prospective cohort study of 10 patients with SSc-PAH enrolled in the University of Colorado Pulmonary Vascular Disease Center biorepository, who had serial echocardiographic measurements and longitudinally banked plasma samples both before and after development of SSc-PAH. Demographic, hemodynamic, clinical, and survival data were analyzed. Biomarker discovery, verification, and validation were performed using SOMAlogic proteomic technology (Boulder, Colorado), which simultaneously measures over 1100 proteins in unfractionated biologic samples. We discovered 52 candidate protein biomarkers. Ingenuity Pathway Analysis (QIAGEN, Redwood City, California) was utilized to identify proteins and pathways of interest. Selection criteria included a minimum of 1.2 fold change and a P < 0.01 by t-test to account for multiple comparisons. Among the 52 candidate proteins, five were identified as targets of interest. Each protein was differentially expressed at least a 1.2-fold change with a corresponding p < 0.01 when pre- and post- SSc-PAH samples were compared.

Results: Baseline characteristics included a mean age of 51.2 ± 8.5 years, median time since diagnosis of SSc of 4.9 ± 3.6 years, with 8/10 being female. Echocardiographic characteristics showed a right ventricular systolic pressure of 41 ± 8.4mmHg, tricuspid annular plane systolic excursion of 1.96 ± 0.38cm, with 1/10 showing RV dilation. Protein expression changes from pre- to post-SSc-PAH for ErbB3 (-1.2031, p=0.0004), IL-1β (1.2796, p=0.1226), Thrombospondin-1 (1.54542, p=0.1447), EGFR1 (-1.25895, p=0.0038), and ESM-1 (1.91804, p=0.0042) were all highly significant. To date, enzyme-linked immunosorbent assay for thrombospondin-1 has confirmed increased plasma levels following development of SSc-PAH (p=0.0091).

Conclusions: In a longitudinally followed, highly unique patient cohort with SSc who subsequently developed PAH, significant differences were noted in protein expression in target protein pathways. Among those proteins examined, ErbB3, IL-1β, Thrombospondin-1, EGFR1, and ESM-1 were most strongly correlated with the development of SSc-PAH.
Figure 1. Differential plasma protein changes in matched pre- and post- SSc-PAH samples
Pulmonary Arterial Hypertension (PAH) Associated with Interferon (IFN) Therapy: A Population Based Study

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Purpose: To examine the incidence of pulmonary arterial hypertension (PAH) associated with interferon therapy in a privately insured group of patients prescribed interferon for treatment of hepatitis or multiple sclerosis.

Background: Development of pulmonary arterial hypertension (PAH) has been associated with ingestion of medications such as anorexigens. Case reports implicate alpha and beta interferon as possible medications associated with development of PAH. These case series have described an association between interferon use and development of PAH the frequency, however the frequency of this event remains unknown. Thus, the aim of this study was to determine the incidence of PAH after initiation of interferon therapy in a privately insured US population prescribed interferon for treatment of hepatitis or multiple sclerosis.

Methods: We used Clininformatics™ Data Mart (CDM) Database to identify subjects between 20 and 65 years who received alpha or beta interferon therapy between April 2001 and December 2012. National Drug Codes (NDCs) and Healthcare Common Procedure Coding System (HCPCS) codes were used to identify drug prescriptions and diagnostic procedures. ICD-9 codes were used to identify subjects with Hepatitis C or multiple sclerosis as an indication for treatment with interferon. Patients were followed one year prior to the medication prescription to initial diagnosis of pulmonary hypertension. ICD-9 codes 416.0 and 416.8 were used to identify subjects that developed pulmonary hypertension while receiving interferon therapy. Age, gender, co-morbidities and prescription of PAH medications were recorded. For those subjects diagnosed with pulmonary hypertension, we recorded whether PAH specific medications were prescribed.

Results: We identified 20,113 subjects that received interferon therapy and carried a diagnosis of either hepatitis C or multiple sclerosis (Table 1). Females comprised 50.8 % of the group and 78 % were >40 years of age. Hepatitis C was the primary indication for interferon therapy and comprised 64.3% of the group. The median follow up was 20 months and pulmonary hypertension was noted to occur in 71 (0.35%) subjects. Of these 71 subjects, PAH specific medications were prescribed to 7 (9.9%) subjects.

Conclusions: In patients with hepatitis C or multiple sclerosis treated with interferon therapy development of pulmonary hypertension was a rare event.

Table 1. Baseline characteristics of patients, newly initiated on interferon therapy from 2001 to 2012

<table>
<thead>
<tr>
<th>Patient characteristics</th>
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<td>Congenital heart disease</td>
<td>8</td>
<td>0.04</td>
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<tr>
<td>Atrial fibrillation and flutter</td>
<td>74</td>
<td>0.37</td>
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<tr>
<td>Sleep apnea</td>
<td>338</td>
<td>1.68</td>
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<tr>
<td>PH diagnosis before end of follow-up</td>
<td>71</td>
<td>0.35</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean ± STD (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Follow-up time, month</td>
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</table>
Targeting the Prostacyclin Pathway in the Treatment of Connective Tissue Disease Associated Pulmonary Arterial Hypertension (PAH): Insights from the Randomized Controlled GRIPHON Trial with Selexipag

McLaughlin V1, Gaine S2, Channick RN3, DiScala L4, Galiè N5, Ghofrani HA6, Hoeper MM7, Lang I8, Preiss R4, Rubin LJ9, Simonneau G10, Sitbon O10, Tapson VF11, Chin K12

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2Mater Misericordiae University Hospital, Ireland
3Massachusetts General Hospital
4Actelion Pharmaceuticals Ltd, Switzerland
5University of Bologna, Italy
6University of Giessen, Germany
7Hannover Medical School, Germany
8Medical University of Vienna, Austria
9University of California, San Diego
10Hôpital Universitaire de Bicêtre, France
11Cedars-Sinai Medical Center
12University of Texas Southwestern

Purpose: Since connective tissue disease (CTD) subtypes have different pathogeneses and prognoses, we further explored this cohort and examined the effect of selexipag vs placebo in patients with PAH associated with systemic sclerosis (PAH-SSc), systemic lupus erythematosus (PAH-SLE) and mixed CTD (PAH-MCTD).

Background: Despite available therapies, patients with CTD-associated PAH (PAH-CTD) have a particularly poor prognosis, even poorer than other PAH etiologies. The global phase III GRIPHON study (NCT01106014) enrolled 1,156 PAH patients including 334 with PAH-CTD. In GRIPHON, compared with placebo, selexipag significantly reduced the risk of the primary outcome composite of morbidity/mortality up to end of treatment by 41% (hazard ratio [HR] 0.59; 99% CI: 0.37–0.96) among patients with PAH-CTD.

Methods: Patients (18–75 years) were randomized 1:1 to placebo or selexipag. HRs (95% CI) were calculated using Cox regression models to determine the effect of selexipag vs placebo on morbidity/mortality.

Results: Of the 334 PAH-CTD enrolled, 170, 82, 47 had PAH-SSc, PAH-SLE and PAH-MCTD, respectively. In 35 patients, the CTD sub-classification was not reported, therefore data from these patients are not included. In the 3 PAH-CTD subgroups, the majority of patients were female (84–99%) and were receiving an endothelin receptor antagonist, a phosphodiesterase type-5 inhibitor or both at baseline (73–83%). In the PAH-SSc, PAH-SLE and PAH-MCTD groups, the mean (SD) age was 60.0 (10.6), 39.0 (11.3) and 48 (14.7) years, respectively, and 65%, 33% and 45% were in WHO functional class III, respectively. Selexipag reduced the risk of morbidity/mortality events by 44% (0.56; 0.34–0.91) in PAH-SSc, by 34% (0.66; 0.30–1.48) in PAH-SLE, and by 53% (0.47; 0.15–1.48) in PAH-MCTD patients. The treatment effect was consistent across the PAH-CTD subgroups (interaction test indicated no heterogeneity; p=0.6737). By the end of study, 22 PAH-SSc, 7 PAH-SLE and 3 PAH-MCTD patients in the placebo and 17 PAH-SSc, 4 PAH-SLE, 8 PAH-MCTD patients in the selexipag group had died. Common prostacyclin-associated side effects observed with selexipag in PAH-CTD patients (e.g. headache, diarrhea, nausea) generally occurred at a similar incidence to PAH-non-CTD patients and within the PAH-CTD subgroups.

Conclusions: The GRIPHON study included the largest randomized cohort of PAH-CTD patients to date. The treatment effect of selexipag on the time to first morbidity/mortality event was consistent across the PAH-SSc, PAH-SLE and PAH-MCTD sub-groups. These data suggest that targeting the prostacyclin pathway with selexipag is an effective therapeutic option in these difficult-to-treat patients.
Pulmonary Arterial Hypertension Patients’ Treatment Patterns After Initial Therapy in the United States

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3Truven Health Analytics, Ann Arbor, MI
4University of Rochester Medical Center, Rochester, NY

Purpose: To provide a characterization of PAH treatment patterns in the real-world setting, which may be of value given rapidly evolving treatment options and recommendations.

Background: Despite multiple treatment options, the prognosis of pulmonary arterial hypertension (PAH) remains less than ideal. Results from the recently completed AMBITION study suggest that initial combination therapy with ambrisentan and tadalafil reduces the risk of PAH-related hospitalization and improves exercise ability compared with either initial monotherapy.

Methods: This retrospective study identified PAH patients in the Truven Health MarketScan Commercial and Medicare Supplemental Databases between 2010 and 2014 who initiated treatment with endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE-5Is), or a soluble guanylate stimulator (sGC). The index date was the date of the first PAH pharmacy claim preceded by a 90-day period without claims for PAH medications to ensure patients were new to treatment. We included patients with ≥2 medical claims with diagnoses for PAH (ICD-9-CM: 416.0, 416.8) or PAH-related conditions, such as portal hypertension, connective tissue diseases, congenital heart disease, or HIV and continuous enrollment in medical and pharmacy benefits for the six months before and after the index date. Treatment patterns were assessed at class level (ERAs, PDE-5 Is, sGC and prostacyclins) from outpatient pharmacy claims during six months post-index period.

Results: 3,908 patients met the selection criteria. The study sample was majority female (63%), with a mean age of 63 ± 15 years. The sample’s most prevalent baseline comorbidities included cardiovascular disease (92%), systemic hypertension (60%), chronic obstructive pulmonary disease (36%), lipid disorder (31%), and type 2 diabetes (29%), with nearly one-third of patients utilizing oxygen therapy in the 6 months pre-index period. Only 5% of patients initiated treatment with combination therapy, defined as claims for ≥2 medication classes within the first 30 days of treatment, while the majority (95%) initiated a PAH monotherapy regimen. Among patients treated with monotherapy, a majority initiated treatment with PDE-5Is (78%) compared to ERAs (22%). Treatment interruption (≥30 day gap in days’ supply) of any medication class in initiating regimen or augmenting class was observed in 38% of patients. For patients who discontinued treatment, approximately one out of three re-started therapy.

Conclusions: These results provide a baseline real-world prescription pattern which will allow future studies to measure the impact of recent data supporting an initial combination therapy strategy on future prescribing patterns. The data reveals that a majority of PAH patients initiated treatment with monotherapy and that treatment interruption was common during the first six months. We note that the age and co-morbidities of this cohort raise the possibility of group 2 or 3 pulmonary hypertension contributing to their PAH.
Predicting Outcomes in Pulmonary Arterial Hypertension Based on Estimated Glomerular Filtration Rate in the REVEAL Registry

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2Allegheny General Hospital
3Baylor College of Medicine
4Mayo Clinic
5Actelion Pharmaceuticals US, Inc.
6Mayo Pulmonary Hypertension Clinic
7ICON Clinical Research
8Boston University

Purpose: To investigate the prognostic value of baseline and change in estimated glomerular filtration rate (eGFR) on survival in patients with pulmonary arterial hypertension (PAH).

Background: Renal dysfunction is associated with abnormal cardiopulmonary hemodynamics, in-hospital death, and poor survival in PAH.

Methods: The CKD-Epidemiology Collaboration equation was used to derive eGFR at baseline and quarterly intervals for patients enrolled in the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL). Kaplan-Meier (KM) estimates ± standard error, stratified by eGFR at enrollment, were calculated for 1-year survival and the composite of survival and freedom from hospitalization. Survival at 1 year by eGFR threshold and by change in eGFR from the first measurement after enrollment or first quarterly measurement were also examined. Multivariate Cox regression models assessed the effect of eGFR worsening on 1-year survival, adjusted for baseline characteristics.

Results: Baseline eGFR was measured for 2368 PAH patients (653 newly and 1715 previously diagnosed) and was associated with age, 6-minute walk distance (6MWD), functional class (FC), REVEAL Risk Score, and PAH etiology. Patients with eGFR <60 mL/min/1.73m2 at enrollment experienced worse survival than those with eGFR ≥60. Patients with a 10% decrease in eGFR had worse estimated survival than patients with an increase in eGFR. A 10% worsening from baseline eGFR at 1 year, adjusted for change in 6MWD and change in FC from baseline, had a hazard ratio (HR) of 1.27 (95% confidence interval [CI] 1.10–1.46, p = 0.001) for survival and HR of 1.30 (95% CI 1.09–1.56, p = 0.004) for the composite of survival and freedom from hospitalization. However, a 10% improvement from baseline eGFR at 1 year, adjusted for the same variables, did not correlate with improved survival or composite survival and freedom from hospitalization.

Conclusions: In REVEAL, a 10% decline in eGFR independently predicted worse survival and a decrease in the composite of survival and freedom from hospitalization, driven mainly by an effect on survival rather than hospitalization. eGFR may be a simple and economical biomarker in PAH.
The Patterns of Healthcare Utilization and Prevalence of Pulmonary Arterial Hypertension Patients on Prostacyclin Therapy in the United States

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2Evidera, Lexington, MA

Purpose: The purpose of this study is to describe recent PGI2 use, patterns of utilization, and provide an estimate of the prevalence of PAH patients treated with parenteral and non-parenteral PGI2 in the United States (US).

Background: Prostanoids (PGI2) are regarded as the gold standard treatment for patients with severe forms of PAH; however, prostanoid therapy is underutilized, particularly in later stages of the disease. In registries that enrolled patients prior to 2010, including REVEAL and PAH-QUERI, PGI2 use was relatively low. For example, in the REVEAL registry at the time of a PAH-related death, 44% of patients were not receiving parenteral PGI2 and 6% were not receiving any PAH-specific therapy. In the PAH-QUERI at 1 year follow-up, 67% and 45% of patients in Functional Class (FC) III and FC IV, respectively were not receiving a PGI2.

Methods: A retrospective observational cohort study was conducted using claims data from Truven® commercial and Medicare databases, which contain medical and pharmacy claims data for over 15 million persons annually from health plans throughout the US. The study period was January 1, 2010 to October 31, 2014.

Results: During the observation period, a total of 12,306 PAH patients were identified, of which 2,670 (21.7%) were treated with PGI2s. Approximately 900 to 1,100 PGI2 treated PAH patients (20.2% to 21.7%) were represented in each calendar year (CY). There was a shift over time in the type of PGI2 being used, with a downward trend in patients initiated on parenteral PGI2 (IV, SQ) starting in 2012. Around the same time, there was an increase in non-parenteral (inhaled) PGI2 use. In 2010, nearly even numbers of patients initiated parenteral PGI2 and non-parenteral (inhaled) PGI2 use. In 2010, nearly even numbers of patients initiated parenteral PGI2 and non-parenteral PGI2; however, from 2011–2014 there were 33%–54% more non-parenteral PGI2 initiators than parenteral PGI2 initiators per year.

Conclusions: PGI2 use in the U.S. has remained consistent at 21% over the five year period. The use of parenteral PGI2 decreased and non-parenteral PGI2 increased through the study interval. The data from this recent retrospective data review supports the earlier findings from the REVEAL and PAH-QUERI registries. Utilization of the PGI2 pathway to treat PAH patients may be underutilized due to the challenges of parenteral and inhaled administration.
Characterization of Centers Accredited by the Pulmonary Hypertension Association (PHA) in the Pulmonary Hypertension Care Centers (PHCC) Initiative during Programmatic Year One

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\(^2\)Division of Pulmonary and Critical Care Medicine, University of South Alabama, Mobile, AL, U.S.A.
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\(^4\)Santa Barbara Cottage Health System, Santa Barbara, CA, U.S.A.
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\(^7\)Division of Pediatric Cardiology, Department of Pediatrics, Columbia University Medical Center, College of Physicians and Surgeons, New York, NY, U.S.A.
\(^8\)Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO, U.S.A.

On behalf of the PH Care Centers Review Committee

**Purpose:** To characterize PH programs accredited as Centers of Comprehensive Care during program year one of the PH Care Centers initiative.

**Background:** Pulmonary arterial hypertension (WHO Group 1 PH, PAH) and chronic thromboembolic pulmonary hypertension (WHO Group 4 PH, CTEPH) are rare, progressive diseases characterized by an increase in pulmonary artery pressure (PAP) and increased pulmonary vascular resistance with high morbidity and mortality. Over the past twenty years, advances in medical and surgical therapies have led professional societies to develop consensus recommendations on the diagnosis and management of these conditions. However, studies have shown variable utilization of guidelines in both the community and academic practice settings. To address these care management concerns and to improve overall quality of care and outcomes nationally, the Pulmonary Hypertension Association (PHA) launched the PH Care Centers (PHCC) initiative in order to identify guideline-compliant Centers with a focused interest in pulmonary hypertension (PH).

**Methods:** PHCC is designed to evaluate and accredit two types of centers, Centers of Comprehensive Care (CCC) and Regional Clinical Programs (RCP). PH programs interested in evaluation by the PHCC initiative submit a comprehensive application describing the multi-disciplinary center. Applicant programs then complete a day-long site review, conducted by a physician and allied health care professional member of the PHCC Review Committee. Applications and site reviews assess the candidate program based on the program director, non-physician coordinator, program staff and support services, facility, and clinical research activities through 67 criteria. Additionally, a chart review is completed directly assessing guideline adherence in PAH patients on oral, inhaled, and parenteral therapies; CTEPH patients; and a recently deceased patient.

**Results:** In September 2014, after performing a pilot program including six PH centers, PHA began accepting applications for PHCC accreditation. In the first year of the program, 29 Centers received CCC accreditation, including 26 adult and 3 pediatric PH programs. Preliminary descriptive data of these programs, based on self-reporting and PHCC Review Committee verification, is presented in Table 1.

**Conclusions:** An initial characterization of CCCs accredited in the first programmatic year shows diversity in many areas of practice setting, structure, and resource availability. Ultimately, the PHCC accreditation structure is expected to provide centers with the infrastructure for their own quality improvement initiatives, community clinicians with a network of experts for co-management, and patients with further information to empower them in their care.
## TABLE 1: Characteristics of a PHA-Accredited Center of Comprehensive Care Accredited in Year 1 of the Program

<table>
<thead>
<tr>
<th>Criteria Type</th>
<th>Characteristic</th>
<th>Adult CCC No. (%) or Median (IQR)</th>
<th>Pediatric CCC No. (%) or Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accreditation Decision</strong></td>
<td>Accreditation Outcome</td>
<td>26 (92.9%)</td>
<td>3 (75.0%)</td>
</tr>
<tr>
<td></td>
<td>Approved</td>
<td>2 (7.1%)</td>
<td>1 (25.0%)</td>
</tr>
<tr>
<td><strong>Overview</strong></td>
<td>Program existence (years)</td>
<td>16 (8,19)</td>
<td>20 (4,30)</td>
</tr>
<tr>
<td></td>
<td>Number of PAH and CTEPH patients on submitted patient roster</td>
<td>240 (147,338)</td>
<td>180 (137,191)</td>
</tr>
<tr>
<td><strong>Center Director</strong></td>
<td>Subspecialty</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiology</td>
<td>6 (23.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Pediatric Cardiology</td>
<td>1 (3.8%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td></td>
<td>Pediatric Critical Care Medicine</td>
<td>0 (0%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary / Critical Care Medicine</td>
<td>18 (69.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary Diseases</td>
<td>1 (3.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Experience with PH</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>0–4 years</td>
<td>3 (11.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>5–9 years</td>
<td>23 (88.5%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td></td>
<td>10 or more years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenure as Center Director (years)</td>
<td>8 (7,13)</td>
<td>15 (4,15)</td>
</tr>
<tr>
<td></td>
<td>Physician FTE in PH treatment and research</td>
<td>1.7 (1.25,2.7)</td>
<td>1.8 (1.6,2.0)</td>
</tr>
<tr>
<td></td>
<td>PAH/CTEPH patients per physician FTE</td>
<td>142 (86,216)</td>
<td>95 (86,100)</td>
</tr>
<tr>
<td><strong>Center Coordinator</strong></td>
<td>Credential</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Advanced Practice Registered Nurse</td>
<td>11 (42.4%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td></td>
<td>Physician Assistant</td>
<td>2 (7.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Registered Nurse</td>
<td>11 (42.3%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>Registered Nurse / Respiratory Therapist</td>
<td>1 (3.9%)</td>
<td>0 (0%)</td>
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<td></td>
<td>Respiratory Therapist</td>
<td>1 (3.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Clinical coordinator FTE</td>
<td>2.0 (1.4,3.0)</td>
<td>3.0 (1.4,3.0)</td>
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<tr>
<td></td>
<td>PAH/CTEPH patients per clinical coordinator FTE</td>
<td>166 (79,217)</td>
<td>127 (60,137)</td>
</tr>
<tr>
<td></td>
<td>Research coordinator FTE</td>
<td>1.3 (0.75,2.0)</td>
<td>1.5 (0,1.2,6)</td>
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<tr>
<td><strong>PH Diagnostic Guidelines</strong></td>
<td>Percent of patients on PAH-specific therapy that underwent RHC</td>
<td>99 (99,100)</td>
<td>98 (94,100)</td>
</tr>
<tr>
<td></td>
<td>Percent of PAH cases undergoing acute vasodilator testing</td>
<td>90 (80,95)</td>
<td>100 (100,100)</td>
</tr>
<tr>
<td></td>
<td>Percent of PH cases undergoing pulmonary function testing</td>
<td>98 (90,100)</td>
<td>30 (13,60)</td>
</tr>
<tr>
<td></td>
<td>Percent of PH cases undergoing nocturnal oximetry or polysomnography testing</td>
<td>68 (45,85)</td>
<td>50 (36,60)</td>
</tr>
<tr>
<td></td>
<td>Percent of PH cases undergoing testing to exclude CTEPH</td>
<td>96.5 (93,100)</td>
<td>100 (80,100)</td>
</tr>
<tr>
<td><strong>PH Medical Therapies</strong></td>
<td>Number of patients center manages on PAH-targeted therapy over the past 3 years(^2)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>210 (150,300)</td>
<td>133 (74,185)</td>
</tr>
<tr>
<td></td>
<td>Inhaled</td>
<td>37 (24, 50)</td>
<td>20 (17,25)</td>
</tr>
<tr>
<td></td>
<td>IV/SQ Prostacyclin</td>
<td>41 (35,87)</td>
<td>34 ± 20</td>
</tr>
<tr>
<td><strong>PHCC Site Visit Chart Review</strong></td>
<td>Percent of pre-defined chart review components successfully identified</td>
<td>95.8 (92.7,97.1)</td>
<td>97.7 (97.2,98.8)</td>
</tr>
<tr>
<td><strong>PHCC Chart Review</strong></td>
<td>Most frequent chart review deficiencies (No. of centers with &gt;1 deficiency)</td>
<td>5 (19.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Nocturnal oximetry</td>
<td>1 (3.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Acute vasodilator testing</td>
<td>1 (3.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Functional Class Assessment</td>
<td></td>
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</tbody>
</table>

(Footnotes)
1. Self-reported statistics from the PHCC Application
2. Includes patients on combination therapy
Evaluation of Quality of Care and Quality of Life of Pulmonary Hypertension Patients Seen in PH Care Centers: PHA Registry Study Design


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4Cedars-Sinai Medical Center, Los Angeles, CA, U.S.A.
5Department of Biostatistics, University of Washington – Seattle, Seattle, WA, U.S.A.
6Division of Pulmonary and Critical Care, University of Washington, Seattle, WA, U.S.A.
7Department of Medicine, Penn Cardiovascular Institute, and the Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, U.S.A.

Purpose: To describe the U.S.-based, multicenter, prospective, observational registry of incident WHO Group 1 and WHO Group 4 PH patients managed at PHA-Accredited PH Care Centers.

Background: Pulmonary arterial hypertension (PAH) is a progressive disease, characterized by pulmonary vascular remodeling, high morbidity, and high mortality. Several drugs for PAH have been developed over the last two decades and professional societies have developed guidelines for the evaluation and treatment of PAH; however, these recommendations are often based on limited evidence and key knowledge gaps persist. Adherence to published guidelines, even at expert centers, has not been well studied. It is also unknown whether adherence relative to non-adherence at an expert center is associated with better outcomes. The Pulmonary Hypertension Association (PHA) has established the PHA Registry (PHAR) in order to improve the quality of care for patients with PH and improve outcomes.

Methods: PHAR is a U.S.-based, multicenter, prospective, observational patient registry being conducted at PHA-Accredited Pulmonary Hypertension Care Centers (PHCC). Twenty-nine PHCCs have been accredited as Centers of Comprehensive Care to-date. Patients newly evaluated at a PHCC with PAH (WHO Group 1 PH) or CTEPH (WHO Group 4 PH, CTEPH) who speak English or Spanish and are able to provide informed consent are able to participate in the PHAR. Demographics, medical history, symptoms, medication use, social history, and health-related quality of life are collected using electronic case report forms at baseline (Table 1). Longitudinal follow-up will be collected approximately semi-annually coincident with regularly scheduled clinical follow-up. Both baseline and follow-up assessments include the Medical Outcomes Study Short Form (SF)-12 and the emPHasis-10 questionnaires.

Results: In August 2015, PHAR started subject enrollment in a pilot at six PHCC clinical sites. Baseline data from the pilot will be presented. More than 5,000 patients are expected to be eligible for enrollment over the next five years.

Conclusions: Initial data suggest variability in adherence to published guidelines at expert centers. PHAR will allow an increasingly rich national assessment of trends in medical practice patterns, adherence to consensus guidelines on the diagnosis and management of PAH and CTEPH at PHA-Accredited PH Care Centers, and patient-reported outcomes. Data from this study will provide infrastructure for center-, regional-, and national quality improvement initiatives seeking to improve patient quality of life and outcomes.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Collection</th>
<th>Follow-up Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUID number</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Primary PH diagnosis</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Right heart catheterization <em>(indicate if performed)</em></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Ventilation/perfusion lung scintigraphy <em>(indicate if performed)</em></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Chest CT <em>(indicate if performed)</em></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Pulmonary function test <em>(indicate if performed)</em></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Overnight oximetry/sleep study <em>(indicate if performed)</em></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray <em>(indicate if performed)</em></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>CTEPH surgical evaluation <em>(indicate if completed)</em></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>PAH-targeted medication(s)</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Concomitant medication(s)</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>WHO functional class</td>
<td>Y</td>
<td>Y</td>
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### TABLE 1: Baseline Variables Collected for Enrolled Patients, continued

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Factors Affecting Accuracy of Transthoracic Echocardiography in the Evaluation of Pulmonary Hypertension

Allen L1, Collins C1, Heidel RE2, Swisher J1
1Summit Medical Group
2University of Tennessee Graduate School of Medicine

Purpose: The objective of the current study was to evaluate factors that influence the reliability of transthoracic echocardiography in the assessment of pulmonary hypertension.

Background: Transthoracic echocardiography (TTE) is widely used for the detection and management of pulmonary hypertension. Right heart catheterization (RHC) is the standard for accurate measurement of pulmonary arterial pressure (PAP), while TTE provides a calculated estimate of the PAP based on the systolic velocity of tricuspid valve regurgitation. The objective of the current study was to evaluate factors that influence the reliability of transthoracic echocardiography in the assessment of pulmonary hypertension.

Methods: We conducted a retrospective analysis of patient data from a regional, community-based pulmonary hypertension referral center. Patients included in the analysis were over 18 years of age and had undergone TTE and pulmonary artery catheterization within a 12-month period of time. Accuracy of systolic PAP (sPAP) determined by TTE was assessed by comparison with sPAP measured during right heart catheterization. Systolic pulmonary artery pressure measured by RHC was used as the reference standard for this analysis. Relationships of TTE measurements with body mass index (BMI), severity of pulmonary arterial hypertension as measured by RHC, and TTE service location were investigated to determine factors that might affect accuracy of TTE measurements. Non-parametric between-subjects tests were used.

Results: A total of 79 patients were identified from the referral center database who met the basic inclusion criteria and had documentation of all data required to complete the analysis. The difference between TTE sPAP and RHC sPAP exceeded 10mmHg in 47 patients (59.5%). Of those, echocardiography underestimated sPAP by more than 10 mmHg in 21 patients (44.7%) and overestimated by more than 10 mmHg in 26 patients (55.3%). The variance between TTE and RHC sPAP was evaluated across four severity groups based on the true sPAP as determined by RHC (sPAP < 35 mmHg, 35–55 mmHg, 56–75 mmHg, and > 75mmHg). Using the Kruskal-Wallis test, a significant main effect of sPAP grouping was found (p = .002). Further, there was significantly higher variance between TTE vs RHC sPAP when true sPAP was < 35 mmHg in comparison to 35-55 mmHg (Mann-Whitney U, p = .003). The true sPAP was consistently overestimated in the under 35 mmHg group. There was also significantly higher variance when the > 75 mmHg group was compared to 56–75 mmHg group, (p = .02), with the true sPAP being underestimated by echocardiography in this range. There was no significant difference in TTE vs RHC variance between the two mid-range groups, 35–55 mmHg and 56–75 mmHg (p = .35). There was no significant effect of BMI or service location on the degree of variance between TTE and RHC determinations of sPAP.

Conclusions: Based on our analysis, transthoracic echocardiography provided a more accurate estimate of sPAP when true sPAP was in the range of 35–75 mmHg. True sPAP was overestimated at levels under 35 mmHg and underestimated at levels over 75 mmHg. Caution should be used when employing TTE estimates of sPAP to manage patients with low and high range sPAP. BMI did not influence the accuracy of TTE estimated sPAP. Likewise, accuracy of TTE estimates did not appear to be affected by any of the four different service locations where TTE was performed.
Right Heart Catheterization in Patients Initiated on Pulmonary Arterial Hypertension Therapies: A Population Based Study

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Pulmonary, Critical Care and Sleep Medicine, University of Texas Medical Branch, Galveston, TX

Purpose: Performance of a right heart catheter study is recommended before prescribing PAH-specific medications. However, there is little data, outside of clinical trials, regarding the use of right heart catheterization in clinical practice. Consequently, we designed a study to determine the frequency of right heart catheterization in patients with newly diagnosed pulmonary hypertension prescribed PAH-specific medications.

Background: Pulmonary hypertension represents a heterogeneous collection of conditions classified into five groups according to pathology, pathophysiology and response to treatment. Right heart catheterization is required to classify patients and prior to initiation of specific therapy for treatment of pulmonary arterial hypertension. The aim of this study was to determine performance of right heart catheterization in patients prescribed pulmonary arterial hypertension (PAH)-specific medications.

Methods: A retrospective review of administrative claims was performed using Clininformatics DataMart. Individuals with an encounter diagnosis for pulmonary hypertension were identified by ICD-9 codes. Individuals were continuously enrolled 12 months before and 15 months after the initial diagnosis of pulmonary hypertension. Patient characteristics, comorbidities and performance of echocardiography within 12 months of encounter diagnosis were determined. Performance of a right heart catheterization was assessed in patients prescribed PAH-specific medications.

Results: From 2002 to 2011, 15,772 patients had an outpatient visit with a diagnosis of pulmonary hypertension with the majority being female over 50 years of age. Within one year of encounter diagnosis, 969 (6.1%) patients were prescribed PAH-specific medications. Oral PAH-specific medications were prescribed to 94.2 % of patients. In patients prescribed PAH-specific medications, 91 % had an echocardiogram within one year of encounter diagnosis. Cardiac catheterization was performed in 407 patients (42 %) within three months of initial prescription and in 583 patients (60.2%) during the entire study period.

Conclusions: In this population based study, performance of a right heart catheterization prior to initiation of PAH-specific therapy was low.
What is the Prognostic Value of the Baseline Serum Sodium Level in PAH?

Fares WH, Tonelli AR, Adonteng-Boateng P, Bazan IS, Kholdani CA, Rao Y, Dweik RA

Background: Predictive models in PAH have known limitations. Hyponatremia has prognostic value in other diseases that include fluid retention including left heart failure and advanced liver disease states. Based on these data and limited data in PAH, we hypothesized that low sodium levels are associated with poor outcomes in PAH.

Methods: We performed a secondary analysis of a well characterized PAH cohort included in United Therapeutics’ clinical trials. We only included adult (> 18 yo) WHO group 1 PH patients who had a baseline sodium level. The 1st objective was to establish whether there is an association between baseline sodium level & 1-year mortality.

Results: The mean age of the total cohort (n=820) was 47 years, of whom 184 patients had a sodium level of < 137 mmol/liter. The average sodium level was similar in the different etiology subgroups of PAH: 139, 139, 140, and 139 mmol/liter for the idiopathic, CTD, congenital heart disease, and PoPH respectively.

Patients with hyponatremia (defined as Na level of < 137 mmol/liter) tend to be older (p=0.02), have higher proportion of functional class IV (p<0.001), have higher baseline mean right atrial pressure (RAP) (p=0.036), have higher baseline RAP/PAWP ratio (p=0.038) (PAWP= pulmonary artery wedge pressure), and have lower right ventricular stroke work index (RVSWI) (p=0.017).

Baseline Na level is negatively correlated with functional class (r=−0.15; p<0.0001) and baseline mean right atrial pressure (r=−0.09; p=0.018). In unadjusted analyses, sodium level (as a continuous variable) is associated with 1-year mortality (Hazard ratio=0.94; p=0.035). Hyponatremia status loses its significance (p=0.12) in the multivariable regression Cox model when adjusted for functional class (after applying a stepwise model selection procedure to identify the confounding variable whose presence turns the effect of baseline sodium level into insignificant). Secondary analyses using a cut-off value of < 135 mmol/liter to define hyponatremia showed overall similar results.

Conclusions: Although baseline hyponatremia is associated with 1-year mortality, it loses its significance when adjusted for functional class in the multivariable regression Cox model. Further studies are needed to better establish the correlation between hyponatremia, central hemodynamics, and functional class in PAH patients.
## Table:

<table>
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<tr>
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<th>Na &gt; 138</th>
<th>Na &lt; 137</th>
<th>p-value</th>
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<tr>
<td><strong>Total # of patients</strong></td>
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<td>184</td>
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<tr>
<td><strong>Sodium level</strong></td>
<td>141</td>
<td>135</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>46 ± 14</td>
<td>49 ± 13</td>
<td>0.020</td>
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<tr>
<td><strong>Female gender (%)</strong></td>
<td>79%</td>
<td>75%</td>
<td>0.321</td>
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<td><strong>Caucasian Race (%)</strong></td>
<td>84%</td>
<td>79%</td>
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<td><strong>PAH etiology</strong></td>
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<td>0.556</td>
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<tr>
<td>Idiopathic (n=435)</td>
<td>53%</td>
<td>55%</td>
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<tr>
<td>CTD (n=173)</td>
<td>21%</td>
<td>21%</td>
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<tr>
<td>Congenital syst-to-Pulm shunts (n=168)</td>
<td>22%</td>
<td>16%</td>
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<tr>
<td>PoPH (n=42)</td>
<td>4%</td>
<td>8%</td>
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<td><strong>Mean 6MWD (meters) at baseline</strong></td>
<td>331 ± 86</td>
<td>322 ± 89</td>
<td>0.282</td>
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<td><strong>Baseline NYHA/WHO functional class</strong></td>
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<tr>
<td>Class II</td>
<td>16%</td>
<td>11%</td>
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<tr>
<td>Class III</td>
<td>77%</td>
<td>72%</td>
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<td>Class IV</td>
<td>7%</td>
<td>17%</td>
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<tr>
<td><strong>Mean Borg dyspnea score at baseline</strong></td>
<td>4.3 ± 2.4</td>
<td>4.5 ± 2.2</td>
<td>0.414</td>
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<tr>
<td><strong>1-year Mortality (%)</strong></td>
<td>10.1%</td>
<td>15.3%</td>
<td>0.048</td>
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<td><strong>Right atrial pressure (mmHg)</strong></td>
<td>10</td>
<td>12</td>
<td>0.036</td>
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<td><strong>RAP/PAWP ratio</strong></td>
<td>1.2</td>
<td>1.3</td>
<td>0.038</td>
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<td><strong>PVR (Wood units)</strong></td>
<td>13.7</td>
<td>12.8</td>
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<td><strong>RVSWI (grams/m2/beat)</strong></td>
<td>19.7</td>
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<td><strong>PAWP (mmHg)</strong></td>
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<td>9.6</td>
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<td><strong>Cardiac index (liters/min/m2)</strong></td>
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<td><strong>Pulmonary artery compliance (ml/mmHg)</strong></td>
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<td>1.1</td>
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Right-to-Left Ventricular End Diastolic Diameter Ratio in Severe Sepsis and Septic Shock

Huston J1, Sardar P2, Suksaranjit P2, Hatton N2, Ryan JJ2

1Veteran’s Affairs Medical Center, Salt Lake City, UT
2University of Utah, Salt Lake City, UT

Purpose: The purpose was to evaluate the prognostic value of right ventricular end-diastolic diameter (EDD) to left ventricular EDD in severe sepsis and septic shock.

Background: The ratio of right ventricular end-diastolic diameter (EDD) to left ventricular EDD (RV/LV) is becoming more commonly used to predict right ventricular failure. We performed a retrospective chart review of medical intensive care unit (MICU) patients at a quaternary referral center diagnosed with severe sepsis or septic shock, who had an echocardiogram within 48 hours of ICU admission.

Methods: Patients were identified by the ICD-9 codes: 995.92 for severe sepsis and 785.52 for septic shock. Increased RV/LV ratio was defined as RV/LV > 1. Un-paired t-tests for continuous variables were used and continuous variables are presented as mean± SD.

Results: We included 147 patients admitted with septic shock (71) or severe sepsis (76) to the ICU. Patient characteristics are displayed in Table 1. There was no significant difference for in-hospital mortality in patients with RV/LV ratio > 1 (p= 0.411). There were associations between increased mortality and higher creatinine (2.6 mg/dL vs. 4.3 mg/dL; p= 0.0009), leukocytosis (17 K/µL vs. 25 K/µL; p= 0.0003) and lactate (2.5 mmol/L vs. 9.5 mmol/L; p= 0.001) (table 2).

Conclusions: To our knowledge, this is the first study to report RV/LV ratio as a prognostic measure in ICU patients with severe sepsis or septic shock. We found no difference in mortality in ICU patients with severe sepsis or septic shock who had increased RV/LV.
Risk Factors for Chronic Thromboembolic Disease in Patients with Newly Diagnosed Pulmonary Hypertension: A Community Based Study

Kanwar M, Raina A, Gladowski P, Benza R
Allegheny General Hospital, Pittsburgh, PA, U.S.A.

Purpose: In this population based study, we sought to evaluate the incidence of venous thromboembolism and/or pulmonary embolism, diagnostic work-up, as well as risk factors for chronic thromboembolic pulmonary hypertension in patients newly diagnosed with pulmonary hypertension (PH).

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) remains an underdiagnosed cause of PH in clinical practice. Although screening with ventilation-perfusion (V/Q) scan is considered the gold standard for screening PH patients for CTEPH, it continues to be underutilized as a diagnostic tool.

Methods: We analyzed the medical records of all patients in the Western Pennsylvania Highmark insurance network who had newly diagnosis PH between January 2012 to December 2013. To be included in this analysis, each subject had to be continuously enrolled in medical coverage from one year prior to their date of initial PH diagnosis through October 2015. From this population, each subject’s claims were reviewed to identify any previous risk factors and diagnostic tests for CTEPH. These included a history of PE diagnosed in the last 5 years, other incidences of venous thrombosis, splenectomy, malignancy, hypercoaguable disorders etc. Diagnostic tests reviewed included echocardiogram, right heart catheterization, CT angiogram, V/Q scan and pulmonary angiogram.

Results: A total of 10,518 subjects were identified with the index diagnosis of PH in the last 2 years, of whom 49% (n=5,193) had at least one known risk factor for CTEPH. Approximately 15% (n=1,554) had a prior diagnosis of PE in the last 5 years, 30% (n=3,121) patients had a previously known or current malignancy, 10% (n=1,057) were on levothyroxine, and 1% (n=97) had undergone a splenectomy or had a infected shunt. An echocardiogram was performed in 93% of patients, right heart catheterization in 10% and V/Q scan in <1% patients.

Conclusions: A significant portion of patients with newly diagnosed PH have risk factors for CTEPH. Despite this, both right heart catheterization and V/Q scan are significantly underutilized suggesting poor community adherence to published diagnostic guidelines and a potential for both mis- and under-diagnosis of CTEPH in community practice.

<table>
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<th>Risk Factor for CTEPH</th>
<th>n</th>
<th>Right Heart Cath</th>
<th>Echo</th>
<th>Ventilation/Perfusion Scan</th>
<th>CT Angiography</th>
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<tr>
<td>PE</td>
<td>1,554</td>
<td>166 (10.6%)</td>
<td>1,514 (97.4%)</td>
<td>9 (1%)</td>
<td>1,318 (83.4%)</td>
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<tr>
<td>Malignancy</td>
<td>3,121</td>
<td>375 (12%)</td>
<td>3,049 (97.6%)</td>
<td>1 (&lt;1%)</td>
<td>2,126 (68.1%)</td>
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<tr>
<td>Others risk factors for CTEPH</td>
<td>1,575</td>
<td>203 (12.9%)</td>
<td>1,529 (97.1%)</td>
<td>8 (&lt;1%)</td>
<td>962 (61.6%)</td>
</tr>
<tr>
<td>No risk factors for CTEPH</td>
<td>4,296</td>
<td>580 (13.5%)</td>
<td>4,068 (94.6%)</td>
<td>9 (&lt;1%)</td>
<td>2,304 (53.6%)</td>
</tr>
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<td>All members combined</td>
<td>10,518</td>
<td>1,324 (12.6%)</td>
<td>10,160 (96.5%)</td>
<td>27 (&lt;1%)</td>
<td>6,710 (63.8%)</td>
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</table>
A Computer Simulation Model for Atrial Fenestration Sizing in Pulmonary Arterial Hypertension with Right Ventricular Failure

Kurup HKN1, Broomé M2, Vettukattil JJ1, Kuruvilla J1
1Helen DeVos Children’s Hospital of Spectrum Health, U.S.A.
2Karolinska University Hospital, Sweden
Karolinska Institutet, Sweden
KTH Royal Institute of Technology, Sweden

Purpose: We sought to evaluate hemodynamics after atrial septostomy in pulmonary arterial hypertension (PAH) by means of a computer model. The specific objective was to derive the size of atrial fenestration to achieve predetermined hemodynamic parameters, for varying degrees of PAH.

Background: There have been significant advances in the medical management of PAH. Atrial septostomy continues to play a role in prolonging survival in severe PAH with right ventricular failure, as a bridge to transplantation or as an early intervention in combination with medical therapy. The procedure is associated with significant mortality due to severe hypoxemia, presumably due to inability to control the size of atrial communication and spontaneous closure rates after septostomy approach 50%. As the degree of atrial decompression will depend on the severity of PAH and atrial pressures, atrial fenestration of varying sizes may be required. The concept of atrial fenestration sizing for achieving desired hemodynamics has not been addressed.

Methods: The Aplysia Cardiovascular Lab (Aplysia Cardiovascular Lab, Aplysia Medical AB, Sweden) provides an overview of the complex real-time interactions between myocardial, valvular and vascular function in the human cardiovascular system. The pulmonary vascular resistance (PVR), atrial and ventricular compliances were altered in this model to simulate varying degrees of PAH. Creation of an atrial fenestration of diameters varying from 4 to 10 mm was simulated. The desired hemodynamics following the procedure were: right atrial pressure (RAP) < 15 mm Hg, left atrial pressure (LAP) to not exceed 15 mm Hg, saturation (SaO2)> 85%, and Qp:Qs ratio more than 0.75.

Results: There was greater fall in RAP compared to the increase in LAP for the same atrial fenestration size. An atrial communication of 8 mm diameter and 5 mm thickness caused an increase in LAP by 3.7 mm Hg, decreased RAP by 4.0 mm Hg, decreased Qp:Qs by 35% and also caused a 13% decrease in SaO2 (to 80%) in a model of severe PAH (PVR-10 Woods Unit). This trend persisted for more severe degrees of PAH, except that the SaO2 reached 72% (19% fall) when PVR was 17 WU. There were no significant hemodynamic differences related to the thickness of the atrial communication. The ideal diameter of atrial communication for the desired hemodynamics was calculated.

Conclusions: A 4–6 mm atrial fenestration would be ideal when PVR > 10 WU. A fenestration size more than 8 mm is unlikely to be of benefit due to severe hypoxemia. Severe degrees of PAH would require fenestration of lesser diameters to prevent inadvertent hypoxemia and decompensation. The pre-determination of the hemodynamics by means of a computer simulation model may be useful for interventional planning in PAH.
Slope of 6MWD as a Predictor of Clinical Outcome in PAH

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1Division of Pulmonary Allergy and Critical Care Medicine, University of Pittsburgh, U.S.A.
2United Therapeutics, Durham, NC, U.S.A.

Purpose: To determine if the slope of change in the 6MWD after initiation of pharmacologic therapy may identify subjects with worsened or improved clinical outcomes.

Background: The 6-minute walk distance (6MWD) used to track therapeutic progress in patients with pulmonary arterial hypertension (PAH) correlates with peak O2 consumption and reflects activities of daily living. The change in 6MWD from baseline however may not always reflect clinical outcomes. The rate of change in 6MWD during a clinical trial has not been evaluated.

Methods: Slopes of the 6MWD from the PHIRST-1 clinical trial were individually calculated via linear regression for the 161 Group I PAH subjects on therapeutic doses of tadalafil (20mg, 40mg). The first and third quartiles for the slopes of 6MWD were calculated to define subjects with a deep slope (DS), shallow slope (SS) and a non-responder (NR). Five 6MWTs were used to calculate each slope up to 16 weeks (Table/Figure). Clinical outcomes were compared.

Results: There were no baseline differences between the slope groups for gender, race, BMI, duration of diagnosis or invasive hemodynamic values. The SS group had a higher baseline 6MWD compared to the NR and DS group. After therapy the DS group demonstrated the largest mean change in 6MWD at 16 weeks compared to baseline (Mean±SD, DS (+)106±39.7, SS (+)35.3±22.9 and NR (-)15±18.5 meters, p<0.001). The DS group demonstrated the largest reduction in uric acid levels from baseline to week 16 (p=0.006) without a significant change in cardiac output or serum creatinine. Log-rank test showed that the slope of the 6MWD by week 16 predicted significant differences in time to clinical worsening for the three slope groups (p=0.0003) at 68 weeks. Cox proportional hazards model demonstrated a hazard ratio of 3.79 for clinical worsening for the NR group versus SS group (p=0.0002) and 2.44 for clinical worsening for the NR group versus DS group (p=0.032). There was not a difference between DS and SS.

Conclusions: The slope of the line based upon serial 6MWD up to 16-weeks predicts 6MWD at 16-weeks and clinical outcome at 68 weeks. This study demonstrates a novel approach to identifying patients at-risk for clinical worsening despite adequate PAH-specific therapy. Three specific groups were identified. The DS group may represent a population with a robust 6MWD response to the initiation of PH specific therapy. The SS group may represent a population of less sick individuals with a modest 6MWD response or possible long-term PAH non-progressors. The NR group represents a group that had minimal response to therapeutic intervention who experience significant clinical worsening and may benefit from intensified therapy.

Figure 1:
Table 1

<table>
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<tr>
<th>Table 1</th>
<th>Non-responder</th>
<th>Shallow Slope</th>
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<td><strong>n</strong></td>
<td>41</td>
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<td><strong>Age, years</strong></td>
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<td>Mean ±SD</td>
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<td><strong>Baseline WHO Functional Class (%)</strong></td>
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<td>I</td>
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<td><strong>Baseline Bosentan use (%)</strong></td>
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<td>Mean ±SD</td>
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<td>32.8 (-10, 92.9)</td>
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<tr>
<td>Mean ±SD</td>
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<td>6.3 ±1.9</td>
<td>7.0 ±2.5</td>
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<td>7.0 (3.4, 11.4)</td>
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<td><strong>Change in UA, baseline to week 16</strong></td>
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<tr>
<td>Mean ±SD</td>
<td>-0.1 ±1.1</td>
<td>-0.2 ±1.0</td>
<td>-0.9 ±0.9</td>
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<tr>
<td>Median (min, max)</td>
<td>-0.2 (-2.0, 3.9)</td>
<td>-0.2 (-3.2, 3.3)</td>
<td>-0.8 (-3.7, 0.3)</td>
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<td><strong>Rate of clinical worsening (%)</strong></td>
<td>41.5</td>
<td>17.2</td>
<td>27.3</td>
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Circulating Aldosterone Levels and Disease Severity in Pulmonary Arterial Hypertension

Safdar Z1, Thakur A1, Singh S1, Ji Y1, Guffey D2, Minard CG2, Entman ML3
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2Dan L. Duncan Institute for Clinical and Translational Research, Baylor College of Medicine
3Division of Cardiology, Baylor College of Medicine

Purpose: It is not known whether aldosterone levels are associated with increased mortality in patients with pulmonary arterial hypertension (PAH). The primary goal of this study was to determine whether circulating aldosterone levels predict severity of PAH in terms of hemodynamic characteristics and mortality.

Background: PAH is a disease in which increased right ventricular pressure leads to right heart failure and decreased cardiac output. Neurohormonal activation by the renin-angiotensin-aldosterone system (RAAS) is an important regulatory mechanism in the presence of low cardiac output associated with heart failure. Aldosterone is released in response to decreased cardiac output. Recent data suggests that hyperaldosteronism may have predictive role in patients with PAH. Based on a small number of studies, debate about the role of aldosterone as a marker of disease severity and mortality in PAH is ongoing since RAAS maybe activated to maintain cardiovascular homeostasis. In this study we investigated whether circulating aldosterone levels, undertaken in an outpatient setting, can be predictive of disease severity and of mortality in stable PAH patients.

Methods: Patients with stable PAH were enrolled at the Baylor PH program. The plasma levels of aldosterone and BNP were measured. Clinical, hemodynamic, and outcome data was collected by chart review. Mean follow up time from study enrollment was 39 ± 102 months. Cox proportional hazards model was used to assess time to death.

Results: There were 125 PAH patients with plasma aldosterone levels. Median aldosterone level was 9.9 pg/ml (25th-75th percentile: 4.1 pg/ml, 27.1 pg/ml) and median brain natriuretic peptide (BNP) level was 67.5 pg/ml (25th-75th percentile: 31 pg/ml, 225 pg/ml). Aldosterone levels were not significantly associated with BNP levels, six-minute walk distance, Borg dyspnea score, right ventricular systolic pressure, cardiac output and cardiac index. Interestingly, the association between aldosterone and right atrial pressure was dependent on mineralocorticoid receptor blocker treatment (Coef. =2.88, 95CI: 1.19, 4.56, p=0.001). By log-rank statistic there was no statistical difference between the survival of patients divided by median aldosterone level (p=0.914). However, there was a significant difference in patient survival between the BNP categories (p<0.001) such that those with high BNP level (>180 pg/mL) had a shorter survival time.

Conclusions: The aldosterone level was not associated with increased mortality in PAH but was a marker of disease severity.
Microfluidic Chip-Based Quantification of Circulating Endothelial Cells in Patients with Pulmonary Arterial Hypertension

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²Department of Chemical Engineering, Northeastern University, Boston, MA, U.S.A.
³Barnett Institute of Chemical and Biological Analysis, Northeastern University, Boston, MA, U.S.A.
⁴Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany

Purpose: Circulating endothelial cells (CECs) have been discussed as potential biomarkers in patients with pulmonary arterial hypertension (PAH). Current protocols for isolation and quantification of these cells are laborious and time-consuming.

Background: We recently developed a disposable microfluidic platform capable of selectively capturing and enumerating endothelial progenitor cells directly from human whole blood. The aim of this study was to apply this microfluidic chip on CECs and to test whether CECs measured by this device may serve as potential biomarker in PAH patients.

Methods: Human whole blood was collected and injected into polymeric microfluidic chips containing microcolumns pre-coated with anti-CD146 antibody. Captured cells were immunofluorescently stained for additional stem and endothelial cell markers.

Results: The CEC capture chip was validated against conventional flow cytometry (r=0.89). In a cohort of 37 patients with three forms of PAH (idiopathic/heritable, drug-induced, and connective tissue disease), CEC numbers are significantly increased ≈ 400 % in PAH subjects vs. matched controls. However, CEC numbers between different PAH etiologies did not differ significantly. CEC numbers were not related to body mass index or to postmenopausal status.

Conclusions: The CEC capture chip requires 200 µL of blood and may serve as a bedside test for the screening and monitoring of patients with PAH and other diseases related to vascular injury.
Pulmonary Artery Pulsatility: Potential Prognostic Marker in Pulmonary Hypertension Due to Left Heart Failure


University of Virginia

Purpose: The purpose of this study is to use cardiac magnetic resonance to evaluate pulmonary artery pulsatility in patients with heart failure with reduced and preserved ejection fraction who are at risk for development of pulmonary hypertension due to left sided heart disease.

Background: There are many causes of pulmonary hypertension (PH), the most common being PH due to left sided heart disease including systolic and diastolic dysfunction as well as mitral and aortic valve disease. Despite being more common than pulmonary arterial hypertension (PAH), it is less well understood, mainly due to the heterogeneity of left heart disease processes. In the PAH population, increased pulmonary artery stiffness is associated with right ventricular (RV) dysfunction and increased mortality. Pulmonary artery stiffness can be measured non-invasively using cardiac magnetic resonance (CMR), specifically measuring proximal pulmonary artery pulsatility over the cardiac cycle. We hypothesize that a subset of patients with PH due to left sided heart disease develop similar changes in the pulmonary arteries as seen PAH, which ultimately confer a worse prognosis. We aim to use CMR to study PA pulsatility, a marker of these pathological changes.

Methods: Between August 2015 and January 2016, 275 patients underwent CMR evaluation for clinical and other research indications. Forty four patients had cine imaging of the proximal main pulmonary artery cross section and were evaluated for this study, including 20 with systolic dysfunction (left ventricular ejection fraction ≤ 40%), 8 with clinical heart failure and normal systolic function (heart failure with preserved ejection fraction, HFpEF), and 16 normal controls. Patients with congenital heart disease were excluded from analysis. Maximum and minimum pulmonary artery areas were measured over 1 cardiac cycle and pulmonary artery pulsatility was calculated as the relative area of change (RAC) (maximum area-minimum area)/minimum area. Pulmonary artery pulsatility and RV function were compared between patients with HF and normal controls.

Results: The etiology of systolic heart failure was ischemic cardiomyopathy in 42.9%; other etiologies included acute myocarditis, sarcoidosis, and unclassified non ischemic cardiomyopathy. Forty six percent of the HF patients had been hospitalized for HF management within the 12 months prior to CMR. Mean left ventricular ejection fraction in the systolic HF group was 26.6%, HFpEF 56.4%, and 58.9% in the controls, p=0.001. There was a stepwise decrement in RV function in the 3 groups, right ventricular ejection fraction 42.0% in systolic HF, 50.8% in HFpEF, and 51.0% in controls, which did not meet statistical significance. The proximal main pulmonary arteries were more distended in patients with systolic HF, minimum pulmonary artery area 576.2 mm2 vs 554.6 mm2 in HFpEF vs 437.2 mm2 in controls, p=0.001, and there was reduced pulmonary artery pulsatility in the systolic HF group, RAC 24.2% vs 30.4% in HFpEF vs 39.4% in controls, p=0.02.

Conclusions: In patients with heart failure with reduced and preserved ejection fraction, there was an observed increase in pulmonary artery minimal area and reduction in pulmonary artery pulsatility when compared with normal controls. These findings of decreased pulmonary artery pulsatility is similar to what has been documented in the PAH population. A larger study in patients with left heart disease correlating CMR and invasive hemodynamic measurements with clinical outcomes is needed.
Supine Exercise Stress Echocardiography (ESE) Assessment of Right Ventricular (RV) Structure and Function in Normal Individuals

Stokem K, Rancourt D, Atherton D, Lucas L, Wirth JA

Purpose: To determine the reproducibility and factors influencing measurement of RV ESE measurements in normal individuals to guide future studies relative to the noninvasive diagnosis of pulmonary hypertension.

Background: Echocardiography is a widely used screening tool for pulmonary hypertension (PH). The American Society of Echocardiography provides specific recommendations or reference values for RV parameters at rest but not during exercise. We hypothesize that evaluating ESE parameters of RV function might have utility to assess PH. We sought to determine the reproducibility and factors influencing measurement of RV ESE measurements in normal individuals.

Methods: Normal healthy subjects of both genders aged 18–66 yrs, with predetermined baseline activity levels were progressively exercised by recumbent bicycle ESE using a specific protocol. Twelve RV echocardiographic parameters [Tricuspid regurgitation velocity (TRV), RV outflow tract acceleration time (RVOT AT), RV time velocity integral (RV TVI), tissue Doppler index velocity index (TDI VI), isovolumetric contraction time (TEI index), RV end systolic area (RVESA), RV end diastolic area (RVEDA), RV basal diameter (RVBD), RV mid diameter (RVMD), RV longitudinal diameter (RVLD), and right atrial area (RAA)] were recorded. Exercise was completed at a rate-pressure product of 20,000 or stopped early for limiting symptoms. Each echocardiographic parameter was subsequently measured from the recordings by two observers independently. The Intraclass Correlation Coefficient (ICC) was used to assess inter-rater reliability for continuous measures and the Kappa statistic to assess inter-rater reliability for categorical measures. Those echocardiographic parameters found to have acceptable inter-rater reliability were analyzed by Mann-Whitney U test to determine statistical differences between resting vs. exercise parameters.

Results: Thirty eight subjects were enrolled. The exercise RV echocardiographic parameters of TRV, RVOT AT, RV TVI, TDI VI, TEI index, RVESA, RVEDA, RVBD, RVMD, RVLD, and RAA had acceptable inter-rater reliability (K>0.50). Exercise TRV and TDI VI were significantly increased while RVOT AT, RVESA, RVEDA, RVBD, RAA (all p<0.01) and RVMD (p<0.05) significantly decreased. Factors of age, body surface area, gender and baseline activity level did not correlate with RV ESE parameters by univariate analysis (all p > 0.01).

Conclusions: The test characteristics of 12 RV echocardiographic parameters were determined for normal individuals of varying ages and baseline activity levels. Eleven of 12 RV ESE parameters were reproducible. Eight RV structure and functional tests were statistically different between resting and exercise conditions. These results should guide future studies relative to the noninvasive diagnosis of pulmonary hypertension.
End Tidal CO2 as a Predictor of Outcomes in Patients with Pulmonary Arterial Hypertension

Welch CE, Robbins IM, Brittain EL, Newman JH, Hemmes AR
Vanderbilt University Medical Center

Purpose: The purpose of this study was to evaluate the association between end tidal CO2 and long term outcomes in patients with pulmonary arterial hypertension.

Background: Pulmonary arterial hypertension (PAH) is a disease of dead space ventilation and this can be measured by end tidal CO2. Prior data suggest that end tidal CO2 is reduced in patients with PAH and that end tidal CO2 correlates with hemodynamic markers of disease severity. The association between end tidal CO2 and long-term outcomes in PAH patients has not been studied. We hypothesized that lower end tidal CO2 measurements in patients with pulmonary hypertension would correlate with worse long term outcomes.

Methods: Patients with PAH seen in our referral clinic were prospectively recruited for end tidal CO2 measurement between September 2009 and February 2010. Vital status and lung transplantation occurrence as of July 2015 was documented using the medical record and the social security death index. Survivors were censored on the date of last medical contact.

Results: Eighty-two patients were followed for a median of 1836 days. Two patients were lost to follow up. Twenty-six patients died. Patients who died were more likely to be older (58.5 ± 14.9 years vs. 47.6 ± 12.2 years, p<0.05) and to have lower six minute walk distances (296 ± 127m vs. 401 ± 92m, p<0.05). Mean end tidal CO2 in survivors was 30.52mmHg ± 4.815 while mean end tidal CO2 in patients who had died at follow up was 27.05mmHg ± 4.179 (p=0.004). After stratification by mean end tidal CO2 of 29mmHg, survival in each group was analyzed. Patients with lower end tidal CO2 had shorter survival, (p=0.006). In 52 patients in whom two end tidal CO2 measurements were obtained, an average of 508 ± 160 days after initial measurement, end tidal CO2 was unchanged, including when analyzed separately by vital status.

Conclusions: Our single center data suggested that end tidal CO2 is stable over time in patients with PAH and that a lower end tidal CO2, a marker of more severe dead space ventilation, is associated with worse outcomes in patients with PAH. Further studies are needed to validate the prognostic utility of end tidal CO2 in patients with PAH.
Recognition and Clinical Importance of a Newly Identified Interatrial Shunt (Tunneled Atrial Septal Defect) in Patients With Pulmonary Hypertension

Zwieke D, Paulus S, Pinninti M, Khandheria B, Bajwa T, Kramer C, Thohan V
Aurora Saint Luke’s Medical Center, Milwaukee, WI

Purpose: Substantiate that patients with tunneled atrial level shunts (T-ASD) represent a population with treatable/reversible pathophysiology of PAH and/or Eisenmenger Syndrome permitting medical and interventional therapies in lieu of heart/lung transplantation.

Background: The prevalence, pathophysiology, and clinical outcomes of tunneled atrial level shunts (T-ASD) among patients with Pulmonary Arterial Hypertension (PAH) are unknown. Tunnel-like Patent Foramen Ovale defects (PFO) have been identified among patients with cryptogenic stroke by three dimensional echocardiography. An autopsy case series has anatomically described a ‘slit-like defect’ with length and depth that represents a T-ASD.

Methods: We performed a prospective study of 575 consecutive patients who were referred to our single center Pulmonary Hypertension Clinic, and underwent an entry echocardiographic study with agitated saline injection between January 2012 and November 2015. Ninety-seven patients had T-ASD’s.

Results: Of 97 patients with T-ASD’s (mean age 65.7 years [range 20−89]; 66% female), 70 (72.2%) were diagnosed with PAH, 57 (58.8%) received targeted PAH therapies, and 3 (3%) were observed. Clinical follow-up for the patients with PAH was 16.3 ± 6.4 months. Of the 70 PAH patients, 10 (10.3%) demonstrated spontaneous shunt closure and 24 (24.7%) underwent therapeutic shunt closure (21 catheter based, 3 surgical). The remaining 32 patients continued active PAH therapy. Of the 34 patients who had either spontaneous or interventional shunt closure, 9 were able to completely wean off infusion therapies, 6 were able to wean off inhaled therapies, and 3 were able to wean off an oral therapy. One patient was able to discontinue all PAH therapies.

Conclusions: The described T-ASD’s were commonly observed in this population, with the majority of patients presenting with PAH or Eisenmenger Syndrome. We have demonstrated that treatment of this patient population is identical to that of other patients with congenital heart disease and/or PAH. Their PAH was successfully treated, permitting closure of the shunts, and eventual down titration/cessation of the PAH medications, with reversal of the PAH pathophysiology and resolution or marked improvement of the symptoms.
Evidence of Shared Genetic Architecture Between Combined Pulmonary Hypertension and Pulmonary Arterial Hypertension

Assad TR, Hemnes AR, Larkin EK, Glazer AM, Wells QS, Farber-Eger EH, Xu M,Brittain EL
Vanderbilt University, Nashville, TN

Purpose: We wanted to determine if patients with combined post-capillary and pre-capillary pulmonary hypertension (Cpc-PH) have genetic similarities to patients with pulmonary arterial hypertension (PAH), a feature that may explain the disproportionate pulmonary vascular disease seen in these patients.

Background: Cpc-PH is distinguished from isolated post-capillary pulmonary hypertension (Ipc-PH) by a pulmonary diastolic to wedge pressure gradient ≥7mmHg. We previously showed that Cpc-PH patients are younger than Ipc-PH patients despite similar severity and chronicity of left ventricular impairment. As no biologic data exists in the Cpc-PH population, it is unknown if Cpc-PH and PAH patients share a molecular predisposition to pulmonary vascular remodeling. We hypothesized that shared genetic variants with PAH may contribute to pulmonary vascular disease in Cpc-PH.

Methods: We used Vanderbilt’s de-identified medical record (Synthetic Derivative) linked to a DNA bio-repository (BioVU) to identify patients who underwent right heart catheterization between 1998−2014 with PAH, Ipc-PH, and Cpc-PH. Genotyping was performed with the Illumina Human Exome BeadChip. Significant single nucleotide polymorphisms (SNPs) were identified by genome-wide association testing comparing Cpc-PH and PAH to Ipc-PH controls. Pathway analysis was performed on significant SNPs using the Database for Annotation, Visualization, and Integrated Discovery (DAVID). We used the Genotype-Tissue Expression (GTEx) database to assess tissues in which genes of interest are highly expressed.

Results: We analyzed 254 subjects: 79 with PAH (31%), 139 with Ipc-PH (55%), and 36 with Cpc-PH (14%). We identified 96 exonic SNPs in 96 genes associated with shared risk for both Cpc-PH and PAH versus Ipc-PH (odds ratio>1 for both, p<0.05), including genes previously associated with PAH (COL18A1 and SMCR7). Only 44 SNPs would be expected by chance. Pathway analysis revealed enrichment in genes related to cytoskeletal function, smooth muscle, and metabolism. A highly significant pathway included calponin-like actin-binding (p<0.001 with a false discovery rate <10%). On GTEx analysis, genes represented by these 96 SNPs were expressed on average 45% higher in lungs relative to other tissues (2nd highest expression levels out of 53 tissues). When GTEx analysis was restricted to genes in the statistically significant pathway (SYNE2, MACF1, LIMCH1, PARVB, PARVA), expression was increased 118% in the lung, 1st amongst all tissues.

Conclusions: An initial genetic analysis of Cpc-PH identified genes and biologic pathways known to contribute to PAH pathophysiology. Pathways related to actin function were significantly affected and predicted to have increased expression in lungs, suggesting that genetic variations involving smooth muscle and cytoskeletal function may contribute to Cpc-PH pathophysiology. These findings suggest shared molecular and genetic underpinnings between Cpc-PH and PAH, but further replication and functional validation are needed.
Evidence of Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension


Background: The mechanisms of right ventricular (RV) failure in pulmonary arterial hypertension (PAH) are poorly understood. Abnormalities in fatty acid (FA) metabolism have been described in experimental models of PAH, but systemic and myocardial FA metabolism have not been studied in human PAH. We hypothesize the FA metabolic defects are present in human PAH and contribute to RV lipotoxicity.

Methods: We used human blood, RV tissue, and non-invasive imaging to characterize multiple steps in the FA metabolic pathway in PAH subjects and controls. Human plasma and RV long-chain acylcarnitines, ceramides, and carnitine palmitoyltransferase I activity were quantified using standard liquid chromatography/mass spectrometric methods. High resolution respirometry was used to measure ex vivo right ventricular oxygen consumption. Proton magnetic resonance spectroscopy was used to quantify in vivo myocardial lipid content.

Results: Circulating FFAs and long-chain acylcarnitines were elevated in PAH patients versus controls after adjusting for multiple comparisons (both \( p < 0.001 \)). Human RV long-chain FAs were increased and long-chain acylcarnitines were reduced nearly 100-fold in PAH versus controls (\( p < 0.001 \)). In vivo intramyocyte lipid content was 7-fold higher in human PAH versus controls (Figure 1; \( 1.4 \pm 1.3 \) %TG vs. \( 0.22 \pm 0.11 \) %TG, \( p = 0.02 \)). Ceramide, a mediator of lipotoxicity, was increased in human PAH RVs versus controls (\( p = 0.006 \)). Using an animal model of heritable PAH (BMPR2R899X), we demonstrated reduced fatty acid oxidation via failure of palmitoylcarnitine to stimulate oxygen consumption in the PAH RV (Figure 2; \( p < 0.001 \)). Carnitine transporter gene expression and activity were similar between PAH and control RVs.

Conclusions: Abnormalities in fatty acid metabolism can be detected in the blood and myocardium in human PAH and are associated with RV steatosis and lipotoxicity. Murine data suggest that lipotoxicity may arise from impaired fatty acid oxidation. This study highlights specific metabolic pathways of potential therapeutic interest in PAH and establishes a tool to study their activity in vivo.
Heritability in Chronic Thromboembolic Pulmonary Hypertension: Pedigree Analysis Suggests a High Prevalence of Venous Thromboembolism in Family Members of CTEPH Patients, But a Low Prevalence of CTEPH

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Purpose: To estimate the role of heredity in CTEPH.

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) complicates 3–5% of cases of acute pulmonary embolism (PE), but also occurs in patients with no history of venous thromboembolism (VTE). Genetic factors have a strong influence on VTE risk, but it’s unknown whether heritable factors contribute to risk of CTEPH. The known inherited thrombophilias have not been clearly associated with CTEPH risk. To estimate the role of heredity in CTEPH, we performed detailed pedigree analyses in CTEPH patients, focusing on the presence or absence of a family history of CTEPH and VTE.

Methods: We identified a cohort of 63 consecutive patients diagnosed with CTEPH at Intermountain Medical Center over the last 20 years. CTEPH was surgically confirmed in 37 cases and strongly suggested in 26 based on right heart catheterization and imaging. Details about the diagnosis of CTEPH and clinical course, CTEPH-associated medical conditions, and family history were obtained for all patients through chart review. To date, we have performed detailed family history interviews to augment family history data obtained through chart review in 33 patients.

Results: Of the 33 patients interviewed, 66.7% report a family history of VTE, 60.6% report a history of VTE in a first degree relative, and 33.3% report a history of VTE in multiple first degree relatives. 45.5% of CTEPH patients report a family history of PE. Interestingly, a positive family history of VTE significantly correlates with operable CTEPH, with only 3.6% of patients with a positive family history of VTE being deemed inoperable, while 36.4% of patients without a family history of VTE were deemed inoperable (p=0.002). Five patients in our cohort have a known inherited thrombophilia (2 with Factor V Leiden, 2 with prothrombin G20210A, and 1 with protein C deficiency), but only 2 of these 5 have a positive family history of VTE. In only 2 of the 33 pedigrees analyzed was there a positive family history of CTEPH, giving a frequency of “familial CTEPH” of 6.1%. In both of these pedigrees there was a strong family history of VTE, but testing for the known inherited thrombophilias was negative.

Conclusions: In patients diagnosed with CTEPH, a positive family history of CTEPH is rare. In contrast, a positive family history of VTE is common, and indeed even more common than previously reported from pedigree analysis in VTE patients. In our cohort, a positive family history of VTE is significantly associated with having operable CTEPH.
Galectin-3 and Aldosterone as Potential Tandem Biomarkers in Pulmonary Arterial Hypertension

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Background: Several studies have identified circulating biomarkers to be associated with the presence and severity of pulmonary arterial hypertension (PAH). Recent evidence supports a role for galectin-3 (Gal-3) and the mineralcorticoid aldosterone in left ventricular failure. However, studies on aldosterone together with Gal-3 in PAH are lacking.

We investigated a novel Aldosterone-galectin-3 (Gal-3) tandem and several other potential PAH biomarkers and their association with the disease severity.

Methods: A total of 57 patients, 41 with idiopathic PAH (IPAH) and 16 with PAH associated with connective tissue disease (CTD), and 8 age-matched, non-relative controls were studied. Gal-3, aldosterone and other potential protein plasma concentrations were measured by single ELISA and multi-array MSD (Meso Scale Discovery) technology.

Results: Gal-3 values were increased in both patients with IPAH (12.2±0.6 ng/mL; p<0.05) and with PAH-CTD (14.1±1.6 ng/mL; p<0.05) versus control (8.5±0.9 ng/mL), while aldosterone was significantly elevated in IPAH only (248.5±38.8 pg/mL vs control 71.9±18.2 pg/mL; p<0.05). In addition, aldosterone, Gal-3, and N-terminal pro-brain natriuretic peptide (NT-proBNP) values were all higher in patients in WHO functional class II-III versus PAH functional class I or controls. The vascular injury marker intercellular adhesion molecule 1 (ICAM-1) was increased in IPAH and PAH-CTD versus controls (559.5±18.2 pg/mL and 734.1±59.4 pg/mL vs controls 394.8±39.3 pg/mL, p<0.05, p<0.0001, respectively), whereas vascular cell adhesion molecule 1 (VCAM-1) and proinflammatory, anti-angiogenic interleukin-12 (IL-12) were elevated in PAH-CTD only (879.5±110.0 pg/mL and 391.2±70.3 pg/mL vs controls 489.8±44.6 pg/mL, p<0.01, and 102.1±15.2 pg/mL, p<0.01, respectively).

Conclusions: Heightened Gal-3 and aldosterone plasma concentrations in PAH patients indicate a role for Gal-3 signalling in the pathobiology of IPAH and PAH-CTD, and may serve as biomarkers for functional status and progression of disease.
Pulmonary Microvascular Recruitment Occurs During Supine Bicycle Exercise

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Purpose: To investigate if pulmonary microvascular recruitment occurs during supine bicycle exercise in normal human subjects.

Background: Because it normally operates at low blood pressure and a low resistance, the human pulmonary circulation strongly depends on gravity and demonstrates gravity-induced gradients in perfusion from the apex to base, in the upright body position. Thus, there are normally “unrecruited” unperfused capillaries in the vertical upper lung at rest. These capillaries can normally be recruited during high pulmonary blood flow states, such as during exercise. Despite the fact that recruitment has been demonstrated in experiments with animals in supine position, it has been proposed that, in humans in supine position, gravitational gradients are minimized and the supine lung at rest may be “maximally or nearly maximally recruited.” Using an indicator-dilution type technique that sensitively measures the perfused functional capillary surface area (FCSA), we are testing whether FCSA recruitment is possible during supine exercise in humans. There have previously been no such studies in normal subjects and, in the course of studies to evaluate patients with presumed pulmonary hypertension, we have identified two rare normals that underwent exercise-heart catheterization.

Methods: Using a bicycle ergometer during cardiac catheterization, we quantified FCSA in the aforementioned 2 normal subjects at rest and at peak exercise, by measuring first-pass transpulmonary metabolism of the biologically inactive, highly specific for angiotensin converting enzyme (ACE) synthetic substrate 3H-benzoyl-Phe-Ala-Pro, by pulmonary endothelium-bound ACE.

Results: The subjects exercised for a mean of 792 seconds to a mean workload of 52 Watts. They had normal levels of FCSA at rest. Cardiac output doubled from mean 5.8 L/min to 12.1 L/min. FCSA increased from mean 3729 mL/min to 5800 mL/min, a 56% increase. The increases in FCSA in relation to flow were parallel and identical in both subjects.

Conclusions: Although the increase in FCSA was not fully proportionate (i.e. 1:1) to increased pulmonary blood flow (cardiac output), these studies provide the first evidence that in exercising normal supine humans, FCSA recruitment occurs. This validated technique can therefore be used to study abnormal patterns of recruitment in pulmonary hypertension.
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EIF2AK4 Mutations in Pulmonary Arterial Hypertension


Purpose: To described the frequency of EIF2AK4 mutations in patients diagnosed with idiopathic or heritable pulmonary arterial hypertension.

Background: Differentiating pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) from idiopathic or heritable pulmonary arterial hypertension (IPAH and HPAH) is important. Mutations in eukaryotic translation initiation factor 2 α kinase 4 (EIF2AK4) cause heritable PVOD and PCH whereas mutations in other genes cause HPAH. The aim of this study is to describe the frequency of pathogenic EIF2AK4 mutations in patients diagnosed with IPAH or HPAH.

Methods: We performed Sanger sequencing and deletion duplication analysis by multiplex ligation-dependent probe amplification (MLPA) to detect mutations in BMPR2 in 81 patients diagnosed with IPAH (n=72) or HPAH (n=9) at 30 North American medical centers. We sequenced the other genes known to cause HPAH for 68 patients without BMPR2 mutations. We sequenced EIF2AK4 for 67 patients without mutations known to cause HPAH. We assessed the pathogenicity of EIF2AK4 mutations and reviewed clinical characteristics of patients with pathogenic EIF2AK4 mutations.

Results: Pathogenic BMPR2 mutations were identified in 7 of 72 (9.7%) IPAH patients and 6 of 9 (66.7%) HPAH patients. We identified a novel homozygous EIF2AK4 mutation (c.257+4A>C) in 1 of 9 (11.1%) patients diagnosed with HPAH. The novel EIF2AK4 mutation (c.257+4A>C) was homozygous in two sisters with late onset of severe pulmonary hypertension. None of the 72 IPAH patients had bi-allelic EIF2AK4 mutations.

Conclusions: Pathogenic bi-allelic EIF2AK4 mutations are identified rarely in patients diagnosed with HPAH. Identification of pathogenic bi-allelic EIF2AK4 mutations can aid clinicians in differentiating HPAH from heritable PVOD or PCH.
The Central Valley Pulmonary Hypertension Support group – A Remarkable Journey

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Purpose: The Central Valley Pulmonary Hypertension Support Group (CV-PHSG) was founded in 2010 and is based in Fresno, CA. We would like to present data pertaining to its impact on the people of Central Valley of California (CVC).

Background: Pulmonary arterial hypertension (PAH) is a devastating illness which carries serious morbidity and mortality if left undiagnosed or untreated. Pulmonary Hypertension Support groups (PHSG) play a pivotal role in provision of education, understanding and coping mechanisms with this severe disease state for the patients and their caregivers. The Central Valley Pulmonary Hypertension Support Group (CV-PHSG) was founded in 2010 and is based in Fresno, CA. We would like to present the data pertaining to these meetings over the last 5 years and its impact on the people of Central Valley of California (CVC).

Methods: A Retrospective descriptive study

Results: The CV-PHSG serves as the main Support group for the patients & caregivers of CVC. Members travel many a mile to attend these meetings. Figure-1 illustrates data with regards to registered attendees from various counties of CVC. Average mileage traveled by the attendees is 19.1 miles (SD ± 18) (Median mileage: 10.8 miles). The CV-PHSG Roster has registered 113 members (PH patients: 52, Caregivers: 61). Of the 52 PH patients – 28 (Non-Hispanic), 19 (Hispanic). There have been 26 meetings held from May 2010 to Jan 2016. The reported average attendance of these meetings being 50 (Non-factual/Estimate). “Guest” speakers (characterized by speakers from outside of the PH center’s framework) constituted 15 of the 26 meetings and “native” speakers (Characterized as within the PH center’s framework) accounted for the remainder (11). In addition to the above PHSG meetings, there were a total of 9 Special events considered Inspirational & Motivational and co-sponsored by the PHA - Annual Fun Walk (4 events), Annual Holiday Celebration event (3), Tom Lantos Grant sponsored Art project (1), Other event (1). The first annual fun walk event (Nov 2012) registered 88 RSVP’s and the most recent Fun walk event (Nov 2015) registered 420 RSVP’s – A 477% increase in attendance!

Conclusions: PHSG’s play a crucial role in promoting education & morale to patients and caregivers. Creating awareness in the community (CVC) of this relatively rare disease state is another crucial impact. Active participation is also likely to promote improved compliance and outcomes which we wish to evaluate prospectively henceforth.
Multi-Dimensional Fatigue in Pulmonary Hypertension: Prevalence, Severity and Predictors

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Purpose: The purpose of this study was to examine clinical factors in adults with PH with query into 1) the prevalence and severity of fatigue, conceptualized as a multidimensional symptom, 2) differences in relationship to demographic characteristics and PH severity indicators and 3) PH therapy associated with and predictive of fatigue.

Background: Pulmonary hypertension (PH) is a progressive, potentially fatal disease. Despite pharmacologic advances, fatigue remains common in patients with PH. This cross-sectional study examines the prevalence and severity of fatigue, conceptualized as a multidimensional symptom in patients with PH.

Methods: A convenience sample of 120 participants between 21 to 79 years old were recruited from the Pulmonary Hypertension Association’s 11th International Conference and completed the Multidimensional Fatigue Inventory Scale (MFI-20). New York Heart Association classification, Body Mass Index, oxygen use and medication type and use were also assessed.

Results: There was a high prevalence of ‘severe’ to ‘very severe’ fatigue for each of the 5 dimensions of fatigue measured: General Fatigue (60%), Physical Fatigue (55.8%), Reduced Activity (41.7%), Reduced Motivation (32.5%), and Mental Fatigue (27.5%).

The mean overall score of the MFI-20 was 58 ± 5.1. Dimensions with the highest averaged levels were General (13.40±3.61), Physical (13.23±3.67) and Reduced Activity (11.33±4.16) dimensions. BMI correlated with higher fatigue scores.

Phosphodiesterase-inhibitors/Endothelin Receptor-Antagonist combination negatively predicted General Fatigue, Physical Fatigue, Reduced Motivation and Reduced Activity. Triple therapy was a significant predictor of General Fatigue, Physical Fatigue and Reduced Activity. There were no significant predictors of Mental Fatigue.

Conclusions: Multi-dimensional fatigue is common and severe in patients with PH. Phosphodiesterase-inhibitors/Endothelin Receptor-Antagonist combination resulted in lower scores in most fatigue dimensions. Comprehensive assessment of fatigue should be considered in the clinical care of patients with PH and clinical research to develop formal interventions that target this disabling symptom.
Impact of Treatment Initiation on Healthcare Utilization and Direct Costs Among Pulmonary Arterial Hypertension Patients in the United States

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Purpose: This study’s objective was to assess the impact of treatment initiation on the economic burden of PAH by comparing patients’ healthcare utilization (HRU) and direct costs in the six months before and after PAH medication initiation.

Background: Patients with pulmonary arterial hypertension (PAH) experience a high economic burden due to comorbidities, hospitalizations and medication costs.

Methods: This retrospective study identified patients in the Truven Health MarketScan Commercial and Medicare Supplemental Databases who initiated PAH treatment with endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE-5Is), or a soluble guanylate stimulator (sGC). To ensure patients were new to treatment, the index date was the first ERA, PDE-5I or sGC outpatient pharmacy claim between 2010 and 2014, after a 90-day pre-index period without PAH medication claims. Patients included in the study had ≥2 medical claims with diagnoses for PAH (ICD-9-CM: 416.0, 416.8) or PAH-related conditions, such as portal hypertension, connective tissue diseases, congenital heart disease, or HIV. All-cause and PAH-related utilization and costs were measured. McNemar’s and paired t-tests were used to compare patients’ HRU and costs in the six-month pre- and post- treatment periods.

Results: Of the 3,908 patients who met the selection criteria, the majority initiated monotherapy with PDE-5Is (78%) or ERAs (22%). Compared to the six-month pre-index, the proportion of patients in the six-month post-index period with any inpatient admission decreased, 42% vs. 30% (p<0.001). In addition, PAH-related inpatient admissions decreased in the six-month post-index period from 7% to 3% (p<0.001). In the pre- and post-index periods, almost all patients had outpatient office visits (98% vs. 99%, p=0.327); however, in the post-index the proportion with PAH-related outpatient office visits increased (59% vs. 70%, p<0.001). After treatment initiation, patients’ average medical costs (excluding pharmacy costs) decreased from $48,200 to $33,962 (p<0.001), which was driven by a reduction in inpatient admissions and corresponding costs. However, total average medical costs including pharmacy costs remained steady after treatment initiation (pre-:$51,455 vs. post-:$53,923; p=0.213). As expected, after PAH treatment initiation, average PAH-related total costs including pharmacy costs increased significantly in the six-month post-index period, $6,100 vs. $21,142 (p<0.0001), while average PAH treatment inpatient admission and medical costs decreased, $2,129 vs. $1,316 (p<0.0001).

Conclusions: This study found that while patients’ PAH-related pharmacy costs increased after treatment initiation, their total healthcare costs remained constant. After initiating treatment, the majority of patients in this real-world cohort experienced lower rates of inpatient admissions and associated cost. While the majority of patients in this study received monotherapy, results from the recently completed AMBITION study indicate that initial combination therapy would provide a superior reduction in PAH-related inpatient admissions. Therefore, future cost analysis of patients treated with combination therapy will be intriguing.
Specialty Pharmacy Experience with Transitioning Patients from Infused to Oral Prostacyclin Therapy in Patients with Pulmonary Arterial Hypertension

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Purpose: The aim of this review is to increase understanding of the variability in the prescribing practices for transition from infused prostacyclin to oral treprostinil in patients with pulmonary arterial hypertension.

Background: Prostacyclin therapy was commercially introduced in 1995 with the FDA approval of epoprostenol to treat pulmonary arterial hypertension (PAH). In the years since, additional infused and inhaled prostacyclins have entered the market. The need for unique devices, frequent intermittent dosing or requirement for continuous infusion has created undue burdens to patients requiring prostacyclin therapy. In December of 2013, FDA-approved treprostinil extended-release tablets, the first oral prostacyclin indicated for the treatment of patients with WHO Group I PAH – offering a new option for prostacyclin-based therapy in progressive disease. Data from a 33-subject multi-center open label phase II study was recently published in the product package insert (PI), but little is known regarding patients who transition in a non-study setting with commercially-available medication.

Methods: Data was retrospectively reviewed to evaluate patients on infused prostacyclin (index therapy) who attempted transition to oral treprostinil using a specialty pharmacy for outpatient care. A board-certified pharmacist with over 17 years of clinical experience in PAH reviewed electronic medical records (EMR) to capture data. Patients were included in the analysis if: both the index prostacyclin and the oral treprostinil were dispensed by the specialty pharmacy, they were on the index drug for at least 30 days prior to the transition, and dispensing dates did not show a gap in days of service between use of the infused and oral therapies. Adjudication of some data required further chart analysis of narrative information to rectify any inaccuracies or omissions in the objective data fields of the EMR. Analysis of data was performed using Microsoft Excel 2010, and was intended to be descriptive rather than show statistical significance in any group or subgroup. Results were rounded to the nearest integer.

Results: Records of 133 patients met the inclusion criteria, 14 (11%) of which were subsequently excluded (infused therapy managed by an alternate SP, transition incomplete, short-term use of infused therapy due to surgery). The remaining 119 patients were analyzed. The results are as follows: Gender [F:M] 94(79%):25(21%); Mean age 48 years (range 8−85); WHO group [I:IV] 111 (93%):8 (7%); functional class at time of transition (adjudicated by prescriber); Class I = 8 (7%), Class II = 46 (39%), Class III = 56 (47%), Class IV = 4 (3%), unspecified = 5 (4%); Index drug: epoprostenol = 2 (2%), treprostinil intravenous = 35 (29%), treprostinil subcutaneous = 82 (69%); length of time on index therapy: 1−3 months = 6 (5%), 4−6 months = 3 (3%), >6 months = 104 (87%), unknown = 6 (5%); place of transition: home = 51 (43%), hospital = 68 (57%). The average time to transition was collected for the 51 patients who transitioned in the home setting. The average transition time was 47 days (range 0−330). The number of patients in this subgroup who transitioned in ≤5 days was 9 (18%).

Conclusions: Transition of patients from infused to oral prostacyclin therapy is feasible in collaboration with a specialty pharmacy. Specific titration orders are required to facilitate this transition. Further data review is needed to better understand the speed at which transitions may safely occur and the long-term outcomes associated with transitions from infused to oral prostacyclins in a non-study setting. While the PI for oral treprostinil states that the majority of patients transitioned from infused prostacyclin to oral treprostinil in ≤5 days (94%), real-world experience shows a much longer timeline to transition when occurring in the home setting. More information is needed to establish if a prolonged time to transition is a benefit or detriment to the long-term success with oral treprostinil.
An Evaluation of Intravenous Treprostinil Waste at a Large Academic Medical Center

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Purpose: To evaluate the amount of treprostinil medication for intravenous administration that is wasted due to changing the medication bags at a specified interval based on the rate.

Background: Treprostinil is a prostacyclin therapy used to treat pulmonary arterial hypertension (PAH). It is a costly medication, and creates an expenditure burden on the institution, specifically to the pharmacy department. At The Ohio State University Wexner Medical Center (OSUWMC), treprostinil used for preparation of intravenous (IV) bags for continuous infusion is prepared using a 1mg/ml multidose vial. The quantity required, based on the desired concentration, is diluted with normal saline to a total volume of 100ml. At OSUWMC, if the rate is 0–1.5ml/hr we change the treprostinil IV bag every 48 hours and if the rate is greater than 1.5ml/hr we change the treprostinil IV bag every 24 hours (at specified times).

Over $475,000 was budgeted in the OSUWMC pharmacy department for purchasing of treprostinil therapies in fiscal year 2016. This project was focused on evaluating the amount of treprostinil medication for intravenous administration that is wasted due to changing the IV bags at a specified interval based on their rates. This waste could be viewed as preventable waste if we allowed the nursing staff to change the IV bags on demand instead of on a scheduled 24 or 48 hour basis.

Methods: This retrospective cost analysis was conducted by running a report of all treprostinil IV bag dispenses for hospital inpatients from July 1, 2014 to June 30, 2015 (FY15).

To begin the cost analysis, the total milliliters (mL) of treprostinil dispensed in FY15 was multiplied by the cost per mL to determine the total amount spent on IV treprostinil.

The next step was to determine how much of this amount is wasted with each IV bag change at 24 or 48 hours depending on the infusion rate. A chart review was conducted on these patients to determine the concentration of each bag, the rate of infusion of the bags and how often these bags were changed for each hospital stay. The amount of medication wasted, in milligrams, with each IV bag change was determined for each IV bag dispensed in FY15, and the total amount wasted was multiplied by the cost per ml of the 1mg/ml treprostinil to determine the total amount that was thrown away in FY15 due to scheduled IV bag changes.

Results: OSUWMC wasted approximately $127,022.40 by changing treprostinil IV bags at specified times during FY15.

Conclusions: Treatment of PAH with treprostinil can be complex and patient safety with use of the prostacyclin medications is of highest priority. A proposal to change our current process so that nurses could request a new IV bag on demand when appropriate, instead of on a specified schedule, requires a thorough evaluation of risk versus benefit. In this case, the risk of changing our current process would be that if a new IV bag was not requested in enough time by the nursing staff, the current IV bag could run dry and cause an abrupt discontinuation of the therapy. The benefit to changing our current process would be the cost-savings obtained by preventing wasted treprostinil medication with each IV bag change.
Assessing the Need for a Multiple Pathway Modulating Therapy for Pulmonary Hypertension Treatment

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Purpose: This study is aimed to evaluate the need for a multiple pathway modulating therapy for PH management.

Background: Pulmonary hypertension (PH) is a rare, life-threatening disease that is commonly associated with various comorbidities. Although multiple therapies are approved by FDA in recent years, less than significant improvement is seen in patient survival. A primary reason for suboptimal therapeutic benefits can be attributed to ability of current therapies to merely ameliorate PH symptoms without limiting the vasculopathy associated with disease progression. Due to existence of overlapping and interconnected pathological pathways, PH management has been a cumbersome task as the current therapeutic interventions only target one of the many pathological pathways involved. This study is aimed to evaluate the need for a multiple pathway modulating therapy for PH management.

Methods: To assess the need for multiple pathway modulating therapy, a survey was designed and distributed to PH clinicians and experts. The survey contained a total of 10 questions on a Likert scale of 1−5, and focused on issues surrounding current PH therapies: efficacy, safety, patient compliance and the need for a therapy modulating multiple pathways. Quantitative and qualitative responses were recorded, and the obtained data were analyzed.

Results: Preliminary results of the study showed that there was unanimous acceptance among PH healthcare professionals of the need for a therapy modulating multiple pathways (Fig. 1). Furthermore, the current therapies were only moderately successful in terms of patient compliance (3 on a scale of 1−5) (Fig. 2). In addition to the issues with patient compliance and need for multiple pathway modulating therapy, it was also discovered that there are tremendous cost implications of PH treatment on payers (Fig. 3). Based on preliminary calculations, a new therapy modulating multiple pathogenic pathways will minimize the number of prescription medications and mitigate re-hospitalization occurrences, thus saving each patient upwards of $150,000.

Conclusions: Overall, we found that in consideration of disease outcome and cost burden of PH, there is great potential for a new multiple pathway modulating therapy to be successful in the PH market.
Review of Treprostinil Dosing Following Complete Transition from the Infused to Oral Route of Administration

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Purpose: A specialty pharmacy with PAH experience reviewed transitions occurring prior to the FDA-approved update to the oral treprostinil PI to evaluate if patients were dosed closely to the infused equivalent calculation within the PI.

Background: Prostacyclin therapy was commercially introduced in 1995 with FDA approval of epoprostenol to treat pulmonary arterial hypertension (PAH). In the years since, additional infused and inhaled prostacyclins have entered the market. The need for unique devices, frequent intermittent dosing or requirement for continuous infusion has created undue burdens to patients requiring prostacyclins. In December of 2013, FDA approved treprostinil extended-release tablets, the first oral prostacyclin indicated for the treatment of patients with WHO Group I PAH. Data from a 33-subject, multi-center, open label, phase II study was recently published in the product package insert (PI) for oral treprostinil; prior to this, little was known regarding how to optimally transition from infused to oral treprostinil. A specialty pharmacy with PAH experience reviewed transitions occurring prior to the FDA-approved update to the oral treprostinil PI to evaluate if patients were dosed closely to the infused equivalent calculation within the PI.

Methods: Data was retrospectively reviewed to evaluate the method by which patients stable on infused treprostinil (index therapy) were transitioned to oral treprostinil in clinical practice using a specialty pharmacy for outpatient care. A board-certified specialist pharmacist with over 17 years of clinical experience in PAH reviewed electronic medical records (EMR) to capture data. Included patients had at least 3 months of infused prostacyclin experience and orders to titrate current infused prostacyclin therapy to oral. Adjudication of some data required further chart analysis of narrative information to complete any inaccuracies or omissions in the objective data fields of the EMR. Analysis of data was performed using Microsoft Excel 2010, and was intended to be descriptive rather than show statistical significance in any group or subgroup. Maintenance infused dose was compared to the infused equivalent dose achieved of oral therapy at the time the infused therapy was fully discontinued. The calculation for infused equivalent was obtained from Section 2.5 of the PI: [infused treprostinil (ng per kg per min) = 139 x oral treprostinil total daily dose (mg) ÷ weight (kg)].

Results: A total of 105 patients completely weaned from infused treprostinil and were successfully transitioned to oral treprostinil. The following histogram depicts the results.

The x-axis represents oral dosing on final transition (based upon the infused equivalent calculation) as a percentage of the maintenance dose of infused treprostinil at the start of transition. Average difference between infused dose to infused equivalent for oral treprostinil is −15% (median: −11%).

Conclusions: The data shows that most prescribers tend to dose oral treprostinil conservatively based upon the infusion equivalent equation used to calculate the comparison dose of oral-to-infused. While clinical assessment and patient-reported measures should guide final dosage of therapy, more studies may be needed to see if patients maintain long-term adherence to oral treprostinil following transition from infused treprostinil when dosed lower than the infused equivalent.
Thrombocytopenia Independently Predicts Death in Idiopathic PAH

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Purpose: This study serves to evaluate the prognostic significance of thrombocytopenia in pulmonary arterial hypertension.

Background: Pulmonary arterial hypertension (PAH) is a progressive vascular disorder characterized by insidious dyspnea culminating in right heart failure and high mortality. Clinical experience and small case series suggest thrombocytopenia may be frequent in this population and associated with a poor prognosis.

Methods: Single center cohort study of 714 incident adult patients (pts) with Group 1 PH. Platelet (plt) count closest to initial PAH diagnosis (±180 days) was utilized in this analysis. Pts were stratified into three groups: normal plt count (>150x10\textsuperscript{9}/L), Grade 1 thrombocytopenia (75−149x10\textsuperscript{9}/L) and Grade 2−4 thrombocytopenia (<75x10\textsuperscript{9}/L).

Results: The median plt count was 209 x10\textsuperscript{9}/L (IQR 163, 264). There were 572 (80%) pts without thrombocytopenia, 107 (15%) with Grade 1 and 35 (5%) with Grade 2−4 thrombocytopenia. The median pt age was 55 yrs (IQR 44-65) with no difference between plt groups (p=0.85). Men were more likely to have thrombocytopenia (62, 34%) than women (80, 15%, p<0.0001). Thrombocytopenia was frequent with portopulmonary PAH (PoPH; 84%) as opposed to idiopathic PAH (iPAH; 14%) or connective tissue disease associated PAH (cPAH; 12%).

Plt counts were not associated with functional class symptoms, the degree of right ventricular enlargement or dysfunction or tricuspid regurgitation by echocardiography. Invasive hemodynamics of right atrial pressure, mean pulmonary artery pressure and pulmonary vascular resistance index were also similar between plt groups.

While plt counts were not associated with outcome in pts with cPAH or PoPH, thrombocytopenia was associated with higher mortality in iPAH patients (age- and sex-adjusted 5 year mortality [HR 1.95 (1.20, 3.08) p=0.008]. In a multivariate model (adjusted for age, sex, FC and 6MW distance) thrombocytopenia was most predictive of 5-year mortality [HR 1.84 (1.11, 2.96), p=0.02]. Five year survival curves are shown in the figure.

Conclusions: Thrombocytopenia in the context of iPAH portends a poor prognosis and is a simple independent factor to consider in judging severity of disease.

Figure 1:
Report of Central Line Infections in PAH Patients on IV Prostacyclin: Single-Center Experience

Aurora Saint Luke’s Medical Center, Milwaukee, WI

Purpose: Report our center’s rates of central line infections, treatment received, and risk factors for infection over the past 3 years.

Background: Pulmonary arterial hypertension (PAH) is a devastating disease that can require treatment with intravenous prostacyclin. A major concern with long-term, indwelling catheters for delivery of intravenous prostacyclin is central line infections. We report our center’s rates of central line infections, treatment received, and risk factors for infection over the past 3 years.

Methods: We retrospectively reviewed charts of patients treated with intravenous prostacyclin and prevalence of central line infections from January 2013 through February 2016.

Results: A total of 64 patients (mean age 57.0 [range 27 to 87]; 47 females) with PAH (33 IPAH, 13 collagen vascular, 5 CTEPH, 11 CHD, 1 hepatopulmonary, 1 HIV) were treated with intravenous prostacyclin. Seven out of 64 patients (10.9%) had bacteremia with the suspected source being their central lines. These patients received IV antibiotics and their central lines were replaced for treatment. An additional 7 patients (10.9%) had cellulitis or tunnelitis without bacteremia related to their central lines. Six out of these 7 patients received oral antibiotics and/or topical antibiotic ointment without central line replacement. One out of these 7 patients received 1 dose of IV antibiotic and had her line replaced. All 14 patients that suffered central line associated infections (bacteremia, cellulitis, or tunnelitis), were either not following proper sterile technique during dressing changes/catheter site cleaning or were not bleaching their shower head as recommended. Fifty out of 64 patients (78.1%) never had a line infection. Of note, one patient having an indwelling catheter for over 10 years and never had a line infection.

Conclusions: In our center’s experience, line infections occurred only in patients who did not follow sterile techniques or did not bleach their shower heads. IV prostacyclin is a necessary treatment in many patients with severe PAH, and if proper preventative measures are taken, line infections can be avoided.
Who, Where and When: The 3W’s World Experience in Pulmonary Hypertension Clinical Research

Roberts D, Khanal C, Stone E, Zaman H, Jimenez J
MCVi-Baptist Health

Purpose: Little has been published about the site source of clinical trial research in pulmonary hypertension. For future planning and to emphasize the value of academic versus non academic and when- change with time, clinical research in pulmonary hypertension is being performed.

Background: We reviewed 11 landmark clinical trials in pulmonary hypertension performed over the last 17 years and identified all sites participating in each study. We determined location, institutional affiliation, functional class of patients enrolled, sample size, year of completion and drug being studied. Data was analyzed and displayed as percentage of total.

Methods: Clinical landmark studies in pulmonary arterial hypertension were selected. Data referring to participating sites were obtained using the original publication and any on-line appendix available. Sites were classified according to location nationally (USA) and internationally. Sites were classified into academic, non academic or military/government according to their published affiliation.

Results: A total of 11 landmark studies were identified and published between 1996 and 2013. Most, except 1, were 12 week studies. A total of 4,360 were included (81-1156) and a total of 570 participating sites (9-176). 525(92%) academic, 43 (7.6%) non-academic and 3 (0.4%) government/military. 5/11 sites included patients with advanced functional class (III/IV).

Location was identified as follows: Europe 214 (37%), Australia 15 (3%), So. America 26 (4%), Asia 62 (10%), No America (Non USA) 30 (6%) and United States 218 (38%). Regional location within the United States was as follows: South 59 (27%), Southeast 5 (2%), Southwest 8 (4%), North 10 (5%), Northeast 55 (25%), West 43 (20%) and Northwest 38 (17%).

Conclusions: Pattern locations of clinical research in pulmonary hypertension across the world varies. Efforts need to be established to include more patients from different locations across the word and within the United States, thus providing an untapped source of patients and racial/ethnic and social diversity. This study also identifies the need to include non academic sites in pulmonary hypertension research since they represent a source of real-life experience in pulmonary hypertension.
Rapid Switch to Macitentan from Bosentan in Pulmonary Arterial Hypertension Patients

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Purpose: Pulmonary arterial hypertension (PAH) is a progressive disease with several therapies currently available. Macitentan was the latest endothelin receptor antagonist (ERA) that was approved for PAH treatment. We present our experience in switching between ERAs (macitentan from bosentan) in PAH patients to determine tolerability and clinical efficacy associated with this switch.

Background: Bosentan and macitentan are dual ETA/ETB antagonists. While bosentan lacked inhibitory activity at high ET-1 concentrations, studies suggest that macitentan receptor binding remain high due to its slow dissociation. In addition while bosentan clearly impacts phosphodiesterase 5-inhibitor (PDE5-I) pharmacokinetics, no such effect has been demonstrated with macitentan. This implies that transition from bosentan to macitentan in patients on background PDE5-i therapy would result in increased exposure with potentially increased side effects attributable to the PDE5-I. Currently, there is no published data to guide physicians regarding switching to the new ERA, macitentan.

Methods: At Baylor PH Program, 26 PAH patients were identified as having been on bosentan. One patient was excluded as this patient was previously enrolled in a clinical trial and another patient was excluded as this patient was a new macitentan start. Data from twenty-four patients who switched from bosentan 125 mg orally twice a day to macitentan 10 mg orally daily (between October 2013 and February 2015) when macitentan became commercially available is presented. Baseline data and post-switch data was collected including 6-minute walk distance (6MWD), BNP, ALT and AST levels, WHO functional class, Borg dyspnea score, and presence of peripheral edema. All analyses are two sided and significance judged as p-value < 0.05.

Results: At the time of switch, age of the patients was 59 ± 11 (mean ± SD) years, duration of disease was 7 ± 4 years, 21 were females, 12 were Caucasians, 12.5% had idiopathic PAH. At baseline, 6MWD was 344 ± 106 meters, BNP was 91 ± 170 pg/ml, AST was 20 ± 8 U/L and ALT was 17 ± 8 U/L. At baseline, WHO FC II status was noted in 10 of the patients and edema was present in 52% of patients. After switch to macitentan, data was collected at a follow-up of 5.7 ± 1.5 months. As compared to baseline, follow-up BNP was 90 ± 137 pg/ml (p=0.159), AST was 20 ± 7 U/L (p=0.940), ALT was 19 ± 10 U/L (p=0.624), 55% had edema and 6MWD was 319 ± 85 meters (p=0.023). Two patients did not tolerate this switch and had to be switched back to bosentan. One patient with portopulmonary hypertension had macitentan stopped due to increase in AST and ALT. Another patient had macitentan stopped due to malaise and tachyarrhythmia. A third patient underwent a successful liver transplant.

Conclusions: Rapid switch from bosentan to macitentan was well tolerated and safe with maintained WHO FC with no significant change in edema and liver function status. There were no adverse events limiting tolerability attributable to altered pharmacokinetic effects of background therapy with PDE5-I.
Novel Analysis of the Oral Treprostinil Combination Therapy Trial Data

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Purpose: Provide new information about short term efficacy of oral treprostinil when used in combination with PAH-specific background therapy.

Background: Pulmonary arterial hypertension (PAH) is a rare but fatal disease with rapidly evolving treatment paradigms. Sequential combination therapy with oral or inhaled agents has achieved the primary outcome in four registration studies. Two of these were smaller, short-term studies of exercise tolerance while two were large, event-driven trials. In 2013, the FDA approved an oral form of treprostinil to improve exercise capacity. The two trials in which oral treprostinil was studied as sequential combination therapy did not achieve statistical significance for the primary endpoint of exercise tolerance.

Methods: We analyzed the patient-level data from the two separate combination trials as one entity. These two trials were essentially identical in the critical attributes: duration (16 weeks), design (primary and secondary endpoints), participant demographics, and dosing. The studies were done at overlapping geographic sites in two consecutive timeframes (2006–2008, 2009–2011) (6). In the second study, all participants had access to low dose tablets for titration, but this did not influence the average dose achieved. The pre-specified plan for each study was to impute worst rank for those who had disease progression or were ‘too ill to walk’ and to impute last observation carried forward (LOCF) for participants who had an adverse event and dropped out before Week 16’s 6-minute walk (6MW) assessment. We used this generally accepted imputation strategy.

Results: Analyzing the combined population, the Hodges-Lehman estimate of treatment effect was 10m (3 – 19m, p < 0.004, nonparametric analysis of covariance adjusted for baseline 6MW). This was attributable to greater improvement in 6MW for actively treated participants (15 m, IQR −12 ± 50) as placebo treated participants also improved (7 m, IQR −19 ± 37). Different statistical approaches yielded similar estimates of treatment effect and significance. A sensitivity analysis including only observed cases (no imputation, 79% of actively treated and 85% of placebo subjects) estimated a treatment effect of 13m (95% CI +5 ± 22, p =0.001). We hypothesized that participants tolerating higher doses of drug would achieve larger improvements. An unbiased division of the actively treated completers into three groups by dose yielded 95, 81, and 87 participants taking twice daily doses < 2 mg, 2 – 3.5 mg, and > 3.5 mg, respectively. Figure 1 shows steady improvement in 6MW for the higher dose group and a difference between the high and low dose groups (p = 0.01, Week 16). In two different sensitivity analyses of this main finding, the median change in 6MW at Week 16 for the high dose group was ≥ 34 m and statistically different than the low dose group (p ≤ 0.006 for both).

Conclusions: A combined analysis of the two studies demonstrates a statistically robust 10 m treatment effect after 16 weeks of oral treprostinil therapy for a group of 660 participants who were taking one or two background PAH therapies. The pattern in Figure 1 does not suggest that these differences would have waned by Week 24, and indeed, shorter term benefits observed in the registration studies for ambrisentan and tadalafil were recently confirmed at Week 24 in the AMBITION study. As expected for treprostinil, benefits in exercise capacity were greater at higher dose, and several approaches estimated an improvement ≥ 34m at higher dose for these participants on background therapy. Improvements in exercise tolerance correlate with improvements in physical functioning, and for the participants achieving higher doses, oral treprostinil produced a difference that likely is clinically important.
Contemporary Approach to Pulmonary Arterial Hypertension in Pregnancy

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Purpose: The purpose of our study is to show that women with pulmonary arterial hypertension (PAH) when treated for PAH can have successful outcomes with their high risk pregnancies.

Background: The management of pregnant women with pulmonary arterial hypertension is difficult, with many centers continuing to report high mortality rates (>50%). We report our experience with 128 consecutive pregnancies between 2000 and 2015, with 100% maternal survival.

Methods: Simple assembly of data for 128 consecutive patients treated at our center or distant consultation (27-US states and 17 other countries).

Results: We were involved with 128 pregnant women who birthed 128 live babies. The etiology of the PAH included all causes. The average maternal age was 27 years, average mean pulmonary artery pressure was 47mmHg, average length of hospital stay was 5 days, 1 elective termination at 22 weeks, 17 Cesarean sections and 111 vaginal deliveries, with 128 live babies including one set of twins. Seven women have had multiple pregnancies while on PAH treatment. Medications included all PAH therapies available in the US, excluding the ERA group. All deliveries were completed between 29 and 36.5 weeks of gestation. Two patients had general anesthesia and 126 had epidural anesthesia.

Conclusions: An aggressive, high risk team approach, early deliver, and meticulous post-partum fluid management resulted in successful outcomes in this high risk population, with no fetal or maternal deaths.
Successful Delivery of Multiple Pregnancies in Women with Pulmonary Arterial Hypertension

Zwicke DL
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Purpose: The purpose of our study is to show that women with pulmonary arterial hypertension (PAH) when treated for PAH can have successful outcomes with multiple, high risk pregnancies.

Background: Management of pregnant women with pulmonary arterial hypertension (PAH) is difficult. Many centers continue to report high mortality rates. We have been successful with the safe delivery of 128 consecutive pregnancies at our center or distant consultations (27 US states and 17 other countries).

Methods: Simple assembly of data from seven women with PAH, who delivered multiple pregnancies.

Results: Seven women with PAH delivered a total of 15 babies after the established diagnosis and initiation of treatment for PAH. Six women had two pregnancies each and one woman had a total of three pregnancies. Five of the seven women were unaware of their PAH diagnosis at the time of their first pregnancy. Two were aware of their PAH diagnosis and chose to electively plan their next pregnancies. One patient had three separate pregnancies over a six year period. Etiologies of the PAH were: 4 idiopathic, 2 lupus, and 1 congenital heart disease. Treatment included the use of prostacyclins and PDE5 inhibitor medications. There was a need for escalation of drug therapy with the second and third pregnancies.

Conclusions: Seven women were able to successfully deliver healthy infants without mortality or significant decompensation of their right heart hemodynamics. Drug therapy was significantly escalated with a second or third pregnancy. Although these were successful pregnancies extreme caution is recommended and multiple pregnancies are not advised.
Efficacy and Safety of Riociguat in Patients with Pulmonary Arterial Hypertension (PAH) Associated with Congenital Heart Disease (CHD) (PAH-CHD)

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6Cologne University Heart Center, Germany

Purpose: Subgroup analysis of PATENT-1 and -2 in patients with persistent or recurrent PAH following complete surgical repair of CHD.

Background: Riociguat has shown beneficial effects in patients with PAH in the Phase III PATENT-1 trial and PATENT-2 open-label extension. We report a subgroup analysis of PATENT-1 and -2 in patients with persistent or recurrent PAH following complete surgical repair of CHD.

Methods: In PATENT-1, treatment-naïve or pretreated patients with PAH received placebo, riociguat up to 2.5 mg tid (2.5 mg–max group), or riociguat up to 1.5 mg tid (1.5 mg–max group; exploratory) for 12 weeks. Eligible patients went on to enter PATENT-2, in which all patients received open-label treatment with riociguat.

Results: In PATENT-1, 35 patients had persistent or recurrent PAH after complete surgical repair of CHD; mean time since last corrective surgery was 16.8 years. Of these, 57% were treatment-naïve, most had atrial (40%) or ventricular septal defects (34%), and all were in WHO FC II (60%) or III (40%). At Week 12, patients in the riociguat 2.5 mg–max group showed greater improvements from baseline in 6MWD (primary endpoint) and secondary efficacy endpoints vs placebo (Table). Four (11%) patients reported SAEs during PATENT-1; none were considered drug-related. One patient died owing to right ventricular failure and worsening PAH (riociguat 1.5 mg–max group; not drug-related) and two patients discontinued treatment, one owing to supraventricular tachycardia and hypotension (riociguat 2.5 mg–max group; drug-related) and one owing to pneumothorax (placebo group; not drug-related). In 33 (94%) patients with PAH-CHD who entered PATENT-2 (median treatment duration 139 weeks), improvements in 6MWD and WHO FC with riociguat persisted for up to 2 years.

Conclusions: In PATENT-1 and PATENT-2, riociguat improved a range of clinical outcomes in patients with persistent or recurrent PAH after complete surgical repair of CHD.

Table. Change from baseline to Week 12 in patients with persistent or recurrent PAH after complete surgical repair of CHD (observed values).

<table>
<thead>
<tr>
<th></th>
<th>Riociguat 2.5 mg–max</th>
<th></th>
<th>Riociguat 1.5 mg–max</th>
<th></th>
<th>Placebo</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n Change</td>
<td>n Change</td>
<td>n Change</td>
<td></td>
<td>n Change</td>
<td></td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>13 +39±60</td>
<td>7 +43±54</td>
<td>12 0±42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyn-s-cm–5)</td>
<td>13 −250±410</td>
<td>7 −126±368</td>
<td>11 −66±632</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>12 −164±317</td>
<td>6 −872±1147</td>
<td>12 −46±697</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO FC, improved/stabilized/worsened (%)*</td>
<td>14 21/79/0</td>
<td>7 29/71/0</td>
<td>12 8/83/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borg dyspnea score</td>
<td>13 −0.3±1.3</td>
<td>7 −0.8±0.8</td>
<td>12 −0.1±2.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EuroQol Group 5-Dimension self-report questionnaire score</td>
<td>14 +0.03±0.18</td>
<td>7 +0.09±0.14</td>
<td>12 −0.05±0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with pulmonary hypertension score</td>
<td>14 −8.0±15.9</td>
<td>7 −13.7±13.2</td>
<td>12 −0.1±15.8</td>
<td></td>
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</tbody>
</table>

Data are mean±SD unless otherwise indicated. *Percentages may not add up to 100% due to rounding.
Efficacy and Safety of Riociguat in Patients with Pulmonary Arterial Hypertension (PAH) Associated with Connective Tissue Disease (CTD) (PAH-CTD)

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8Bayer Healthcare Pharmaceuticals Inc, U.S.A.
9Clinic of Rheumatology, Lübeck, Germany
10La Sapienza University of Rome, Italy

Purpose: Subgroup analysis of patients with PAH-CTD from the PATENT studies investigating the soluble guanylate cyclase stimulator, riociguat, for the treatment of PAH

Background: PAH-CTD has a worse prognosis than idiopathic/familial PAH. We report a prospective subgroup analysis of patients with PAH-CTD from the PATENT studies investigating the soluble guanylate cyclase stimulator, riociguat, for the treatment of PAH.

Methods: In the 12-week PATENT-1 Phase III trial, patients with PAH received placebo or riociguat individually dose-adjusted to a maximum of 2.5 mg tid or 1.5 mg tid (exploratory). The primary endpoint was change from baseline in 6-minute walking distance (6MWD). The PATENT-2 open-label extension assessed long-term safety and outcomes.

Results: In PATENT-1, 111 patients had PAH-CTD (66 PAH associated with systemic sclerosis [PAH-SSc], 39 PAH-other defined CTD, 6 unspecified CTD; PAH-SSc and PAH-other defined CTD subgroups were derived post-hoc from the medical history using MeDRA preferred terms). At Week 12, there was an improvement in 6MWD with riociguat in the 2.5 mg–maximum arm (+18 m from 348 m at baseline) and a deterioration with placebo (–8 m from 361 m at baseline; Figure). By March 2014, 70 patients with PAH-CTD had received treatment for ≥2 years in PATENT-2 and improvements in 6MWD were maintained in patients receiving riociguat. At 2 years, similar survival rates (95% CI) were observed for patients with PAH-CTD, PAH-SSc, idiopathic/familial PAH, and the overall population: 93% (85–97%), 94% (82–98%), 93% (89–96%), and 93% (90–95%), respectively. Riociguat had a similar safety profile in PAH-CTD as in the overall population.

Conclusions: In patients with PAH-CTD, riociguat was associated with long-term improvements in 6MWD; 2 year survival rates were high and similar to patients with idiopathic/familial PAH.
Health Outcome Assessment in Pulmonary Arterial Hypertension (PAH) Patients Treated with Riociguat: 2-year Results from the PATENT-2 Long-Term Extension Study

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2Chrestos Concept GmbH & Co. KG, Germany
3Bayer Pharma AG, Germany
4Johns Hopkins School of Medicine, U.S.A.
5Southside Regional Medical Center, U.S.A.

Purpose: An analysis from PATENT-2 on the long-term HRQoL benefits of riociguat.

Background: PAH is a chronic, life-threatening disease that causes impaired physical function and diminished health-related quality of life (HRQoL). The 12-week Phase III PATENT-1 study and the long-term PATENT-2 extension study demonstrated the positive sustained clinical benefit of riociguat as a treatment for PAH. We present here an analysis from PATENT-2 on the long-term HRQoL benefits of riociguat.

Methods: In PATENT-1, treatment naïve PAH patients or those receiving treatment with endothelin-receptor antagonists or (non-intravenous) prostanoids were randomized to receive placebo, riociguat individually dose adjusted up to 2.5 mg tid, or riociguat individually dose adjusted up to 1.5 mg tid (exploratory arm) for 12 weeks. Eligible patients enrolled in PATENT-2 all received riociguat up to 2.5 mg tid after a blinded 8-week dose adjustment period. The EQ-5D is a standardized generic instrument that measures patient-reported health in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). HRQoL was assessed using the EQ-5D in PATENT-1 (baseline and Week 12) and PATENT-2 (Week 12, and Months 6, 9, 12, and 24). Responder analyses were performed to put EQ-5D scores into context with clinical outcomes (6-minute walking distance [6MWD] and WHO functional class [FC]). EQ-5D utility scores were summarized using descriptive statistics and 95% confidence intervals (CIs). We report EQ-5D patient data after at least 24 months of participation in PATENT-2.

Results: Of 443 randomized patients who received at least one dose of study medication or placebo, 396 entered PATENT-2. Former riociguat 2.5 mg–maximum-treated patients and former placebo-treated patients saw increases in EQ-5D from PATENT-1 baseline maintained at both Month 12 and Month 24 (Table). Responder analyses in the total population indicate that, from baseline to Month 24, patients who were in WHO FC I/II and III/IV at PATENT-2 Week 12 both benefitted from an increase in EQ-5D utility score of +0.059 (CI 0.021 to 0.096) and +0.073 (CI 0.002 to 0.144), respectively. Patients who showed a 6MWD improvement from baseline of at least +40 m after 12 weeks in PATENT-2 saw increases in EQ-5D utility score of +0.08 (CI 0.035 to 0.125).

Conclusions: Patients with PAH treated with riociguat showed an improvement in their health outcome status across a 2-year period in the PATENT-2 extension study. The results also highlight the consistency of findings between clinical and HRQoL endpoints.

Table. Mean EQ-5D utility score in former riociguat and former placebo patients receiving riociguat in PATENT-2.

<table>
<thead>
<tr>
<th>EQ-5D, mean (CI)</th>
<th>n</th>
<th>PATENT-1 baseline</th>
<th>n</th>
<th>Month 12</th>
<th>n</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>392</td>
<td>0.682 (0.658 to 0.706)</td>
<td>351</td>
<td>0.754 (0.731 to 0.777)</td>
<td>221</td>
<td>0.733 (0.700 to 0.766)</td>
</tr>
<tr>
<td>Former riociguat</td>
<td>230</td>
<td>0.688 (0.658 to 0.719)</td>
<td>203</td>
<td>0.753 (0.721 to 0.785)</td>
<td>128</td>
<td>0.753 (0.711 to 0.795)</td>
</tr>
<tr>
<td>2.5 mg–maximum arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former placebo</td>
<td>107</td>
<td>0.693 (0.649 to 0.737)</td>
<td>94</td>
<td>0.760 (0.720 to 0.800)</td>
<td>59</td>
<td>0.742 (0.682 to 0.802)</td>
</tr>
</tbody>
</table>
Health Outcome Assessment in Chronic Thromboembolic Pulmonary Hypertension (CTEPH) Patients Treated with Riociguat: 2-year Results from the CHEST-2 Long-Term Extension Study

Bonner N1, Brockman B2, Busse D2, de la Orden M3, Gater A1, Mathai SC4, Minai OA5, Teal Simon3

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2Chrestos Concept GmbH & Co. KG, Germany
3Bayer Pharma AG, Germany
4Johns Hopkins School of Medicine, U.S.A.
5Southside Regional Medical Center, U.S.A.

Purpose: We report EQ-5D patient data after at least 24 months of participation in CHEST-2.

Background: Approximately 40% of patients with CTEPH are deemed unsuitable for surgery due to co-morbidities or the presence of distal disease, and 10–34% experience recurrent or persistent disease post-surgery with pulmonary endarterectomy (PEA). The 16-week Phase III CHEST-1 study and the long-term CHEST-2 extension study demonstrated the positive sustained clinical benefits of riociguat as a treatment for CTEPH. We present here the results of health outcomes assessment collected during CHEST-2.

Methods: In CHEST-1, CTEPH patients who were inoperable or had persistent/recurrent pulmonary hypertension post-surgery were randomized to receive placebo or riociguat individually dose adjusted up to 2.5 mg tid. Eligible patients enrolled in CHEST-2 where former placebo patients received riociguat after an 8-week, blinded, dose adjustment period and former riociguat patients remained on their dose. Health-related quality of life (HRQoL) was assessed using the EuroQol Group 5-Dimension self-report questionnaire (EQ-5D) in both CHEST-1 (baseline and Week 16) and CHEST-2 (Week 12, and Months 6, 9, 12, and 24). Responder analyses were performed to put EQ-5D scores into context with clinical outcomes (6-minute walking distance [6MWD] and WHO functional class [FC]). EQ-5D utility scores were summarized using descriptive statistics and 95% confidence intervals (CIs). We report EQ-5D patient data after at least 24 months of participation in CHEST-2.

Results: Of the 243 patients who completed CHEST-1, 237 entered CHEST-2. Former riociguat-treated patients and former placebo-treated patients saw increases from CHEST-1 baseline in EQ-5D maintained at both Month 12 and Month 24 (Table). Responder analyses in the total population indicate that, from baseline to Month 24, patients who were in WHO FC I/II at CHEST-2 Week 12 saw a greater increase in EQ-5D (+0.102 [CI 0.042 to 0.163]) compared with patients in WHO FC III/IV at CHEST-2 Week 12 whose EQ-5D remained relatively constant over 2 years (+0.007 [CI –0.097 to 0.111]). Patients who showed a 6MWD improvement from baseline of at least +40 m at CHEST Week 12 saw increases in EQ-5D utility score of +0.1 (CI 0.037 to 0.164).

Conclusions: Our findings demonstrate that the positive benefit in patient-reported health outcome of riociguat is maintained across the 2-year period in all patients regardless of initial treatment arm. We also show that the increase in 6MWD translated into a sustained improvement in HRQoL.

Table. Mean EQ-5D utility score in former riociguat and former placebo patients receiving riociguat in CHEST-2.

<table>
<thead>
<tr>
<th>EQ-5D, mean (CI)</th>
<th>n</th>
<th>CHEST-1 baseline</th>
<th>n</th>
<th>Month 12</th>
<th>n</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>235</td>
<td>0.646 (0.614 to 0.678)</td>
<td>201</td>
<td>0.724 (0.692 to 0.756)</td>
<td>97</td>
<td>0.717 (0.674 to 0.761)</td>
</tr>
<tr>
<td>Former riociguat</td>
<td>154</td>
<td>0.641 (0.601 to 0.681)</td>
<td>130</td>
<td>0.744 (0.709 to 0.778)</td>
<td>63</td>
<td>0.733 (0.685 to 0.781)</td>
</tr>
<tr>
<td>Former placebo</td>
<td>81</td>
<td>0.657 (0.601 to 0.713)</td>
<td>71</td>
<td>0.688 (0.621 to 0.754)</td>
<td>34</td>
<td>0.688 (0.598 to 0.778)</td>
</tr>
</tbody>
</table>
Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension (CTEPH): 2-year Results from the CHEST-2 Long-Term Extension

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11UT Southwestern Medical Center, U.S.A.
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**Purpose:** 2-year data analyses from the CHEST-2 extension study and analyses of correlation between efficacy endpoints and long-term outcomes.

**Background:** CTEPH is a rare and potentially fatal disease caused by organized fibrous material obstructing pulmonary artery branches. In the 16-week CHEST-1 study, riociguat, a soluble guanylate cyclase stimulator, significantly improved 6-minute walking distance (6MWD) and other secondary endpoints in patients with CTEPH. Improvements persisted for a further 1 year in CHEST-2. We present 2-year data analyses from the CHEST-2 extension study and analyses of correlation between efficacy endpoints and long-term outcomes.

**Methods:** Patients with inoperable CTEPH or persistent/recurrent pulmonary hypertension after pulmonary endarterectomy entered CHEST-2 after completing CHEST-1 without ongoing riociguat-related serious adverse events (SAEs). All patients received riociguat adjusted up to 2.5 mg three times daily. Primary endpoints were safety and tolerability; secondary endpoints included 6MWD, World Health Organization functional class (WHO FC), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), survival, and clinical worsening-free survival. Correlation between efficacy parameters and long-term outcomes was assessed using Kaplan–Meier analyses and a Cox proportional-hazards regression model.

**Results:** Of 243 patients completing CHEST-1, 237 (98%) entered CHEST-2. At this cut-off (March 2014), 172 (73%) patients were ongoing, 171 (72%) had received ≥2 years of treatment, and 18 (8%) had switched to the commercial drug. Riociguat was well tolerated; 5% of patients withdrew due to adverse events (AEs). There were 7 (3%) drug-related SAEs of syncope. All SAEs reported were within the range of the known safety profile for riociguat. At 2 years, mean±SD 6MWD had increased from CHEST-1 baseline by +50±68 m (n=162) and WHO FC improved/stabilized/worsened in 39/58/3% (n=170). The 2-year survival and clinical worsening-free survival rates were 93% and 82%, respectively. 6MWD and NT-proBNP at baseline and follow-up correlated significantly with long-term survival. WHO FC showed no significant association with survival, but did correlate with clinical worsening-free survival.

**Conclusions:** Riociguat has a good long-term safety profile and is the first therapy to show sustained clinical effect in patients with CTEPH. The correlation of 6MWD and NT-proBNP with long-term survival emphasizes the prognostic value of 6MWD and NT-proBNP for patients with CTEPH.
Riociguat for the Treatment of Pulmonary Arterial Hypertension (PAH): 2-year Results from the PATENT-2 Long-Term Extension

Fritsch A1, Ghofrani HA2, Grimminger F3, Grünig E4, Huang Y4, Humbert M5, Jansa P6, Jing Z7, Kilpatrick D8, Langleben D9, Menezes F10, Nikkho S1, Rosenkranz S11, Torres F12

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Purpose: Analyses from the long-term PATENT-2 extension study and analyses of correlation between efficacy endpoints and long-term outcomes.

Background: PAH is a chronic condition with a poor prognosis that is characterized by increased pulmonary vascular resistance. Riociguat, a soluble guanylate cyclase stimulator, is the first member of this novel class of PAH therapies. In the 12-week PATENT-1 study, riociguat significantly improved 6-minute walking distance (6MWD), and other secondary endpoints in patients with PAH. We present analyses from the long-term PATENT-2 extension study and analyses of correlation between efficacy endpoints and long-term outcomes.

Methods: PAH patients who were treatment-naïve or pretreated with endothelin receptor antagonists or prostanoids entered PATENT-2 after completing PATENT-1 without ongoing riociguat-related serious adverse events (SAEs). All patients received riociguat individually adjusted up to 2.5 mg three times daily. Primary endpoints were safety and tolerability; secondary endpoints included 6MWD, World Health Organization functional class (WHO FC), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), survival, and clinical worsening-free survival. Correlation between efficacy parameters and long-term outcomes was assessed using Kaplan–Meier analyses and a Cox proportional-hazards regression model.

Results: Of 405 patients completing PATENT-1, 396 (98%) entered PATENT-2. At this cut-off (March 2014), 275 (69%) patients were ongoing, 307 (78%) had received ≥2 years of treatment, and 13 (3%) had switched to the commercial drug. At 2 years of PATENT-2, 258/307 (84%) patients were receiving the maximum riociguat dose of 2.5 mg tid, 31/307 (10%) were receiving 2 mg tid, 12/307 (4%) were receiving 1.5 mg tid, 3/307 (1%) were receiving 1 mg tid, and 3/307 (1%) were receiving 0.5 mg tid. Riociguat was well tolerated; 10% of patients withdrew due to adverse events (AEs). There were 13 (3%) drug-related SAEs of syncope and 4 (1%) drug-related SAEs of pulmonary bleeding. All SAEs reported were within the range of the known safety profile for riociguat. At 2 years, mean±SD 6MWD increased from PATENT-1 baseline by +47±85 m (n=296) and WHO FC improved/stabilized/worsened in 33/58/9% of patients (n=306). At 2 years, survival was 93% and 17% of former therapy-naïve patients were receiving additional PAH therapy. Measurements of 6MWD, WHO FC, and NT-proBNP at baseline and after 12 weeks of treatment with riociguat correlated significantly with long-term survival and clinical worsening-free survival.

Conclusions: Riociguat has a good long-term safety profile and shows sustained clinical effect for up to 2 years in PAH patients. The correlation of 6MWD, WHO FC, and NT-proBNP with long-term survival and clinical worsening-free survival emphasizes the prognostic value of 6MWD, WHO FC, and NT-proBNP for patients with PAH.
**OPsumit® USers Registry (OPUS): Insights into the Safety and Tolerability of Opsumit®**

**Kim NH¹, Chin K², Muros-Le Rouzic E³, Brand M³, Selej M³, Channick RN⁴, McLaughlin VV⁵**

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**Purpose:** To evaluate the safety profile, clinical characteristics and outcomes of patients newly treated with macitentan (Opsumit®) at one year of follow-up.

**Background:** Macitentan is an oral, dual endothelin receptor antagonist (ERA) approved in the US to delay disease progression and reduce hospitalizations in patients with pulmonary arterial hypertension (PAH). The OPsumit® USers registry (OPUS) evaluates the safety profile, including potential hepatic risks, of macitentan in the real-world post-marketing setting and further characterizes its use in routine clinical practice. The registry is a FDA post marketing requirement for macitentan 10 mg tablets (NCT02126943).

**Methods:** OPUS is a long-term, prospective, multicenter, observational drug registry of patients newly-treated with macitentan (≤30 days of enrollment) in the US. Data collected at enrollment or during observation include: demographics, clinical characteristics and outcomes, adverse events (AEs) and hepatic AEs (HAEs), macitentan treatment, and registry discontinuation. All assessments are performed per routine clinical practice at each study center and at intervals determined by the treating physician.

**Results:** By April 17, 2015, one year after initiation of OPUS, 274 patients were enrolled in the registry of which 200 patients have follow-up information available. Of the 200 patients, 167 (83.5%) are still in the study; 19 (9.5%) patients discontinued macitentan, 6 (3%) died, and 8 (4%) discontinued the OPUS registry for other reasons. The median (Q1, Q3) exposure of macitentan was 3 (1, 7) months with a maximum of 13 months; all patients received the approved 10 mg macitentan dose. Thirty-nine (19.5%) patients were previously treated with a different ERA which was stopped ≤30 days prior to macitentan initiation (87% bosentan, 13% ambrisentan). The majority of patients were reported to have switched for the reason “further improvement expected”. Of the 19 patients who discontinued macitentan; 12 did so due to an AE, 2 due to other reasons, and no reason was provided for 5 patients. Overall, 6 (3%) patients had at least one HAE including 4 patients with an abnormality in liver function tests. All HAE were assessed as unrelated to macitentan, and none led to discontinuation of macitentan.

**Conclusions:** One year into this ongoing OPUS registry, 274 newly macitentan-treated patients have been enrolled, providing follow-up data for 200 patients. The safety profile observed so far is consistent with previously published data.
Individualized Dosing of Selexipag Based on Tolerability in the GRIPHON Study Shows Consistent Efficacy and Safety in Patients with Pulmonary Arterial Hypertension (PAH)

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8Hannover Medical School, Germany
9Medical University of Vienna, Austria
10University of California, San Diego
11Hôpital Universitaire de Bicêtre, France
12Cedars-Sinai Medical Center

Purpose: To further examine GRIPHON study data according to selexipag dose.

Background: Selexipag is an oral, selective IP receptor agonist targeting the prostacyclin pathway. In the randomized, controlled, event-driven GRIPHON study in patients with PAH, selexipag, when titrated to an individualized highest tolerated dose, reduced the risk of a morbidity/mortality event (primary endpoint) up to the end of treatment by 40% vs placebo (PBO); hazard ratio (HR) 0.60; 99%CI: 0.46–0.78; log-rank p<0.0001.

Methods: Patients (18–75 years) were randomized 1:1 to selexipag or PBO. Study drug was titrated weekly, in 200 mcg b.i.d. increments, to an individualized highest tolerated dose (maximum 1600 mcg b.i.d.). The individualized maintenance dose (IMD) was defined as the dose to which each patient was exposed for the longest duration. Based on their IMD, patients were assigned to pre-specified dose groups; low (200, 400 mcg b.i.d.), medium (600, 800, 1000 mcg b.i.d.) or high (1200, 1400, 1600 mcg b.i.d.). HRs for the effect of selexipag vs PBO on the primary endpoint were calculated using Cox regression models.

Results: In total, 1156 patients were randomized to selexipag (n=574) or PBO (n=582). Of those randomized to selexipag, 133 (23%), 180 (31%) and 246 (43%) were in the low-, medium- and high-dose groups, respectively. The effect of selexipag on the primary endpoint was consistent across dose groups; HR (95%CI; log-rank p-value) vs overall PBO was 0.60 (0.41–0.88; p=0.0038), 0.53 (0.38–0.72; p<0.0001) and 0.64 (0.49–0.82; p=0.0002) in the low-, medium- and high-dose groups, respectively. Median treatment duration, weeks (range), was 52 (1–217), 71 (3–183) and 79 (7–200) in the respective low-, medium- and high-dose groups, and 64 (1–192) in overall PBO. The IMD did not appear to be influenced by baseline characteristics including background PAH therapy, functional class or body mass index. The most frequent adverse events observed with selexipag in all IMD dose groups were headache, diarrhea, nausea and jaw pain.

Conclusions: Patients’ baseline characteristics did not appear to influence the highest tolerated dose of selexipag. The approach to individually titrate selexipag based on tolerability resulted in consistent efficacy and safety in patients with PAH.
An Open-Label, Uncontrolled Study of the Safety and Efficacy of Ambrisentan in Patients with Exercise Induced Pulmonary Arterial Hypertension (EiPAH)

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Background: A growing body of evidence suggests that EiPAH (mPAP>30mmHg at peak exercise, PVRmax>80dynes-sec-cm-5, and PCWPmax<20mmHg in the absence of resting pulmonary hypertension) may represent an early form of PAH. Identifying the disease at an early, potentially more responsive phase, and initiating treatment may improve functional status and prevent progression to severe forms of PAH.

Methods: Single-center, open-label 6-month study to evaluate the effect of ambrisentan on exercise capacity utilizing invasive cardiopulmonary exercise testing (iCPET) in EiPAH. Patients recruited after having a clinically indicated iCPET for evaluation of unexplained exertional dyspnea. After 6 months of treatment, patients repeated iCPET; exercise capacity, symptoms, and hemodynamics were assessed. We compared change from baseline in peak exercise values of mPAP, PCWP, transpulmonary gradient (TPG), PVR, CO, Ca-VO2, and VO2; in addition, categorical improvements of WHO Functional Class were evaluated.

Results: 22 patients (age 58.6±2.1 years) completed the 6-month treatment phase and undergone repeat iCPET. Baseline peak hemodynamics were mPAP=38.0±1.4mmHg, PCWP=12.9±0.9mmHg, TPG=24.4±1.5mmHg, PVR=182.2±15.4dynes-sec-cm-5, CO=10.9±0.8L/min, Ca-VO2=12.8±0.6mL/dL, and VO2=1429.8±117.3mL/min. After 6 months of treatment there was a significant decline in peak mPAP (-5.2±1.2mmHg, p=0.001), TPG (-7.1±1.7mmHg, p=0.001), PVR (-71.8±12.7dynes-sec-cm-5, p=0.0002), and Ca-VO2 (-1.8±0.5mL/dL, p=0.0002), with significant increases in peak PCWP (+2.9±1.2mmHg, p=0.02), CO (+2.3±0.3L/min, p=0.0001), and VO2 (+82.6±35.9mL/min, p=0.04). In addition, there was a significant decrease in WHO Functional Class, from 2±0.1 at baseline, to 1.5±0.1 after 24 weeks of treatment (p=0.002).

Conclusions: Patients with EiPAH provide a unique window into the pathogenesis of PAH, as they represent an early phase of disease with an abnormal vascular response to exercise. Our findings suggest that treatment of EiPAH with ambrisentan results in improved hemodynamics and functional status over a 6-month period. Treatment of EiPAH may prevent the progression of vascular remodeling and development of established PAH. Further study of EiPAH treatment is warranted, especially with regards to functional capacity, disease progression, and quality of life.
Baseline Demographics of the Prospective, Multicenter, Single-Arm, Open-Label, Phase IV MOTION Study of Riociguat in Pulmonary Arterial Hypertension

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Purpose: The MOTION study is designed to explore patient-reported outcomes (PROs) in pulmonary arterial hypertension (PAH) patients treated with riociguat.

Background: Pulmonary arterial hypertension is a progressive and fatal disease that affects people of all ages and genders. It has a debilitating impact on exercise capacity and health-related quality of life (HRQoL). Patients experience dyspnea, fatigue, peripheral edema, cyanosis, chest pain, and heart palpitations. Treatment studies typically aim to improve functional capacity—measured by treatment-related change in the six-minute walk test (6MWT)—and prevent progression of disease. No trials have evaluated treatment-related change in patient-reported outcomes (PROs) such as HRQoL.

Methods: MOTION is a prospective, multicenter, single-arm, open-label, phase IV, 24-week trial designed to assess whether riociguat monotherapy will result in improved PROs among treatment-naïve PAH patients. Patients will receive riociguat over a 10-week titration phase, increased q2wk at 0.5-mg increments up to 2.5 mg TID max. The primary endpoint is change from baseline (BL) in the Living with Pulmonary Hypertension (LPH) questionnaire after 24 weeks of treatment. Secondary variables include change from BL to week 16 in the LPH, change from BL at weeks 16 and 24 in the Work Limitation Questionnaire-8 (WLQ-8), the SF-12, WHO FC, Borg Dyspnea Index, and 6MWD. Accelerometer activity will be recorded at screening, BL, and weeks 16 and 24. Higher LPH and WLQ-8 scores indicate worse HRQoL.

Results: Study recruitment began in September 2014 and is ongoing. As of November 2015, 82 patients had been screened (18 failed screening, 22 completed study). Here we report baseline data (mean ±SD) for enrolled patients (N=61). The population was predominantly female (87%, n=53) and non-hispanic/latino (79%, n=48) with mean/median age of 61 and 63 years, respectively. Total LPH score was 46.3±24.4 (n=59) and the majority of patients were WHO FC III (WHO FC I/II/III/IV; 11.5%/27.9%/59.0%/0.2%, respectively), the mean 6MWD was 313±92 m (N=61). Supplemental oxygen was needed in 20 subjects during 6MWT; use ranged from 2–10 L. WLQ-8 time management, and physical, interpersonal, and output tasks scores were 4+1.5, 3+1.5, 4+1, and 4+2, respectively. Completer data is expected by time of presentation.

Conclusions: The MOTION trial will provide information on the effect of riociguat on PROs in PAH patients in the United States who are not currently on active treatment through the use of disease-specific and generic HRQoL measures.
A Study of Referral Patterns of Pulmonary Arterial Hypertension Patients

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Purpose: To determine the referral pattern of our PAH patients at time of first evaluation at our center in association with disease severity.

Background: Pulmonary arterial hypertension (PAH) is a rare and devastating disease that is characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance which eventually leads to right ventricular failure and death. The most common presenting symptoms of PAH is dyspnea. In general dyspnea in community setting is initially managed by primary care providers (PCPs). PAH is considered when common causes of dyspnea are ruled out by the PCP and in turn patients are referred to a specialist center.

Methods: All PAH patients WHO Group I with a mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure (PCWP) < 15 mmHg (confirmed via right heart catheterization) at our center from were considered for the study. Demographics, WHO Functional Class (WHO FC), and referring physician data were obtained from retrospective chart review. Referring physician specialty was obtained from retrospective chart review. Referring physician category was broken down into Primary Care Physicians and Specialists (i.e Pulmonologists, Cardiologists, Rheumatologists, Infectious Disease, and Nephrology). IRB approval was obtained for this study.

Results: There were a total of 116 PAH patients (Male n=32 (27.6%), Female n=84 (72.4%). Of these patients 70 (60.3%) were referred by a specialist experienced with managing PAH and 46 (39.7%) by primary care physicians. Of the patients referred by specialist physicians, 27 (38.6%) were WHO FC I/II at presentation, 43 (61.4.4%) were functional class III/IV. As for those referred by PCPs/Others 11 (23.9%) were functional class I/II, 35 (76.1%) were functional class III/IV. Of the referring physicians 46 (39.7%) were pulmonologists, 42 (36.2%) were primary care physicians, 17 (14.7%) were cardiologists, 7 (6.0%) were rheumatologists 3 (2.6%) other specialists and 1 (0.9%) infectious disease specialist.

Conclusions: Our results indicate that approximately one third of our patients are being referred by primary care providers. This seems to be a suggestion that patients referred by PCPs a greater number were presenting to us at a later disease state. As the number primary care providers increases (not only physicians but nurse practitioners and physician assistants) this argues for further education for providers in the primary care setting for dyspnea with an unknown origin with a special emphasis on diagnosis of pulmonary hypertension.
Initial Combination Therapy with Ambrisentan (AMB) and Tadalafil (TAD) in Treatment Naïve Patients with Pulmonary Arterial Hypertension (PAH): Efficacy and Safety in the AMBITION Study Intent to Treat (ITT) Population


Gilead Sciences, Inc.

Introduction: AMBITION was an event driven trial investigating efficacy and safety of initial combination (COMB) therapy compared with monotherapy in a heterogeneous PAH patient population.

Aims and objectives: We present the results from the entire study population (ITT).

Methods: 605 patients were randomized to COMB (n=302), AMB (n=152) or TAD (n=151) monotherapy. Patients were categorized into two populations based on revised eligibility criteria in a protocol amendment; those that met revised criteria (Primary Analysis Set=PAS, n=500), and those that did not mainly due to the presence of cardiovascular comorbidities (Ex-PAS, n=105). The primary endpoint was time to clinical failure (TTCF; all-cause death, hospitalization for worsening PAH, disease progression and unsatisfactory long term clinical response). Secondary endpoints at Week 24 included NT-proBNP, % achieving satisfactory clinical response, 6MWD, WHO FC, and Borg Score.

Results: The TTCF was significantly reduced with COMB vs. pooled monotherapy (HR 0.532, 95% CI: 0.385, 0.733; p<0.0001) and vs. each monotherapy (AMB, p=0.0002; TAD, p=0.0023). A reduction in PAH hospitalizations drove the treatment effect. The primary outcome in the Ex-PAS population showed a similar trend. Results for secondary endpoints will be presented. Peripheral oedema, headache, nasal congestion, and anaemia were more common in COMB than either monotherapy.

Conclusion: Initial combination therapy (AMB + TAD) significantly reduced the risk of a clinical failure event compared with monotherapy in the AMBITION ITT population.
PHA Resources for Medical Professionals

PHA Medical Membership Networks

**PH Clinicians and Researchers (PHCR)** – PHA’s medical membership network for PH-treating physicians and PhD-level researchers interested in pulmonary hypertension.
www.PHAssociation.org/PHCR

**PH Professional Network (PHPN)** – PHA’s medical membership network for nurses, nurse practitioners, physician assistants, pharmacists, respiratory therapists, social workers and other healthcare professionals who care for PH patients.
www.PHAssociation.org/PHPN

PHA Medical Education Fund Programs for Medical Professionals

**PHA Preceptorship Program** – This program facilitates direct CME education and training of medical professionals. Led by experienced pulmonary hypertension specialists at nationally recognized PAH centers, this day-long, comprehensive program instructs front-line clinicians in the highest quality of care for PAH patients.
www.PHAssociation.org/Preceptorship

**PHA Medical Education On-Demand Program** – This program allows medical professionals to design a CME program that meets the PH educational needs for their local medical community. The medical professional requesting the program chooses the topic, speaker, format and date, and PHA takes care of the rest.
www.PHAssociation.org/OnDemand

**PHA Online University** – A comprehensive online platform for PH education for medical professionals, **PHA Online University** meets the needs of healthcare professionals at all levels in their careers and studies. **PHA Online University** includes resources, CME/CE-accredited content and networking opportunities for healthcare professionals.
www.PHANOlineUniv.org

PHA Medical Meetings

**PHA’s International PH Conference and Scientific Sessions** – This biennial conference is the largest gathering of PH patients, family members and medical professionals in the world featuring educational opportunities and networking.
www.PHAssociation.org/Conference

**PH Professional Network Symposium** – The only program of its kind, this symposium brings together pulmonary hypertension non-physician clinicians from across the globe to discuss the latest advances and research in PH.
www.PHAssociation.org/Symposium

**Building Medical Education in PH (BME) Program** – This program, an exclusive benefit for members of PHCR and PHPN, and their affiliate PH centers, creates partnerships between PHA and PH programs across the country to provide continuing education in the medical community.
www.PHAssociation.org/BME

PHA’s Research Program

**PHA’s Research Program** This program provides grants to promising researchers in the field of pulmonary hypertension. The program fosters new leaders in the field by supporting their interest in PH research and providing them with opportunities to work with mentors and learn new skills.
www.PHAssociation.org/Research

PH Care Centers (PHCC)

**PHCC** – The purpose of the PHA-Accredited Pulmonary Hypertension Care Centers (PHCC) initiative is to establish a program of accredited centers with expertise in pulmonary hypertension that aspires to improve overall quality of care and ultimately improve outcomes of patients with pulmonary hypertension, particularly pulmonary arterial hypertension, a rare and life-threatening group of diseases. The PHCC website can help patients locate accredited centers in their area.
www.PHCCareCenters.org/Patients/AccreditedCenters
**PHA Registry (PHAR)**

**PHAR** – One of the requirements of being accredited as a PHCC is to enroll PH patients into the Pulmonary Hypertension Association Registry (PHAR). PHAR collects data from WHO Group I PH (pulmonary arterial hypertension [PAH]) and WHO Group IV PH (chronic thromboembolic pulmonary hypertension [CTEPH]) who are starting evaluation and/or treatment at a PHCC. Over time, PHAR will help researchers evaluate trends and practice patterns to determine which treatments work best. Also, doctors and nurses will learn what treatments other clinicians are using that could potentially benefit their patients.

www.PHAssociation.org/PHAR

**For Your Patients**

**Envelope of Hope** – This free, patient-friendly packet includes an overview of pulmonary hypertension and a snapshot of everything that PHA has to offer. Order referral postcards for your office or request packets for patients and caregivers.

www.PHAssociation.org/EnvelopeOfHope

**Pulmonary Hypertension: A Patient’s Survival Guide** – PHA’s comprehensive guidebook for patients and caregivers features candid information about the latest treatments, patient care, lifestyle issues and much more.

www.PHAssociation.org/SurvivalGuide

**Empowered Patient Online Toolkit** – Templates, checklists and tips to help patients manage their healthcare.

www.PHAssociation.org/OnlineToolkit

**PHA Classroom** – This online education tool is a resource for patients and families to learn about diagnosis of PH, treatments on the horizon and other popular topics through live online events and recordings.

www.PHAssociation.org/Classroom

**PHA on the Road: PH Patients and Families Education Forum** – This is a free, day-long educational forum that seeks to provide education and support to patients and their family members across the country living with pulmonary hypertension. This patient-focused program offers interactive presentations, educational sessions and networking opportunities for patients, caregivers and PH medical experts in the region.

www.PHAssociation.org/OnTheRoad

**Patient-to-Patient Support Line: 800-748-7274** – This toll-free line is answered by friendly volunteer patients who are there for anyone who needs someone to talk to about PH. Local, online and telephone support groups offer hope to PH patients and families. Use PHA’s website to help your patients locate a local group or refer patients to PHA’s online communities and telephone support groups.

www.PHAssociation.org/Community
Research Grant Award Recipients

Barst Fund Award Winners

2015
David Brian Frank, MD, PhD
“Wnt Signaling Progenitor Cells in Late Lung Development, Regeneration, and Repair”
The Matthew and Michael Wojciechowski Pediatric PH Research & Mentoring Grant
December 1, 2015 – November 30, 2016
Instructor/T32 Grant Trainee, Cardiology
The Children’s Hospital of Philadelphia, University of Pennsylvania

Vitaly Oleg Kheyfets, PhD
“The Cause and Effect of Decreased Wall Shear Stress in Pediatric Pulmonary Arterial Hypertension”
Cordelia’s Pediatric PH Research and Mentoring Grant
December 1, 2015 – November 30, 2016
Assistant Research Professor, Medicine
University of Colorado Denver | Anschutz Medical Campus

Kara Nicole Goss, MD
“Right Ventricular-Pulmonary Vascular Interactions Following Postnatal Hyperoxia Exposure”
The Joel Belt Pediatric PH Research and Mentoring Grant
December 1, 2015 – November 30, 2016
Assistant Professor, Pulmonary and Critical Care
University of Wisconsin

2014
Rebecca Johnson Kameny, MD
“Right Ventricular Performance in Pediatric Pulmonary Hypertension and Congenital Heart Disease”
Cordelia’s Pediatric PH Research and Mentoring Grant
December 1, 2014 – November 30, 2015
University of California, San Francisco

PHA Proof of Concept Award

2015
Ke Yuan, PhD
“The Role of Lung Pericytes as a Source of Occluding Pulmonary Artery Smooth Muscle Cells in PAH”
December 1, 2015 – November 30, 2016
Instructor, Pulmonary Critical Care Medicine
Stanford University

Soban Umar, MD, PhD
“Y Chromosome Confers Protection Against Pulmonary Arterial Hypertension”
The Jerry Wojciechowski PH Proof of Concept Grant
December 1, 2015 – November 30, 2016
Resident Physician, Molecular Medicine
University of California Los Angeles

Frances S. de Man, PhD
“A New Tool to Obtain Novel Insights in PAH-Induced Right Heart Failure”
The Jerry Wojciechowski Pulmonary Hypertension Proof of Concept Grant
December 1, 2014 – November 30, 2015
VU University Medical Center Amsterdam

Fiona Murray, PhD
“A Novel G-Protein Coupled Receptor (GPCR) Target in Pulmonary Arterial Hypertension”
American Thoracic Society Foundation/Pulmonary Hypertension Association Proof of Concept Research Grant
University of Aberdeen, UK

Marc de Perrot, MD, MSc
“Photodynamic Therapy for the Treatment of Pulmonary Arterial Hypertension”
December 1, 2014 – November 30, 2015
University of Toronto, Canada

2014
Daniel L. Fox, MD
“SSc-PAH Risk Score: Early Identification of Scleroderma-associated PAH by RV Strain, GDF-15 & IL&”
December 1, 2014 – November 30, 2015
University of Colorado Denver
ATS/PHA RESEARCH FELLOWSHIP IN PULMONARY ARTERIAL HYPERTENSION

2015
William M. Oldham, MD, PhD
“Metabolic Flux Analysis in Pulmonary Arterial Hypertension”
December 1, 2015 – November 30, 2017
Associate Physician, Pulmonary and Critical Care
Brigham and Women’s Hospital

2014
Ankit A. Desai, MD
“Enhanced Risk Profiles of Sickle Cell-Related Pulmonary Hypertension – Integrating Genomics & Imaging”
American Thoracic Society Foundation/Pulmonary Hypertension Association Research Fellowship
University of Arizona

PHA/NHLBI K08/K23 Award Winners

2015
Laura Mercer-Rosa, MD, MSCE
“Right Ventricular Remodeling and Outcome in Tetralogy of Fallot”
September 1, 2015 – November 30, 2019
Assistant Professor, Cardiology
The Children’s Hospital of Philadelphia

2014
Tien Peng, MD
“The Role of Hedgehog Signaling in Pulmonary Arterial Hypertension”
July 1, 2014 – June 30, 2019
Postdoctoral Fellow, Pulmonary Care Division
Hospital of the University of Pennsylvania

2013
Bradley A. Maron, MD
“Aldosterone Impairs Endothelin B-Dependent Synthesis of Nitric Oxide to Promote Pulmonary Arterial Hypertension”
July 1, 2013 – June 30, 2018
Division of Cardiovascular Medicine
Department of Medicine
Brigham & Women’s Hospital

2012
Vinicio A. de Jesus Perez, MD
“The Role of the Wnt/Planar Cell Polarity Pathway in Pulmonary Angiogenesis”
Oracle Corporation Community Grant
July 1, 2012 – June 30, 2017
Division of Pulmonary and Critical Care Medicine
Department of Medicine
Stanford University Medical Center

2011
Edda Spiekerkoetter, MD
“Modulating BMPRII Signaling in Pulmonary Arterial Hypertension”
September 1, 2011 – August 31, 2016
Division of Pulmonary and Critical Care Medicine
Department of Medicine
Stanford University Medical Center
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Notes:
The Pulmonary Hypertension Association would like to thank ACTELION for sponsoring the 2016 International PH Conference Program Book.
Centers of Comprehensive Care (CCC) are required to participate in the PHA Registry (PHAR). For more information, visit www.PHAssociation.org/PHAR.

Regional Clinical Program (RCP) online application opening in Summer 2016

www.PHCareCenters.org