The Journal
PVRI Chronicle (ISSN number forthcoming) is a non-peer reviewed journal published on behalf of the Pulmonary Vascular Research Institute. The journal publishes articles, reviews, and commentaries on the subject of pulmonary vascular diseases and actions within the PVRI. The journal is published biannually online and is available in print on request.

Information for Authors
There are no page charges for submission to the journal. All manuscripts are solicited by the Editorial Board, but submissions may also be made to Executive Editor Nikki Krol at nkrol@pvri.info or to Editor in Chief Dr. Sachindra Joshi at sachindraraj_joshi@nymc.edu

Subscription Information
Copies are provided to Fellows and members of the PVRI free of charge. PVRI members and Fellows must notify Executive Editor Nikki Krol of a change in their address in order to continue to receive the journal. She can be contacted at nkrol@pvri.info. PVRI Chronicle is published and distributed by the Pulmonary Vascular Research Institute. Requested print copies are sent to subscribers directly from the publisher's address. It is illegal to acquire copies from any other source. If a copy is received for personal use as a member of the association/society, one cannot resale or give away the copy for commercial or library use.

Advertising Policies
PVRI Chronicle accepts display and classified advertising. Frequency discounts and special positions are available. Inquiries about advertising should be sent to Nikki Krol at nkrol@pvri.info.
PVRI Chronicle reserves the right to reject any advertisement considered unsuitable according to the set policies of the journal. The appearance of advertising or product information in the various sections of the journal does not constitute an endorsement or approval of the journal and/or its publisher of the quality or value of said product or of claims made by its manufacturer.

Copyright
The entire contents of the PVRI Chronicle are protected under international copyrights. PVRI Chronicle, however, grants to all users a free, irrevocable, worldwide, perpetual right of access to, and a license to copy, use, distribute, perform and display the work publicly and to make and distribute derivative works in any digital medium for any reasonable non-commercial purpose, subject to proper attribution of authorship and ownership of the rights. The journal also grants the right to make small numbers of printed copies for their personal non-commerical use.

Permissions
To request permission to reproduce articles/information from this journal, please contact Miss. Krol at nkrol@pvri.info or adminpvri@gmail.com.

Disclaimer
The information and opinions presented in the Journal reflect the views of the authors and not of the Journal and its Editorial Board or the Publisher. Publication does not constitute endorsement by the Journal. Neither the PVRI Chronicle nor its publishers nor anyone else involved in the preparation or the material contained in the PVRI Chronicle represents or warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from such material. Readers are encouraged to confirm the information contained herein with other sources.

Addresses
Editorial Office
Miss. N. Krol
Pulmonary Vascular Research Institute
Enterprise and Innovation Hub
Giles Lane, Canterbury,
CT2 7NJ Canterbury, Kent
United Kingdom
nkrol@pvri.info

Published By
Editorial Office
PVRI Chronicle
Pulmonary Vascular Research Institute
Enterprise and Innovation Hub
Giles Lane, Canterbury,
CT2 7NJ Canterbury, Kent
United Kingdom
# Table of Contents

**PVRI CHRONICLE**  Volume 1, Issue 2  
**July - December 2014**

## 1 Editorial

**Looking Through the Heart of Pulmonary Vascular Disease**  
**Sachindra Raj Joshi**  
1

## 2 Guest Editorial

**PVRI and the PVRI Young Council: The Heart of the Matter**  
**Stephanie Barwick**  
3

## 3 PVRI News and Activities

8th PVRI AGM and 7th Scientific Workshops and Debates, Bad Nauheim, Germany  
**Nikki Krol, Ewa Kolosionek**  
4

7th Joint Saudi Association for Pulmonary Hypertension/PVRI Conference in Muscat, Oman  
**Nikki Krol**  
13

**Djuro Kosanovic**  
17

**Medicine and Technology**

Introducing: the first dedicated protanoid calculator app for mobile devices  
**Ben Fox, Chanan Vinitski**  
18

**Interview**

A perspective from clinician and researcher: An interview with Prof. Ardeschir Ghofrani FPVRI  
**Michael Seimetz, Nikki Krol**  
19

## 4 Journal Club

**Interactive Discussion**

Molecular links between pulmonary hypertension and obesity: what else except adiponectin?  
**Balram Neupane, Akylbek Sydykov, Michael Seimetz, Srikanth Karnati, Eveline Baumgart-Vogt, Norbert Weissmann, Ralph Theo Schermuly, Djuro Kosanovic**  
27

PPARγ regulation is cell type dependent: Can it reverse the COPD?  
**Srikanth Karnati, Djuro Kosanovic, Ralph Theo Schermuly, Norbert Weissmann, Eveline Baumgart-Vogt, Michael Seimetz**  
31

Exercise in pulmonary diseases – good or bad? An inflammatory point of view  
**Karsten Krüger, Djuro Kosanovic, Ralph Theo Schermuly, Frank-Christoph Mooren, Norbert Weissmann, Michael Seimetz**  
36
It is with very great sadness that we inform you of the death of Dame Professor Julia Polak, DBE. She passed away Monday 11th August. She was a member of the PVRI Board of Directors and a very valued contributor in the field of pathology and tissue engineering. She will be greatly missed.

"Who knows what will happen in five or ten years. There are lots of hurdles to overcome [but] creating an atmosphere of really multidisciplinary teams including everybody, including patients, to work together with companies and science: it needs work but it’s happening."

- Dame Professor Julia Polak, DBE
“Sometimes the heart sees what is invisible to the eye” - as said by H. Jackson Brown, Jr., an American author best known for his inspirational book Life’s Little Instruction Book. In the context of pulmonary vascular diseases (PVDs) and the treatment thereof, I believe our heart can see changes in our physiology that are invisible to the eye.

Heart and lungs are intricately interrelated. Subtle change in the pulmonary circulation is detected by the patient’s heart in the pulmonary vascular disease pulmonary arterial hypertension (PAH). Increasing pulmonary arterial resistance and progressing pulmonary arteriopathy is sensed by the heart. As the resistance in pulmonary arteries increases due to progressing arteriopathy, the right ventricle is exposed to pressure overload. The right heart adapts to the increased pressure overload by right ventricular dilatation, followed by right ventricular hypertrophy. As a biomedical scientist working in pulmonary hypertension (PH) research, I have witnessed the heart of a mammal adapting to deteriorating lung pathology and increasing resistance to blood flow in the lungs by undergoing anatomical as well as molecular remodeling. Most interestingly, in pulmonary hypertension patients who have undergone a successful lung transplant, the hypertrophied heart reverts back to its original state as a normal heart. This remarkable plasticity of the heart tells us that heart can see what is at first invisible to the eyes.

In essence, despite the progressive deterioration of the lung vasculature, the heart fights until the very end to keep the patient alive. Similarly, the heart of a family audaciously adapts to the changes made to their day to day activities. For a family, pulmonary hypertension is a life-changing experience that brings many difficult challenges and changes. The emotional toll of PH is significant, and when a loved one is diagnosed with the disease, the heart of the family undergoes a lot of emotional transition, be it as a parent, a partner, a child or a friend. Apart from adapting to ever changing daily routines, the ‘family heart’ is increasingly dedicated to helping in any way, including participation in pulmonary hypertension research and awareness programs.

The heart of a clinician and a scientist is no different from a family’s heart. Clinicians work tirelessly to best manage the failing heart. They do intensive research and collaborate with various medical centers around the globe to come up with the best alternative medicine for the disease. Meanwhile, scientists are working tirelessly around the clock to solve the mystery behind the pathology of the disease and find new and alternative therapeutic targets, so that in future, pulmonary hypertension can be detected in its early stage, disease-progression may be prevented, and one day, even cured.

PVRI Chronicle embraces the hearts of patients, family, clinicians and scientists in pulmonary vascular diseases, by providing a dedicated platform for news, discussion, science and medicine from all perspectives. In PVRI Chronicle, the Pulmonary Vascular
Research Institute seizes the opportunity of bringing global expertise in the field of PVDs to find new solutions for improving the lives of patients, family, clinicians and scientists. Through dedicated sections such as PVRI news and activities, Journal Club, Art Club, Learner’s Corner and Patient’s Corner, PVRI Chronicle aims for widespread pulmonary vascular disease awareness.

In this issue, we have presented social and scientific news from the 8th PVRI AGM and 7th Scientific Workshops and Debates, Bad Nauheim, Germany in January; the PVRI American Thoracic Society 2014 Get Together, San Diego, CA in May; and the 7th joint Saudi Association for Pulmonary Hypertension/PVRI Conference in Muscat, Oman, April 2014. The perspective from a clinician and researcher is represented in an interview with Prof. Ghofrani, who speaks about his career path and offers advice and experience for the younger generation of PVD scientists. For the Journal club section, we have selected three interactive discussions covering a wide range of topics, from molecular links between pulmonary hypertension and obesity to the important question on exercise, and whether its benefits outweigh the negatives for pulmonary vascular disease patients. Likewise, in the Learner’s Corner, we present a historical perspective on entothelial glycocalyx & the revised Starling principle, a review article on pulmonary hypertension in pregnancy and its prognostic implications, and a Did You Know article on Pulmonary Hypertension & HIV. The Patient’s Corner holds a Case report on PH as a function of carcinoid heart disease, as well as two perspectives, one on exercise and pulmonary hypertension and the other on the prevalence, causes, clinical characteristics and diagnostic challenges associated with pulmonary hypertension (PH) in African and African-Americans.

Our seven pound heart puts all its effort in the fight against the increasing pressure overload due to increased pulmonary arterial resistance in pulmonary hypertension. Similarly, if each individual in our PVD community puts a little effort in communicating their science, PVD issues, news and scientific debates, these informative works collectively will help improve the heart of the pulmonary vascular disease community. Therefore, I urge you on behalf of our editorial board to send articles for the forthcoming issues of PVRI Chronicle and help in spreading pulmonary vascular disease awareness worldwide.

Dr. Sachindra Joshi FPVRI
Editor in Chief PVRI Chronicle
Department of Pharmacology
New York Medical College
Valhalla, NY, United States
Email: sachindraraj_joshi@nymc.edu
The Heart of the Matter: PVRI & the PVRI Young Council

Stephanie Barwick
Executive Director
Pulmonary Vascular Research Institute
University of Kent
Canterbury, Kent, United Kingdom

When I attended the 8th PVRI Annual General Meeting and the 7th Scientific Workshops & Debates meeting in Bad Nauheim, January 2014, I was very excited and impressed to see the beating heart of the PVRI in action. I was particularly impressed with the many young researchers and clinicians actively involved in the PVRI, and specifically, the work of the Young Council. The Council is very active within the PVRI and helps manage the Institute—a set up which is in many ways quite unusual, but also extremely good news. Most membership organisations struggle to recruit ‘new blood’ into their institutions and if they are fortunate enough to recruit new members, these often do not actively participate or take on responsibility. The PVRI is different, as all members are treated equally and benefit from the same opportunities. There is no hierarchy, nor preferential treatment due to individual status or reputation. As an organisation, this core principle underlies everything we do and it is thanks to these values that the PVRI has been successful in engaging so many of our members and young people in our work, research and activities. The PVRI is fortunate to have all of them on board and the PVRI Chronicle is a testament to the hard work and successful engagement of the Young Council and PVRI members.

I am currently writing the ‘PVRI Strategic Plan’ for the next three years which will be circulated to all our members for consultation later in the year. Support for the ‘young hearts’ (and the young at heart) is a cornerstone in our objectives. Not only do we intend to continue all the existing support, we also want to proactively work on identifying new opportunities for young researchers and clinicians, increase the budget for our travel grants and help to develop the PVRI Chronicle, which is particularly aimed at publishing research from ‘young’ researchers who are embarking on their career, into a second peer-reviewed high quality medical journal with a great reputation. For any young researcher or clinician, we believe that involvement in our Young Council will lay the foundations for an excellent career progression in the future within the scientific community.

Last, but not least, I would like to thank all our young members, in particular the editorial board of the PVRI Chronicle, for their involvement in the PVRI. Without them, our mission cannot be achieved in the future. Our young members will be the future leaders of the organisation, and even at present, they represent the heart of the PVRI as their efforts pump forth into the body of pulmonary vascular research. It is them who will be promoting pulmonary vascular disease related illnesses in the world, publishing articles in our journals and working with like-minded colleagues in many different countries around the globe on extending their knowledge and understanding of the pulmonary vascular diseases, patient needs and potential treatments. The energy and creativity of our young members will ensure further developments of the PVRI initiatives and activities and also help to establish new projects and ideas: vital for any organisation.

Corresponding author:
Stephanie Barwick
PVRI Executive Director
University of Kent
Canterbury, Kent, United Kingdom
Email: sb@pvri.info
For the 8th PVRI Annual General Meeting and 7th Scientific Workshops and Debates, the Pulmonary Vascular Research Institute joined with the ECCPS Symposium Molecular Mechanisms and Treatment of Lung Disease. Congratulations are due to the ECCPS and their administrative staff for organising such a beautiful detailed meeting in the maze located under the Dolce Bad Nauheim. Housing 25 Conference rooms, the Dolce is an impressive business hotel with a solid reputation, and PVRI members, ECCPS members, and other attendees were well-served throughout the week of meetings and socialing.

**Tuesday January 28th**
The meeting started in earnest on Tuesday January 28th, with the PVRI Pre-Symposium on Lung Vascular Compliance and Recruitment, chaired by David Badesch and Anna Hemnes. These included ‘Right heart after load at rest and exercise’, by Robert Naeije, Brussels; ‘PA stiffness and right ventricular-PA coupling’, by Rebecca Vanderpool, Pittsburgh; and ‘Detection and evaluation of the potential for lung microvascular recruitment in PAH’, by David Langleben, Montreal. Those who followed the meeting from home and afar were treated to a steady stream of images, updates, and streams of consciousness from the PVRI Twitter and Facebook social media, and each new speaker was immortalized on the web with their name and topic under the hashtag #PVRI14. Admittedly, Monday also saw some meetings, which were evidenced on the web with images from the PVRI Young Council meeting during their preparations for the week’s lecture, interview and abstract recordings, as well as the Board of Directors meeting in the afternoon.

With 460 registered attendees, PVRI far surpassed last year’s 220 delegates, which was itself a 50% increase of the year before in Cape Town. As the number of delegates continues to rise, so too does the quality of the Conference. A speaker-based meeting, the PVRI Annual Conference is gaining a reputation for its open atmosphere, high quality science, and valuable discussion. Added to that are the efforts of the Young Council, who spent the week soliciting people for lectures and interviews for publication on the PVRI Educational website. The interviews are part of a new initiative, namely the History of Pulmonary Vascular Diseases,
as told by the people who lived through and continue to be immersed in its changes, frustrations, and successes. All interested PVRI attendees were invited to sit down for a 20-30 minute interview with a member of the Young Council, to talk about their initial and current interest in PVDs, how the labs and methodologies have changed for them over the years, to identify the most essential support for their career, and their advice for young scientists entering the field today.

After the Lung Vascular Compliance session followed Anticoagulants and angioplasty in PH, which included the sessions ‘Pro and con of anticoagulants in PAH’, by Marius Hoeper from Hannover, ‘The role of novel anticoagulants in CTEPH’, by Irene Lang from Vienna, and a pro and con debate on ‘Angioplasty for CTEPH’, with Pro presented by Hiromi Matsubara from Okayama, and Con presented by Eckhard Mayer from Bad Nauheim. This was followed by the session Pulmonary Hypertension in Children, which featured the following sessions: ‘The lung vasculature in bronchopulmonary dysplasia’ by Dick Tibboel from Rotterdam; ‘PH classification in children post-Panama and Nice’ presented by Maurice Beghetti from Geneva; and ‘Current and future therapy of PH in children’ by Steven Abman from Aurora.

By the time of the Peter Raymond Memorial Lecture ‘Adaptation to high altitude living’, delivered very well by Cynthia Beall from Cleveland, the Young Council had recorded 7 interviews and 1 lecture, Pulmonary Circulation had completed a successful editorial lunch meeting, the new PVRI Women’s Health Taskforce was just finishing up their inaugural (face to face) meeting, and the new PVRI Exercise Taskforce was connecting to India and the US in a Skype meeting. This very active and productive first day had another highly important installment in the form of the Annual General Meeting, where the current PVRI Committee announced a number of significant changes in the PVRI Structure and their ways. In a nutshell, these included:

- Prof. Sheila Glennis Haworth from London, UK, was announced as the new PVRI President, taking over from Prof. Martin Wilkins.
- Prof. Ghazwan Butrous was named Treasurer of the PVRI, and presented slides on the PVRI finances for 2013.
- Miss Stephanie Barwick was revealed as the new PVRI Executive Director, as per the goals identified in the 2013 PVRI business plan. She will begin in April 2014, but was already in Giessen to meet the membership and detail her plans for the future success of the PVRI.
- Chairman of the Board Stuart Rich introduced the PVRI BOD to the membership.
- Dr. Aaron Waxman was named as the PVRI Director of Scientific Affairs, placing him in charge of the educational website and scientific agenda.
- Managing Editor for Pulmonary Circulation (PC) Miss Christina Holt presented the changes for PC in 2014, which include a new publisher, a new submission website, and an
online-only publishing policy with an option for print on demand. She also demonstrated PC’s success in the 57,000 article downloads since 2011, further strengthened by the very encouraging 375,000 page views generated during the same time.

- The newly formed Central Asia PVRI group (CA-PVRI) was introduced by Prof. Talant Sooronbaev from Kyrgyzstan, who also promoted a number of upcoming meetings in the region and encouraged interest from the membership.
- Dr. Djuro Kosanovic briefly represented the Young Council detailing the PVRI Chronicle and educational website projects, and invited PVRI Fellows and members (35 years and younger) to apply to join the growing group of active members.

The above was met with general approval, and with particular enthusiasm for the appointment of PVRI Executive Director Miss Barwick, who introduced herself with a very strong presentation. She called for more membership participation for promotion of the PVRI, reflected in twitter updates inviting PVRI-ers to answer such queries as ‘PVRI provides great advantages for members. True or false?’, ‘How can PVRI reach the general non-medical audience?’, and ‘How can PVRI effectively demonstrate its value and successes?’ Still mulling over these questions, attendees retired to the dining room for dinner at the end of the first day.

**Wednesday January 29th**

Wednesday was the start of the parallel program, which confused some attendees regarding location. Luckily, the Young Council was on hand to ensure everyone found the ‘Saal’ they were looking for, and to further offer their services for interview, lecture and abstract recordings. Wednesday also marked the first day of the poster presentations, which were well organized and ordered.

The Joint Symposium opened with sessions on Infection, inflammation and pulmonary vascular disease, chaired by Serge Adnot and Friedrich Grimminger, and included presentations from Norbert Voelkel from Richmond, Brian Graham from Denver, Marc Gladwin from Pittsburgh, and Soni Savai Pullamsetti from Bad Nauheim. After the coffee break, the program continued with Stem cells in heart and lung (re)-generation chaired by Norbert Voelkel and Thomas Braun. Ed Morrissey from Philadelphia, Hesham Sadek, Dallas, Jeffrey Whitsett, Cincinnati, and Luca Caputo from Bad Nauheim presented their ideas and findings in concordance with the theme, and each presentation was met with discussion from the attendees before retiring for lunch and the poster sessions.

Simultaneously, the smaller Spiegelsaal started the day with the PVRI Breakout Symposia sessions, which have all been recorded and are available for the PVRI membership under the ‘Learning’, and then ‘Conference Talks’ tab on the PVRI website. On Wednesday morning, these included sessions on Technology progress in cardiopulmonary disease, chaired by Thomas Braun and Ralf Brandes. Sessions included ‘Genomics, proteomics and bioinformatics’, presented by Thomas Braun from Bad Nauheim, ‘Small animal imaging’ by Ralph Schermuly, Giessen, ‘Molecular analysis and high resolution imaging’ by Ralf Brandes from Frankfurt, and...
a presentation of the best selected abstract, in this case ‘Oxygen uptake efficiency slope is a valid sub maximal measure of exercise performance in pre capillary pulmonary hypertension’, presented by Stephen Thomson from Glasgow.

After discussion, the membership had a short break with some refreshments, followed by the PVRI Breakout Symposia session Pregnancy and pulmonary hypertension. Barbara Cockrill, from Boston, presented the excellent ‘Genetics and pathophysiology of PH during pregnancy’, after which Zeenat Safdar from Houston presented ‘Management of PH in pregnancy in PH centers’. Riyadh-based Manal Al Hazmi’s ‘Management of PH in pregnancy in the developing world’ concluded the session, as Mamotabo Matshela, who had been selected for Best Abstract presentation, was unfortunately not able to attend.

After lunch and the first poster session, the theme of pregnancy and pulmonary hypertension was further explored in a PVRI Taskforce meeting of the newly formed ‘Women’s Health Taskforce’, which met in room ‘Bad Homburg’ to discuss their forthcoming consensus document. Simultaneously, the PVRI Pediatric Taskforce and the PVRI Chronic Heart Disease Taskforce met and promptly froze in room ‘Parksaal’, until they were moved into one of the recording rooms with working heating. All taskforces reported productive and efficient meetings, and enthusiastic follow up plans.

The PVRI Chronicle meeting, initially meant to take place during lunchtime, had to reschedule to the evening as a number of its members were involved in the poster presentations. Sadly the evening meeting was necessarily short as Giessen-based members needed to catch the last train home, but in a nutshell, the committee was congratulated on their hard work for the first issue of PVRI Chronicle, and asked to encourage submissions from their colleagues and fellows for the next issue. Overall, the committee felt positive about the content and format of the Journal, but agreed that more frequent Skype meetings should be undertaken (at least six a year).
The afternoon continued at 15:00 with the Joint Symposium main program session Genetics and personalised medicine in cardiopulmonary diseases, chaired by John Newman and Ralph Schermuly, and featuring presentations by Jim Loyd from Nashville, Heribert Schunkert from Munchen, Marlene Rabinovitch from Stanford and Florent Soubrier from Paris. After his impressive talk, the Young Council approached Jim Loyd for a lecture recording, which he graciously agreed to, along with Richard Trembath from the UK. His and Dr. Trembath’s lecture recordings can be found in the PVRI website at ‘Learning’, and ‘Lectures’. Users can search by name once in the ‘Lectures’ section.

The PVRI Breakout Symposia began the afternoon with Post-IMPRESS, what is the future of TKI in PH Therapy?, chaired by Mark Gladwin and Werner Seeger. Ardeschir Ghofrani (Giessen) presented ‘The historical background’, followed by ‘The FDA’s view’ by Stuart Rich (Chicago) and ‘The EMA’s view’ by Amany Elgazayerly. Rounding the session off was Newcastle-based Paul Corris’ ‘A clinician’s view.’ Discussion, which will be transcribed for interested parties, was followed by Pulmonary Hypertension in chronic lung disease in the Breakout symposia, chaired by Joan A. Barbera and Andreas Guenther, whilst the Main Program focused on Left and right heart hypertrophy and maladaptation. The latter was chaired by Ardeschir Ghofrani, and included sessions by Stephan Rosenkranz from Cologne, Paul Hassoun from Baltimore, Georg Ertl from Wurzburg, and an abstract presentation by Rolf Schreckenberg from Giessen. The Breakout symposia included the following presentations: ‘PH concomitant with or due to COPD’ by Yo-chai Adir from Haifa; ‘PH concomitant with or due to ILD’ from Martin Kolb, Hamilton; ‘PH in CPFE and advanced sarcoidosis’ from Vincent Cottin from Lyon; and Giessen’s Matthias Clauss presenting the best abstract, entitled ‘iNOS and EMAPII induction are part of a feed forward loop to promote lung emphysema’. With sessions ending around 19:00, the membership was invited to wander outside for a warming hot wine punch reception, followed by an excellent dinner in the Dolce.

After the first full day of parallel sessions, the dining room was abuzz with conversation, collaboration, ideas, and relaxation, all setting the stage for another full and productive day on Thursday.

Thursday January 30th

Thursday started with fresh energy at 9:00, with the Epigenetics of heart and lung disease sessions chaired by Jim Loyd and Stefanie Dimmler, whilst the Breakout Symposia focused on Novel technologies for healthcare in the developing world. The latter was chaired by Julio Sandoval, and kicked off with a presentation by President of the Saudi Association of Pulmonary Hypertension (SAPH) Majdy Idrees from Riyadh, entitled ‘The challenges for clinical trials in PH in the developing world’. An invigorating lecture, it inspired a lot of discussion, and was followed by ‘The Recife experience’ presented by Angela Bandeira from Recife, and a presentation by the new PVRI President Glennis Haworth from London, entitled ‘PVRI programs to promote pulmonary vascular disease management in the developing world.’ It details
the ways in which PVRI is involved in direct management of pulmonary vascular disease throughout the world, and is also available to the general public on the website. Meanwhile, the main program sessions included lectures from Kevin White, Glasgow; Thomas Thum, Hannover; and Rachel Hopper from Stanford, who presented the best abstract. At 11:00, the PVRI Central Asia Taskforce met in Parksaal to discuss the June 17-18 Bishkek meeting and a co-ordinated effort within the Central Asia region to further promote knowledge and awareness of pulmonary vascular diseases. The High Altitude Taskforce also met in the morning, starting at 8:30 and continuing until nearly noon, when the room was filled instead with members of the Schistosomiasis Taskforce. All in all, these extra rooms have proven very welcome and useful in allowing members of the PVRI to congregate for specific purposes apart from the general conference sessions. A second poster presentation session took place in the mid-morning to early afternoon, and was followed by lunch in the Dolce. At 14:00, the sessions resumed with a vengeance, with Hypoxia and high altitude disease, chaired by Andrew Peacock and Ralf Brandes, kicking off in Kursaal. Larissa Shimoda from Baltimore, Philipp Eaton from London, Erik Swenson from Seattle and Agnes Gorlach from Munchen all presented, though the main program sessions could sadly not be recorded by PVRI. However, the Breakout Symposia focused on Systems biology and bioinformatics in pulmonary hypertension and was chaired by former PVRI President Martin Wilkins, and Patricia Thislethwaite. Some of the following presentations can be found on the PVRI website: ‘Setting the scene 1: the date flow from molecular genetics and systems approaches to pulmonary vascular diseases’ by Stefan Graf, Cambridge; ‘Setting the scene 2: new biomarkers for PH and right ventricular function,’ by Steve Kawut from Philadelphia; ‘How to interrogate Big Data’ by Janine Felix from Rotterdam; and the best abstract, entitled ‘HRQol and Collagen Biomarks in Pulmonary Arterial Hypertension’, presented by Zeenat Safdar from Houston. This spelled the end for the Breakout Symposia sessions for the day, but after the coffee break Nicholas Hill from Boston presented the first PVRI Robyn Barst Memorial Lecture in Kursaal. His talk was titled ‘Pulmonary vascular abnormalities in lung disease from a global perspective’, and was met with approval by the audience, and, Prof. Hill said he hoped, Robyn Barst herself. **GALA DINNER** Afterwards, the membership was reminded that the buses for the Gala Dinner would depart at 17:45 sharp. Four buses were arranged, and after a bit of confusion regarding the pick-up location, eventually all interested attendees were delivered to reception and dinner at castle ‘Burg Gleiberg’, dressed to the nines. Dinner and entertainment, organised by the multi-talented Daniela Weber from the ECCPS, was magical, and consisted of a show of ‘science magicians’ and a fantastic band. But first, Werner Seeger from the ECCPS thanked the membership and all those involved for their contributions to the meeting, including the attendees, discussion participants, and the hard
work of conference organisers Daniela Weber, Regina Lichte and Sylvia Weissmann. Prof. See ger started his talk with the proclamation that he ‘loves PVRI!’, to applause from the room, and continued to explain the PVRI and its mission to those who may not yet be familiar with the Institute. He then went on to proclaim his love for the ECCPS as well, before declaring that the combination of both was what he loved even better, and spoke of his happiness regarding the PVRI/ECCPS collaboration in the form of this joint symposium. However, Prof. Werner’s utmost love was reserved for first, his wife, family and the German soccer team, but a very close second was the Justus-Liebig University Giessen. On that note, he introduced Prof. Joybrato Mukherjee, the President of the Justus-Liebig University Giessen. Prof. Mukherjee gave a brief talk touching upon the importance of giving research-based advice to political leaders where human health, resources management and sustainability are concerned, and the significance of the University, the ECCPS and similar organisations in the sight of this mission. He then thoroughly surprised former PVRI President Martin Wilkins, by awarding him with the title of Liebig-Professor of the University of Giessen for his outstanding academic and scientific achievements. After calls for a ‘speech, speech!’, Prof. Wilkins charmed the audience with a very concise few German words which included ‘gute abend’, ‘danke schon’, and ‘das ist gut’, before speaking of his honour at receiving the title of Liebig-Professor and thanking his wife, family and the English soccer team.

**Achievement Awards**

Following this, the PVRI continued its tradition of presenting the PVRI Achievement Awards during the Gala Dinner. PVRI President Sheila Glennis Haworth and PVRI President Emiritus and Treasurer (formerly Managing Director) Ghazwan Butrous took to the stage to announce the PVRI Achievement Award 2013, which was presented to the Saudi Association of Pulmonary Hypertension (SAPH), in recognition of their distinguished efforts in enhancing clinical practise and research in the Eastern Mediterranean Region. SAPH President Majdy Idrees and colleague Manal Al Hazmi were asked to the stage and presented with this PVRI honour, which is also announced on the SAPH website. Prof. Haworth detailed the many projects the SAPH is involved in on a yearly basis, and the excellent response to their multiple awareness days, courses and initiatives, as well as their very well attended meetings of high scientific quality. Prof. Butrous further expounded that the achievement award nomination for SAPH had been unanimously backed by the PVRI Executive Committee, and felt it was fully and thoroughly deserved.

Next was the Certificate of Recognition, established in 2011. The 2013 plaque was awarded to Prof. Chen Wang, in recognition of his work promoting scientific advances in pulmonary vascular diseases throughout China and beyond. Prof. Haworth introduced Prof. Wang as being ‘the director of basically most of Chinese medicine’, and as a central figure in the health delivery system in the people’s republic of China. ‘He is nationally responsible for medical education and medical research, as well as an outstanding clinician in respiratory medicine, and was the initiator of a very successful tobacco control program- and all this is really just the beginning.’ Prof. Haworth then wished him a happy
new year, as the Gala Dinner coincided with the Chinese New Year, and said that she looked forward to working with him further throughout 2014 to prepare for the 2015 PVRI AGM and Scientific Workshops and Debates in Guangzhou, China. Prof. Wang responded with a few words thanking the PVRI for the Certificate, and mentioned that he looked forward to seeing all attendees at the Guangzhou meeting.

Prof. Butrous then announced the PVRI Lifetime Achievement Award, which was introduced last year at the Istanbul meeting. The award for 2013 was unanimously appointed to Prof. E. Kenneth Weir, who unfortunately could not be present for the ceremony. Prof. Haworth jokingly admonished the audience that they should feel very sorry for Prof. Weir, as he was currently on vacation in the Galapagos Islands. She went on to describe him as the epitome of the ideal clinician scientist, as “he is a wonderful clinician, erudite, compassionate, and successfully combines the art and science of a really good clinician”, and specifically named his work on potassium channels and mitochondrial function as revolutionary.

This concluded the speeches for the evening, and opened the floor to the second course of dinner, and later, magic and dancing. All in all, a very good night, dutifully recorded by the hard-working PVRI Young Council.

Friday January 31st

Despite Thursday’s late night, Friday’s program took no prisoners and started early at 9, with Adaptive and maladapted angiogenesis, chaired by Duncan Stewart and Ingrid Fleming in Kursaal, and High Altitude Medicine, chaired by Norbert Weismann and Almaz Aldashev in Spiegelsaal. The former included talks from Eli Keshet, Jerusalem; Bernard Thebaud from Ottawa; John Cooke, Stanford; and the best selected abstract. Spiegelsaal saw the following presentations: ‘Hypoxia sensing,’ from Paul Schumacker, Chicago; ‘HIF and erythropoietin: functions in the cardiopulmonary system’ by H. Franklin Bunn, Boston; ‘Chronic mountain sickness’ by Aaron Waxman, Boston, and the best abstract entitled ‘Acquired and genetic alterations of the miR-210-ISCU axis to promote iron-sulfur cluster deficiency and pulmonary hypertension’. All the Spiegelsaal talks (excepting the abstract) are available on the PVRI website.

The poster sessions that had taken place over the previous few days now culminated in the mid-morning poster price awards. The afternoon sessions were kept short in the understanding that many attendees would have to leave early to catch trains, planes and automobiles to get back home, or in some cases, onwards to the next meeting. Spiegelsaal featured the Hot Topic Session on ‘Emerging issues of paediatric pulmonary hypertension’, after which the PVRI Paediatric Taskforce and interested parties retreated to another room for

Prof. Chen Wang, middle, receives the PVRI Certificate of Recognition from professors Sheila G. Haworth and Ghazwan Butrous FPVRI

Drs. Ioana Preston and Harrison Farber bring the fun during the Gala Dinner
an in depth discussion on the week’s sessions. Meanwhile, Kursaal held a session on Molecular imaging in heart and lung disease, chaired by Paul Hassoun and Andreas Zeiher. Lectures included different angles and perspectives within the main topic. Joseph Wu from Stanford, Frank Bengel from Hannover, David Newby from Edinburgh, and finally Christian Schonfeld from Hannover rounded off the 7th PVRI Scientific Workshops and Debates, and marked the end to the Joint Symposium ECCPS/PVRI 2014.

Overall, the feedback was very positive, specifically regarding the quality of the science. Some members did indicate that they preferred the more intimate feel of previous PVRI meetings, something which is being considered for the 2015 China meeting. For the Young Council, the meeting proved fruitful with recordings of 11 lectures, 17 interviews, and 22 abstract presentations, as well as 34 conference talks. However, for next year, the Young Council aims higher, and needs your help. I would like to urge you all to consider bringing slides ready for a lecture recording (or two) to the China meeting, which takes place 15-18th of January 2015. The Young Council is responsible for populating the PVRI educational website for the benefit of the whole membership, but cannot do so without your help. A big thank you to everyone who participated, and we hope to see the lecture, interview and abstracts recordings grow year after year! Please have a look at the Gallery here to again savour the Bad Nauheim meeting.

Corresponding Author
Nikki Krol
PVRI Executive Administrator
PVRI Chronicle Executive Editor
Canterbury, Kent
United Kingdom
Email: nkrol@pvri.info

The most senior and the very youngest attendees and delegates to the 8th PVRI AGM and 7th Scientific Workshops and Debates, Jan 28-31st 2014, in Bad Nauheim, Germany, gather for a group photo.
This year the SAPH2014 Conference, also known as the Saudi Association for Pulmonary Hypertension and the PVRI Eastern Mediterranean Region 7th Annual Joint Pulmonary Hypertension Assembly, took place in Muscat, Oman.

Spanning three days from May 1st to May 3rd, the program promised sessions on classifications and updates, new developments in PAH therapy, insights in pulmonary hypertension due to left heart disease, a detailed look at CTEPH, management challenges in PAH patients and pregnancy challenges in PH patients, as well as practical clinical scenarios and more specific PAH management particularities, such as pericardial effusion and CTD associated PAH- and it certainly delivered.

As usual with SAPH, the high quality scientific program was accompanied by a flawless and aesthetic organisation, this year in the Ritz Carlton Al Bustan Palace in Muscat, Oman. A jewel on the coast of Oman, the hotel is situated right on the beach, whilst some of the rooms are located right at the edge of the pool—a near necessity in a country where May temperatures reach well into + 45°C.

The meeting kicked off on such an evening, when the temperatures rose high outside and attendees retreated into the cool blast of the hotel airconditioning. After registration, which included name tags, PVRI/SAPH pins and mocktails, attendees took a seat in the impressive ballroom. The Opening Ceremony included a welcome from Conference Chairman Dr. Saleh Al Dammas, followed by an introduction to PVRI* by PVRI President Sheila G. Haworth, an introduction to SAPH by Head of SAPH Majdy Idrees, and a more detailed look at the program from Head of SAPH Scientific Committee Abdullah Al Dalaan.

Then followed the talks, focusing on ‘Classification & Updates,’ chaired by Drs. Mohamed Al Hajjaj and Saleh Al Dammas. These presentations covered the basic physiobiological and genetic aspects of pulmonary arterial hypertension, and were spearheaded by Prof. Ardeschir Ghofrani, FPVRI, with ‘PH phenotypes: Distinct Inflammatory Pathways’.

---

**PVRI Chronicle: Volume 1 Issue 2, July - December 2014**

* Please note that link compliance may depend on your PDF reader settings. If links fail to open, please right click to copy the URL destination into your browser, or open the PDF in your browser.
Originally due to give two talks, Prof. Stephan Rosenkranz, FPVRI had a change in schedule which meant he would leave earlier than expected. As such, he combined both talks ‘Pulmonary Vascular Changes in PH Due to Left Heart Disease: Closer Look at the Histopathological Level’ and ‘Insight into RV assessment: Size and Function as Predictors of Clinical Worsening (Echo & MRI)’ into one, entitled ‘Pulmonary Vascular Changes Due to Left Heart Disease’, a two-part talk which can be found at the link.

His presentation was followed by Prof. Ghazwan Butrous, who provided an update on the genetics of PH, which will become available on the PVRI website at a later date.

Each lecture was followed by discussion amongst presenters and attendees, which continued during dinner and made for an excellent, involved and interesting start to the Conference.

The Friday Morning Sessions focused on topics ‘PAH Therapy: New Developments’, chaired by Drs. Abdullah Al Dalaan and Hussam Sakkijha, and ‘Definitions: New Changes’, chaired by Drs. Nasser Al Busaidi and Bader Al Ghamdi. The former looked at new publications concerning the indications of macitentan (the potent dual endothelin receptors antagonist), riociguat (sGC stimulator), and the role of anti-neoplastic TKI. It included talks by Prof. Ardeschir Ghofrani, FPVRI, Dr. Nazzareno Galie, Dr. Marius Hoeper, FPVRI, with ‘Inoperable CTEPH: Medical Treatment ‘CHEST 1’ and ‘CHEST 2’ Studies’, and Dr. Majdy Idrees, who presented ‘Targeting Tyrosine Kinase Pathways: Where do we stand?’.

After coffee, Dr. AbdelGhafour Gari opened ‘Definitions: New Changes’ with ‘Borderline PH: Does it exist?’. His presentation was followed by Dr. Marius Hoeper, FPVRI, who presented ‘Out
Discussion ensues during the scientific sessions presented on ‘The Role of Specific Pulmonary Vasodilator Therapy in PH Due to Left Heart Disease’. Originally scheduled for Dr. Stephan Rosenkranz, Dr. Hoeper instead filled the next slot with ‘PH Guidelines: What is New after the 5th World Congress?’

After a quick coffee break, the sessions resumed with ‘CTEPH’, which was overseen by Drs. Mohamed Bader Al Salad and Hadeel Al Otair and focused on the selection criteria of operable patients, and the best peri-operative, operative and post-operative management. Dr. Eckhard Mayer, FPVRI, set the tone with ‘Evaluating Operability of CTEPH: Important Decision!’ and ‘Advancements in Surgical Treatment of CTEPH, PEA and Beyond: The Role of Pulmonary Angioplasty’. Dr. Talant Sooronbaev ended the day’s scientific programme with ‘PH Due to High Altitude, a Special Condition’, an informative talk which featured details on the upcoming Bishkek meeting in Kyrgyzstan.

The sessions overran by about an hour, which is always a good indicator of an involved audience and many discussions. Nonetheless, delegates were given about an hour to relax at the pool and get ready for the Gala Dinner, which took place outside on hotel grounds. Big fans sprayed cool droplets onto the dressed up delegates, who found their places at the round tables in the picturesque and exciting setting. A small stage was formed at the front, whilst attendees enjoyed ice water and fruit juices, and chatted amongst themselves. Before long, Conference Chairman Saleh Al Dammas and Head of SAPH Majdy Idrees took to the stage to thank the speakers, attendees and organisers for their presence and contributions. They presented an award to each speaker and honourable guest, and announced a new tradition of recognising one particular SAPH member at each meeting, based on their hard work for SAPH throughout the year. However, this year they chose to honour two, namely Head of SAPH Scientific Committee Abdullah Al Dalaan, and Head of the SAPH Pediatric Taskforce, the unofficial Queen of SAPH, Maha Al Dabbagh, FPVRI.

Shortly after the ceremony, dinner was served, much to the delight and enjoyment of all attendees.

Saturday’s scientific programme started at 9am, with a focus on ‘Challenges in PAH Management’. It was chaired by Drs. Abdulmajeed Al Otay and Amjad Kouatli, and looked at PH management challenges and new strategies that might be adopted by PH-treating physicians. Dr. Robert Levy, FPVRI, started the day off right with ‘Upfront Combination Therapy for Severe PAH: Should it be the Standard of Care?’ He was followed by Prof. Ardi Ghofrani FPVRI, who presented ‘Treatment Goals: Review of Evidence’. Next was Nazzareno Galie with ‘PH in hemolytic anemia, why was it removed from Group I?’, and the session ended as it started, with Robert Levy presenting ‘Timing of Lung Transplant in advanced PAH: A Critical Decision!’

After coffee, ‘Practical Clinical Scenarios in PH’ was chaired by Drs. Nazzareno Galie and Maha al Dabbagh, and focused on different challenging clinical scenarios of interest to PH physicians in the EMR region (and beyond). This included a talk on Pregnancy Challenges in PH patients by Dr. Manal Al Hazmi, and a presentation by Dr. Abdullah Al Dalaan on ‘Pericardial Effusion and CTD Associated PAH.’
Then it was time for the best abstract winner, Dr. Stephen Chan FPVRI, to make his presentation, entitled ‘Acquired and Genetic Alterations of the MiR-210-ISCU Axis Promote Iron-Sulfur Cluster Deficiency and Pulmonary Hypertension.’ He was honoured in the abstract ceremony afterwards, and presented with a Certificate by Drs Saleh Al Dammas, Abdullah Al Dalaam and Ghazwan Butrous. Another Certificate was presented to Ellsa Booysen, a PH-patient of Maha Al Dabbagh who attended the SAPH 2014 Conference with her husband Ronnie Booysen to share her story.

With nearly a hundred attendees and a wide variety of topics, high quality presentations and discussion, the Joint SAPH/PVRI Conference 2014 was a real success. Thanks are due to the organising committee of Drs. Majdy Idrees, Saleh Al Dammas, Abdullah Al Dalaan, Nasser Al Busaidi and Hassan Alorainy, as well as to each speaker and attendee who made the SAPH2014 conference a reality. Special thanks also go to the Global Access team, who once again worked tirelessly to ensure excellent organisation and a faultless experience for all.

All links in this story are recordings of the conference talks, and can be viewed by PVRI members only. The images featured in this blog can be seen here, along with many others from the SAPH 2014.
PVRI held their traditional annual Get-Together meeting during the American Thoracic Society (ATS) conference in San Diego on May 19th from 9-11 pm. Hosted by the W Hotel, the informal meeting was enriched by coffees, teas, soft drinks and cakes, with alcoholic drinks (wine, beer...) as a delightful bonus for this year. Around 30 PVRI members were present at the meeting and took the opportunity to discuss and chat in a relaxed atmosphere. Hosted right in the middle of the weeklong ATS Conference, the mini-break was timed perfectly to allow members a chance to recharge their batteries and PVD enthusiasm amongst similar ilk. Importantly, the meeting was also a unique chance to meet old and long-time-no-see friends. Although there was no official talk, all PVRI members exchanged their valuable experiences, those related to the science and research in the field of the pulmonary vascular diseases, as well as those related to everyday life. The majority of attendees were younger PVRI members, supported by our renowned and leading experts in the field such as professors Drs. Ralph Schermuly, Norbert Weissmann and Werner Seeger- a heartening reminder of the PVRI’s durability and capacity for growth.

The PVRI Get-Together event also proved an excellent opportunity for the PVRI Young Council to hold a separate 30 minute meeting. During this time, new members Drs. Natascha Sommer and Oleg Pak were welcomed into the fray by other Young Council members, and introduced themselves with a small summary on their scientific and academic background. Drs. Sommer and Pak joined the Educational Website Board and expanded on their future plans regarding the active involvement in the PVRI Young Council-based activities. The Young Council then proceeded to discuss the general strategy for the rest of the year, touching specifically on a need for more educational recordings focusing on methodological, theoretical and conceptual contents, and the context/basic philosophy of the following PVRI Chronicle volumes/issues. In order to maximise elearning content, the Young Council will be available all week during the 8th PVRI Annual World Congress meeting (formerly the 9th PVRI AGM and 8th Scientific Workshops and Events) in Guangzhou, China, Jan 15-18 2015, to record lectures, abstracts and interviews with willing PVRI members. Interested PVRI members are encouraged to contact Admin Nikki at nkrol@pvri.info

The Get-Together slowed down around 11 pm, at which point members, fortified by talk but tired from the long day, retired to their rooms (or potentially the downstairs bar).

We would like to thank to Dr. Michael Yeager, FPVRI, for his valuable efforts to organize this informal meeting, which has become a well-attended traditional PVRI event. Similarly, we would also like to thank all participants to the PVRI Get-Together ATS 2014 meeting and hope to see more PVRI members and friends, both juniors and seniors, during the future ATS conferences.

Corresponding Author
Djuro Kosanovic, PhD
Universities of Giessen and Marburg Lung Center
Excellence Cluster Cardio-Pulmonary System
ECCPS, Auweg 130; 35392 Giessen; Germany
Email: Djuro.Kosanovic@innere.med.uni-giessen.de
We are excited to launch CliniCalc.net, the first dedicated prostanoid calculator app for mobile devices - and it’s free to use. Our aim is to simplify the lives of healthcare professionals and patients who use prostanoids to treat pulmonary arterial hypertension. Further details can be found in the app itself.

Please go to http://CliniCalc.net through your mobile device browser or desktop browser. We’d love you to use the app, link to us on your blog, social media and website, and share our app with your colleagues and patients. Please let us know what you think by writing to the corresponding author, or by commenting in the PVRI website.

Corresponding author:
Ben Fox
Rabin Medical Centre
Petach Tikva, Israël
Email: drbenfox@gmail.com
Dr. Michael Seimetz (MS): Hello Prof. Ghofrani, thank you very much for coming here and taking the time for this interview. Prof. Ghofrani, in profession you are a physician, a clinician. But in addition, you also work as a scientist. The question is why. It is very time-intensive, why do you that? Why do you think it’s important?

Prof. Ardeschir Ghofrani (AG): Well, you may know this already, but I had a previous history, starting as a scientist. Then in parallel to my medical studies, I worked in the laboratory quite extensively, both on acute models of lung injury and chronic models of pulmonary vascular disease. So this was my heritage basically, before I re-started doing my clinical work. When med school was finished and my doctoral thesis was finalised, I then became more and more interested in both patient care and clinical studies, clinical science. And I found it, at least for myself, quite fulfilling, and also basically the goal of my career would be more in the interface between basic science and clinical application, what we nowadays call translational medicine. Before this new title was invented, in our working group we were already living this translation from bench to bedside. So that was the start of the kind of work that I’ve been doing the last couple of years until now. I think that mainly the beauty of it and the reward you can personally get from it, when you are involved- it is of course a team effort, but still, when you are part of the train that delivers new treatment to patients- that is the ultimate goal you can have, in my view at least, when you follow the career of a physician scientist.

MS: I think in the last ten to fifteen years the methodology and equipment have really improved. It has become more efficient and allows us to do more complicated things. But can you remember back when you first started working- what did the lab look like? What was the methodology?

AG: So, I started in a physiological lab. We worked in the group of Werner Seeger and Fritz Grimminger, in those times we were very much interested in the basic physiology of lung function, and particularly the interaction between the ventilatory and the circulatory system. From there on, of course, the experimental setting became more and more complex. So in these physiological and also
we became interested in the metabolism of these organs, in the inflammatory responses, in the signalling cascade and cells that were involved. That was the reason why, for instance, the morphology and histology was implemented in the technologies of the laboratory. That was also at a time when the molecular biology aspects became more and more interesting and also available to our laboratory. You said very rightly that this was an incremental process for which none of us was a, let’s say, ‘generalised expert’ for all the fields that had to be addressed. But fortunately, with the growth of the group, we were able to hire and also to engage new members of the research group who came to us with a given level of expertise in particular technologies. That’s how the group gradually grew, and of course it was also necessary to be able to keep the scientific standard- sometimes even be ahead of the scientific standard and technologies- to be able to be innovative and original. So that was basically how it started- it was very basic settings with quite- at that time it was advanced technology, compared to nowadays we’d say quite basic technology, but then of course there was this gradual evolution of expertise in different areas, and that is I think also one of the secrets of this group, that it steadily grew. The new additions to the group were very carefully chosen and nicely complimented, I think, the existing expertise.

MS: If you look at recent publications, let’s say from the last years, you can see the New England Journal of Medicine papers, which contain very nice clinical studies, and most people know, for example, the Sildenafil studies, very exciting stories, the work that you and your colleagues did. What would you like to tell us about the story, the Himalaya story?

AG: *laughs* Yeah, I think that was nice piece of translational success, as you said. The intermediate step was basically a volunteer study in otherwise healthy people, who simulated a disease situation, which basically happens to all of us if we expose ourselves to prolonged periods of environmental hypoxia. What you basically do is take an otherwise healthy person, put him or her into an environment in which you become sick. In this case, you develop pulmonary hypertension and consecutive right heart loading. In fact, that’s a very attractive way to build in an intermediate step if you have already uncovered a new signalling mechanisms, a new molecular target- maybe a new medication- could be useful to a certain disease, but the proof is currently limited to in vivo animal models, or even ex vivo but in the respective organ chronic animal models. And then you really want to go to the patient. Sometimes you are hesitant, because you are not quite sure whether undesirable effects could occur, which you haven’t seen in the animals but you’d really like not to expose your patients to before you really know if the concept works. And to prove the concept, in the sildenafil story that you mentioned, we decided to build-in an intermediate step in otherwise healthy volunteers who undergo a transient period of a disease which fortunately resolves in all of them once they come back down to sea level, but which very closely resembles the situation of the patients. Before that, there
was a three or four years very sophisticated basic research program that strengthened the hypothesis and also the identification of the involvement of phosphodiesterase 5 in the evolution and the promotion of pulmonary vascular disease. In fact, our lab was amongst the first to show that PDE 5 is much stronger regulated and important for maintenance of normal pulmonary vascular function than it is in the erectile organ of the man for which the drug was originally invented and clinically approved. So we were able to show that this enzymatic system plays a much more important role in the lung circulation than it does, as I said, on demand in the erectile male organ.

But to be able to show the concept that this inhibitor of the phosphodiesterase 5, which in that case was sildenafil, displays beneficial effects in the lung circulation required and disturbed lung circulation. You cannot find out in a normal pulmonary circulation whether PDE 5 inhibitors have a desirable effect, because the effects can only be displayed once there is a disturbance in the pulmonary circulation, namely if the pressure is elevated, if the resistance is higher, and also if the cardiac function is impaired. So we took Sildenafil, and we could have given it to healthy volunteers whom we put into a pressure chamber. But for the disease to evolve you need many days up to several weeks so you can't do this just by exposing volunteers to short-term hypoxia. And I think at that time at least no institutional review board or ethics committee would have granted approval for a clinical study protocol in which you caged in 20 healthy people in a pressure chamber for 8 weeks- that's not ethical. But it is ethical to accompany people who expose themselves voluntarily to a hypoxic state for a long period of time- and these are mountaineers. So we accompanied a highly trained group of professional mountaineers, who aimed to summit the Mount Everest in 2003. And in agreement with them, and according to best clinical trial protocols and clinical practise guidelines, we conducted a randomised, double-blinded, placebo-controlled trial in those healthy volunteers that exposed themselves to become pulmonary hypertensive. And we were able to show, and that was one of the major concept that it works, were able to show that the PDE 5 inhibitor, under conditions of hypoxia-induced pulmonary hypertension, reduces pulmonary hypertension. In turn, cardiac function improves, and not only at rest, but also during exercise. So it was the first proof that you could pharmacologically improve exercise capacity under hypoxic conditions. And of course, if you translate this to the patient situation, you can easily imagine that a patient who has either an underlying lung disease, but goes along with – in this case- internal hypoxia which has an effect on the pulmonary circulation, that you could overcome this mechanism. Of course, also for other patients with chronic pulmonary vascular disease, this could be a good option.

Once we saw that it worked, we had good experiences with a few patients who received the PDE 5 inhibitor sildenafil, in a kind of compassionate treatment use. We and others published data in the early 2000s in a larger series of patients, of course uncontrolled data so far, and controlled that it was an efficacious treatment from which a lot of patients could benefit. Ultimately, of course, the randomised phase III placebo controlled study aiming to gain approval was conducted and was highly significantly positive. This led to the approval of sildenafil which, since then, is amongst the most frequently prescribed, if not the most frequently
prescribed drug for pulmonary hypertension.

**MS:** The sildenafil story is really a fantastic story- it started from the basic science and finally went to patients, and the sildenafil was also approved for treatment of pulmonary hypertension. But if you look at recent publications, you and your group were not just a one-hit wonder. You also contributed to other potential treatments and even treatments, let’s say for example the recent soluble guanylate cyclase stimulator riociguat, which is now also near approval to treatment for pulmonary hypertension. What do you think is the difference between your group, the Giessen group, and others? Because it is very rare that you can find treatments, especially for pulmonary hypertension.

**AG:** Well, if there is a difference at all, and I don’t know that there is, I think that the whole community of so-called PH specialists worldwide is a very powerful community. In fact, as a worldwide network we work very closely together, at least at the final stages of clinical approval. So this network is key for the last step before a new treatment is a really deliverable to patients, after it has undergone very strict study protocols, placebo controls, with all the requirements according to the international guidelines. This is a collaborative effort, and really all the PH centres worldwide are united under this same philosophy that new treatments should be tested before they are given to patients, and for that purpose we have a clinical trials network. I think the exclusive situation in Giessen is that we have the fortunate situation that we have a very powerful basic research group, interested in many aspects of lung diseases, of which of course the core-interest is centred around the pulmonary vasculature. But also a lot of work is ongoing to increase our understanding of chronic lung diseases, parenchymal lung diseases, airway diseases- there is a lot of work ongoing with regards to animal models that provide us with clinically relevant information for human disease. There is a lot ongoing to try and decipher signalling pathways that are involved in different lung diseases. And all the evidence then comes together because many people inside this very large group interact very actively. We have regular sessions with our junior faculty, with the PhD students, with the post-docs who present the ongoing work- and that allows the group to generate collective ideas, basically. And from those you can even make a choice, depending on how ‘at reach’ a potential treatment is. The easiest way, of course, is if you identified for a disease a hitherto unknown signalling pathway, for example: you’ve clearly identified a molecular target. And then you go and screen the available therapies, and find out that there is already a medication, a molecule, available that is currently used for a completely different application. No one ever thought that it may play a role in your disease of interest. And that shortens the development time considerably, as was the case of sildenafil: the drug was already marketed for the treatment of erectile dysfunction. And then we and others found that it plays a potentially even more important role in the pulmonary circulation, but you didn’t have to invent the molecule from scratch, you did not have to investigate on all the pre-clinical science that is necessary, toxicology studies, first in man studies to prove the tolerability and safety and so forth; there was a marketed drug which was safe to be used in man. So that was a true shortcut, the same that of course occurred in the development of tyrosine kinase inhibitors, which were of course approved at that time for the treatment of oncological disorders. And then we could take the agents that were clinically available and forward it to patients, because we found out that the PDGF pathway signalling may play an important role. Slightly different from that was the story of riociguat, because riociguat is a molecule which has never been used before in patients. But we knew from research that was
done in our group and in collaboration with colleagues from the company which produces riociguat, and also the inventor of the molecule, Johannes-Peter Stasch, we had very early interaction. And together we figured out that it may also play a role for pulmonary hypertension. That was the start of the clinical development, when we received this novel compound which was not clinically available, and that subjected it to all necessary steps until two independent randomised phase III controlled trials, which led ultimately and fortunately to the approval of this new compound.

**MS:** You mentioned that as a clinician you work together with basic scientists, and pharmaceutical companies. And somehow, obviously, you are successful. Do you think it is necessary nowadays for clinicians to engage with the corporate network?

**AG:** Well, I think that we first of all have to acknowledge that academic research is still a very powerful tool, because you can investigate, you can design study protocols, you can follow concepts, more or less without any restrictions. The only restriction may be financial, but depending on the success of the group, and the rate of success of the grant applications, you're basically not limited in what you're doing as long as you have a reasonable concept, and you don't waste money, but really invest it properly. That's the first thing.

The second thing is that academia has to acknowledge that we are not yet drug-makers. We cannot design and develop and produce drugs from scratch. And because of that we are very grateful for a very fruitful and early collaboration with the pharmaceutical industry, which has the capability to design drugs - even custom made. If you come up with a new concept, they can even screen their pipelines, and then find molecules that are designed in a way that they match the therapeutic needs, and become an eligible treatment for patients, for instance. So acknowledging the strengths but also the weaknesses inherent to academic research, I personally believe that it can be very fruitful to have early collaboration with pharmaceutical industry for the mutual interests and benefit of both sides. After a certain intellectual step has been undertaken from academia, from there on to develop in a collaborative fashion new treatments for patients - in my view this is quite an efficacious approach. Interestingly, there is a new trend which you may have followed, in which some pharmaceutical companies downscale their in-house research, and instead set-up collaborations with specific academic centres, which they know are 1. Much more specialised, 2. Much more streamlined in their particular field of interest. Additionally, the costs-effect for the entire healthcare system may be reduced by this approach, if not every single pharmaceutical industry, let's say, has to provide the whole variety of exponential/experimental settings, programs, staff, but rather selectively cooperate with academic centres which are known to have a certain pre-clinical and clinical expertise. So that may shorten the duration of new drug development, may save resources overall, and may even help make drugs a little bit cheaper.

**MS:** Maybe, hopefully! I think based on your success in Giessen, different initiatives were founded, such as the Excellence Cluster Cardio-Pulmonary System, the German Lung Centre - these centres show somehow that the importance of research is nowadays recognised by the country. And in addition, based on your research, you were one of the founders of the PVRI. So we now have this annual meeting - what do you think is the benefit for patients derived from the institute and the meetings?

**AG:** Well, in the very early days of the Pulmonary Vascular Research Institute, there was a very small group of people who thought that, despite the achievements in the field of pulmonary vascular diseases that had been achieved until then, that there was still a high unmet need to be addressed, particularly in the disease entities, that were not addressed sufficiently, at least in our view, a couple of years ago, namely, pulmonary hypertension associated with high altitude; pulmonary hypertension in associ-
ation with inflammatory disease or infectious diseases, such as schistosomiasis or HIV. But there was also a big educational gap regarding awareness of pulmonary vascular diseases, and the impact it may have on the general public's health. The founders of the Institute, and the main driving forces at that time of course were Ghazwan Butrous, colleagues such as Stuart Rich, Martin Wilkins and Evangelos Michalakis- all the founding members- and from our group Werner Seeger, Fritz Grimminger and myself, we thought that there were many gaps to close. And that became the philosophy of this Institute. First of all, we wanted to be as inclusive as possible. So the Institute is very liberal in including members: basically anybody who is interested in the subject can apply and becomes a member; and becomes as valuable and important as any presumably ‘eminent’ person in the Institute. So it is a very collegial atmosphere.

Secondly, one of the major achievements of the leadership group is that from the first day, the aim was to become global. To really try to encourage colleagues around the world to utilise their own expertise locally, to build up satellites of the PVRI, to become their own Pulmonary Vascular Research Institute. And this has now been achieved in many areas of the world, very successfully. They are very active branches and chapters of the PVRI, now spread all over the world- so it becomes a real world-wide network of people interested in pulmonary vascular diseases. And then of course comes the question of how we can cross-fertilise each other with the knowledge we have, how can we, let’s say, provide expertise regarding basic research with our group, but to collaborate with groups who have a geographic advantage and/or interest in a disease that is not so prevalent in our area. So this is already something the PVRI is executing on a daily level. There are many many fruitful collaborations, and therefore I think that the whole concept of the PVRI is already very successful. In addition, some initiatives have been undertaken inside PVRI to fulfil the goals that the Institute has set for itself- namely, educational purposes. PVRI is very active in using modern technology such as e-learning; web-based databases and registries, to increase the knowledge about PH also for people living in developing countries, who may not have all the resources to travel to international conferences, yet now get a handle on very important lectures and data, and even some histological specimen that are stored online that can be reviewed and learned from. So there is a lot ongoing in the field of clinical research, collaborative research on the basic research level, as well as on the level of education. And all that, with very very small resources. I think this is one of the secrets of success- there is not a lot of money needed to potentially achieve great success with that kind of concept. And that, for sure, is something that particularly Ghazwan Butrous is the driving force for the success of this Institute in that way.

MS: I fully agree- I think Ghazwan did a great job, for example if you see the amount of members, which is steadily increasing every year. What role do you think the PVRI will play in ten years, even just in the future of pulmonary hypertension?

AG: Well, for me it’s crystal clear that the PVRI is the main platform for people who are interested in the pulmonary circulation, starting from the very basic research up to clinical trial design and conductance, also with regards to educational purposes and exchange of information and thought and building up global networks and databases- I think that PVRI is really our main society for people who are interested in the pulmonary vascular disease area in general. I also believe that PVRI can offer more and more as a clinical trial platform, as we have collaboration and access to many many sites around the world, and have deep insight into the quality of work that our colleagues are doing, and it’s excellent in many many places around the world. But with this insight, we can
recommend and even include clinical trial sites around the world for particular trials - that is another strength. But as you said, one of the biggest treasures we inherit is the interest of our colleagues in this Institute, and the steadily growing numbers of members, considering this institute started with 7 or 10 founding members and has now grown to a membership number in the upper 3-digits- and hopefully we'll have a couple of thousands when we do this interview again in five years.

**MS:** Okay. Coming back to the quality of work that you mentioned; you've published in very high-ranking journals, but do you really think the impact factor reflects the quality of the work? For example, Aaron Chiechanover, he got a Nobel Prize for the discovery of ubiquitin-mediated protein degradation, and he published his data in a low-ranking journal. What do you think about that?

**AG:** Well personally I believe that the impact factor is helpful. The journals that have a very high impact factor have this impact factor for good reason, because they proved that they publish science that is both of interest to a large readership, it's frequently cited, and in most cases it is also durable. Because the quality criteria that were set for the papers that are finally published in those journals are very strict and very high. Having said that, sometimes fundamentally new ideas, that are against the mainstream, at a very early stage do not find their way into those high impact journals. Because of course, it is inherent to the system that current experts review the papers, and they value them, and sometimes they disagree with a completely different paradigm, or a completely different view on something that appears to be clear, and therefore the paper may be rejected due to the advice of the reviewers. And then it gets published in a lower-ranking journal, or a new journal that has not yet collected an impact factor due to technical reasons. Still, the research published there can be fundamental. So, not everything is dependent on the impact factor. Still, as a rough measure of quality and importance, the impact factor will remain important and certainly also a selection criteria. Having said that, I think with reference to the Pulmonary Circulation journal, I'm very sure, knowing about the quality of the research that is already published at a time when the journal, just because it's so new and so young, does not yet have an impact factor, just because it needs time to accumulate a certain number of published articles and also a certain time over which statistics can be conducted to get an impact factor, I'm sure that we will have a good impact factor to begin with, and I'm sure the impact factor will further increase over time as the papers are already highly cited because of the quality of the work and the excellent job of the editorial board of Pulmonary Circulation. It is already, despite the fact that it does not have an impact factor, the most concerted and specific organ for people interested in the field of pulmonary vascular research. And that's why I think that it's a self-fulfilling prophecy to say it will become one of the most important organs that we will have for publication of topics related to the pulmonary circulation.

**MS:** Okay. One last question. You are very successful but you started as a young unknown scientist. What would you suggest to young unknown scientists and investigators today as important for their career?

**AG:** That's a very difficult question! I mean, part of success, however you measure it, is also related to chance and luck. My chance and luck was that I started in an already very active and successful group of scientists and researchers. I had excellent peers and role models in my PI's, who were Fritz Grimminger and Werner Seeger at that time, but also I had excellent colleagues whom I started to work with in the very early days, who are still very good friends.
and still active collaborators, such as Norbert Weissmann and Ralph Scher-muly. I think if you’re part of an interested and active group, that’s already a key to success. That way you can really develop things collaboratively, and compensate maybe for things that your partner is not as good in but on the other hand you benefit from the special abilities that your collaboration partner has. That’s one thing. The other thing is of course that we had a very supportive environment in Giessen. The university was always of help. The university hospital supported much of what we did. This also enabled us to conduct our studies with a lot of support from the environment. And ultimately of course, it needs passion, and you need a vision to really be able to overcome frustrations and drawbacks, which are inherent to research and everyone, young and old scientists alike, will repeatedly experience drawbacks and frustrations. But to over-
come these, because you have a vision, a long-term vision, it keeps you on track and keeps your performance high, and you must never lose the trust that you can achieve your goals; you just have to be sustainable, you just have to not let yourself get frustrated and discouraged, even if you don’t have continuous success. At the end of the day, I think you should follow your vision, follow your goals, and partner with good friends. If you are lucky enough, find a good place, because the environment is of course also very very important.

**MS:** Thank you very much for this nice talk.

---

**Corresponding Author**
Nikki Krol
PVRI Executive Administrator
PVRI Chronicle Executive Editor
Canterbury, Kent
United Kingdom
Email: nkrol@pvri.info

---

*Justus-Liebig University Giessen, Germany*
Molecular links between pulmonary hypertension and obesity: what else except adiponectin?

Balram Neupane1, Akylbek Sydykov1, Michael Seimetz1, Srikanth Karnati2, Eveline Baumgart-Vogt2, Norbert Weissmann1, Ralph Theo Schermuly1, Djuro Kosanovic1

1Universities of Giessen and Marburg Lung Center (UGMLC) 
Member of the German Center for Lung Research (DZL)
2Institute for Anatomy and Cell Biology II, Division of Medical Cell Biology, Justus Liebig University 
Giessen, Germany

Despite the significant advances in the profound understanding of the disease pathobiology and identification of the potential therapeutic approaches/strategies during the last decade, pulmonary hypertension (PH) in all its forms still remains enigmatic and represents a noticeable health burden for one hundred million patients worldwide1,2. Obesity, a medical condition often recognized to be associated with different adverse cardiovascular consequences regardless of the existence of the “obesity paradox”, is increasingly prevalent in the modern age, especially in the developed world3-5. Obesity, a medical condition often recognized to be associated with different adverse cardiovascular consequences regardless of the existence of the “obesity paradox”, is increasingly prevalent in the modern age, especially in the developed world3-5. Although the recent literature implicates the potential role of obesity in the development of PH and indicates adiponectin as a potential molecular link, the research in this direction is still in its dawn and requires future studies6,7. Considering this, we would like to hypothesize that a plethora of different molecular mediators/signals mostly related to altered inflammation and augmented oxidative stress may represent a pathological bridge between the obese condition and PH. This interactive discussion aims to mobilize scientists and other persons interested in the field to express their perspectives in order to identify new potential molecular links shared amongst severe pulmonary vascular disease and obesity.

Adiponectin, a protein exclusively synthesized by adipose tissue, is found to be reduced in the obese condition (Figure 1) and its deficiency alters the vascular homeostasis in the lungs with promotion of pulmonary vascular disease development3,8. Furthermore, the literature demonstrates that over-expression of this anti-inflammatory adipokine is associated with attenuation of the pulmonary vascular remodeling in animal models of PH, in response to inflammatory and hypoxic stimuli7,9,10. Therefore, adiponectin may represent a potential molecular link between the obese condition and PH, and its protective role for the pulmonary vasculature is strongly indicative7,11. In addition to adiponectin, we would like to point out that a plethora of different molecular signals/mediators may be potentially shared between PH and increased adipose tissue/obesity (Figure 1). In the context of obesity and its cardiovascular consequences, Musaad and Haynes systematically reviewed a variety of bioactive molecules mostly focusing on altered inflammation and enhanced oxidative stress, as two major mechanisms suggested to be involved in the cardiovascular pathology associated with the obese condition3. It is worth mentioning that both pathological events, such as augmented inflammation and oxidative stress, are also important culprits in the pathogenesis of PH9-14. Increased adipose tissue and obesity lead to elevation in the levels of interleukin-6 (IL-6), tumor necrosis factor alpha...
(TNF-α), monocyte chemoattractant protein-1 (MCP-1), angiotensinogen (Ang), F2 isoprostanes (F2 IsoPs), C-reactive protein (CRP), fibrinogen, resistin, serum amyloid A, oxidized low density lipoprotein (oxLDL) and homocysteine (for details, see the review article from Musaad and Haynes). Resistin is another adipose tissue-derived candidate, in addition to adiponectin, with visible properties to be associated with pathologies of both obesity and PH. In particular, resistin induces the proliferation of the human smooth muscle cells via activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase signaling pathways, and promotes the proliferation and migration of human endothelial cells, suggesting the potential involvement of this adipose tissue-derived molecule in pulmonary vascular remodeling.

IL-6 is a cytokine which dysregulates the normal proliferation and apoptosis of the pulmonary arterial smooth muscle cells and endothelial cells, and therefore represents an important player in the pathogenesis of pulmonary arterial hypertension (PAH). TNF-α is a cytokine which is also involved in the pathology of PH, and TNF-α antagonism exerts beneficial therapeutic effects in the monocrotaline model of PAH. MCP-1, a pro-inflammatory chemokine, is increased in the plasma of idiopathic PAH (IPAH) patients. Additionally, its plasma level correlates with the disease severity in patients with chronic thromboembolic PH (CTEPH), clearly suggesting this chemokine as
a potential player in the pathology of PH\textsuperscript{19,20}. Furthermore, a therapeutic blockade of the MCP-1 signaling results in the attenuation of the experimental PH\textsuperscript{11}. Considering the above, and knowing that IL-6, TNF-α and MCP-1 are also augmented in obesity, it is tempting to speculate that these three pro-inflammatory mediators may represent a potential pathological bridge between PH and obesity\textsuperscript{3}. Ang levels are increased in obesity, and in the context of PH the role of angiotensin system is as previously described, thereby indicating another potential link between these two medical conditions\textsuperscript{12,13,23}. Enhanced oxidative stress is indeed an important pathological feature in both PH and obesity, and some biomarkers for oxidative stress, such as oxLDL and F2 IsoPs, may further illuminate the search for the common themes among the pulmonary vascular disease and obesity\textsuperscript{3,12,24-27}.

Finally, the available literature indicates additional molecular signals/mediators which are suggested to be increased in the obese condition, as potential biomarkers and/or active players in the pathology of different clinical forms of PH, such as homocysteine, fibrinogen, serum amyloid A and CRP\textsuperscript{3,28-32}. In details, augmented levels of: 1) homocysteine are found in patients suffering from PAH associated with congenital heart disease, as well as in IPAH patients\textsuperscript{28,29}; 2) serum amyloid A are demonstrated in the patients with sickle cell disease complicated with PH\textsuperscript{30}; 3) fibrinogen Aα in CTEPH patients\textsuperscript{31}; and 4) circulating CRP in both CTEPH and PAH forms\textsuperscript{32}.

**THE QUESTION FOR INTERACTIVE DISCUSSION**

We would like to postulate the following question to the scientific community worldwide:

**What else except adiponectin may represent a molecular link between PH and obesity?**

All experts and other persons interested in the field are welcome to reply and express their views on this topic, in the next volume of PVRI Chronicle.

**References**


Corresponding Author
Djuro Kosanovic, PhD
Universities of Giessen and Marburg Lung Center
Excellence Cluster Cardio-Pulmonary System
Member of the German Center for Lung Research
ECCPS, Aulweg 130; 35392 Giessen; Germany
E-mail: Djuro.Kosanovic@innere.med.uni-giessen.de
**Prelude**

Chronic obstructive pulmonary disease (COPD) is a devastating, non-reversible, global health disease affecting millions of people worldwide. Although significant understanding of the COPD pathomechanisms and identification of new valid candidates for potential therapeutic approaches are increased during last years, the clinical studies showed disappointing results, amongst others based on elevated comorbidities and systemic inflammation in extra pulmonary organs. Thus, there is still a need for alternative therapeutic possibilities. Peroxisome proliferators activated receptor γ (PPARγ) is an emerging anti-inflammatory and anti-oxidative gene and its role in the pathomechanisms of COPD is not well understood. The expression and activity of PPARγ is pulmonary cell type-dependent. This interactive discussion describes the multiple roles of PPARγ in different lung cell types and a possible treatment of COPD with PPARγ agonists. Although the recent literature implicates the potential role of PPARγ in the pathomechanisms of COPD, the research in this direction requires future studies to enlighten the hidden molecular pathways. This interactive discussion aims to challenge scientists and other persons who are interested in this field to express their views about the potential of PPARγ-associated treatments of COPD.

Chronic obstructive pulmonary disease (COPD) is a chronic condition of airflow limitation characterized by abnormal inflammation and impairs respiratory gas exchange that is not fully reversible and is progressive in nature. The main risk factors that are associated with COPD are tobacco smoke. However, other factors such as air pollution, occupational hazards and infections are also important. Although COPD is primarily a lung disease, this disease exerts systemic manifestation and comorbidities in extra pulmonary organs and tissues such as heart, bone, pancreas and skeletal muscle dysfunction.

The worldwide prevalence of COPD is estimated to be approximately 10% of individuals older than 40 years of age. Further, due to the lack of effective treatments, COPD is the seventh-leading cause of disability and fourth-leading cause of death internationally according to the world health organization. At present, the accepted treatment for most inflammatory diseases is glucocorticoid therapy. However, this treatment is beneficial only to acute exacerbations of COPD patients, and unfortunately produce unwanted side effects whilst exhibiting limited efficacy. Additionally, some COPD patients develop a resistance to corticosteroid treatment, further underscoring the need for an alternative therapeutic approach.

Peroxisome proliferator activated receptors (PPAR-α, -β, -γ) are members of the ligand-activated nuclear hormone receptor super family.
PPARγ agonists exert strong anti-atherogenic, anti-inflammatory and anti-oxidant effects by inhibiting several inflammatory mediators such as TNFα, IL-1, IL-6, iNOS and transcription factors such as nuclear factor-κB (NF-κB), Nrf2, FOXO, Egr-1, AP-1 and other pro-inflammatory transcription factors via multiple mechanisms.

In recent years, several hundreds of publications on the PPARγ receptor were published suggesting its importance in controlling the complex cellular mechanisms by regulating the transcription of genes (transactivation) that are involved in lipid metabolism, adipogenesis, inflammation and metabolic homeostasis. PPARγ can also inhibit gene transcription, through transrepression mechanisms that involve interactions with other transcription factors and their coactivators to prevent effective DNA binding. In addition, various preclinical studies have already shown that PPARγ ligands have pleiotropic effects preventing cardiovascular complications. PPARγ is also used as therapeutic drug target for chronic inflammatory diseases such as atherosclerosis. This has led to increased interest of this receptor and to its therapeutic role in a variety of diseases including type 2 diabetes, atherosclerosis, inflammatory bowel disease, asthma, arthritis, myocarditis, cancer, fibrosis and endotoxin shock.

PPARγ exerts its function depending on the cell type. Thus, Figure 1 summarizes the functional roles of PPARγ protein in a variety of pulmonary cell types such as the airway epithelium, bronchial smooth muscle cells, endothelial cells, macrophages, fibroblasts, T-lymphocytes, eosinophils, alveolar epithelial cells type II (AECII) and dendritic cells. Though PPARγ ligands exhibit cell type dependent functions, the most common anti-inflammatory effects were observed in various animal models of airway diseases such as asthma and COPD.

Although PPARγ has been known for more than 25 years, the mechanism that triggers the anti-inflammatory potentials of PPARγ protein in cigarette smoke exposure and COPD have not been elucidated. Further, the functional role of PPARγ in the pathomechanisms of smoke-induced COPD is still poorly understood.
Recently, Lakshmi et al. showed that the PPARγ protein and DNA binding activity was reduced in human bronchiolar epithelial cells of COPD patients. In addition, downregulation of GRα and HDAC2 was observed, whereas pro-inflammatory NF-κB was upregulated. Interestingly, treatment with a PPARγ agonist (rosiglitazone) reversed cigarette smoke extract (CSE)-mediated effects by strong up-regulation of PPARγ expression and activity, suppressed cytokines and reversed the activation of NF-κB by promoting direct inhibitory binding of PPARγ to NF-κB. Thus, the authors claimed that downregulation of epithelial cell PPARγ expression and activity plays an important role in cigarette smoke-induced inflammation and the pathophysiology of COPD37.

Since Lea et al. showed that PPARγ levels were not altered in alveolar macrophages (AM) of COPD patients28, lung epithelial cells were suggested to be a key locus for the pathogenesis of COPD. However, Malur et al. showed that alveolar macrophages and lung myeloid dendritic cells (mDC) are important antigen presenting abundant inflammatory cells of the lungs of smokers that are strongly associated with emphysema38. Macrophage-specific PPARγ deficient mice showed spontaneous lung inflammation and increased Th1 polarization38. Interestingly, a recent publication from Shan et al. showed a reduced expression of PPARγ in human mDCs in smokers with emphysema. Moreover, smoke-exposed mice showed a reduced PPARγ expression in lung alveolar macrophages suggesting that PPARγ deficiency in antigen presenting cells leads to spontaneous development of emphysema. These authors showed that mice treated with a PPARγ agonist (ciglitazone) in an early emphysema model or CD11c-specific deletion of PPARγ or ablation of the Spp1 gene reversed emphysema, which suggests targeting the Osteopontin/PPARγ axis as a new therapeutic option39. However, it is not clear whether this treatment could reverse the effects by a late stage or end stage smoking-related diseases. Based on existing literature and heterogeneous regulation of PPARγ in different pulmonary cell types, we would like to postulate the following question to the scientific community worldwide:

Is a PPARγ-mediated regulation in individual cell types sufficient to reverse the emphysema or COPD?

We would like to invite all experts and other persons interested in this field to reply and express their views on this topic, in the next volume of PVRI Chronicle.

REFERENCES

flammation control: molecular mechanisms and patho-
allergy: journal of the British Society for Allergy and
obstructive pulmonary disease. Clinical and experimental
tential anti-inflammatory agents in asthma and chronic
proliferator-activated receptor-gamma agonists as po-
22. Spears M, McSharry C, and Thomson NC. Peroxisome
of the peroxisome proliferator-activated receptor-gam-
Kurokawa R, Rosenfeld MG, Willson TM, Glass CK, and
therapeutic role of peroxi-
isisome proliferator-activated receptor-gamma in dendritic
Pretolani M. Regulation of peroxisome proliferator-ac-
Clinical Immunology. 2006;36(12):1494-504.
23. Benayoun L, Letuve S, Druilhe A, Boczowski J, Dom-
bret MC, Mechighel P, Megret J, Lesege C, Aubier M, and
Pretolani M. Regulation of peroxisome proliferator-ac-
ted receptor-gamma expression in human asthmatic
ways: relationships with proliferation, apoptosis, and
airway remodeling. Am J Respir Crit Care Med. 2001;164(8
Pt 1):1487-94.
proliferator-activated receptor-gamma regulates air-
way epithelial cell activation. Am J Respir Cell Mol Biol.
25. Patel HJ, Belvisi MG, Bishop-Bailey D, Yacoub MH,
and Mitchell JA. Activation of peroxisome proliferator-ac-
tivated receptors in human airway smooth muscle cells
has a superior anti-inflammatory profile to cortico-
steroids: relevance for chronic obstructive pulmonary disease.
CM. Peroxisome proliferator-activated receptor gamma
ligands increase release of nitric oxide from endothelial
cells. Arteriosclerosis, thrombosis, and vascular biology.
27. Reddy AT, Lakshmi SP, Kleinhzenz JM, Sutliff RL,
Hart CM, and Reddy RC. Endothelial cell peroxi-
osome proliferator-activated receptor gamma reduces endotox-
2012;189(n):5341-20.
Fox JC, and Singh D. The effect of peroxisome prolifera-
tor-activated receptor-gamma ligands on in vitro and in
vivo models of COPD. The European respiratory journal.
29. Chinetti G, Griglio S, Antonucci M, Torra IP, Delerive
Activation of proliferator-activated receptors alpha and
gamma induces apoptosis of human monocyte-derived
30. Belvisi MG, and Hele DJ. Peroxisome proliferator-ac-
tivated receptors as novel targets in lung disease. Chest.
31. Hammad H, de Heer HJ, Soullie T, Angeli V, Trottein F,
Pretolani M. Regulation of peroxisome proliferator-ac-
tivated receptor-gamma expression in human asthmatic
airways: relationship with proliferation, apoptosis, and
airway remodeling. Am J Respir Crit Care Med. 2001;164(8
Pt 1):1487-94.
32. Trifilieff A, Bench A, Hanley M, Bayley D, Campbell
E, and Whittaker P. PPAR-alpha and -gamma but not
-delta agonists inhibit airway inflammation in a mu-

34. Michael LF, Lazar MA, and Mendelson CR. Peroxi-
Staels B, Capron M, and Dombrowicz D. Peroxisome
proliferator-activated receptors alpha and gamma down-reg-
ulate allergic inflammation and eosinophil activation. J
some proliferator-activated receptor gamma expression is induced during cyclic adenosine monophosphate-stimulated differentiation of alveolar type II pneumonocytes. Endocrinology. 1997;138(9):3695-703.


Corresponding author:
Dr. Srikanth Karnati (PhD)
Institute for Anatomy and Cell Biology II,
Division of Medical Cell Biology,
Justus Liebig University,
Aulweg 123, D-35385 Giessen, Germany
Email: Srikanth.karnati@anatomie.med.uni-giessen.de

PVRI CHRONICLE

“Coming together is a beginning; keeping together is progress; working together is success.”

- Henry Ford

CALL FOR PAPERS

A brand new Journal, PVRI Chronicle needs your help to grow.

To that end, please encourage your junior physicians, medical students, graduate students and post doctoral fellows to contribute case reports, interactive discussion articles, fellows activities, Did you Know facts, PVD images and book reviews, and don't hesitate to submit your own!

Convinced?
Then please submit your work to:
Sachindra Joshi at sachindraraj_joshi@nymc.edu and Nikki Krol at nkrol@pvri.info

Thank you!
Exercise in pulmonary diseases: good or bad? An inflammatory point of view

Karsten Krüger², Djuro Kosanovic¹, Ralph Theo Schermuly¹, Frank-Christian Mooren², Norbert Weissmann¹, Michael Seimetz¹

¹Excellence Cluster Cardio-Pulmonary System (ECCPS), Universities of Giessen and Marburg Lung Center (UGMLC), Member of the German Center for Lung Research (DZL) Giessen, Germany
²Department of Sports Medicine, Institute of Sports Sciences, Justus-Liebig-University Giessen, Germany

Prelude
A person’s capacity is arguably essential to their quality of life, as well as overall life expectancy. Sadly, all the above is quite limited for patients with (cardio-)pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), due to several factors. Airflow limitations, alterations in gas exchange and muscle atrophy are predominant phenomena. To improve these disorders, exercise training seems to be a suitable instrument. However, physical activity can be beneficial as well as harmful for the health - dependent on the intensity and duration. For example, acute physical activity can increase the risk for acute coronary syndrome (ACS) and sudden cardiac death. On the contrary, it is known that continuous exercise training leads to decrease of cardiovascular morbidity and mortality⁴⁻³. The following controversial discussion will summarize some further aspects that explain the good and bad effects of exercise training with focus on the role of the inflammatory response in this context. This article should animate experts in the field to comment this topic, either by agreeing or disagreeing with our conclusions/hypotheses. The readers are invited to present arguments either pro or contra exercise training for patients not only with COPD but also with other cardiopulmonary diseases.

Impairments in lung function and breathing represent only one aspect of the disability experienced by individuals with COPD. Secondary consequences like the systemic inflammatory status and skeletal muscle dysfunction are further key limitations in these patients⁴. The systemic inflammation of COPD patients is indicated by dysregulation of both cellular and humoral immune parameters. Patients with stable COPD present a peripheral leucocytosis, enhanced expression of leucocyte activation markers, and neutrophils show an increased oxidative burst. Serum levels of acute phase proteins like C-reactive protein (CRP), and pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α are increased during stable COPD⁴,⁵.

Inflammation and muscle in COPD
In the last years, intense discussion has centered on the contribution of the systemic low grade inflammation in the pathophysiology of COPD. A number of studies focused on the relationship between inflammatory cytokines and skeletal muscle atrophy/dysfunction, since muscle wasting has been identified as a predictor of physical function and increased mortality in obstructive lung diseases⁶. Muscular atrophy is accompanied by structural changes of muscle fibers that include a decreased proportion of oxidative muscle fibers, a loss of mitochondrial density and significant fiber type IIX atrophy⁷⁻⁹. From a functional point of view these changes induce a loss of endurance and deficits in muscle strength⁹. There are several other factors which crosslink the systemic inflammatory status and muscle tissue.
At first, it is suggested that COPD patients tend to be sedentary, which might lead to both muscle atrophy as well as the accumulation of visceral fat, resulting in the activation of an additional network of systemic inflammatory pathways\textsuperscript{10-12}. It is known that the pro-inflammatory cytokines TNF-\(\alpha\) and IL-6 can induce muscle wasting by activating key mediators in the ubiquitin-proteasome pathway\textsuperscript{13,14}. TNF-\(\alpha\) is also known to inhibit skeletal muscle regenerative pathways through the induction of oxidative stress, and via nuclear factor (NF)-\(\kappa\)B-dependent inhibition of MyoD, the transcription factor essential for regeneration of muscle\textsuperscript{15,16}.

**Immunomodulatory effects of exercise**

Exercise training has repeatedly shown itself to be an effective part of COPD therapeutic regimes; improving aerobic performance, muscle function, dyspnea, fatigue, muscle weakness and quality of life\textsuperscript{17,18}. Acute and regular physical exercises are also known to have immunomodulatory effects\textsuperscript{19}. A single bout of concentrated exercise is followed by a pro- or anti-inflammatory response, depending on type and intensity.

**Pro-inflammatory effects of exercise**

Inflammation in skeletal muscle can, amongst others, occur after muscle fiber damage due to physical force and strenuous exercise. This can trigger release of inflammatory cytokines such as TNF-\(\alpha\), IL-1 and IL-6 generated by immune cells and/or damaged muscle tissues. Contracting skeletal muscles, especially if associated with inflammation, produce free radicals, known as reactive oxygen/nitrogen species (ROS/RNS). In the past, these radicals were considered as exclusively harmful for the muscle because of oxidative damage within the fiber. Nowadays, it is clear that both ROS and RNS are essential for signaling events involved in muscle adaptation to exercise and the remodeling that occurs during periods of prolonged inactivity. There is an abundance of evidence that low to moderate levels of ROS influence metabolic pathways in muscles related to glucose transport, ATPase activity, calcium release, creatine kinase activity, mitochondrial biogenesis and muscle fiber differentiation. Inflammation caused by muscle disuse and misuse is sensed by redox-sensitive signaling pathways like NF-\(\kappa\)B and mitogen activated protein kinases (MAPKs)\textsuperscript{20,21}. It was shown that the activity of the MAPK signaling modules is partially dependent on the type, duration and intensity of the contractile stimulus. The main function of MAPK pathway in muscle is the modulation of growth, metabolism, differentiation, transcription, translation and remodeling\textsuperscript{21}. While transient oxidative stress is necessary in inflamed muscles to exert an anti-septic function and activation of signal transduction, extended severe oxidative stress can disturb long-term muscle welfare\textsuperscript{20,21}.

**Anti-inflammatory effects of exercise**

In contrast, moderate acute exercise or regular exercise training are followed by an anti-inflammatory cytokine cascade. Thereby, IL-6 is a predominant cytokine which is produced by contracting muscle fibers in response to muscular glycogen depletion\textsuperscript{22}. IL-6 stimulates the appearance of other anti-inflammatory cytokines such as interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10) in the circulation and inhibits the production of TNF-\(\alpha\)\textsuperscript{23}.

**Exercise and inflammation in COPD**

Interestingly, some studies demonstrated that the immune response to exercise differs in subjects with already increased baseline cytokine levels such as COPD patients\textsuperscript{24,25}. In this context, an increase of inflammatory cytokines was observed even after moderate types of endurance exercise. Therefore, it is suggested that exercise regimes should be highly individualized and controlled according to the patient’s exercise capacity, activity and inflammation level. COPD patients are mostly completely deconditioned and therefore show a significant cytokine response even at low intensity exercise. Thus, activity programs need to start at very low intensities and progress slowly. Then patients might benefit from the anti-inflammatory properties of exercise training. Furthermore, the nutritional status and the carbohydrate ingestion prior to exercise have to be controlled because both affect the exercise-induced cytokine response\textsuperscript{25}.
The question for interactive discussion
We would like to postulate the following questions to the scientific community worldwide:

Does a change of the immunological profile after exercise in patients with COPD mediate the beneficial effects of exercise in COPD patients? Is it necessary to perform exercise training in an individual and low intensity fashion to prevent pro-inflammatory effects of exercise?

All experts and other persons interested in the field are welcome to express their views on this topic, in the next volume of PVRI Chronicle.

References

Corresponding author:
Dr. rer. nat. Michael Seimetz
Justus-Liebig-University Giessen
ECCPS, UGMLC, Aulweg 130 D-35392 Giessen, Germany
Email: Michael.Seimetz@innere.med.uni-giessen.de
Surgical approaches for correcting PAPVR. For anomalous veins connecting portions of the left lung to the left brachiocephalic vein, the anomalous vein is reconnected directly to the LA. For anomalous veins connecting portions of the right lung to the SVC, the SVC is reconnected to the right atrial appendage and blood from the anomalous vein is shunted, with the help of a pericardial patch, though a newly-created (or enlarged) ASD into the LA. Alternatively, there have been reports of GORE-TEX™ grafts being used to create a conduit crossing the right atrium.

Legend:
Surgical approaches for correcting PAPVR. For anomalous veins connecting portions of the left lung to the left brachiocephalic vein, the anomalous vein is reconnected directly to the LA. For anomalous veins connecting portions of the right lung to the SVC, the SVC is reconnected to the right atrial appendage and blood from the anomalous vein is shunted, with the help of a pericardial patch, though a newly-created (or enlarged) ASD into the LA. Alternatively, there have been reports of GORE-TEX™ grafts being used to create a conduit crossing the right atrium.

References:
Different HDAC activity in several PH-animal models


Essential differences are found in HDAC activity between heart and lung. Because lung HDAC activity is decreased in several experimental PH models, remodeling of the pulmonary vascular vessel seems not to require a continued increase in HDAC activity. RV HDAC activity was increased in several models of RV hypertrophy, which suggests that HDAC activity plays an important role in the compensation to pressure overload. The clinical implications of our findings is that the effects of HDAC inhibitors in humans with PAH are unpredictable and may include RV functional deterioration, especially when a reduction in pulmonary vascular resistance is not feasible.

Pulmonary vesselbed

Right ventricle

Healthy

Hypoxia

SuHx

Hypoxia, SuHx & PAB

Intima

Media

Physiological HDAC response

No therapeutic effect of HDACi

Therapeutic effect of HDACi

Worsening due to HDACi


Introduction
It is not often a textbook paradigm that has withstood time for 100 years is put to the test. In 1894, E. H. Starling found discrepancies in data presented by Heidenhain that suggested “lymph was to be looked upon as a secretion rather than a transudation.” Starling was unable to reproduce many of Heidenhain’s experimental data and realized that lymph filtration was not an active process of secretion. Instead, as we learn from any physiology textbook, it is the equilibrium between hydrostatic and oncotic pressures. However, though this is not completely wrong, it is incomplete. These pressure gradients were applied to the overall difference between the lumen of the microvasculature relative to the underlying interstitial space. Eventually it became clear the endothelial glycocalyx (eGCX) has matrix properties restricting larger macromolecules to the vessel lumen. As such, new theories developed challenging the idea that simple filtration was regulated through variable gaps between the cells. A revised Starling Principle, proposed by Michel and Weinbaum (independent research), suggested the Starling forces only be applied across the eGCX since it is now considered the molecular sieve for plasma proteins. When the eGCX is experimentally removed, the hydraulic permeability would rise dramatically. This, they claim, is due to the eGCX which streamlines the flow of plasma away from the paracellular clefts, thereby reducing hydrostatic pressure. Additionally, the eGCX contains a steep solute concentration gradient due to its thickness and diffusion resistance.

To summarize, hydrostatic and oncotic pressure gradients between the microvessel lumen and the interstitium are dependent on the eGCX. The importance for us research scientists is not the revision itself, but the idea that the eGCX holds the power to change our understanding of a fundamental principle for which much of our current knowledge on edema and vascular health is based. Since the presence of the eGCX has not been considered in other physiological studies, unexplained phenomena could be attributed to eGCX function.

Brief History of eGCX discovery
On the path to discovering the eGCX, two developments occurred that eventually merged and led to the revised Starling Principle: (1) The invention of the electron microscope; and (2) Continued research on fluid exchange as well as mathematical models developed to predict or compare experimental data on the Starling forces. The electron microscope was co-invented in 1931 by Max Knoll and Ernst Ruska. After refinements and advancements, the first transmission electron microscope (TEM) was made commercially available in 1939. With this, the fine structure of cells could be visualized; the eGCX could be seen and its function speculated upon. The mid 1950’s saw the first mentions of a homogenous fuzzy coating on the surface of endothelial cells, George Palade being one of them. In 1966, Luft was the first to use ruthenium red to specifically mark the glycocalyx for electron microscopy. Before naming the glycocalyx, there were various descriptions including the cell wall, cell surface layer, mucous coating, cuticle or red cell antigen, as well as others. In 1963, Bennett suggested a unifying term, ‘glycocalyx,’ as the general name...
for this “extracellular, sugary coating, wherever it may be found.” Its Greek translation is “sweet husk.” As indicated in the introduction, the endothelial glycocalyx (Figure 1) is a meshwork of long glycosaminoglycans (GAGs) linked to membrane bound proteins (proteoglycans) as well as glycosylated proteins (glycoproteins). Glycoproteins are usually what we envision as cell surface receptors, selectins, integrins, and other functionally dynamic proteins at the cell surface. Proteoglycans play more of a structural role to the glycocalyx and are made of a core protein anchored to the cell membrane with long GAGs attached to them. Glycoproteins and proteoglycans are synthesized and assembled in a series of steps as they are vesicularly shuttled from the endoplasmic reticulum to the golgi apparatus and finally to the cell membrane. Other GAGs could be considered soluble since they are not assembled as part of protein synthesis but rather assembled extracellularly and later bound to surface proteins or receptors. One example is hyaluronic acid (HA), also called hyaluronan, linked to the endothelial surface receptor, CD44. This HA/CD44 interaction is now known to be a contributor responsible for what is termed the molecular sieve characteristic of the glycocalyx. This means long HA GAGs weave through the eGCX just above the cell surface and create a fence-like meshwork which contribute to size exclusion of plasma molecules. These soluble GAGs are also responsible for the seamless meshwork that bridge the luminal surfaces of one endothelium to the next, thereby creating a semi permeable filter to large solutes.

**Starling Forces**

As you can see, the endothelial glycocalyx (as we know it) has a very short, half-century history. Interestingly, we can look at historical biological findings and see where the glycocalyx had influence. The rest of this paper will take a look what led to the revision of the Starling...
Principle influenced by the eGCX. This aspect is interesting because the research involving fluid exchange was in progress before the eGCX was appreciated, while it was this work on fluid exchange that led to understanding the enormous role of the eGCX. The original Starling Principle refers to the balance between hydrostatic and oncotic pressures relative to the microvascular wall. Hydrostatic pressure is the fluid pressure exerted on the vessel wall, a force generated as a function of the contracting ventricles of the beating heart. Since the vasculature leaks between endothelial cells, the hydraulic pressure forces water out into the surrounding tissue space until the pressure meets the resistance of the interstitium and lymphatics. The oncotic pressure is created by the imbalance of protein concentration on either side of a semi-permeable membrane. A membrane permeable to water, but not large proteins, will cause a pressure increase where the proteins are more concentrated as the water attempts to equalize the concentration. The oncotic pressure favors movement of water into the vasculature where the protein concentration is higher. According to Starling, when these forces are combined, the net force will cause water to filter out of the higher pressure capillaries while causing absorption back into the vasculature at lower capillary pressures.17 The latter has been shown not to be the case (discussed below).18 Starling’s research on fluid exchange began in 1892 and his conclusions were published in 1896. Using the isolated canine hind limb he demonstrated the forces governing the movement of plasma fluid in and out of the blood stream. Amazingly, he hypothesized that this movement was regulated by gaps in the intercellular space but in the same sentence admitted that there was no basis for this conclusion since at the time there was no evidence in support of this theory.17 Even so, this was the prevailing dogma for about 100 years. The familiar equation that exemplifies Starling’s findings is as follows:

\[
\frac{J_y}{A} = L_p \ (\Delta P - \Delta \pi)
\]

\[
\frac{J_y}{A}
\]

is the net filtration volume per area, \(L_p\) is the permeability coefficient for plasma fluid, \(\Delta P\) is the difference in hydrostatic pressure and \(\Delta \pi\) is the difference in oncotic pressures. The actual equation was not created by Starling himself. It was an evolutionary process that follows the history of understanding the nature of these forces.

**Revised Starling Principle**

I. Confirming Starling’s findings

We know the variables in the Starling equation to be derived from the principles that Starling set forth, but the definitive measurements were not made possible until Landis, in 1927, confirmed Starling’s findings.3 Landis began his investigations on capillary permeability in 1925 by modifying a micro-injection apparatus involving a micro pipette of 4 to 8 micrometers in diameter, which allowed the direct measurement capillary pressures relative to lymph pressure.19 These methods are still used in modern experiments for precise measurements of intracapillary pressures.20 In 1948, Pappenhiemer showed the relationship between hydrostatic pressure and oncotic pressure of the microvessels using isogravimetric studies further bolstering Starling’s hypothesis.21

II. Reflection coefficient- determining how, what and why solutes traverse the barrier

The simple Starling Equation mentioned above does not take into consideration the restrictive properties of the barrier to solutes. Meaning, the barrier will allow the passage of water at a certain rate and the same can be said about the passage of solutes, especially solutes determined to be of similar size to the inclusion area of the barrier. Pappenheimer’s 1948 study considered the direct measurements of Landis’ experiments and the idea that the barrier filtered solutes, thought at the time to be the space between the cells where tight junctions are found. From this, he discovered there were discrepancies in calculations of permeability and the actual measured values. This led Pappenheimer to develop both the Pore Theory, and, from Staverman’s osmotic reflection coefficient, a mathematical model that described the permeability of solutes.22,23 A solute with complete restriction would have a value of 1 (100% reflection) while a solute with no restriction would have a value of 0. A solute with 100% reflection at the barrier would exert its maximal oncotic pressure on that barrier.
Pappenheimer’s calculations were based on a cylindrical pore of a certain length and radius. We now think of these pores (or simply the restrictive space through which solutes pass) as a two dimensional fence-like meshwork of the eGCX rather than a series of parallel channels so the natural behavior was in disagreement with mathematical predictions. Over the next decade, Curry, Michel and others called into question the model for the reflection coefficient based on pore theory.24 This prefaced the realization that the relatively newly identified glycocalyx could have relevance to this puzzle.

III. Closer to implicating the eGCX

Up to this point, the glycocalyx had not been considered to be a regulator in the filtration of plasma fluids, despite speculation of this function in the late 1950s and early 1960s. Studying electron micrographs, Palade made his prediction based on the basal lamina and noticed a homogenous surface coating much like the basement membrane.8,10 Most suspicion had been directed to the intercellular clefts between the cells because researchers recognized discontinuous tight junctions could have restrictive properties and thus considered it as the filtering barrier for fluid and solutes (discussed later).24 In 1980, Michel published “A Fiber Matrix Model of Capillary Permeability.” This shed the pore theory and suggested “the endocapillary layer is a three-dimensional network formed by the fibrous chains of the membrane glycoproteins of the endothelial cell coat reinforced by the absorption of plasma proteins.”4,25 This may be the hypothesis that changed the historical importance of the eGCX. This model takes into consideration a random array of fibers of specific diameter, length and density for a given area. These fibers are later shown to be hyaluronan as described in the introduction.26

CHALLENGING THE STARLING PRINCIPLE

I. Steady state filtration– 1st challenge to Starling Principle

From the fiber-matrix model, Michel and Phillips were able to develop the idea of steady-state fluid filtration in 1987. This theory suggests that when the Starling forces have balanced, there is always filtration. The only exceptions are in organs where reabsorption is a function of that organ– such as the kidney and gut.5,18,27 This challenges Starling’s finding that reabsorption occurs on the venous side of capillary beds due to the drop in hydrostatic pressure while the oncotic pressure remains the same. This situation results in a net force that favors absorption of fluid back into the vasculature.3,17,21 The problem is that Starling, and others since, were measuring transient reabsorption as a result of changing experimental conditions. Michel and Phillips showed that when they dropped the arterial pressure, there was a temporary adjustment period during which they found absorption. But within a few minutes, the flow stopped and finally filtration resumed, even at the “new” lower capillary pressure while no change to plasma proteins had been made.18

II. Not the cleft – It’s the eGCX

From Starling’s writings it was assumed that the major factors regulating filtration were tight junctions in the gaps between endothelial cells.
III. Tissue protein concentration not a factor-
2nd Starling Principle challenge

Regarding the movement of macromolecules, 

Based on Weinbaum’s 1998 model and experimentally demonstrated by Adamson in 2004, 

Protein concentration in the tissue, at physiological levels, doesn’t affect the rate of filtration.

This is thought to be due to the washout of the protected space (Figure 2) beneath the eGCX described earlier. 

This space, where the concentration of protein is a function of hydrostatic flow, is said to uncouple the oncotic effect of interstitial concentration from the vessel lumen. Therefore, the protein concentration in the interstitium has little influence on fluid flux.

Summary

In conclusion, the eGCX holds the key to understanding the forces that regulate plasma filtration and the fundamental principles of edema. It may be that studies on vascular permeability would be reconsidered if the GCX was neglected as an experimental condition. Further evidence suggests that the health of the glycocalyx could play a mechanical or signaling role in vascular permeability.

One hypothesis states that the breakdown of the glycocalyx is a first step in barrier disruption to miss-regulated fluid flux. Studies involved in leukocyte rolling and adhesion explain that the breakdown of the eGCX is important in the process of leukocyte migration through the vascular wall.

This shows that the eGCX has a role in this complicated process during a normal immune response. Annecke et al. have demonstrated that ischemia can degrade the eGCX in guinea pig coronary arteries.

In terms of lung biology, perturbation of the eGCX, for example in high altitude pulmonary hypoxia, could lead to pathological pulmonary edema, hypertension and ultimately right heart failure.

Most textbooks dedicate a single paragraph to a description of the GCX as the carbohydrate rich coating on the cell surface. Fewer go on to describe the vesicular shuttling and synthesis of some GCX components, but never suggest this structure is physically and biochemically relevant to vascular function, essentially leaving the reader with its function unknown. In the same textbook, you would find a chapter on the Starling forces which explains the four factors affecting fluid filtration. What is lacking in

---

Starling himself clearly stated this was an assumption. Using Weinbaum’s Junction-matrix model, Adamson and Michel concluded experimentally that tight junctions account for 90% restriction in the continuous frog mesentery capillaries. This left 10% of the space between the cells unrestricted to larger proteins and water. Additionally, these junctions were determined to be 150 nm by 20 nm, much too large to restrict albumin of 7 nm in size (the major plasma protein that contributes to oncotic pressures). They found the restrictive properties of this 10% to contribute only slightly to rates of filtration and solute movement. This means Starling’s century old assumption has been found to have little influence on regulating filtration.

From this finding and Michel’s fiber-matrix theory, Weinbaum proposed a 2-dimensional model in which there are distinct zones about the eGCX that vary in concentration gradients. He suggested the steady-state filtration is due to washout of protein between the eGCX and tight junctions (Figure 2). Once on the tissue side, the back-diffusion of proteins is prevented by the funneled flow of fluid through breaks in the tight junctions. At steady hydrostatic pressures, a small amount of proteins filter through the semi permeable glycocalyx, but then are immediately washed out of this sub-glycocalyx space due to the flow of plasma funneled through the gaps between tight junctions. This sets up a relationship between fluid flux and protein flux. At any capillary hydrostatic pressure greater than interstitial pressure, washout will occur because protein permeation is slower than the flow of fluid in a steady state situation. An abrupt change in pressure or permeability could affect the flux of protein, but only temporarily until equilibrium between solute flux and washout is re-established. Considering this, there might be some question as to the influence of hydrostatic pressures on fluid flux. It may be that studies on vascular permeability would be reconsidered if the GCX was neglected as an experimental condition. Further evidence suggests that the health of the glycocalyx could play a mechanical or signaling role in vascular permeability. One hypothesis states that the breakdown of the glycocalyx is a first step in barrier disruption to miss-regulated fluid flux. Studies involved in leukocyte rolling and adhesion explain that the breakdown of the eGCX is important in the process of leukocyte migration through the vascular wall. This shows that the eGCX has a role in this complicated process during a normal immune response. Annecke et al. have demonstrated that ischemia can degrade the eGCX in guinea pig coronary arteries.

In terms of lung biology, perturbation of the eGCX, for example in high altitude pulmonary hypoxia, could lead to pathological pulmonary edema, hypertension and ultimately right heart failure.

Most textbooks dedicate a single paragraph to a description of the GCX as the carbohydrate rich coating on the cell surface. Fewer go on to describe the vesicular shuttling and synthesis of some GCX components, but never suggest this structure is physically and biochemically relevant to vascular function, essentially leaving the reader with its function unknown. In the same textbook, you would find a chapter on the Starling forces which explains the four factors affecting fluid filtration. What is lacking in
this description is that fluid filtration is always maintained in a steady state condition rather than reabsorbed at lower pressures, nor would you find that the interstitial protein concentration does not affect the filtration rate. These two major diversions from the original Starling Principle make enormous contributions in our understanding of edema, but as of yet they are not a part of mainstream education.

References

Corresponding author:
Edward S. Crockett
College of Medicine, University of South Alabama
5851 USA Drive North,Mobile AL, 36688, USA
Email: esc301@jagmail.southalabama.edu
This article will highlight the educational and learning materials on the PVRI website.

The issue of exercise and pulmonary vascular diseases, particularly pulmonary hypertension, has been of great interest to many these last thirty years (Presentation 1). Exercise has been useful for the diagnosis, the prognosis, and the total management of pulmonary hypertension patients. I would like to concentrate here on the issues of exercise-induced pulmonary hypertension (EIPH), a concept which has been hotly debated for the last twenty years, most notably during the Nice World Congress meeting in 2013 by a special taskforce led by Marius Hoeper, FPVRI1 (Presentation 2). The taskforce agreed that the definition for pulmonary hypertension should remain as follows: ‘pulmonary hypertension is defined as average pulmonary pressure of 25 mm Hg at rest as measured by right heart catheterization’. However, no agreement could be reached on the correct terminology, as referring to a patient who has a PAH level between 20 and 24 mm Hg as ‘borderline pulmonary hypertension’ was not accepted. The ambivalence continued as the debate further considered the concept of exercise induced pulmonary hypertension. Previously, part of the definition of pulmonary hypertension was the presence of 30 mm Hg or more during exercise. However, this definition has a lot of weakness, because the level, exercise type and posture (standing or sitting) was not specified, and further, pulmonary pressure varies with age. It has been noticed that different age groups showed no significant difference in pulmonary pressure at rest, but during exercise PAH was significantly higher in older patients (here defined as fifty years of age and older). Therefore, it was agreed amongst the Nice taskforces that it is impossible to define a cut-off value, and the recommendation was made to eliminate this criteria from the definition of pulmonary hypertension. This decision was not taken lightly, and was considered an interesting and somewhat controversial development. It also created confusion, as the last twenty years have produced many publications in which the cut off value of 30 or 45 mm of Hg by echocardiography was used as a valid definition of the clinical condition EIPH (Presentation 2).
Let us consider for a moment the technical issues of exercise in evaluating patients or volunteers. We know that right heart catheterization is the golden standard. But engaging in proper exercise during catheterization sessions is not at all simple. In contrast, performing exercise during an echocardiographic examination is possible and relatively easier. It is well accepted that echocardiographic measurement of the pulmonary vascular parameters can be used successfully in the pathophysiological studies, but it is insufficient for individual clinical diagnosis, as the cut-off measurements are very wide compared to the right heart catheterization measurements. Recently, some centres began to introduce invasive cardiopulmonary exercise testing (CPET) to assess the pulmonary vascular hemodynamic parameters (Presentation 4 and Presentation 5). CPET has many advantages, but can be considered semi-invasive. Additionally, the major issue concerning CPET is the lack of a globally agreed standardization, which complicates the data interpretation and makes it very difficult to compare different publications and results.

To truly appreciate the role of exercise in the pulmonary circulation, we must return to basic physiology. The pulmonary circulation is (broadly speaking) one simple loop when compared to the systemic circulation, which has multiple open loops each with its own auto-regulation. However, pulmonary circulation has a very high capacity in comparison to the systemic circulation, and in fact has the same cardiac output and the same volume of blood for each cardiac beat as the systemic circulation. It is interesting to note that the cardiac output by echocardiography is correlated to the pulmonary pressure. This correlation was assessed recently by Robert Naeije et al., using both echocardiography and cardiac catheterization and showed some reasonable concordance (see also Presentation 6). The exercise therefore will stress the pulmonary circulation, and that causes an increase in cardiac output and left
arterial pressure. Argiento et al. in an article published two years ago, show that the positive relations of the cardiac index and the pulmonary pressure is slightly but not significantly lesser in females than in males. Additionally, the pulmonary pressure during diverse activities at different times of the day varies a great amount. This indicates that many other factors and stimulations, aside from exercise alone, may also contribute to changes in the pulmonary circulation during exercise. Of great value to our clinical practise was the observation that age is the most important factor with regards to the pulmonary pressure response to exercise. Although there are slight changes in the pulmonary pressures, those changes are exacerbated and more prominent in patients who are over the age of fifty. This was clearly demonstrated in a series of studies by Kovacs et al. Naturally, the individual patient’s position may vary. For example, it has been shown as early as in 1989 by Bob Reeves et al. that the pulmonary pressure changes to the workload vary depending on a number of factors- including even whether exercise is performed in a supine or upright position. Additionally, in a paper published in 2010 Argiento et al. observed that the pulmonary arterial pressure and cardiac output reverted back to its baseline level very quickly within the first five minutes after exercise. This suggests to us the importance of performing the measurement of exercise-induced hemodynamic changes in the pulmonary vasculature at the maximum exercise level, and not during the very early resting period. Admittedly, the period post-exercise is practically more accessible, but due to the fact of the rapid normalization of the hemodynamics, it is not ideal.

The reviews of the literature published regarding changes in the pulmonary pressures in different groups using echocardiography have been of great interest, but unfortunately do not show a consistency, as reviewed recently by Sagger et al.

It has also been observed that other lung diseases and conditions, such as chronic obstructive pulmonary disease (COPD), heart failure or high altitude, will change the relation between cardiac index and pulmonary pressure. This will shift the curve more steeply to the left compared to both controls and patients with primary pulmonary hypertension, suggesting that exercise induced pulmonary hypertension will probably play a more important role in the COPD or lung
Exercise-Induced Pulmonary Arterial Hypertension

- EIPH is a clinical and pathophysiological entry
- EIPH pathophysiologically is complicated
  - Multifactorial variation
  - Gender variation
  - Age Variation
- It is difficult to evaluate clinically
  - Currently it is not possible to define a cutoff value
  - Nice WSHIP recommended eliminating Exercise cutoff criteria
- Although the Guidelines for the Echocardiographic Assessment of the Right Heart in Adults of the American Society of Echocardiography and ACC (2010) included an upper limit of 43 mm Hg should be used in patients at non-increased workloads.
- Technically we do not have standardization technique to evaluate these patients.

Figure 2: Some features of the exercise induced pulmonary hypertension (see text below and Presentation 2)

Figure 3: Hypothetical scenario depicting relationship between the EIPH as an intermediary phase of normal and established pulmonary hypertension (see text below and Presentation 2)

diseases with increased pulmonary pressure, as well as in left heart failure (Figure 1). Therefore, despite all that has been published in the last twenty years, exercise induced pulmonary hypertension is still considered a poorly understood entity. We cannot deny that this condition exists physiologically- but our problems relate to its definition and its clinical value. It is still unclear whether its diagnostic value lays in the pathogenesis, i.e. its contribution to the development of full clinical presentation of pulmonary hypertension, or whether it should be considered an intermediate or early stage for the future development of pulmonary hypertension. Those who believe the latter think that EIPH is an early and more treatable phase of the ensuing pulmonary hypertension. Others believe that with stable guidance, it can probably be considered a pre-clinical situation for pulmonary arterial hypertension in the asymptomatic patient (Figures 2 and 3). In the studies done by Gruning et al., it was found that certain families that had familial exercise-induced PH could help differentiate between those that had a normal pulmonary arterial systemic pressure response to exercise and those who did not. The authors believe that for some of these patients, EIPH could likely contribute to the development of future pulmonary hypertension. Therefore, it would be beneficial to diagnose these patients early, even beyond genetic profiling. It has also been shown, via the standard Bruce protocol exercise, that in certain forms of pulmonary arterial hypertension such as scleroderma, as many as 46% of patients may experience an increase in pulmonary arterial systolic pressure to more than 35 mm of Hg. This has been demonstrated by many authors over the last 10 years. Some believe that this could be very important diagnostic criteria for the evaluation of these patients.

Tolle et al., studied a group of patients who had been referred for testing on dyspnoea and aetiology, to differentiate cardiac from pulmonary limited exercise and many other conditions. They noticed that 48% of patients had pulmonary venous hypertension, whilst only 23% of them would develop pulmonary arterial hypertension with many other conditions. The details of this study can be watched in the presentation by David Systrom on the PVRI website (Presentation 4). The investigators noticed that the patients who had EIPH usually are in between the ‘normal’ and the ‘established PH’ measurements regarding the hemodynamic behaviour of the VO2 versus the main PAP. Further, the VO2 was used as a surrogate for cardiac output, and overall this suggested that the exercise induced pulmonary hypertension was an intermediate phase, strengthening the theory that EIPH is an early stage before full-blown development of pulmonary arterial hypertension (Figure 3 and Presentation 7). Therefore, it is probably considered a continuum of the pathophysiology and the early manifestation of pulmonary arterial hypertension. Although we mainly concentrate on pulmonary arterial hypertension, EIPH also plays a very im-
important part in the diagnosis and management of diastolic heart failure patients, as well as in those with COPD (Presentation 7 and Presentation 8). It has been shown that in patients with diastolic heart failure, exercise-induced pulmonary hypertension has a worse prognosis compared to those who do not have EIPH.

In conclusion, exercise induced pulmonary hypertension should certainly be characterised as a clinical and pathophysiological entity. Its pathophysiology is complicated, and there are multifactorial variations, including gender and age. The major difficulty lies in clinical evaluation, and is firstly due to the lack of a defined cut-off value. Secondly, its removal from the Nice classification, and thirdly, the lack of a standardized technique for patient evaluation further complicate clinical evaluation. Additionally, we do not know EIPH’s clinical significance, whether it’s a pre-clinical stage of pulmonary arterial hypertension or a continuum of the pathophysiological process, or whether it is indeed a separate clinical entity and has any prognostic significance in patients with pulmonary arterial hypertension similar to that seen in heart failure. Moreover, we also do not know if it would help in genetic counselling. Therefore, more active and serious research is urgently needed to improve the definition, assess the methodology and to evaluate the impact of EIPH, the exercise capacity and the performance of the patient, and to assess the role (if any) it plays in the development of right ventricular dysfunction. This leads us to the final point that some form of consensus report or guidelines on exercise stress tests in pulmonary hypertension patients are needed, which has not yet been developed until now.

REFERENCES:

Corresponding Author
Ghazwan Butrous, FPVRI
Professor of CardioPulmonary Sciences
University of Kent, Canterbury
Canterbury, Kent
United Kingdom
Email: g.butrous@kent.ac.uk
Introduction

Pregnancy in women with pulmonary hypertension (PH) is known to be associated with significantly high morbidity and mortality rates, with an estimated mortality between 30% and 56%.1,2,3 The physiological changes that occur during pregnancy and the peripartum period are poorly tolerated. During pregnancy, an index of suspicion should exist for common conditions associated with pregnancy that can be complicated by PH, as these need to be evaluated thoroughly during this critical period. These include pulmonary and amniotic fluid embolisms, which are very common and mostly fatal. Most of the maternal PH-associated deaths occur during labor or within 1 month post-delivery.3 The clinical features of PH are nonspecific during pregnancy, and as a result these patients are often missed. Generally Imaging workups are the gold standard when managing these patients; however they may cause undesirable radiation exposure to the fetus. Pulmonary artery catheterization remains a well-regarded method for diagnosing pulmonary hypertension, although its use in pregnancy and in the intensive care unit has slowly fallen out of favor. Goal-directed bedside echocardiogram and lung ultrasonography are the strongly recommended modalities, and these do provide attractive alternative evaluator approaches in these patients.1

Physiological changes during pregnancy and peripartum period

During pregnancy, multiple physiological changes take place which may further impact on the hemodynamic ramifications in PH.

Virtually every organ in the body is affected during pregnancy. The most important and significant change in the cardiovascular system is increased blood volume, which may increase almost 50% above the non-pregnant level at its peaks, during the second to the third trimester of pregnancy.4 Additionally, there are cardiovascular parameters which have added effects during pregnancy. These include heart rate and stroke volume, which lead to a subsequent increase in cardiac output. During normal pregnancy both the systemic and pulmonary vascular dilate, leading to a decrease in systemic (SVR) and pulmonary vascular resistance (PVR). In the presence of PH during pregnancy, pulmonary vascular disease prevents the fall in PVR, leading to a further rise in pulmonary arterial pressure (PAP) with increased cardiac output.5 All these have significant bearing on the overall cardiovascular system during pregnancy. During the peripartum or post-delivery period, there is subsequent decrease in preload from blood loss and of anesthetic. The converse is also true in that there is increased preload from relief of the inferior caval obstruction (by the uterus), or additional blood return from the contracting uterus and increased fluid intake during labor (iatrogenic). This results in an increase of SVR and PVR and leads to decreased ventricular contractility and function.3 All these changes may be poorly tolerated during this critical period of pregnancy.

Diagnosis approach pulmonary hypertension during pregnancy

I. Clinical parameters

The standard approach during the evaluation of pulmonary hypertension in pregnancy simply starts with a basic symptomatology evaluation. The symptoms of PH in pregnancy can be very non-specific, and similar to those
of normal physiological changes. Generally the symptoms of PH will include chest pain, cough, and shortness of breath or dyspnea, and all these are common in normal pregnancy. Additionally, patients with right heart failure may present with lower extremity swelling, dizziness, fatigue or syncope: all of which may indicate PH, or normal pregnancy. As a result, this will pose a serious challenge to the attending clinician. The physical examination of these patients (including precordial examination) with PH and right ventricular failure would reveal an elevated jugular venous pulse, a palpable and loud pulmonic component of the second heart sound and a palpable right ventricular heave and systolic murmur of tricuspid regurgitation. It is important to evaluate the pulmonary or the lungs as these will rule out any underlying parenchymal disease. In addition, it is very important to determine any underlying left sided valvular heart disease, left ventricular dysfunction or pulmonary venous hypertension.

II. Relevant Blood or Biochemical Tests
It is mandatory to risk stratify any patient with a suspicion or diagnosis of PH during pregnancy as the prognosis might be dismal, especially in those with advanced disease. The most important blood investigations include full screening for rheumatologic or common connective tissues disease, for example systemic lupus erythematosus. In addition to these, there are very important biomarkers used for screening, prognostication and for follow-up of these patients. These biomarkers are also very useful in guiding patients’ management, and may include brain natriuretic peptide (BNP), which is additionally useful for monitoring chronic pulmonary arterial hypertension (PAH). In pulmonary embolism, BNP can stratify patients regarding risk for development of right ventricular failure. Troponin I leak is very useful for predicting mortality. D-Dimers are also very important to rule out pulmonary embolisms in these patients. These biomarkers should be used in conjunction with the attending clinician’s best judgment and as additives to other modalities.

III. Chest Radiography
Chest radiography (CXR) might be helpful with the evaluation of PH patients; however its utility in the high care setting might be limited. The typical findings on CXR in pulmonary hypertension will depend on the chronicity and severity of pulmonary hypertension and these would include right ventricular hypertrophy or enlargement, right atrial enlargement and enlarged pulmonary arteries. The CXR is recommended for identifying parenchymal abnormalities and could be helpful if there is suspicion of a potential pulmonary embolism. However, some of these features may not be obvious on CXR. Other imaging modalities recommended in pregnancy when suspecting pulmonary hypertension/pulmonary embolism would include lung scintigraphy and computed-tomographic pulmonary angiography (CTPA). It is very important to take precautionary measures to prevent radiotherapy exposure to the fetus.

IV. Right Heart Catheterization
Generally the right heart or pulmonary artery (PA) catheterization is the gold standard for the diagnosis of PH. However, its use has fallen out of favor in the critically ill patients. Most studies recommend the placement of PA catheters for patients admitted to the intensive care unit with severe PH and RV failure. Yet its use has not been associated with improved survival and there is an increased risk of pulmonary artery rupture and thrombosis. Right heart catheterization hasn’t been used routinely in pregnancy as it is associated with risks both in the mother and fetus.

V. Ultrasound modalities recommended for pulmonary hypertension in pregnancy
Compression ultrasound (CUS) has a proven sensitivity of 97% and a specificity of 94% for the diagnosis of proximal deep venous thrombosis (DVT) and this should be recommended as a standard assessment in pregnancy. Ultrasound is a useful tool and is important to implement in the critical care setting, and should be used in pregnancy when there is a suspicion of DVT. Echocardiography should also be performed in these patients, as it provides direct visualization of the right ventricle and other additional abnormalities. Lung ultrasonography may help differentiate the causes of PH in critical care and minimizes ra-
Common Causes of Pulmonary Hypertension in Pregnancy

The common causes of PH in pregnancy are reported in Table 1. Pregnancy is a physiological condition which is characterized by an increased risk of thromboembolic complications. Pulmonary embolism is regarded a common cause for further thromboembolic issues, and one of the most crucial risk factors to rule out in pregnancy. It is also essential to rule out amniotic fluid embolism in a patient with PAH, as it is commonly associated with acute right ventricle failure and can lead to death. However, it is important to consider other common causes as highlighted in Table 1 and these include collagen vascular diseases and congenital heart diseases.

<table>
<thead>
<tr>
<th>Cardiac diseases*:</th>
<th>Congenital heart diseases: e.g. atrial septal defect, persistent ductus arteriosus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left sided heart diseases: Mitral valve disease, aortic valve disease, left ventricular dysfunction</td>
</tr>
<tr>
<td>Respiratory diseases:</td>
<td>Obstructive lung diseases (e.g. asthma, bronchiectasis)</td>
</tr>
<tr>
<td></td>
<td>Parenchymal lung diseases (e.g. idiopathic pulmonary fibrosis)</td>
</tr>
<tr>
<td></td>
<td>Thoracic abnormalities (e.g. kyphoscoliosis)</td>
</tr>
<tr>
<td>Thromboembolic diseases, including amniotic fluid embolism*</td>
<td></td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease</td>
<td></td>
</tr>
<tr>
<td>Collagen vascular diseases*</td>
<td></td>
</tr>
<tr>
<td>Primary pulmonary hypertension, including drug-related*, infections like human immunodeficiency virus*</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Causes of Pulmonary Hypertension**

General measures of Pulmonary Hypertension during Pregnancy, Labor, and Postpartum

Improved survival in pregnancy and PH is attributable to the new treatment modalities, including incorporation of a multidisciplinary approach. There is no standardized approach to the management of PH in pregnancy in the current era; successful outcomes are heavily dependent on a methodical approach individualized to each patient in a dedicated clinical care setting. The basic overall approach for the management of PH with right ventricular failure are maintaining right ventricular function and reducing pulmonary vascular resistance, and these principles apply to PH in pregnancy as well. Fluid resuscitation and various vasopressors are used with caution. PH-targeted therapies have been utilized cautiously in pregnant women and require full understanding with regards to their safety in pregnancy. Mainstay therapy for pulmonary embolism is anticoagulation, and the treatment for amniotic fluid embolism predominately supportive care. Multidisciplinary team approach is therefore crucial to achieving successful outcomes in these difficult cases.

Special Management of Pulmonary Hypertension during Pregnancy and Labor

I. Pulmonary embolism

Pulmonary embolism (PE) is the most common cause of acute decompensation during the peripartum period. In patients with risk factors for PE should be managed cautiously during pregnancy and it is mandatory to exclude thromboembolic diseases. Heparin remains the mainstay of therapy in thromboembolic diseases during pregnancy, mainly as it does not cross the placenta and does not have teratogenic effects or carry any potential risk for fetal hemorrhage. Low molecular weight heparin (LMWH) is a recommended alternative as its safety during pregnancy has been demonstrated. The main pitfall however is that the two require anti-Xa levels monitoring with dose adjustments. These issues make them unfavorable in real clinical practice, negating their choice over unfractionated heparin. The next line of therapy is coumadin derivatives; however, these cross the placenta and are associated with embryopathy. Warfarin in particular is associated with embryopathy during the first trimester of pregnancy and can cause fetal hemorrhage; nonetheless, the current evidence suggests that if given at a dose of less than 5mg per day, the risk of embryopathy is quite low.
Pregnancy is commonly one of the exclusions in clinical trials, and as a result there is not enough evidence on use of thrombolytic therapy in pregnant patients and data on thrombolytic therapy is generally limited to case reports. In other conditions, e.g. acute myocardial infarction, thrombolytic therapy is considered, as with pulmonary embolisms or venous thromboembolisms. The risk of major bleeding should be anticipated with the use of thrombolytic therapy.

II. Amniotic fluid embolisms
Supportive measures are the mainstay of treatments in amniotic fluid embolisms (AFE) patients and the treatment modalities should be to maintain adequate cardiorespiratory in the form of oxygenation, fluid resuscitation, vasopressors, and/or inotropes, and correct coagulopathy. It is very important to consider cardiopulmonary bypass, extracorporeal membrane oxygenation, and intra-aortic balloon counterpulsation as these have been used successfully in previous reports. Newer alternatives include the ventricular assist device (RVAD), which should be considered in severe PH, in particular those with right ventricle failure. In such a case, urgent delivery of the fetus should be performed. This will require a multidisciplinary approach including a pediatrician, cardiologist, surgeon and neonatologist.

Special considerations and precautions in patients who present with pulmonary hypertension in the peripartum period
Peripartum period is the most crucial time to closely monitor the PH patients, as that is the time when most maternal deaths occur. It is especially important to pay special attention to pulmonary hypertensive crisis and systemic hypotension. In addition, these patients are prone to develop hypoxemia, bradycardia, pulmonary thromboembolism, and cerebrovascular attack (including convulsions and bleeding tendencies with or without anticoagulant therapy). It is also important to pay special attention to the development of peripartum cardiomyopathy, which may have some influence on post-partum recovery.

Mortality Risk for Mother and Fetus in a Patient with PAH
In the past, the mortality risk in pregnant patients with PH was considered to be significantly high. With retrospective reviews, in a series of 125 pregnancies the mortality risk was reported at 30% in PAH patients, and 36% in pulmonary hypertension associated with Eisenmenger syndrome. However, this was found to be lower than the reported mortality of 56% in patients with PAH associated with other conditions, including those with chronic anorexigen use, collagen vascular diseases, pulmonary thromboembolic disease and chronic liver diseases. These led to more research and subsequently progress in the form of new therapies, which are now available and give hope for further reduction of maternal mortality. However, even though the mortality decreased significantly, maternal mortality rates still remain high. The rate of fetal mortality, heavily associated with maternal death, was also high and reached 7% to 13% in various reports.

Conclusion
Pulmonary hypertension in pregnancy is associated with high morbidity and mortality as pregnancy related changes are poorly tolerated in these patients. Most of the deaths occur during the last month of pregnancy or within the first month post delivery. Most fetal deaths are related to maternal deaths. The symptoms of PH can be very similar to those of normal pregnancy, and as a result these patients can be very easily missed during the evaluation. Though right ventricular catheterization is the gold standard for diagnosing PH, its use in pregnancy is associated with both maternal and fetal risks. Pulmonary embolism and amniotic fluid embolisms (AFE) are regarded as the most common and crucial causes of PH in pregnancy. There are currently no standardized measures to treat pulmonary hypertension in pregnancy. However, anticoagulation and supportive measures are the mainstay of treatment for pulmonary embolism and AFE respectively, as these are quite common in these patients.

References:

Corresponding author:
Dr. Mamotabo R. Matshela, MB, CHB
University of Kwa-Zulu Natal,
Durban, South Africa
Email: mamotabomatsh@gmail.com
Did you know?

Pulmonary Arterial Hypertension and HIV

DID YOU KNOW...

... that incidence of Pulmonary Arterial Hypertension (PAH) is increased in people infected with the Human Immunodeficiency Virus (HIV)?

Since its discovery in the early 1980s, HIV has become a pandemic. In 2008 alone, more than 33.4 million people were living with HIV, whilst over 25 million people died from it¹. Today, the number of infected people is still growing. Because Highly Active Anti-Retroviral Therapy (HAART) is lengthening life expectancy of HIV-positive individuals, there is increased incidence of secondary complications associated with infection, such as Secondary Pulmonary Arterial Hypertension¹. PAH occurs when the lumenal diameter of the pulmonary artery—the blood vessel that carries blood from the right ventricle of the heart to the lungs—decreases due to cell proliferation and migration (Fig 1). This increases the pressure within the pulmonary artery. Normal pulmonary artery pressure is ~15 mmHg, while a hypertensive pulmonary artery pressure is > 25 mmHg at rest. This increased pulmonary artery pressure forces the heart to work harder. As in the case of a bodybuilder “pumping iron”, when the heart works harder, the muscle grows larger. However, this growing heart tissue reduces the amount of blood that can be pumped from the right ventricle and can lead to heart failure. The pathology associated with HIV-related PAH is similar to that found in other forms of PAH, and the cause is unknown². These pathologies lead to shortness of breath, fatigue, and life-threatening complications³. The prospect of one life-threatening illness that destroys immune function is daunting to most, yet for many people, this is a reality worsened further by another fatal disease, which destroys the ability of your heart to pump blood.

Since the first report of HIV-associated PAH in 1988⁴, evidence suggests that there is greater than a million-fold rise in incidence of PAH amongst the HIV-positive population⁵,⁶. Surprisingly, most of the research in this field has only taken place in the past decade, likely due to the increased incidence within this group. One of the challenges in treatment of secondary PAH in HIV patients is the necessity to treat the PAH without having a negative impact on the retroviral treatment⁷. In order to overcome this challenge in a still growing HIV-positive population, we need far more research in this field. Until then, people with HIV will still be at greater risk for developing PAH.

REFERENCES:


Corresponding author: Ryan Viator
Center for Lung Biology, University of South Alabama,
Mobile, Al , USA
Email: ryanjviator@gmail.com
Prevalence, causes, clinical characteristics and diagnostic challenges associated with pulmonary hypertension in African and African-Americans

Epidemiology of pulmonary hypertension in the minority populations
Generally there has been very little data regarding the prevalence of pulmonary hypertension in the general and the minority populations, including African or African-Americans. The prevalence of PH was previously reported at 6.8% in community-based and larger populations, of which the majority were Caucasian (6.6%). Consistent with a recent report, African-American patients had a significantly higher prevalence of pulmonary hypertension compared to other races, both in the entire study population and in patients with idiopathic interstitial pneumonitis (IIP). In the same report, the association or prevalence of pulmonary hypertension in the African-American race was observed in other forms of PH as well. In idiopathic PH, African-American patients demonstrated a substantially increased mortality rate compared with Caucasian patients. Pulmonary hypertension tends to frequently develop at an earlier age in African-American patients with systemic sclerosis. These patients are more likely to have interstitial lung disease-associated pulmonary hypertension, and have a poorer survival compared with Caucasian patients. Due to health care disparities between races, African-Americans may be more likely to be uninsured, have less comprehensive health insurance benefits, and lack adequate access to care and costly treatments than other racial groups. Past research indicates a greater percentage of African-Americans than caucasians dying of PH, a difference which has increased over the past twenty years. Another study showed a higher risk of death for African-Americans with pulmonary arterial hypertension (PAH) compared with other racial groups, even after consideration of severity of disease and use of therapies.

INTRODUCTION
Pulmonary hypertension (PH) is defined as a resting mean pulmonary arterial pressure (PAP) of greater than 25 mm Hg at rest or 30 mm Hg on exercise. Although right heart catheterization is mandatory to make the diagnosis, it is not always feasible or practical to perform in daily practice. Alternatively, due to its easy accessibility and non-invasive nature, Doppler echocardiography is frequently used as a screening tool for PH in populations to estimate the pulmonary arterial systolic pressure.

Pulmonary hypertension is associated with increased morbidity and mortality, with clear cost implications from recurrent hospital admissions, prolonged hospital stay and chronic medical use. Left heart disease and chronic pulmonary diseases are well-recognized risk factors for PH and are prevalent in the minorities, including the African or African-American community. The clinical classification of pulmonary hypertension was revised to identify five major groups (Table 1). The cause of PH is of critical importance as it defines subsequent treatment options, and those with pulmonary arterial hypertension (Table 1, group 1) can be treated with selective pulmonary arterial vasodilators. Yet there is often a delay from first symptoms to diagnosis, as making the diagnosis of pulmonary hypertension can be challenging. This delay can impact negatively on the overall management of PH patients.
### Table 1. Pulmonary Hypertension World Health Organisation (WHO) clinical classification system (Dana Point 2008)\(^\text{11,12}\)

<table>
<thead>
<tr>
<th>Group 1. Pulmonary arterial hypertension (PAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic (IPAH)</td>
</tr>
<tr>
<td>Hereditary (HPAH)</td>
</tr>
<tr>
<td>Bone morphogenetic protein receptor type 2 (BMPR2)</td>
</tr>
<tr>
<td>Activin receptor-like kinase 1 gene (ALK1), endoglin (with or without haemorrhagic telangiectasia)</td>
</tr>
<tr>
<td>Unknown etiologies</td>
</tr>
</tbody>
</table>

| Toxins and Drug Induced                        |
| Associated with other Diseases                |
| Collagen vascular diseases                    |
| Infections, e.g. human immunodeficiency virus (HIV) |
| Chronic liver diseases, e.g. portal hypertension |
| Congenital heart diseases (CHD)               |
| Schistosomiasis                               |
| Chronic haemolytic anaemia                    |

| Persistent pulmonary hypertension of the newborn (PPHN) |

<table>
<thead>
<tr>
<th>Group 1. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Group 2. Pulmonary hypertension secondary to left heart diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valvular heart disease: mitral or aortic valve</td>
</tr>
<tr>
<td>Systolic or diastolic dysfunction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3. Pulmonary hypertension due to lung diseases and/or hypoxemia</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Group 4. Chronic thromboembolic pulmonary hypertension (CTEPH)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Group 5. PH with unclear and/or multifactorial mechanisms</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Haematological disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>myeloproliferative disorders</td>
</tr>
<tr>
<td>post-splenectomy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>sarcoidosis</td>
</tr>
<tr>
<td>pulmonary Langerhans cell histiocytosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycosgen storage disease</td>
</tr>
<tr>
<td>thyroid disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>tumoral obstruction</td>
</tr>
<tr>
<td>fibrosing mediastinitis</td>
</tr>
<tr>
<td>chronic renal failure on dialysis</td>
</tr>
</tbody>
</table>
The cause for these differences in outcomes in developed countries is unknown. Much of the statistical evidence on PH among people of African descent is based on death rates, indicating a lack of diagnosis while there is still a chance to save lives. Pulmonary hypertension was also reported to be common among heart failure patients, and was associated with worse outcomes among Africans. It is recommended that patients presenting with heart failure or symptoms be screened for pulmonary hypertension, and most importantly, precautions should be taken immediately in the presence of pulmonary hypertension in terms of management and for prognostic purposes. Additional epidemiologic initiatives also are needed to ascertain prevalence and incidence of various PH disease entities such as pulmonary arterial hypertension. In a study presented at CHEST 2006, the 72nd annual international scientific assembly of the American College of Chest Physicians (ACCP) revealed that racial disparities exist in PH mortality and morbidity, with African-American women exhibiting the highest mortality rate when compared with all other groups.

Causes of pulmonary hypertension in Africans and African-Americans

Left heart disease and chronic pulmonary diseases are well-known and common risk factors for pulmonary hypertension and are prevalent in the African and African-American community. The existing reports from studies have demonstrated an increased prevalence of PH with increasing age and are independent of comorbidities and cardiopulmonary function. The prevalence ratio increases 10 times in older people compared to those of a younger age ( >65 versus 45 years). Risk factors for increased left atrial pressure are also associated with increased risk for pulmonary hypertension and other related diseases, such as systemic hypertension, diabetes and obesity, in Africans or African-American populations. According to some African reports, human immunodeficiency virus (HIV) is emerging as one of the most common and important causes of pulmonary hypertension in Africans. In some studies, both sexes were affected by idiopathic PAH, whereas significantly more women were affected by HIV and connective tissue related PAH. Based on the Heart of Soweto study, the majority of these cases were of African descent and originated from somewhere other than Soweto, which is more urban. In the same report, women were almost two-fold more likely to present with PAH while those with low levels of education and originating from urban areas were less likely to present with PAH compared with those with higher levels of education.

Demographic & Clinical Characteristics Associated with PH

Based on previous reports, the prevalence ratio of pulmonary hypertension increases with age, female, being obese, or having diabetes, higher pulse pressure, severe left heart valve disease or chronic lung disease. All these are some of the parameters to look for in daily clinical practice when evaluating a patient with (or suspected of having) PH. Pulmonary hypertension is characterized by insidious onset and progressive clinical deterioration. The symptomatology of PH could be very diverse and non-specific. These symptoms would include dyspnea of breath, episodes of chest pains, generalized fatigue, dizziness or syncope, cough and palpitations. Dyspnea has been reported as the most frequently encountered symptom and most importantly the clinical signs in these patients are predominantly those of right sided heart failure. However, the clinical signs are also guided by the chronicity and severity of pulmonary hypertension. Due to lack of access to health facilities and poor socioeconomic backgrounds in most of the minority populations, patients tend to be symptomatic for a longer period of time before they present to the health centers for medical attention. Unfortunately, this means that the window to identify these patients earlier and plan their management accordingly is significantly smaller.

Diagnostic Evaluation of Pulmonary Hypertension, Are There Any Differences?

I. Screening and Diagnostic evaluation

The diagnostic approach for PH should be applied similarly; however this should be guided by the clinical setting and the attending clinicians’ judgment. Patients with PH must be evaluated using a multimodality approach.
to ensure a correct diagnosis and basal evaluation as well as a prognostic assessment. The standard transthoracic echocardiographic examination remains the first line of multimodality imaging and this allows for the evaluation of pulmonary pressure and right ventricular changes in relation to high afterload. However, other imaging modalities are widely used as part of the standard protocol, and include Chest-XR and CT scans (including high resolution computer tomography: HRCT).

II. Noninvasive estimation of pulmonary arterial pressure (PAP) using transthoracic echocardiography (TTE)

With the existence and easy accessibility to standard two-dimensional echocardiography, particularly Doppler echocardiography, the assessment of pulmonary arterial pressures is quite feasible. However, because of its intrinsic operator dependency, screening can be challenging. Transthoracic echocardiography remains the most financially viable and easily accessible modality in the minority population, especially in the rural communities. Yet the challenges remains, as some hospitals lack echocardiography, whilst other centers that have access to this tool still struggle with a lack of expertise in this technology. As such, difficulties remain in the screening and diagnosis of early pulmonary hypertension in most of these patients. However, some of the most important technical challenges include the presence of a tricuspid insufficiency.

III. Exercise Echocardiography

Exercise echocardiography is one of the advanced echocardiographic modalities that is used to assess systolic PAP in several groups of patients. It is predominantly used in patients with chronic lung diseases, congenital heart diseases (including atrial septal defects), valvular heart diseases, cardiac transplantation, and high altitude pulmonary diseases. Exercise echocardiography should be used in PH.

IV. New modalities in noninvasive screening

Cardiac magnetic resonance (CMR) is a reliable modality and can be used both at rest and during exercise or acute vasodilator testing. However, its use as a routine screening test is not mandatory.

V. Biochemical Markers

Biomarkers, such as brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP), may be quite useful in early detection of PAH. The BNP can be used both for monitoring and prognostication depending on the patient’s symptomatology and disease stage. It is important to note that the incidences of PH and clinical characteristics may differ because PH is commonly associated with other conditions, which are also associated with elevated BNP.

VI. Genetic Testing

Performing testing for genetic mutations should be guided by the clinical scenario, as these could have potential risks and benefits following the tests. There are limitations with accessibility of the tests and results thereof. It might be very difficult in some centers for genetic testing and counseling. The molecular testing should ideally be performed in clinically approved and certified molecular genetics laboratory, which may not be available in some centers. This poses a huge challenge to genetic screening as part of the work up for PH.

CONCLUSION

Pulmonary hypertension (PH) is a common entity and can easily be detected with the implementation of echocardiography. PH has been reported to be quite prevalent in minority populations, in particular the African and African-American populations, and more so in women. Apart from the common risk factors for PH, age, chronic obstructive lung disease, and significant left-sided heart diseases (including valvular heart disease), are some of the most common and important determinants of PH in the minority populations. The presence and severity of PH is associated with poor outcomes in African-Americans with underlying cardiopulmonary disease. As a result, it is very important to promptly identify these patients very early in the course of the disease. The better outcomes will obviously be influenced by early diagnosis and treatment.

REFERENCES

1. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary...
Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009;34:1209-1263

PVRI and the CMS/CTS present

8th PVRI Annual World Congress on Pulmonary Vascular Diseases
January 15-18 2015, Guangzhou, China

Click here to register
INTRODUCTION
Carcinoid symptoms typically occur between the fifth and seventh decades of life with a mean age of 55–60 years. Carcinoid heart disease is reported to be a rare but important cause of right sided valvular heart diseases and its occurrence is associated with significant morbidity and mortality due to right heart failure. Cardiac involvement occurs in at least 50% of patients with florid carcinoid symptoms. In patients with carcinoid heart disease, right atrial and right ventricular enlargement is present in up to 90% of cases and ventricular septal wall motion abnormalities are seen in almost half of the cases. The tricuspid valve leaflets and subvalvar structures are often thickened, shortened and retracted, leading to incomplete coaptation and usually moderate or severe tricuspid regurgitation (Figures 1 and 2). The continuous wave Doppler profile of tricuspid regurgitation shows a characteristic dagger shaped spectrum with an early peak pressure and rapid decline. The pulmonary valve may also be thickened and retracted, leading to pulmonary insufficiency and less commonly, pulmonary stenosis. However, the occurrence of pulmonary hypertension (PH) in carcinoid heart diseases is quite rare, unless the patient presents with left heart valve involvement or intracardiac shunt.

CASE PRESENTATION
The clinical case is a 78 year old African male who presented with constitutional symptoms, including associated lower limbs and abdominal swelling for a period of three to four months. Additionally, he reported a history of lower abdominal mass and skin hyperpigmentation, which had progressively gotten worse over the same period of time. At time of presentation, he was a pensioner and previously worked as a domestic worker. He had no significant smoking history, nor prior surgical history. His clinical examination revealed features of pulmonary hypertension (PH), severe tricuspid regurgitation and right heart failure.

DIFFERENTIAL DIAGNOSIS
Based on his initial presentation, he was evaluated for constrictive pericarditis, which was subsequently ruled out. Cor-pulmonale was fully entertained, however carcinoid syndrome and carcinoid heart disease were suspected during echocardiographic assessment. His echocardiographic pictures are shown in Figures 1 and 2.

FURTHER INVESTIGATIONS
His 5- hydroxyindoleacetic acid was elevated more than 10 times the upper limit of normal (ULN) and octreotide scan of his liver and intestines was positive. In addition to his echocardiographic images below, his pulmonary arterial systolic pressure (PAS) was 65 mmHg with no significant left sided valvular heart disease. The transoesophageal echocardiography revealed no intracardiac shunt or significant left sided valve disease. His chest radiography revealed mild hyperinflation with clear lung fields. The CT scan of his abdomen revealed multiple lesions in the liver and ileum.

PATIENTS’ MANAGEMENT AND OUTCOME
Unfortunately the patient refused further management including surgery, and he demised a year later.
Discussion

Even though this patient was diagnosed with having carcinoid syndrome with cardiac involvement, his initial presentation was quite intriguing. The diagnosis of carcinoid syndrome was mainly suspected during work-ups, including transthoracic echocardiography. The echocardiographic features are classical of carcinoid heart diseases; however, the presence of severe pulmonary hypertension could not be easily explained as his clinical and echocardiographic finding ruled out significant left sided heart disease. Additionally, there was no intracardiac shunting noted during neither transthoracic nor transoesophageal echocardiographic evaluations. Even though the occurrence of PH in carcinoid syndrome is thought to be rare, one small study reported four of sixteen patients who presented with mild PH, who were also diagnosed with metastatic gastrointestinal (GIT) carcinoid disease without left sided heart disease or documented intracardiac shunt. The postulate to this is that serotonin is normally taken up by endothelial cells and platelets, and if this process is impaired or overwhelmed then PH can develop.

References


Corresponding author:
Dr Mamotabo R Matshela
University of Kwa-Zulu Natal
Durban, South Africa
Email: mamotabomatsh@gmail.com
Established in 2005, the ENTELLIGENCE Young Investigator Program is a US-based research program consistent with Actelion Pharmaceutical US, Inc.’s commitment to basic science, translational, and clinical research in the area of pulmonary vascular disease. Young investigators at universities and research institutes in the United States and Canada with innovative projects and promising careers in pulmonary vascular disease are supported by the ENTELLIGENCE program.

**ENTELLIGENCE Steering Committee (SC)**

Ronald J. Oudiz, MD  
*Program Chairman*  
LA Biomedical Research Institute  
at Harbor-UCLA Medical Center  
Torrance, CA

Harrison W. Farber, MD  
Boston University School of Medicine  
Boston, MA

Adaani E. Frost, MD  
Baylor College of Medicine  
Houston, TX

Mardi Gomberg-Maitland, MD, MSc  
University of Chicago Medical Center  
Chicago, IL

Maureen D. Mayes, MD, MPH  
The University of Texas  
Health Science Center at Houston  
Houston, TX

Evangelos D. Michelakis, MD  
University of Alberta  
Edmonton, AB, Canada

Harold I. Palevsky, MD  
Perelman School of Medicine of the University of Pennsylvania  
Philadelphia, PA

Richard M. Silver, MD  
Medical University of South Carolina  
Charleston, SC

Jason X-J Yuan, MD, PhD  
University of Arizona College of Medicine  
Tucson, AZ

Award winners receive a research grant of up to $100,000 to fund a 1-year mentored project.

**ENTELLIGENCE Milestones**

- Year established: 2005
- Review cycles completed: 9
- Awards distributed: 46
- Funding: $3,825,000

**2014-2015 Timeline**

- Letter of Intent (LOI) Submission: Sept. 18 – Nov. 6, 2014
- SC Selection Meeting: March 2, 2015
- Notify Applicants: March 23, 2015

Please visit www.ENTELLIGENCEMD.org for more information and to apply.

The Actelion ENTELLIGENCE Young Investigator Program is supported through an educational grant from Actelion Pharmaceuticals US, Inc.