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Introduction

In 2015 the PVRI grew up and became a professional, international organisation capable of addressing the huge challenge of improving the care of patients with Pulmonary Vascular Disease all over the world and facilitating research into this devastating disease.

The infrastructure is now secure. Our very capable CEO Stephanie Barwick has been in post for almost two years and her report details essential improvements in office management, staffing and accounting. But the PVRI is a membership organisation and therefore the two changes which are of central importance are:

i) the approval at the last AGM in China of the ‘Regulations of the PVRI’, the rules by which we govern ourselves, and

ii) the development of a new website which is our face to the world and the hub of our PVRI network.

The unsung heroes and heroines of the PVRI are those working in the Task Forces all over the world. National and local meetings are key to improving clinical care and meetings for 2016 in South America, India and Central Asia are already advertised on our website. Helping emphasise our commitment to finding a cure for Pulmonary Vascular Disease, we have formed a new Disease & Speciality Task Force on ‘Pre-clinical and Molecular Science’, to facilitate research collaboration across the world.

The scientific standard of our international meetings continues to improve. We continue the policy of holding the Annual Congress in a different continent every year, this year in China, in Europe in 2016 and in North America in 2017. The Drug Discovery & Development Symposium is held in North America and Europe in alternate years to encourage collaboration between the PVRI and the FDA and EMA respectively. The aim is to reduce the time from drug discovery to the patient’s bedside. In 2016 we are introducing a third Annual Conference and this will be organised by, and run specifically for, the younger members of the PVRI, the Committee for Young Clinicians and Scientists.

The PVRI’s journal Pulmonary Circulation has maintained a high standard due entirely to the drive and initiative of its Editors, Jason Yuan and Nick Morrell, ably assisted by Annisa Westcott, the journal’s Managing Editor.

The next major initiative to be launched in 2016 will be a PVRI e-learning programme which will be a modular course covering a wide range of topics from basic clinical ‘how to diagnose and treat’ modules to erudite ‘current research’ modules.

The PVRI is very grateful indeed to the Cardiovascular Medical Research and Education Fund for its continued support, and to the pharmaceutical companies and individual donors who understand and support our mission. As President of the PVRI, I would like to thank Stephanie Barwick for all her hard work and unfailing commitment to the PVRI. She is ably supported by Aaron Shefras, our media guru, and Administrative Assistant Margaret Carver. Their contributions have been essential to the advances made in 2015.

The Executive Committee is advised by the Council of the PVRI and their collective wisdom has been a great source of strength during the past two years.

We are only now beginning to exploit the huge potential of the PVRI as a global organisation committed to helping patients with Pulmonary Vascular Disease. There is much work to do, but with an enthusiastic membership and a cohort of bright young colleagues we can expect to go far.

Writing this introduction in December 2015, it’s the time to wish all members of the PVRI a very Happy New Year and success in all their endeavours in 2016.

Review from the PVRI President

2014/2015

Professor Sheila Glenshaw Haworth CBE
President PVRI
2015 has been a year of transition and consolidation. The outline below highlights some of the operational and administrative changes which took place during the year.

**New PVRI Constitution & Regulations**
A new PVRI Constitution & Regulations was compiled and ratified at the last Council Meeting and Members’ Annual General Meeting which was held in China in January 2015. The new organisational chart reflecting the Constitution & Regulations has been uploaded onto the website indicating named PVRI members who have been appointed as Chairs of Committees.

**New PVRI Office in Canterbury, UK**
In March 2015 the University of Kent gave the PVRI notice on all their office rooms due to the building being redeveloped into labs for the School of Bioscience. New suitable premises were found at 33 St George’s Place, Canterbury, Kent CT1 1UT, UK and the lease was signed on 12th May 2015 for a period of 3 years.

**New Members of Staff**
In February 2015 we said ‘Good-bye’ to Nikki Krol who has been with the PVRI for four years as the Charity’s Executive Administrator and we welcomed Aaron Shefras, who joined the PVRI on 9th February as ‘Marketing Officer’ and Margaret Carver, who was recruited on 21st September 2015 as ‘Administrative Assistant’. Both have already made a great difference to the PVRI. Aaron has been working hard on improving all our marketing materials and online communications as well as leading the development of our new website which will go live on 14th January 2016. Margaret has been busy helping out with fundraising activities as well as with content transfer to our new website.

**New Accounting System**
We have invested in a new bespoke Accounting System which allows us to accurately monitor all income and expenditure from all PVRI operations, both UK and USA. We are now in a position to produce regular management accounts for review by the Executive Committee and Finance Committee as well as the PVRI Council. A big thank you to our accountants ‘Kreston Reeves LLP’ who are based in Canterbury and helped us get everything up and running.

**Marketing Activities & New PVRI/PC Website**
**New joint PVRI/PC website**
A lot of hard work has gone into the development of our new joint PVRI/PC website which will be launched on 14th January 2016 during our Members’ Annual General Meeting. We would like to express our thanks to everyone who has been involved in making this happen, especially Aaron Shefras who has overseen the entire development process as well as our partners ‘Yoyo Creative Agency’ who have been appointed to undertake the work.

My sincere thanks go to the Committee for Young Clinicians & Scientists who have been incredibly busy undertaking a complete review of the entire e-learning materials which are available on the current PVRI website. This totals over 600 materials, including interviews, lecture recordings, images and talks. Not only did they rate the materials for content quality, they also ‘tagged’ all materials in readiness for our new website. This was a huge undertaking and we are very grateful to all our young scientists for their help.

**PVRI brochure, leaflets and advertising**
Various marketing materials have been produced during the year including a new PVRI brochure, a double-sided A4 leaflet advertising the London Drug Symposium and Rome Annual World Congress, fundraising leaflets and the 5th May concert programme. Thank you to ‘ABA Creative’ for always being at hand with design and print solutions.

Electronic adverts promoting the PVRI and our Annual World Congress in Rome were placed in the European Respiratory Society website and European Society of Cardiology website reaching out to a total of 20,000 doctors in Europe.

**Social media activities**
Aaron Shefras has taken charge of all aspects of social media including Facebook and Twitter and he also produces regular online communication reports outlining our website and social media activities. During 2015 approximately 31,000 people from across the world have visited and actively searched our website.

Regular new content and updates are now being made consistently which has resulted in an increased Twitter and Facebook following. We now have 476 followers on Twitter and 529 followers on Facebook. Our ‘5th May Charity Concert’ video was viewed by over 3,200 people making it the most popular PVRI item on all our social networks to date.

**International Scientific Meetings**
As has become tradition in the PVRI calendar, during 2015 we held two major international conferences – the 8th PVRI Annual World Congress on PVD which was held in Guangzhou in China in January and the 2nd PVRI Annual Drug Discovery & Development Symposium which was held in London in June. A big thank you to our Meeting Planner, Andrea Rich, for making sure our conferences are organised in great venues and run smoothly.

For more information on our Scientific Meetings, please have a look at pages 09-11.

**PVRI Membership Update**
The PVRI membership has increased to a total of 890 members, which are spread across 60 different countries worldwide. We are immensely proud of our international reach and global representation as the PVRI is the only global charity dealing in PVD. Thank you to everyone for your continued membership and support.

During the year, membership fees were increased to $150, although to accommodate members from poorer countries and trainees, a reduction in fees was agreed for these groups.

The following membership fee structure has been implemented:
* Annual membership fee, developed world: $150
* Annual membership fee, developing world: $75
* Annual membership fee, trainee: $50
Industry Support and Roundtable Membership 2015
I would like to express my sincere thanks to all our industry partners who have supported us during 2015 and engaged in the PVRI Roundtable Membership which is the PVRI-industry alliance. Without their continued sponsorship and support we simply could not fulfil our mission. Roundtable Members for 2015 included Bayer, Gilead, GSK, United Therapeutics.

Particular thanks go to Bayer and United Therapeutics who in addition to the PVRI Roundtable Membership have donated Travel Grants in support of the 8th PVRI Annual World Congress which was held in Guangzhou, China in January 2015. The grant from Bayer has enabled us to sponsor seven speakers to attend our China meeting and the United Therapeutics grant has allowed us to sponsor three speakers to come to China.

Discussions have already started for 2016 and I am delighted to announce that Bayer, Glaxo Smith Kline, United Therapeutics, Gilead and Belleraphon Therapeutics have expressed an interest.

Task Forces Activity
A review of all Task Forces was undertaken by the PVRI President Sheila Glennis Haworth during 2015 and all ‘Regional’ as well as ‘Disease & Speciality’ Task Forces were agreed with appointed leader(s) and updated on the PVRI website. Two new Task Forces were created – ‘Preclinical & Molecular Science’ headed by Mandy McLean, and the ‘PVD Imaging Task Force’ headed by David Kiely. Task Force meetings are planned to take place in January 2016 during the Annual World Congress in Rome. Our thanks go to all Task Force leaders for their hard work and commitment throughout the year.

For more information on our Task Forces, please have a look at pages 15-39.

PVRI Publications
Pulmonary Circulation
During 2015 we have published four editions of our peer-reviewed and flagship journal Pulmonary Circulation featuring articles. Our sincere thanks go to our Chief Editors Jason Yuan in the USA and Nick Morrell in the UK for their immense hard work. A big thank you also to Annisa Westcott, our Managing Editor, and our Publishers, University of Chicago Press.

A full report on Pulmonary Circulation is on pages 12-14.

PVRI Chronicle
Two editions of the PVRI Chronicle have been published online during the year in January and July 2015. My thanks go to the PVRI Committee for Young Clinicians & Scientists and Aaron Shefras for all their hard work in putting this together.

PVRI Grants
During 2015, the PVRI has supported its membership by awarding research and travel grants for speakers to attend various scientific meetings across the globe.

Research Grants
A research grant was awarded to the Central Asia Task Force in support of their high altitude project.

Travel Grants
15 Travel Grants were awarded during the year to various PVRI members in support of national and international PVRI meetings and initiatives. These included the 8th PVRI Annual World Congress on PVD in Guangzhou, China in January 2015, the SAPH 2015 Annual Meeting in Abu Dhabi in April 2015, the Leh Symposium in India and the Central Asia Master Class which was held in April 2015 in Kyrgyzstan.

Travel Grants for the Committee for Young Clinicians & Scientists
The most active three members of the Committee for Young Clinicians & Scientists during 2014 – Djuro Kosanovic, Michael Seimetz and Michiel de Raaf – were awarded with Travel Grants to attend the 8th PVRI Annual World Congress on PVD which was held in Guangzhou, China in January 2015. Winners of the PVRI Travel Grants 2015 will be announced during the Gala Dinner of the 10th PVRI Annual World Congress on PVD in Rome 2016.

2014 PVRI Award Winners
During the Gala Dinner of our 8th PVRI Annual World Congress in China in January 2015, we celebrated the achievements of some of our most distinguished and active members.

• The Lifetime Achievement Award 2014 was presented to Stuart Rich, USA, in recognition of his distinguished contribution to patient care and research in PVD.
• The Achievement Award 2014 went to Qadar Pasha, India, for enhancing high altitude research.
• The Certificate of Excellence 2014 was presented to the Committee for Young Clinicians & Scientists for their outstanding contribution to the PVRI and the publication of the PVRI Chronicle.

Congratulations to all our winners. The prize winners of 2015 will be announced on 16th January 2016 at our Gala Dinner in Rome.

Feasibility Report on E-learning Diploma Course on PVD
The PVRI commissioned a consultant to research the feasibility of a PVRI e-learning course on PVD which was funded by the Cardiovascular Medical Research and Education Fund and submitted by Dr. Tracy Crowther in February 2015. Following the recommendations, the PVRI Executive Committee decided to engage with Cambridge University to start the development of one pilot module to further evaluate the process prior to committing to the production of a whole course. The Executive Committee appointed one of its distinguished members, Professor Andy Peacock, to lead on this project. Discussions with Cambridge University are ongoing and we are hoping to see our first finished module in 2016.
PVRI Fundraising Activities

The PVRI held its first fundraising event, a Charity Concert, on 5th May 2015 in honour of ‘World Pulmonary Hypertension Day’. This was the first event aimed at the general public to raise awareness of the PVRI and PVD. The concert was held at the Colyer-Fergusson Music Hall at the University of Kent campus in Canterbury together with the Festival Chamber Orchestra and internationally acclaimed conductor Stephen Barlow. Over 200 people attended the concert and the total amount raised from sponsorship, donations and ticket sales was £13,549.58. The event was a huge success, receiving considerable positive feedback from attendees and sponsors. The post-concert video which was produced by Aaron Shefras was viewed by over 3,200 people.

Our thanks go to the following corporate sponsors and private donors for their support.
- ABA Creative
- Bob Laslett
- Brett Construction
- Cains Amusements
- David & Claudia Harding Foundation
- Designer Bed Co. Ltd
- Digital Beans
- Dr. Wayne Campbell
- Ian Ogders
- Ian & Sue Brown
- Kent College, Canterbury
- Kreston Reeves
- Margate Football Club
- Mr. J Phipson
- Regeneration UK
- St. Edmund’s School, Canterbury
- St. James’s Place Wealth Management
- The King’s School, Canterbury
- Waitrose, Canterbury
- Woodley Coles LLP
- WP Thompson

We would like to thank Lynette Swift who was appointed the Chair of the PVRI Fundraising Committee. Lynette’s son has been diagnosed with PVD in his early 20’s and she is keen to help the PVRI as a volunteer and raise awareness of the disease. Lynette has approached various UK based Trusts who offer funds to charities and was successful in receiving a £5,000 donation from the ‘David & Claudia Harding Foundation’ as sponsorship for the PVRI Charity Concert. Lynette is now planning our second major event to take place on 21st April 2016. This will be a fundraising dinner, cocktail reception and auction at the prestigious Foundling Museum in London.

International Collaborations

During the year we have received ongoing support from many leading universities and hospitals around the world. In particular, I would like to thank the following organisations for their collaboration during 2015.
- American Heart Association
- American Thoracic Society
- Cambridge University, UK
- Chinese Thoracic Society
- European Respiratory Society
- European Society of Cardiology
- Imperial College London, UK
- International Society for Lung & Heart Transplantation (ISHLT)
- Pulmonary Hypertension Association (PHA) in the USA
- The Royal Society of Medicine, UK
- University of Arizona, USA
- University of Chicago Press

I would like to thank everyone for their support during 2015 – our committed and hardworking staff in the UK and USA, our members all over the world, our active volunteers, our Task Force leaders, our young clinicians & scientists, our industry partners and Roundtable Members, the Cardiovascular Medical Research and Education Fund, all our supporters, corporate sponsors and donors and all members of the PVRI Council. It is all of you who make the PVRI what it is. Thank you for your help, advice and continued commitment.

Last, but not least, a big thank you to our President Sheila Glennis Haworth, for her unflinching commitment to the PVRI, her incredible hard work and her strength to steer us through the past couple of years.

Wishing you all a happy and successful 2016.

Stephanie Barwick
Chief Executive Officer
The 8th PVRI Annual World Congress on Pulmonary Vascular Disease was held this year in the beautiful and futuristic city Guangzhou, China, on 15th-18th January 2015.

The Congress was hosted by the Dong Fang Hotel, and it was organised as a joint meeting together with the 7th National Chinese Congress on Pulmonary Embolism and Pulmonary Vascular Diseases, creating a unique milieu to meet and unite both the Western and Eastern civilizations. Such a multicultural concept resulted in great enthusiasm amongst attendees who took this opportunity to discuss the most important and urgent scientific and clinical issues in the field of Pulmonary Vascular Disease (PVD), and to share valuable experiences.

The conference sessions covered a variety of scientific and clinical topics, paying particular attention to the most interesting and ‘hot’ achievements and novel findings in the recent years with regard to PVD. For example, alteration of the MicroRNAs system was described in the PVD pathology and these molecular regulators have received considerable focus in the recent past, and the lectures from Drs. Schermuly, Chan and Chun provided further insights on their role and potential therapeutic strategies, considering both the pulmonary vasculature and right heart remodeling/failure.

Furthermore, abnormally activated immune system and inflammation were recognised as culprits in the development of pulmonary hypertension (PH). Among different inflammatory cells, the macrophages were of particular interest during this congress, evidenced by valuable talks given by Drs. Zheng, Sternmark, Johns and Leopold. The group 3 of the current clinical classification of PH also received noticeable attention, and Drs. Weissmann and Aldashev shared their knowledge and expertise on the pulmonary vascular abnormalities in the context of COPD and high altitude environment, respectively.

Following the heritage and trace of Dr. Robyn Barst in paediatric research, and knowing that PH in children is very frequent across the world and there is no satisfactory therapy, lectures from Drs. Adatia, del Cerro, Díaz and Ivy further enlightened the current issues on paediatric registries, clinical trials and potential therapeutic approaches. The distinctive ‘face’ of the PH pathology in women, including all aspects from pregnancy, sex differences and hormones, contraception etc., was the subject of the lectures presented by Drs. Cockrill, MacLean, Shafer, Preston and Mandel.

The patients’ registries and novel opinions on clinical trials, covering a variety of indispensable experiences, perspectives and knowledge from all over the world (Africa, Asia, Europe, South America), comprised a large portion of the congress and resulted in interesting and thought provoking talks/discussions given by Drs. Thienemann, Wen, Jian-Guo, Kerkar, Laliberte, Corris, Díaz and MacDonald. Also, the non-pharmacologic approaches to PH, re-synchronizing the right ventricle, and compliance, cardiac output, ventriculo-vascular coupling as targets of choice etc. were the subjects covered by the lectures from Drs. Boogard, Pritzker, Moledina and Thenappan.

Finally, our PVRI Annual General Meeting was also held during the congress. Briefly, PVRI members discussed different topics ranging from the branding and communication (updated PVRI logo, promotional materials, educational website, social media presence...) to fundraising (development of the committee, establishment of a future fundraising strategies and organisation of more frequent fundraising events). In conclusion, the 8th PVRI Annual World Congress on Pulmonary Vascular Disease definitely achieved far more than expected, ultimately leading to greater understanding of PVD pathogenesis and significant improvements of current therapies. However, we still have a long way to go in order to acquire satisfactory curative strategies and options.
Leading scientists in the fields of Pulmonary Vascular Disease, right heart failure, and clinical trial designs presented some novel and futuristic treatments to their colleagues, as well as representatives from the pharmaceutical industry and regulatory authorities from the EMA.

Each topic was critically reviewed by an expert panel, which offered insightful comments and perspectives. The discussions that followed were often spirited and provocative. The programme chairpersons were John H. Newman, M.D., Stuart Rich, M.D., Anton Vonk Noordegraaf, M.D., Ph.D., and Martin Wilkins, M.D.

The meeting spanned three half-days. Some of the more novel presentations that focused on PAH included “osteoprotegerin as a promising target in PAH,” “genetically modified endothelial progenitor cells in the therapy of pulmonary hypertension” and “treating PAH by targeting BMPR2 with BMP9/10.”

The session on other forms of pulmonary hypertension included “the effects of iron supplementation on hypoxic pulmonary hypertension;” “nitric oxide synthase inhibition for COPD;” and “the repetitive use of levosimendan for right ventricular failure from pulmonary hypertension.”

The third session included controversial topics such as “conditional approval and adaptive licensing as possible new pathways for clinical trials in pulmonary hypertension;” and “combination PH therapies should be required background therapy for future registration trials.” Members of the EMA offered many enlightening views about the challenges with regulatory approval with orphan drugs.
Pulmonary Circulation Update
Annual Report 2015
2015 has been a year of growth and positive change for *Pulmonary Circulation*. The most significant change has been the instigation of author publication fees.

**Initiatives**

2015 has been a year of growth and positive change for *Pulmonary Circulation*. The most significant change has been the instigation of author publication fees. As of 1st January 2015, authors are required to pay a publication fee if the manuscript is ultimately accepted for publication (if the manuscript is not accepted, there will be no fee). The fee will be assessed at the time the author receives proofs. Not all article types are subject to the charge: for Original Research articles and Guidelines articles, the publication fee is $1,000. For a traditional Case Report (up to 1,000 words), the fee is $500, and for an Extended Case Report (up to 2,500 words), the fee is $750. For other article types, including invited articles, there is no fee.

In 2015 we published a total of 82 articles, including the final articles in our series of high quality review articles from the 2013 Grover Conference, and one Consensus Statement. We have been in communication with Thomson Reuters and are hopeful that we will receive our Impact Factor in 2016.

**Progress**

As of 1st December 2015, *Pulmonary Circulation* articles have been accessed online almost 479,000 times. This year, our UCP website has received over 96,500 visits on the List of Issues, Table of Contents, Abstracts, and Full Text (both HTML and PDF) pages combined. Cumulatively, our 397 published articles have been downloaded as PDFs over 64,000 times.

This year, *Pulmonary Circulation* has seen an increase of approximately 95% in online usage over last year, with total access to abstracts and full articles at 85,479 as of 1st December 2015, up from a total of 47,770 for all of 2014.

**Promotion**

We have continued various promotional email blasts and are continuing to grow our mailing lists.

In 2015, we have revived our newsletter, providing quality content in the form of Journal Office News, Researcher Spotlights, and Current Topics articles, as well as exciting articles from the Young Scientists Council of PVRI.

We continue to work on developing our social media presence for the journal and increasing its visibility on various platforms.

Additionally, *Pulmonary Circulation*’s Editors-in-Chief and Managing Editor continued to promote the journal at various international conferences, including the American Thoracic Society International Conference 2015, the American Heart Association Scientific Sessions, the 2015 Grover Conference, and the 8th Pulmonary Vascular Research Institute Scientific Workshops and Debates.

**Goals for 2016**

- *Pulmonary Circulation* will launch a fresh, new website as part of the re-launch of the new and improved PVRI website.
- Continue to attract and solicit high-quality article submissions.
- Continue to broaden our readership. With the instigation of social media channels and the re-launch of our website, we will continue to expand our audience and reputation.

- Increase citations made to the Journal. In an effort to ensure an acceptable impact factor for *Pulmonary Circulation*, one of our continuing main goals is to increase citations to the journal.
- Articles posted online immediately after acceptance. With *Pulmonary Circulation*’s publisher, the University of Chicago Press, we have the option to post articles online immediately after acceptance for viewing by the general audience.
- Quicker acceptance to publication date. Our acceptance to publication date goal for 2016 is eight weeks from acceptance of the manuscript to Ahead of Print publication of the final article.

**Statistics**

- N=397 articles
- Pulm Circ. Types of Articles Published
  - Editorials – (33) 8.3%
  - Review – (90) 22.6%
  - Original Research – (185) 46.6%
  - Guidelines & Other – (60) 15%
  - Case Reports – (38) 9.5%
Top 15 most accessed articles published in 2015:

1. The right ventricle under pressure: evaluating the adaptive and maladaptive changes in the right ventricle in pulmonary arterial hypertension using echocardiography (2013 Grover Conference series), Alexis Harrison, Nathan Hatton, and John J. Ryan
   Vol. 5, No. 1, March 2015. # Accesses 1418

2. Bioenergetic shifts during transitions between stem cell states (2013 Grover Conference series), Lianghui Zhang, Glenn Marsboom, Danielle Glick, Yanmin Zhang, Peter T. Toth, Nicole Jones, Asrar B. Malik, and Jalees Rehman
   Vol. 4, No. 3, September 2014. # Accesses 1392

3. Perioperative pharmacological management of pulmonary hypertensive crisis during congenital heart surgery, Nathan Brunner, Vinicio A. de Jesus Perez, Alice Richter, François Haddad, André Denault, Vanessa Rojas, Ke Yuan, Mark Orcholski, and Xiaobo Liao
   Vol. 4, No. 1, March 2014. # Accesses 1088

4. Statement on pregnancy in pulmonary hypertension from the Pulmonary Vascular Research Institute, Anna R. Hemnes, David G. Kiely, Barbara A. Cockrill, Zeenat Safdar, Victoria J. Wilson, Manal Al Hazmi, Ioana R. Preston, Mandy R. MacLean, and Tim Lahm
   Vol. 5, No. 3, September 2015. # Accesses 988

5. The response of the pulmonary circulation and right ventricle to exercise: exercise-induced right ventricular dysfunction and structural remodeling in endurance athletes (2013 Grover Conference series), André La Gerche, Timothy Roberts, and Guido Claessen
   Vol. 4, No. 3, September 2014. # Accesses 958

6. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology, Cyrus Khodadani, Wassim H. Fares and Vahid Mohsenin
   Vol. 5, No. 2, June 2015. # Accesses 849

7. Mechanisms regulating endothelial permeability, Sukriti Sukriti, Mohammad Tauseef, Pascal Yazbeck and Dolly Mehta
   Vol. 4, No. 4, December 2014. # Accesses 819

   Vol. 4, No. 1, March 2014. # Accesses 792

9. Cardiac energy metabolic alterations in pressure overload–induced left and right heart failure (2013 Grover Conference Series), Sowndramalingam Sankaranagam and Gary D. Lopaschuk
   Vol. 5, No. 1, March 2015. # Accesses 792

10. Acute effects of riociguat in borderline or manifest pulmonary hypertension associated with chronic obstructive pulmonary disease, Hossein A. Ghofrani, Gerd Staehler, Ekkhard Grünig, Michael Halank, Veselin Mitrovic, Signur Unger, Wolfgang Mueck, Reiner Frey, Friedrich Grimminger, Ralph T. Schermuly, and Juergen Behr
    Vol. 5, No. 2, June 2015. # Accesses 684

11. Fatty acid metabolism in pulmonary arterial hypertension: role in right ventricular dysfunction and hypertrophy, Megha Talati and Anna Hemnes
    Vol. 5, No. 2, June 2015. # Accesses 673

    Vol. 5, No. 2, June 2015. # Accesses 673

13. Right ventricular long noncoding RNA expression in human heart failure, Thomas G. Di Salvo, Yan Guo, Yan Ru Su, Travis Clark, Evan Brittain, Tarek Absi, Simon Maltais, and Anna Hemnes
    Vol. 5, No. 1, March 2015. # Accesses 591

    Vol. 4, No. 3, September 2014. # Accesses 558

    Vol. 4, No. 3, September 2014. # Accesses 505
Regional Task Force Reports
Annual Report 2015
PVRI Central Asia Task Force
Ghazwan Butrous and Talant Sooronbaev

In Autumn 2014, Ghazwan Butrous visited the Institute of Cardiology and gave two talks on PVD to the staff (attended by about 50 people) and discussed PVRI and PVD issues with the centre head Prof. Berkinbaev and other invasive cardiology staff, notably Dr. Algerim Yeshtay, Head of the Dept. of Interventional Cardiology and recently appointed to run a pulmonary hypertension clinic.

They are keen to make the institute the PVRI Centre of Excellence for PVD in Almaty. Other centres will be in Astana (the new capital) with almost 700,000 inhabitants and growing. Ghazwan Butrous visited between 29 September - 1 October 2015 and agreed it should be another PVRI centre of excellence. Doctors and technicians have good experience, although they could benefit from more targeted training. The centre is mainly used for congenital heart diseases and left heart catheterisation. Ghazwan Butrous also visited the Institute of Paediatric Surgery and had a lengthy discussion with Dr. Abzaliev Kuat who is involved in the iloprost study to assess reversibility of pulmonary hypertension in congenital heart disease, a protocol they share with a centre in South Korea.

The centre is heavily involved in the correction of congenital heart diseases with the majority of patients of an older age group (>9 years old). Many of these patients are still suffering from high pulmonary pressure despite correction. The Cath Lab is well equipped and sufficient for the purpose and they also have two well equipped cardiac surgery theatres.

From Almaty Ghazwan Butrous travelled to Bishkek, to assess the possibility of establishing the Excellence Centre at the National Centre Cardiology and Internal Medicine (NCCIM). There they have reasonable echocardiography supported by six ultrasound doctors and scientists, some with more than 15 years’ experience. The cardiac catheterisation lab is reasonably well equipped and carries out mainly work on congenital heart disease and left heart catheterisation. However, drug availability is limited to generic sildenafil.

PVRI Excellence Centre for Pulmonary Hypertension
We have discussed and made a decision that a PVRI excellence centre for Pulmonary Vascular Disease (based in the National Centre Cardiology and Internal Medicine (NCCIM) should be created. The Kyrgyz Republic Ministry of Health and the head of the NCCIM, (Prof. Dzhumagulova) have promised to allocate the newly refurbished wing of the NCCIM. Their new PVRI excellence centre for Pulmonary Vascular Disease in Bishkek was officially opened in January 2015. This centre is now the pilot project for the CA PVRI Task Force - now called CAPH (Central Asia Pulmonary Hypertension Group).

The facility has four rooms (one is an Echolab), the centre will support the high altitude research which is the main research activity in Kyrgyzstan. Dr. Talant Sooronbaev and Dr. Batyr Osmonov will be running the centre.
The CAPH Excellence Centre in Bishkek main function:
1. Appoint trained doctors (main staff) to the PVRI/CAPH Excellence Centre for Pulmonary Vascular Disease and manage their main responsibilities and activities.
2. Create a team of consultants from the following disciplines: infectious diseases, rheumatology, cardiology, paediatrics, cardiac surgeons, pulmonologists, CT specialists and others to work within the Centre.
3. Provide the necessary equipment for the management of Pulmonary Vascular Disease (ECG, spirometry, Echocardiography, DLCO and others).
4. Organise a right heart catheterisation in the department of interventional cardiology of NCCIM.
5. Create and organise a PVRI EC PVD outpatient room for examination of out patients with Pulmonary Vascular Disease. Allocate four beds in the hospital for patients with Pulmonary Vascular Disease.
6. Develop a referral system for patients with Pulmonary Vascular Disease from other centres and clinics.
7. Create a database (register) of patients in the PVRI Excellence Centre for Pulmonary Vascular Disease; develop a simple programme to register all patients seen in the centre. The main function of this database is to assess the efficiency of the centre and the referral pattern and to identify issues that can direct further training and awareness programme.
8. Professor Butrous and Dr. Majdy Idrees to be consultant and advisor of the PVRI excellence centre for Pulmonary Vascular Disease in Kyrgyzstan.
9. Develop national guidelines for the management of pulmonary hypertension
10. Organise and hold educational and awareness programmes for PH in all regions of Kyrgyzstan, involving many other disciplines and specialties.
11. Produce brochures for patients and the public on pulmonary hypertension.
12. Establish an organisation for patients with PH in Kyrgyzstan.
13. The Saudi Association Of Pulmonary Hypertension (SAPH) can support this new initiative, in both an advisory and training capacity.

PVRI Excellence Centre for Pulmonary Hypertension at SCP & PS in Almaty.
The second PVRI excellent Centre was established at The Scientific Centre of Paediatrics and Paediatric Surgery (SCP&PS) in Almaty, Kazakhstan. The SCP&PS was founded in 1932 and included various for specialities for Paediatric Cardiology, Cardiac Surgery, Oncology, Haematology, Pulmonology, Rheumatology, Neonatology, and Urology. The PVRI Excellent Centre for Pulmonary Hypertension SCP&PS was established in July 2015 by Dr. Aigerim Kuat and was approved by the Professor Boranbayeva, Director of Scientific Centre of Paediatric Surgery. The funding for SCP&PS is covered by the central budget of the Ministry of development.

The centre will:
1. Become a centre for further medical education in the field of Pulmonary Vascular Diseases by organising seminars, training programmes and masterclasses at local and regional levels.
2. Enhance scientific communications with other medical organisations in the region to exchange experience and expertise.
3. Organise a Paediatric Pulmonary Hypertension awareness day for local physicians in Kazakhstan.
4. Establishing a patient data collecting system to assess the pattern and distribution of Pulmonary Vascular Diseases in Kazakhstan to help future clinical and policy strategies of the paediatric population.
5. Establish a specialist referral clinic to deal with pulmonary hypertension and its complication and advance therapies.
6. Support graduate and postgraduate students and doctors in training to pursue further research in Pulmonary Vascular Disease.
7. Enhance clinical research collaboration with international centres of excellence.
8. Work with the PVRI paediatric and congenital heart disease task force and support its activities.

PVRI Trainings and Masterclasses
Two masterclasses took place in: Bishkek, Kyrgyzstan 23-25 April organised by Dr. Sooronbaev, and Astana, Kazakhstan 1-2 October 2015 organised by Dr. Murat Mukarov.

The general structure of the two masterclasses:
1. One day general training course (mainly in Russian) on pulmonary vascular diseases. Main participants were local consultants with lectures from guest speakers Ghazwan Butrous, Stefano Ghio and Tarek Kashour.
2. This was followed by a full day of two separate groups:
   a. Echocardiography, with participation by a panel of experts (lead by Dr. S. Ghio from Italy), which involved theory and live demonstration of clinical cases.
   b. Right heart catheterization with participation by a panel of experts (lead Dr. T. Kashour from Saudi Arabia), which involved theory and live demonstration of clinical cases.

CAPH Young Group
Professor Butrous met a group of young physicians interested in pursuing careers in pulmonary hypertension and in further research.
PVRI China Task Force
Chen Wang and Martin Wilkins

PVRI China Task Force continues its active participation in organising national pulmonary hypertension (PH) meetings and education courses in China, aiming to extend and update the understanding of PH among Chinese physicians, exchange clinical experience and create future international collaboration opportunities. The PVRI China Task Force has encouraged collaboration at international level. This has brought in several international joint publications and promoted both clinical and basic science PH research in China.

Jan 15th - 18th, 2015
The 8th PVRI Annual World Congress collaborated between Pulmonary Vascular Research Institute (PVRI) and the Chinese Thoracic Society (CTS) was held together with the 7th National Congress on Pulmonary Embolism and Pulmonary Vascular Diseases in Guangzhou, China. The conference covered a broad range of topics through the expertise of leaders in Pulmonary Vascular Diseases. The topics covered the most updated guidelines of venous thromboembolism (VTE) and pulmonary hypertension, especially the updated antithrombotic and prevention of thrombosis guidelines and pulmonary hypertension guidelines, which provided the latest knowledge of diagnosis, treatment and prevention of Pulmonary Vascular Diseases. PVRI also enhanced its educational programme during the meeting.

Jan 10th - 14th, 2015
Prof. Michael Madani visited Beijing Chao Yang Hospital, Beijing Institute of Respiratory Medicine, to evaluate the operability for chronic thromboembolic pulmonary hypertension (CTEPH) patients. A half day symposium on CTEPH and PAH was held. Prof. Madani, and his assistant gave talks covering the diagnosis, image evaluation, medical and surgical management of CTEPH.

May 5th -10th, 2015
World Pulmonary Hypertension Day on a national scale, physicians from different cities organized meetings to raise awareness of the disease by staging various events involving both the scientific community and the general public. A series of educational and social activities on pulmonary hypertension were held in Beijing with the support of the I-seek pulmonary hypertension advisory group. More than 200 multidisciplinary physicians participated in the activities. The issues of health education, social support, medical insurance and standardised treatment for Chinese pulmonary hypertension patients were discussed.

July 25th - 26th, 2015
The 5th Chinese SLE Treatment and Research (CSTAR) Forum was held in Beijing, organised by Beijing Union Hospital. Around 800 physicians participated. Professors Qian Wang and Lan Zhao gave lectures on the ‘Precision (Personalised) Medicine’ session, with a focus on SLE-PAH clinical management and biomarkers.

Aug 6th - 9th, 2015
China Heart Congress. The one and a half pulmonary vascular disease session was attended mostly by cardiology physicians. Professors Jason Yuan, Xiansheng Chen, Lan Zhao and Zhenguo Zhai gave lectures at the meeting, covering topics in advances in PAH, as well as congenital heart disease and medical and surgical treatment of CTEPH.

Sep 3rd - 6th, 2015
The 15th National Conference of Chinese Thoracic Society was held in Zhengzhou, China. This meeting provided a communication stage that would ensure further progress in the diagnosis and treatment of Pulmonary Vascular Disease including pulmonary embolism and pulmonary hypertension for physicians, scientists and other health care providers in China.

Feb and Aug 2015
Two education programmes on standardising the diagnosis and treatment of Pulmonary Vascular Diseases were organised by the Chinese Medical Journal. These courses provided updates on several important aspects, including diagnosis and treatment of pulmonary hypertension, diagnosis technology, and standard thrombolytic and anticoagulant therapy, and clarified a standardised operational procedure for imaging pulmonary hypertension. More than 10 multidisciplinary physicians jointly explored and distributed some special points on the clinical practice of evaluation and management of pulmonary embolism and pulmonary arterial hypertension.

Multidisciplinary consultation platform
A Multidisciplinary consultation platform for diagnosis and management of Pulmonary Vascular Diseases was set-up in Beijing China-Japan Friendship Hospital in Sep 2015. More than 50 complicated PVD patients were discussed since its set-up. This platform provides good support for individualised diagnosis and treatment of pulmonary embolism and pulmonary hypertension. The platform also provided an excellent learning and communication opportunity for physicians.

China Day of ISTH
The China Day of ISTH was held in Toronto in May 2015, and more than 200 multidisciplinary physicians, including attendees from USA, Canada and China, joined the event, which explored China’s clinical practices in antithrombotic therapy and thrombosis prevention. Dr. Zhenguo Zhai gave a talk about progress in the management of pulmonary embolism and deep venous thrombosis in China. A detailed discussion of the cooperation was also explored during the meeting.

Collaborative Research Programme
The Collaborative Research Programme on ‘Pathomechanisms of high altitude pulmonary hypertension and genetic basis of adaptation to high altitude hypoxia’, led by Professor Ghofrani of Justus Liebig University of Giessen and Professor Chaoying Cui of Tibet University Medical College, has completed two large held studies (Lhasa 3680m and Naqu >5000m) with a focus on cardiopulmonary phenotyping using echocardiography. PVRI provided the basis for a strong international collaborative team.

Publications


PVRI North American Task Force
Kurt Stenmark & Stephen Archer

The North American Task Force was created in late Spring 2015. In this inaugural year, we hosted the Annual PVRI gathering in Denver, Colorado at the International Meeting of the American Thoracic Society.

In the coming year we will plan and then host the International PVRI Meeting in Miami in January 2017. In addition, in July 2016 we will host the 3rd Annual Pulmonary Hypertension Drug Discovery and Development Symposium in Washington, DC. This will create another opportunity to stimulate greater involvement of the North American community in the PVRI.
Names of Task Force leaders
• Task force leader: Paul Hassoun, MD (USA)
• Task force co-leader: Majdy Idrees, MD (KSA)

Changes in the task force in 2014-2015:
The total number of local/regional members was 111 in 2013, 137 in 2014, and 159 members as of July 2015. This consistent increase in the number of members reflects the increased awareness among local health care providers in the region about the disease.

Educational events/meetings:
The following scientific and educational activities took place in 2015:
• The 8th annual conference for EMR (SAPH 2015), April 2015, Abu Dhabi, UAE
• Awareness Day for PH for interns & family physicians.
  - March 2015, Riyadh, KSA
  - June 2015, Jeddah, KSA
  - June 2015, Madinah, KSA
  - September 2015, Dammam, KSA
• Awareness Day for PH for public (PH Annual Day)
  - May 2015, Jeddah 2014
• PH Patients’ Support Day.
  - May 2015, Riyadh, KSA

Publications

Research (current research initiatives)
• The prevalence of PH in Sickle-cell disease in the Eastern Provence in Saudi Arabia
• Inhaled Iloprost in severe pulmonary hypertension in COPD patients.
• Genetic studies in Saudi patients with congenital heart disease
• Bronchiectasis & PH in Saudi patients
• Prevalence of PH in the high altitude in Saudi Arabia
• Prevalence of CTEPH in Saudi Arabia
• Phenotyping of pulmonary hypertension
• PAH in scleroderma patients in Saudi Arabia
• PAH in CHD in Saudi patients
• Morbidity and mortality of right heart cath in a tertiary care centre in Saudi Arabia
• Contribution in the PVRI consensus statement for the management of pulmonary hypertension in the developing world.
Other initiatives:
• SAPH/EMR is working on establishing further collaboration with PHA Europe and PHA Canada.
• SAPH/EMR is also planning to expand its collaboration and share experience through working with PHA South Africa and many early initiatives/groups in North African countries
• SAPH has established a partnership with the Central Asian PH group (CAPH).

Summary of goals for 2016:
• To hold the 9th Annual Joint (SAPH/PVRI) meeting in Jordan, Amman in the period between 4-6 February 2016. For more information about this meeting, please visit the conference website (www.saph2016.com) or the SAPH website (www.saph.med.sa).
• To continue holding the paediatric PH masterclass in February and the Adult PH masterclass in October 2016.
• To continue holding frequent awareness days in different regions in the EMR region.
• To continue to participate in the international PH annual day on 5th May 2016.

Further goals for year 2016:
SAPH/EMR is planning to continue to expand its activities quite rapidly. It is now recognised regionally and somewhat internationally for its services in the field of PH.

SAPH will continue to strive to increase the number of active members, improve awareness and create a positive environment between physicians and healthcare providers interested in the field. Attracting more nurses, paramedics, and patients is now an important SAPH target.

PVRI Sub-Saharan & Africa Task Force
Professor Ana Olga Mocumbi & Professor Karen Sliwa

During 2015 the activities of the Sub-Saharan Task Force were concentrated on consolidating the network created for the Pan-African Pulmonary Hypertension Cohort (PAPUCO) Study in the previous years, in publishing the results of this continental project and in seeking new funding for regional research projects.

Leaders
• Professor Ana Olga Mocumbi
• Professor Karen Sliwa

Summary
During 2015 the activities of the Sub-Saharan Task Force were concentrated on consolidating the network created for the Pan-African Pulmonary Hypertension Cohort (PAPUCO) Study in the previous years, in publishing the results of this continental project and seeking new funding for regional research projects.

Through funding allocated to other projects, researchers from different countries were able to organize opportunistic meetings for discussion of PAPUCO results. New collaborative projects are being designed to maintain this dynamic network and several grant proposals are being submitted to potential funders.

The goal for next year is to scale up some of the clinical research activities to other countries in the region and work towards the development of some projects involving basic research.

1. Background
The PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) STUDY GROUP was able to prepare and submit to a peer-review journal the results of the study which has the title below and includes the participants of all centres that recruited patients.

Title:
The causes, treatment, and outcome of pulmonary hypertension in Africa: Results of the Pan-African Pulmonary Hypertension Cohort (PAPUCO)

Authors:
Friedrich Thienemann, MD, MScIH, DTM&H; Anastase Dzudie, MD; Ana O. Mocumbi, MD, PhD; Lori Blauwet, MD; Mahmoud U. Sani, MD; Kamilu M Karaye, MD; Okechukwu S. Ogah, MBBS, MSc; Irina Mbanze, MD; Amam Mbakwem, MD; Patience Udo, MD; Kemi Tibazarwa, MD, PhD; Albertino Damasceno, MD, PhD; Simon Stewart, PhD; Karen Sliwa, MD, PhD
**Affiliations:**

1. Institute of Infectious Diseases and Molecular Medicine and Department of Medicine, Faculty of Health Science, University of Cape Town, Cape Town, South Africa.
2. Department of Internal Medicine, Douala General Hospital and Buea Faculty of Health Sciences, Douala, Cameroon.
3. Instituto Nacional de Saúde, and Universidade Eduardo Mondlane, Maputo, Mozambique.
4. Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55902, USA.
5. Department of Medicine, Bayero University Kano & Aminu Kano Teaching Hospital, PMB 3452, Kano Nigeria.
6. Department of Medicine, Bayero University & Aminu Kano Teaching Hospital, Kano, Nigeria.
7. Division of Cardiology, Department of Medicine, University College Hospital Ibadan, Oyo State, Nigeria.
8. Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique.
9. Department of Medicine, College of Medicine, University of Lagos, Lagos, Nigeria.
10. Department of Paediatrics, University of Uyo Teaching Hospital, Uyo, Nigeria.
11. Department of Cardiovascular Medicine, Mulhumili National Hospital, Dar es Salaam, Tanzania.
12. Hatier Institute for Cardiovascular Research in Africa and Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.
13. Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique.
14. Mary MacKillop Institute for Health Research and NHMRC Centre for Research Excellence (CRE) to Reduce Inequality in Heart Disease, Australian Catholic University, Melbourne, Australia.
15. Soweto Cardiovascular Research Unit, University of the Witwatersrand, Johannesburg, South Africa.

**2. Research Activities**

**2.1. Scientific Meetings**

Abstract presented by F Thienemann at PVRI 2015 Meeting in China.

**Title:**

Clinical profile and outcomes of sub-Saharan African patients with pulmonary hypertension due to left heart disease: data from the Pan African Pulmonary Hypertension Cohort (PAPUCO) study.

**Authors:**

A. Dzudie, MD, F. Thienemann, MD, Lori Blauwet, MD, Ana O. Mocumbi, PhD, Kamulu M Karaye, MD, Mahmoud U. Sani, MD, Okechukwu S. Ogah, MD, Irina Mbanze, MD, Amam Mbakwem, MD, Patience Udo, MD, Kemi Tibazarwa, MD, PhD, Leopold AMINDE, MD, Jules Ndjebet, MD, Cabral Tantcho Tchouni, MD, Andre Pascal Kengne, MD, PhD, Karen Sliwa, PhD.

**Purpose:**

The Pan African Pulmonary Hypertension Cohort (PAPUCO) is a multinational prospective observational registry involving 13 university centres across four SSA countries. Cases with signs and symptoms of PH underwent echocardiographic assessment for cardiac disease and PH. PH was classified as mild (right ventricular systolic pressure [RVSP]: 35-45 mmHg), moderate (RVSP: 46-60 mmHg) and severe (RVSP: >60 mmHg). Regressions models were used to determine predictors of outcome (hospital admissions and all-cause mortality) during follow-up.

**Results:**

Of 209 patients diagnosed with any PH, 144 (mean age 53.3±18.5 years, 40.4% men) had PHLHD. Mean RVSP was 60.4±16.7 mmHg overall, and 41.6±3.4, 51.9±4.4, 78.1±12.5 for mild (n=47), moderate (n=32) and severe PH (n=62) respectively. In multivariable analysis, left atrial diameter (OR=0.55; 95%CI 0.28-0.82; p<0.001) and TAPSE (OR=0.99; 95%CI -1.51—0.47; p=0.001) were predictors of RVSP. Heart failure with preserved ejection fraction was the most frequent (56%) cause of PH but valvular heart disease was associated with more severe PH (p=0.009). In all, 35 deaths and 41 hospital admissions were recorded after a median follow-up of 9.3 (25th-75th percentiles 6.8-15.2) months. There was a positive and graded association between WHO-FC and mortality (p=0.01), RVSP and admissions (p=0.03) but not RVSP and mortality.

**Conclusions:**

Among patients with PHLHD in SSA, left atrium size and TAPSE were significant predictors of RVSP. RVSP predicted admissions but not death after a short-term follow-up. A long-term follow-up of a larger sample is necessary to confirm these observations.

NRF-FNI Meeting, 4-6 November 2015 - Pretoria, South Africa

The Task Force participated through its two leaders presenting the results of PAPUCO study and the challenges and lessons from this web-based registry involving several African countries. (National Research Foundation South Africa – Fundo Nacional de Investigação, Mozambique; grant 2013-2015; PIs: A Mocumbi, K Sliwa)

**2.2. Research Projects**

Cardiovascular manifestations of HIV in children and adults

In Mozambique the INS developed a study project on cardiovascular manifestations of HIV with emphasis on PAH in cohorts, which was implemented in a local HIV clinic recruiting 320 patients with access to HAART. The results of this study will be soon be published.

Markers of endothelial dysfunction in HIV

A collaborative project between UEM/INS and UCSD (PIs: A Mocumbi, K Kim) was submitted for funding and is currently being implemented in Maputo City, Mozambique aimed at describing the occurrence of coagulation markers in HIV ART-naive patients (CFAR grant).

**2.3. Research Training**

Dr. Anastase Dzudie from Cameroon finished his PhD training at University of Cape Town, South Africa under the supervision of Professor Karen Sliwa.

**3. Publications**


Disease & Speciality Task Force Reports

Annual Report 2015
To improve knowledge, encourage research and optimise delivery of clinical care of neonates, children and adolescents with Pulmonary Vascular Disease, through:

1. Facilitating the growth of networks for research and clinical care between professionals from different medical specialties, institutions and countries especially in less privileged communities.

2. Disseminating knowledge about the paediatric pulmonary vascular phenotype in clinics caring for adults with Pulmonary Vascular Disease and facilitating smooth transition of childhood survivors of Pulmonary Vascular Disease to adult clinics.

3. Promoting concepts about the fetal and developmental origins of Pulmonary Vascular Disease.

2015 Activities

Activities on Paediatric Pulmonary Hypertensive Vascular Disease organized by pediatric Task Force members and with major contributions from paediatric Task Force members.

- Paediatric Task Force Meeting in Guangzhou (China), January 2015
- American Thoracic Society International Postgraduate Course Paediatric Pulmonary Vascular Disease Organised by Steve Abman Denver, CO, USA.
- Plenary Session at PHPN (PHANUSA) meeting Arlington Virginia September 2015.

2016 Goals

1. Publication of two consensus documents: “Cardiac Catheterisation in Children with Pulmonary Vascular Disease” (already submitted to Pulmonary Circulation), and “Management of Pulmonary Vascular Disease in Bronchopulmonary Dysplasia”.

2. Collaborate in the organisation of and participate in the “2nd Latinamerican Pediatric Pulmonary Hypertension” conference in Buenos Aires in 2016 (date still to be settled).

3. 9th Neonatal & Childhood Pulmonary Vascular Disease Conference, 10-12 March 2016.

Abstracts & Publications

On pediatric pulmonary vascular disease FROM TASK FORCE MEMBERS.

A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI Pediatric Task Force, Panana 2011.

Repair of congenital heart disease with associated pulmonary hypertension in children: what are the minimal investigative procedures? Consensus statement from the Congenital Heart Disease and Pediatric Task Forces, Pulmonary Vascular Research Institute (PVRI).


Leukotriene B4 Activates Pulmonary Artery Adventitial Fibroblasts in Pulmonary Hypertension.

Non-invasive determination by cardiovascular magnetic resonance of right ventricular-vascular coupling in children and adolescents with pulmonary hypertension.

[Updated clinical classification of pulmonary hypertension].

Intrapulmonary vascular shunt pathways in alveolar capillary dysplasia with misalignment of pulmonary veins.

Real-time magnetic resonance assessment of septal curvature accurately tracks acute hemodynamic changes in pediatric pulmonary hypertension.

Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension.

Fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension: a proof of principle study.


Updated clinical classification of pulmonary hypertension.

Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia.

Short-Term Treprostinil Use in Infants with Congenital Diaphragmatic Hernia following Repair.

Right ventricular nitric oxide signaling in an ovine model of congenital heart disease: a preserved fetal phenotype.

Measurement of oxygen consumption in children undergoing cardiac catheterization: comparison between mass spectrometry and the breath-by-breath method.

Assessing pulmonary hypertensive vascular disease in childhood.
Data from the Spanish registry.

Longitudinal assessment of right ventricular myocardial strain in relation to transplant-free survival in children with idiopathic pulmonary hypertension.

Pulmonary venoocclusive disease in childhood.
Implications of the U.S. Food and Drug Administration warning against the use of sildenafil for the treatment of pediatric pulmonary hypertension.

Diagnostic evaluation of paediatric pulmonary hypertension in current clinical practice.

Clinical features of paediatric pulmonary hypertension: a registry study.

Pediatric pulmonary hypertension.

Childhood idiopathic pulmonary arterial hypertension: a national cohort study.
Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG, Heart. 2010 Sep;96(17):1401-6

Clinical trials in neonates and children: Report of the pulmonary hypertension academic research consortium pediatric advisory committee.

Implications of the U.S. Food and Drug Administration warning against the use of sildenafil for the treatment of pediatric pulmonary hypertension.

Pulmonary interstitial glycosogenosis: an unrecognized etiology of persistent pulmonary hypertension of the newborn in congenital heart disease?

Pulmonary interstitial glycosogenosis associated with pulmonary hypertension and hypertrophic cardiomyopathy.

Atrial septostomy in patients with pulmonary hypertension: should it be recommended?

The world of pulmonary vascular disease.
Yuan JX, Morrell NW, Harikrishnan S, Butrous G. Pulm Circ. 2011 Jul-Sep;11(3):303-4

Hospitalizations of Children With Pulmonary Hypertension: Implications for Improving Care.

Impaired pulmonary vascular development in bronchopulmonary dysplasia.

Early determinants of pulmonary vascular remodeling in animal models of complex congenital heart disease.

Sildenafil therapy for neonatal and childhood pulmonary hypertensive vascular disease.

Meandering right pulmonary vein associated with severe and progressive “idiopathic-like” pulmonary hypertensive vascular disease.
Cuenca S, Brett M, Del Cerro M. J Cardiol Young. 2015 Sep 16;14.

Pulmonary hypertension and congenital heart disease: An insight from the REHAP National Registry.

Alveolar capillary dysplasia with misalignment of the pulmonary veins associated with aortic coarctation and intestinal malrotation.

Pulmonary hypertension in bronchopulmonary dysplasia: clinical findings, cardiovascular anomalies and outcomes.

Inhaled iloprost as a rescue therapy for transposition of the great arteries with persistent pulmonary hypertension of the newborn.

Pulmonary hypertension in bronchopulmonary dysplasia: clinical findings, cardiovascular anomalies and outcomes.

Inhaled iloprost as a rescue therapy for transposition of the great arteries with persistent pulmonary hypertension of the newborn.

Add-on therapy with subcutaneous treprostilnil for refractory pediatric pulmonary hypertension.

Pulmonary Vasodilators in the Management of Low Cardiac Output Syndrome after Pediatric Cardiac Surgery.

Nonketoic hyperglycinemia presenting as pulmonary hypertensive vascular disease and fatal pulmonary edema in response to pulmonary vasodilator therapy.
PVRI HIV-Associated Pulmonary Hypertension
Task Force  Sharilyn Almodovar

Leaders:
• Nicola Petrosillo, M.D.
• Sharilyn Almodovar, Ph.D.

Mission:
Pulmonary Hypertension (PH) continues to rise as an important complication of HIV infection (HIV-PH). Several studies have enlightened the field with knowledge of the pathophysiology of PH, making pulmonary circulation-specific pharmacotherapies available. However, the clinical management of PH may represent a global challenge in daily practice, particularly in the context of HIV disease.

Our mission is to:
1 Increase awareness of HIV-PH
2 Convene the HIV specialists, Pulmonologists, Cardiologists, and Basic scientists including experts in Vascular Biology to discuss current needs and future clinical and biomedical research directions.
3 Disseminate information regarding tools available to create and nurture international collaborations.

Highlights of 2015:
1 Online survey:
   We created an online questionnaire that aims to survey practice patterns among experts in the field of PH and HIV in all the countries reached by the PVRI. The questionnaire, which contains 50 items, may be completed in approximately 5-10 minutes. We hope to use the results of the survey to identify gaps in knowledge in the field and assess differences in the patterns of clinical practice among healthcare professionals in the field of HIV-PH. The survey is available to all the professional scientific and clinical community.

2 Publications:

3 Activities:
   a. Dr. Cicalini served as speaker (Clinical case of HIV-associated PH) at a conference on Pulmonary Hypertension in Rome, Italy in September 25, 2015
   b. Dr. Petrosillo participated as moderator at the Conference on Pulmonary Hypertension in Rome, Italy in November 19-20, 2015.
   c. Dr. Almodovar presented at the Palm Springs Symposium on HIV/AIDS “HIV Disease: From Cause to Cure”; March 4-7th, 2015 in Palm Springs, California, USA.
   d. Dr. Almodovar presented her work at the American Thoracic Society 2015 International Conference, May 15-20, 2015 in Denver, Colorado, USA.

Goals for 2016
   a. In order to identify the specific gaps in knowledge and resources available to clinicians caring for HIV-PAH, the completion of the online survey will be encouraged at the PVRI Annual Congress in Rome and in several professional conferences throughout 2016.
   b. Revamp the HIV-PH Task Force website to include information about Registries of HIV-associated hypertension in countries reached by the PVRI, opportunities for career development and links to the latest research articles in the field and interactive opportunities for education and research-showcasing purposes.
   c. Call for new members. The Task Force needs to increase the number of members. After a new interactive website is implemented, our efforts will be focused on inviting new members globally.

PVRI Right Heart Failure & Exercise
Task Force  David Systrom and Aaron Waxman

Mission:
Develop guidelines for:
1 Definition of exercise pulmonary hypertension
2 Standardized cardiopulmonary exercise test administration, data collection and reporting
3 Deep phenotyping of exercise pulmonary hypertension

Leader(s):
• David M Systrom, MD

Members:
• Brad Maron MD
• Aaron Waxman MD, PhD
• Jane Leopold MD
• Marco Guazzi MD
• Andy Peacock MD
• Ron Oudiz, MD
• Rajan Saggar MD

What has been achieved over the years, in particular updates during 2015.
We have published guidelines for standardised invasive exercise testing and the first large study of the upper limits of normal for exercise pulmonary hemodynamics in a “true” normal population, across a wide spectrum of age.

Goals/Aims for 2016
Deep phenotyping of exercise PH, including imaging and transpulmonary flux of biomarkers (metabolomics, proteomics, transcriptomics and coagulomics).

Research activities & collaborations

a) Ongoing research activities: Our laboratory has shown the selection of few variants of EGLN1 with respect to adaptation and HAPE. With those interesting results in hand, we commenced another project further to investigate the O2-sensing pathway. We hypothesized that two hydroxylases of the same pathway, individually and interactively, influence the regulation of body physiology. Hence, we started working on the project. This research project was awarded by a USA based funding agency called 'The Cardiovascular Medical Research and Education Fund (CMREF)', Philadelphia. As a consequence, we investigated the role of the two HIF-hydroxylases in adaptation and maladaptation/disease susceptibility under hypobaric hypoxia. We have some really interesting and intriguing results.

b) In view of our continuing efforts to screen newer ethnic groups in relation to altitude adaptation and maladaptation, we have been able to forge collaborations with two new hospitals in another Himalayan state, namely Himachal Pradesh. Both hospitals cater to the local population and national and international tourists. The Govt hospital at Keylong has already arranged samples, whereas the hospital at Palampur is in the process of collecting samples. Incidentally, both the locations are highly scenic. These hospitals are open to international collaborations.


In analogy, Max Gassmann was also invited by Prof. Peter Wagner, editor-in-chief of the J Applied Physiol, to submit a review - together with Prof. M. Muckenthaler - on the interactions between Iron and Oxygen at high altitude: Gassmann M. and Muckenthaler M.U. (2015). Adaptation of iron requirement to hypoxic conditions at high altitude. J Appl Phys; in press.

c) Likewise, the faculty at the College of Sports Science and Technology, Mahdol University, Bangkok, Thailand, which I visited recently, was ecstatic to know about PVRI and willing to participate in its activities.
Iron meets hypoxia at high altitude
Max Gassmann 1 and Martina U. Muckenthaler 2

A daptation of iron requirement to hypoxic conditions at high altitude

Iron's crucial role in sensing hypoxia equally critical. Thus, in this review we focus on the interaction between oxygen and iron homeostasis. We review the role of iron (i) in the oxygen sensing process and erythropoietin (Epo) synthesis, (ii) in gene expression control mediated by the hypoxia-inducible factor-2 (HIF-2), and (iii) as an oxygen-carrier in haemoglobin, myoglobin and cytochromes. The blood hormone Epo that is abundantly expressed by the kidney under hypoxic conditions stimulates erythropoiesis in the bone marrow, a process requiring high iron levels. To ensure that sufficient iron is provided Epo controlled erythrophorone that is expressed in erythroid precursor cells acts in the liver to reduce expression of the iron hormone hepcidin. Consequently, suppression of hepcidin allows for elevated iron release from storage organs and enhanced absorption of dietary iron by enterocytes. As recently observed in sojourners at high altitude, however, iron uptake may be hampered by reduced appetite and gastrointestinal bleeding. Reduced iron availability, as observed in a hypoxic mountaineer, enhances hypoxia-induced pulmonary hypertension and may contribute to other hypoxia-related diseases. Overall, adequate systemic iron availability is an important prerequisite to adjust to high-altitude hypoxia and may have additional implications for disease-related hypoxic conditions.

Key words (not already present in the title):
Low oxygen, prolyl hydroxylase, PHD2, hypoxia-inducible factor, erythropoietin, erythroferron, hepcidin, ferroportin, transferrin, iron homeostasis, oxygen sensor, iron sensor, pulmonary hypertension, HAPE, mountaineer

Hypoxia and iron: essentials
Iron and oxygen are both essential for life. The regulatory mechanisms that maintain their homeostasis, influence each other in a tightly coordinated manner. In excess, however, their interaction generates toxic compounds, especially reactive oxygen species (ROS). Before submerging into the topic we summarise some facts about iron and oxygen. When do we face hypoxia? While the oxygen concentration in atmospheric air is always about 21%, at high altitude the oxygen partial pressure declines leading to systemic hypoxia. But hypoxic conditions can be also reached at sea level as exemplified by an exercising athlete whose body's oxygen supply does not meet its demand. As a consequence, cells need to respond very fast to reduced oxygenation in an organ-specific manner (78). How much iron does the body need? Iron is a key element in iron-containing proteins and as such is crucially involved in a wide variety of pathways. These include oxygen transport (haemoglobin) and storage (myoglobin), the mitochondrial electron transport chain (a critical requirement for energy production), as well as DNA replication and cell proliferation (10, 77). Most iron is required in erythrocytes for oxygen transport (1800mg) and in the muscle's myoglobin (300mg), while approximately 1000mg of iron are stored in the liver. Only 3mg circulate in the serum bound to transferrin to provide iron to most cell types (30). Interestingly, there is no regulated pathway for iron excretion. Iron that is lost either by desquamation of cells or bleeding is compensated for by absorption of dietary iron by duodenal enterocytes (1-2 mg per day). Most iron required for erythropoiesis is provided by reticuloendothelial mechanisms that cope with reduced oxygen supply. However, during sojourns to high altitude adjustment to elevated iron demand is
body’s response to hypoxia. Note that the cabin air pressure of a commercial airplane flying at around 10,000 m is usually set to mimic the oxygenation occurring at altitudes of 1,700 to 2,500 m (18, 72). What is our first response to hypoxia? The fall in atmospheric pressure hampers oxygen uptake by the alveolae, which causes arterial hypoxaemia. To cope immediately with this threatening condition we increase ventilation. At the same time perikular fibroblasts in the renal cortex (47) synthesize the blood hormone erythropoietin (Epo) that via the circulation reaches the bone marrow and promotes red blood cell maturation (16). Reduced oxygenation stabilizes the &subunits of the hypoxia-inducible factor-1 and -2 (HIF-1 and HIF-2) that heterodimerize with the constitutively expressed common partner ARNT (aryl hydrocarbon receptor nuclear translocator, also termed HIF-α) to form the HIF-1 or HIF-2 complex, respectively (reviewed in (19, 61)) (Fig. 1). Importantly, the severity and duration of hypoxia required to induce HIF-stabilization is organ-specific (78). Once formed, the HIF complexes are able to upregulate hundreds of genes that promote adaptive responses to hypoxia (reviewed in (67)). The transcription factor HIF-2 is able to bind to the hypoxia-response element (HRE) present in the regulatory region of the Epo gene as well as additional genes involved in the molecular response to continuous hypoxic exposure (84) to markedly enhance their expression. What mechanism controls expression of HIF’s &subunits? It is the oxygen sensor that consists of one of the four so far described prolyl hydroxylases (PHDs, predominantly PHD2) (34, 61). Apart from 2-oxoglutarate, ascorbate and oxygen, these dioxygenases require a divalent iron to become activated. Upon activation, PHDs hydroxylate HIF’s &subunit, and by doing so, make HIF less for poly-ubiquitination followed by proteasomal degradation (reviewed in (17)). Indeed, the targeting of iron by either transitional metals such as cobalt (46) or iron chelators such as desferrioxamine inhibit activity of the PHDs and as a consequence the HIFs are stabilized. It is intriguing to realize that evolution has come up with a very efficient but expensive response to cope with hypoxia exposure in every cell of our body: our cells constantly synthesize HIF &subunits that under normoxic conditions are immediately degraded (and thus are experimentally hard to detect). This synthesis is energetically a burden but allows the cell to instantaneously stabilize HIF &subunit when oxygen supply is low (22). This enables the hypoxic cell to respond in an accelerated manner compared to the usual slow transcription/translation process.

Increasing ventilation at high altitude

A fast way to reach high altitude is by car - driving to very high passes such as Ticlio in Peru (4843 m) or Khardung La in Ladakh, India (5359 m) - or by gondola to Klein Matterhorn in the Swiss Alps (3883 m). When leaving the gondola and being immediately faced with the lack of oxygen, it is little solace to know that in about 8-10 days more erythrocytes will be readily available to compensate for reduced oxygen availability (see below). Thus, the body initially responds to the reduced oxygen partial pressure by enhancing ventilation, a process known as the hypoxic ventilatory response. Interestingly, this process is partially regulated by Epo (25). It is worth mentioning here that (functional) Epo receptors (EpoR) are not exclusively expressed in erythropoietic cells but are detected in a wide variety of other cell types such as cerebral cells (24, 26, 45). Accordingly, serum Epo seems to bind the EpoR present in the carotid bodies that in turn forwards this information via the carotid sinus nerve to the respiratory centre of the brain stem (74, 75). In addition, Epo is synthesized in the brain in response to hypoxia and binds to its receptor located in brain stem neurons of the central ventilatory centre. Thus, EpoEpoR interactions in the carotid body and brain stem increase ventilation when our body is exposed to hypoxia. But how is iron involved here? Most probably, Epo’s upregulation in the brain is mediated by HIF-2 that in analogy to the renal situation is controlled by PHD2 in an iron-dependent manner (see above).

Iron-dependent expression of hypoxia-regulated genes

Cellular iron levels are balanced by the iron regulatory protein (IRP) and iron response element (IRE) system. Two homologous IRPs (IRP1 and IRP2) sense cellular iron levels by distinct mechanisms. Under iron-replete conditions, a cubic iron-sulfur [4Fe-4S] cluster assembly in IRP1, preventing IRE binding of IRP1. During iron deficiency however, IRP1 binds to IREs as an apoprotein. In contrast, IRP2 does not contain a iron-sulfur cluster and is regulated by iron via proteasome degradation. IRPs bind to RNA stem loop structures (IREs) located in untranslated regions of genes involved in iron uptake, export, storage and utilization to control their expression at the posttranscriptional level. IRP target genes are further involved in cellular functions not immediately related to iron metabolism (10, 59, 73). A key target gene of IRP1 is HIF-2, that harbours an IRE within its 5’-UTR, that upon binding IRP1 blocks HIF-2 translation (66) (Fig. 1). (49). IRP1-deficient mice that lack this repressor of HIF-2 translation show derepressed HIF-2 translation in the kidney, elevated Epo serum levels and a marked transient polycythaemia (4, 27). It is remarkable, however, that mutations within the HIF-2-IRE have been excluded as a frequent cause of congenital secondary erythrocytosis/polycythaemia (58). To further strengthen the link between iron and oxygen homeostasis IRP1 is mainly active when cellular iron levels are low but oxygen levels are sufficient. Hypoxic conditions, however, override the signal generated by low iron and markedly reduce IRP1 activity allowing for increased HIF-2-translation (12). It should be mentioned that the RNA-binding activity of IRP2 is elevated when facing both low iron and low oxygen conditions (see below). Mice deficient for IRP2 show altered body iron distribution and microcytosis (22). Thus, the two major control systems of cellular iron homeostasis (IRE/IRP) and oxygen levels (HIF) tightly interact at the molecular level to control iron and oxygen homeostasis.

Control of dietary iron uptake and macrophage iron-recycling in hypoxic conditions

Complex interactions of the oxygen/iron sensing systems ensure tight regulation of Epo levels in the kidney. Besides the well-known compensatory effect of erythrocytosis to iron availability. While the IRE-mediated control of HIF-2 levels is expected to be operational in the kidney where most Epo synthesis occurs, the same mechanism will work in all those tissues where HIF-2-mediated expression of oxygen-dependent genes occurs (Fig.1). An often neglected but important organ for an ascending mountaineer is the intestine. There, HIF-2 coordinates dietary iron absorption by regulating the transcription of key factors involved in iron uptake (43). These include the ferrireductase dcytb that converts ferric (Fe3+) to ferrous (Fe2+) iron, the divalent metal transporter 1 (DMT1) that imports ferrous iron from the diet into the duodenal enterocyte and the iron exporter ferroportin (Fpn) that transports iron out of the duodenal enterocyte into the blood stream (reviewed in (69)) (Fig.1). Consistent with the negative regulation of the expression of duodenal HIF-2 by IRP1, expression of the duodenal iron uptake machinery is elevated in homozygous irp1-deficient mice due to increased HIF-2 levels (4). Apart from their HIF-2-mediated transcriptional control, the expression of both, DMT-1 and Fpn is regulated in an iron-dependent manner. These two genes also contain iron-responsive elements (IRE) in their transcripts and thus are prone to iron-dependent IRE/IRP mediated control (reviewed in (49)). While HIF-2 translation is mainly controlled by IRP1, gene expression of the dietary iron transporters DMT-1 and Fpn is additionally regulated by IRP2 (70). Interestingly, IRP1 protein levels do not change in hypoxic conditions while the abundance of IRP2 proteins is elevated when oxygen is limiting (29, 87). In summary, cellular iron and oxygen homeostasis are tightly interconnected in the sense that the activities of the corresponding sensors, of the IRPs and of HIF-2 are controlled by iron and oxygen availability. In addition, expression of genes that regulate appropriate cellular and systemic iron levels is maintained by
interaction of the iron and oxygen control systems and ultimately determine the extent of erythropoiesis as well as the rate of intestinal iron absorption.

As mentioned earlier, most iron utilised for erythropoiesis is recycled from damaged erythrocytes by tissue macrophages. The heme moiety is catabolized by heme oxygenases resulting in iron release and subsequent iron export into the circulation (31). Once iron enters the blood stream it binds to the transport protein transferrin (Tf). Iron-loading of Tf may be facilitated by gastrins in mice exposed to hypoxia (10% oxygen for 10 days), when circulating gastrin levels are increased. Tf expression is also regulated in an oxygen-dependent manner by HIF-1 (44). Unexpectedly, macrophage-specific deletion of HIF-1 and HIF-2 did not affect iron recycling. While HIFs are critical regulators of DMT-1 and Fpn in duodenal enterocytes (see above) and of heme oxygenase-1 in some cell types (36), it is not essential for the regulation of the same genes in macrophages during iron recycling (44). Obviously, HIF-mediated transcriptional control of iron genes seems to be a more general principle and may explain the hypoxia-controlled expression of transferrin receptor 1 (39) or ceruloplasmin (50) among others.

In hypoxia, iron controls Epo that controls erythroferrone that controls hepcidin that controls ferroportin that controls iron levels

As described above, the IRE/IRP system that controls cellular iron metabolism is tightly connected to the HIF-mediated hypoxic response. But what occurs at the systemic level when a mountaineer is gaining altitude? The key to systemic iron homeostasis is the amount of iron-bound transferrin in the circulating blood that supplies the expanding mass of erythrocytes defined as the erythron (31). A physiological concentration of ferric iron-bound Tf that is usually specified in percentage (normal values being between 15-45% Tf saturation) is maintained by the hepcidin/ferroportin regulatory system (31). The small liver-derived peptide hormone hepcidin (25 amino acids) controls dietary iron uptake as well as iron release from iron-recycling macrophages by binding to its target receptor, the iron exporter ferroportin (Fpn) and subsequently triggering Fpn’s internalization and degradation (51). In other words: hepcidin leads to cellular retention of iron in enterocytes and macrophages and therefore to reduced levels of circulating iron. The hepcidin level itself is controlled by systemic iron availability, inflammatory cues, the erythropoietic drive, and hypoxia (31). As for mountaineers ascending to high altitude several studies have shown that hepcidin serum levels decrease, thereby enhancing Fpn-mediated iron uptake (see for example (3, 60, 82)). The underlying mechanisms have been under extensive debate in recent years, but it became evident from many studies (some performed in mountaineers) that Epo exerts an indirect effect on hepcidin expression (e.g. (5, 9, 23, 38, 62)).

How can erythroid expansion forward signals to the liver to control hepcidin synthesis? The answer may be through one or most probably several soluble factors that are secreted from erythroblasts. Epo binds to its receptor present on erythroid progenitor cells (see below) and drives maturation and proliferation of red blood cells via the JAK/STAT5 signaling pathway (88). In addition, the team of E. Nemeth and T. Ganz recently discovered that once it reaches the bone marrow, Epo triggers expression of erythroferrone (ErFe), a protein that subsequently is secreted by (pro)erythroblasts to ultimately suppress expression of hepcidin in the macrophage (33). The ErFe protein is expressed from the BFU-E (burst-forming unit erythroid) cells to erythroblasts, but only CFU-E cells (colony-forming unit erythroid) and proerythroblasts are Epo-responsive, at least in terms of erythropoiesis (91-93). Elevated ErFe mRNA levels have been found in proerythroblasts and most abundantly in basophilic, polychromatonic and orthochromatonic erythroblasts (33). Note that although erythroblasts still harbor the Epo receptor (Fig.2) it does not further regulate erythropoiesis (reviewed by (14)) but upon binding Epo might induce ErFe expression.

Another important observation is that the Epo-driven maturation from CFU-E to erythroblasts takes - at least in vitro - about 7 days to occur. Few additional days are then required for final maturation to adult erythrocytes (Fig.2). This delay between hypoxia-induced Epo gene expression and increased number of circulating red blood cells is mirrored in the ascending mountaineer. While serum Epo concentrations reach maximal values 19-39 h following ascent to 4559 m of altitude, hematocrit and hemoglobin levels only showed a tendency to increase during ten days of stay at that altitude (1). Very similar observations in the kinetics of Epo and hematocrit were made in mountaineers staying at 4500 m for 7 weeks (48). Iron-bound Tf is delivered to the erythroblast via transferrin receptor 1 for hemoglobin synthesis and as a consequence serum iron levels decrease (Fig.2). Indeed, a reduction in iron levels is observed for at least up to 4 days at high altitude, indicating that in this acute hypoxic condition dietary iron absorption by enterocytes and release by macrophages cannot match the increased requirements for erythropoiesis. The magnitude and time course of changes differed between studies likely because of different speeds of ascent and level of high altitude (3, 28, 42, 60, 73). Most studies do not report a change in ferritin levels during a 2-4 day stay at high altitude, suggesting that tissue iron stores are not detectably depleted within this short time period at high altitude.

Hepcidin production is suppressed at high altitude. Low hepcidin serum levels enhance iron export from macrophages and duodenal enterocytes and as a consequence iron will be supplied to the blood stream to satisfy the erythroid demand for this metal. Kautz and co-workers showed increased Erfe mRNA expression in (pro)erythroblasts of mice already 4h after phlebotomy or Epo injection (8,000 IU/kg body weight) that preceded hepatic hepcidin suppression (33). Of note, Erfe expression kinetics appear to be Erp dose-dependent, as another group detected elevated ErFe mRNA levels in liver and spleen only 4d after injecting about 1/5 of the Epo concentration used in the original study (23). Using a transgenic mouse line that expresses Epo receptor exclusively in hematopoietic tissue (79), the latter group confirmed that Epo’s impact on hepcidin expression is indirect by showing that the presence of the Epo receptor on liver cells is not required for hepatic iron upregulation by hypoxia. Moreover, homozygous ErFe-deficient mice failed to suppress hepatic hepcidin expression after phlebotomy or Epo supply and showed delayed recovery from anemia as compared to wild-type controls (33). Interestingly, apart from the bone marrow, ErFe is expressed in multiple mouse tissues, including tests, intestine and skeletal muscle. Thus, it will be interesting to investigate whether ErFe expression in these organs, especially in the exercising muscle, ultimately contributes to the regulation of iron homeostasis (see below). So far, ErFe’s impact on hepatic expression upon elevated serum Epo levels has been demonstrated only in mice, but it is expected that ascents to high altitude would also induce this erythroid regulator in man. To this end, a working ELISA to detect ErFe in human serum should be established soon.

Most probably ErFe is not the only circulating factor repressing hepcidin expression under hypoxic conditions. Previous studies indicate that in healthy volunteers, during a 7-day sojourn to altitude (4340 m above sea level) Epo and hepcidin levels did not correlate (82). In another study 23 healthy volunteers were subjected to exercise under hypoxic conditions, equivalent to an altitude of 5600 m (76). Six hours after exercise performance an elevated concentration of platelet-derived growth factor (PDGF)-BB was observed showing a significant correlation with hepcidin levels in these individuals. Importantly, PDGF-BB was also increased in mountaineers ascending to 4550 m within 2 days (3). A causal relationship between PDGF-BB levels and hepcidin expression could be demonstrated in mice injected with PDGF-BB in which hepcidin was suppressed and circulating iron levels...
increased (76). Additional erythroid factors that may down-regulate hepcidin expression in response to an expanding erythron under hypoxic conditions have been discovered (e.g., GDF15) when studying diseases of ineffective erythropoiesis, such as thalassemia (83). While GDF15 levels are increased in mountaineers at high altitude, they do not seem to correlate with hepcidin levels (82). Furthermore, analysis of GDF15-deficient mice demonstrate that GDF15 is essential for the regulation of iron homeostasis in response to phlebotomy (11). In summary, apart from ErFe, PDGF-BB and GDF15 there may be more hepcidin-regulating factors to be detected in the serum of individuals acutely exposed to hypoxia.

Iron regulation in the exercising mountaineer
The muscles of a mountaineer are exercising when ascending. Of note, skeletal muscles harbour about 1/8 of the body’s iron, mainly in myoglobin and cytochromes. How does exercise influence iron regulation? As mentioned above, ErFe, the newly identified repressor of hepcidin, is expressed in the skeletal muscle, too. In fact, ErFe is identical to the recently discovered muscular factor termed myonectin/CTPR15 that connects skeletal muscle activity to systemic lipid homeostasis in liver and adipose tissue (68). There are conflicting data as to when and how exercise induces ErFe gene expression in the skeletal muscle. In the original paper, Seldin and co-workers report that wild type mice given access to a running wheel for 2 weeks, presented with higher myonectin/ErFe mRNA levels in the muscle as well as higher protein levels in blood (68). In contrast, others observed that serum myonectin/ErFe concentration dropped in 28 women after a ten weeks period of aerobic exercise performance at submaximal oxygen consumption (37). To make it even more confusing, a very recent study on aerobically trained rats reported that after 9 weeks of exercise, myonectin/ErFe mRNA was downregulated in the skeletal muscle while protein level increased (59). Thus, the impact of exercise on ErFe serum levels has yet to be sorted out. If it turns out that muscular ErFe synthesis does not interfere with serum ErFe levels, then the latter could possibly be used as a new biomarker to detect Epo abuse (G. Cairo, personal communication).

How else is iron homeostasis challenged in our exercising mountaineer during ascent? Both exposure to high altitude (reviewed in (15)) and exercise performance (13) elevate inflammation markers, especially that of Interleukin-6 (IL-6) that is well known to activate hepcidin expression (53-57, 86). Inflammation thus counteracts the hypoxia-induced hepcidin decrease that may cause lower serum iron levels than expected upon exposure to oxygen depletion. Low iron conditions may ultimately reduce physical performance and, in addition, may also disturb neuronal function and immune response (9). This is caused by decreased oxygen transport to the exercising muscle and by deficits of the nonheme iron associated enzymes, respectively.

Stomach and intestine at high altitude
Finally the mountaineer reaches the Italian study hut Capanna Regina Margherita at 4559 m above sea level, a famous place for high altitude research, and stays there for 5 days. What happens to iron uptake? First, one has to note that over 50% of mountaineers suffer from acute mountain sickness (AMS) at altitudes over 4000m and that nausea is a classical AMS symptom (65, 89). Thus, general appetite will be reduced in relation to the AMS severity, but interestingly, gastrointestinal satiation hormones are not involved in appetite loss (2). Gastrointestinal changes also occur at high altitude such as general downregulation of duodenal solute carrier (SCL) transporters (90). A study performed on Tibetan railroad construction workers showed a 0.5% incidence of life-threatening gastrointestinal bleeding due to ulceration (94). In keeping with this, another recent study revealed that patients suffering from inflammatory bowel disease risk exacerbation of their symptoms upon high altitude journeys or even commercial flights (85).

Unexpected was the recent observation that 14 out of 23 (61%) healthy mountaineers staying their fourth night at 4559 m displayed peptic mucosal lesions such as erosions, ulcers and haemorrhagic gastritis/duodenitis (21). It is of interest to learn whether these gastrointestinal lesions disappear after longer acclimation periods to high altitude and whether highlanders such as Tibetans or Quechuas are well adapted and thus unaffected. Nevertheless, in acutely acclimatizing mountaineers all these effects will lead to iron loss. Consequently iron uptake has to be upregulated, but how? There is convincing evidence that relevant mechanisms include an increase of dietary iron absorption. By analysing blood samples and duodenal biopsies obtained from 25 healthy mountaineers upon reaching the Capanna Regina Margherita, a Zurich team reported a rapid decline in serum iron and ferritin levels, the latter being indicative for iron mobilization stored in various tissues. As expected, the decline in iron and ferritin levels was paralleled by an up to 10-fold elevation of duodenal DMT-1 and Fpn mRNA levels (28). On the other hand, serum Epo levels peaked at the second day spent in the hut, while hepcidin levels were markedly reduced. It is tempting to speculate that the Epo -> hepcidin signal is linked by ErFe – which unfortunately cannot be measured (yet). Most probably, these responses to hypoxic exposure allow elevated dietary iron uptake and the release of iron stores ultimately covering the elevated iron demand at high altitude. However, within short study periods (up to 4 days), serum iron levels remain low (see above).

Iron’s impact on pulmonary hypertension and HAPE
Reduced oxygen availability as occurring at high altitude leads to pulmonary arterial hypertension due to pulmonary vasconstriction (63). Under chronic hypoxic conditions the latter represents the consequence of pulmonary vascular remodeling due to endothelial cell proliferation and exercise performance (13) elevate inflammation markers, especially that of Interleukin-6 (IL-6) that is well known to activate hepcidin expression (53-57, 86). Inflammation thus counteracts the hypoxia-induced hepcidin decrease that may cause lower serum iron levels than expected upon exposure to oxygen depletion. Low iron conditions may ultimately reduce physical performance and, in addition, may also disturb neuronal function and immune response (9). This is caused by decreased oxygen transport to the exercising muscle and by deficits of the nonheme iron associated enzymes, respectively.
development of iron deficiency over time, although this was not seen during the short observation period of the mentioned study (3).

Conclusions
Regulation of cellular and systemic iron and oxygen homeostasis are so closely connected at the molecular level that it is difficult to discern what regulates what. Are the PHDs iron sensors that require oxygen or oxygen sensors that require iron to ultimately control stabilization of the α-subunit of the transcription factor HIF-2α? Notably, P. Robbins formulates a similar question in his accompanying review article (20). In addition, HIF-2α orchestrates the expression of genes that maintain iron homeostasis but likewise controls adaptation to chronic hypoxic exposure. Surprisingly, it is not only low iron levels that predominately control expression of the iron hormone hepcidin, but rather the oxygen-responsive blood hormone Epo. Knowledge about this tight relationship between iron and oxygen should increase the motivation to study hypoxic responses in those diseases and mechanisms that are predominantly related to iron metabolism, and vice versa to consider the involvement of iron in medical conditions associated with tissue hypoxia.

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Conflict of interest
Both authors have no conflicts of interest to declare.

Figure 1: The role of iron in oxygen homeostasis
Upon ascent to high altitude a fall in atmospheric pressure inhibits oxygen uptake by the alveolae and causes arterial hypoxemia. Systemic oxygen levels are monitored by prolyl hydroxylases (PHDs, exemplified by PHD2) in peritubular fibroblasts in the renal cortex. Iron is a critical co-factor for these dioxygenases. Thus, reduced oxygen or iron levels suppress the activity of PHD2 and cause stabilisation of the α-subunit of the hypoxia-inducible factor-2 (HIF-2α) that heterodimerizes with its partner ARNT (aryl hydrocarbon receptor nuclear translocator, also termed HIF-1β) to stimulate erythropoietin (Epo) transcription. A second iron-dependent process adjusts Epo levels to iron availability: HIF-2α contains an iron responsive element (IRE) in its 5' untranslated region. Under iron-deficient conditions - when no further haemoglobin synthesis can occur - this RNA structure binds to the iron regulatory protein-1 (IRP1) to inhibit HIF-2α translation. In other words, these mechanisms ensure that Epo synthesis is adjusted to iron availability. Once Epo reaches the bone marrow it promotes red blood cell maturation and proliferation, a process that consumes high amounts of iron. To make sure that sufficient iron is provided systemically, hypoxia-induced soluble factors - such as the Epo-controlled erythroferrone (ErFe) or the growth differentiation factor 15 (GDF15) that are both expressed in erythroid precursor cells, as well as the platelet-derived growth factor BB (PDGF-BB) reach the liver where they reduce expression of hepcidin, the iron hormone that binds the cellular iron exporter ferroportin (Fpn) leading to its internalization and degradation. Thus, suppression of hepcidin allows both, elevated iron release from storage organs including macrophages and enhanced absorption of dietary iron by enterocytes. In addition, tissue hypoxia or iron-deficiency further augments dietary iron absorption in the intestine. Similar to the situation in the kidney, these conditions stabilize the α-subunit of HIF-2α that stimulates transcription of proteins that control iron absorption: the ferrireductase (dcytb), the apical divalent metal transporter-1 (DMT-1) and the iron exporter ferroportin (Fpn). The iron released from macrophages and duodenal enterocytes is transported bound to transferrin (Tf) to ultimately satisfy the iron requirements of erythropoiesis in the bone marrow. For further details see text.
Erythropoiesis occurs in the bone marrow and describes the process by which erythroid progenitors proliferate and differentiate into reticulocytes and erythrocytes. Two distinct erythroid progenitors, the early-stage burst-forming unit-erythroid (BFU-E) and the later stage colony-forming unit-erythroid (CFU-E) progenitor have been defined. The so-called proerythroblast is the earliest morphologically recognizable erythroblast that undergoes mitosis to produce basophilic, polychromatized, and orthochromatized erythroblasts. The latter expel their nuclei to become reticulocytes. The phase in which Epo stimulates this differentiation process is indicated. Additionally Epo in proerythroblast and mainly in erythroblasts activates the expression of erythroferrone (ErFe), a critical suppressor of hepcidin expression in the liver. Ultimately, Tß-bound iron is taken up via the transferrin receptor-1 (CD71), that is highly expressed during all maturation stages but is absent in the mature red cell (52).

References


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PVRI Women’s Health & Pregnancy in Pulmonary Hypertension Task Force
Barbara Cockrill & Anna Hemnes

Task Force Leader:
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Task Force Members:
• Anna Hemnes, USA
• Karen Sliwa, South Africa
• Ioana Preston, USA
• Barbara Cockrill, USA
• Manal Alhazmi, Saudi Arabia
• Tim Lahm, USA
• Zeenat Safdar, USA
• Ghazwan Butrous, UK

Initiatives:
We are a working group with a focus on women’s health and pregnancy in pulmonary hypertension. This is a multidisciplinary collaborative effort to address issues important to women’s health in the context of Pulmonary Vascular Disease including:

1. State of knowledge of the effects of female sex hormones on Pulmonary Vascular Disease
2. Challenges of pregnancy in pulmonary hypertension including complications, therapy of pulmonary hypertension, delivery and post-partum care
3. Options and recommendations for contraception and sterilisation in pulmonary hypertension
4. The potential implications of hormone replacement therapy

Future plans:
Dr. MacLean will present a discussion on sex differences in response to medication at the upcoming PVRI 10th Annual World Congress in Rome.

Goal Summary 2016:
The Task Force will be meeting in Rome to plan our next projects. We are considering a statement on hormone replacement therapy, as exploring other issues specific to women, including focusing on specific risk factors for women to develop PH worldwide.

Educational Activities:
Published consensus statement:

The statement paper on pregnancy and pulmonary hypertension was published in September 2015. Lead by Anna Hemnes, this manuscript was a collaborative effort of all members of the task force.

Symposium at the 8th PVRI Annual World Congress in Guangzhou, China:
Chaired by Barbara Cockrill and Zeenat Safdar, the symposium, “Pulmonary hypertension in women” featured a presentation of the Task Force document (Dr. Cockrill), and talks by Mandy MacLean (Sex differences in PH), Ioana Preston (Contraception and termination in PH), and Jess Mandel (Anticoagulation in pregnancy).
New Task Forces for 2015 Reports

Annual Report 2015
The Preclinical and Molecular Science Task Force was set up in January 2015 and featured at The World Annual Congress in Rome 2016.

This Task Force will bring together basic scientists and clinicians researching into the molecular mechanisms behind the pathobiology of PAH as it applies to cellular and animal models and their responses to therapeutic strategies.

The aims of the task force are:

1. To understand the mechanisms behind the drugs we use to treat PAH.
2. To promote discussion on future drug development through our knowledge of basic science and animal models.
3. To inform clinicians about how prescribed drugs work.

The first formal meeting of the Task Force will take place at the PVRI conference in Rome, 2016. This will involve over 20 oral and poster presentations on animal models of PAH, biomarkers, mechanisms of existing drugs and new therapeutic targets.

The new Task Force has already attracted several new members to the PVRI from across the world.
PVRI Imaging Task Force
David G Kiely, Jim M Wild, Andrew J Swift

Summary statement Nov 2015

Leader:
• David G Kiely

Task Force Members:
• Jim W Wild (UK)
• Andrew J Swift (UK)
• David Levin (USA)
• Edwin Van Beek (UK)
• Jens Vogel-Claussen (Germany)
• Mark Schiebler (USA)
• Anton Vonk Nordegraaf (Netherlands, tbc)

Note: Membership to date represents international experts in field of imaging drawn primarily from Academic Radiology and PH Physicians with an interest in Imaging. The aim of the initial recruitment was to identify key experts with experience in imaging modalities including fluoroscopy, nuclear medicine, CT and CMR both clinical and academic. It is anticipated that the group will recruit up to 20 members from all 5 continents including senior and more junior members of the PVRI. There will be a call made for members of this task force at the Rome meeting (the first meeting of this group) and the membership will be broadened at this time.

Mission:
• Harmonise imaging protocols to improve international clinical and research collaboration.
• Help to develop a network of international PH Imaging centres to allow dissemination of best practice.
• Include clinicians, radiologists, imaging scientists and industry partners, to facilitate a step change in how we use imaging and translate this into clinical practice.

Strategy:
Exhaustive review of established and emerging imaging modalities:
• Plain x-ray and fluoroscopy (DSA).
• Echocardiography (2D, 3D, Doppler).
• Nuclear medicine imaging (V/Q, SPECT, PET, shunt studies).
• CT imaging (CT pulmonary angiography, high resolution CT, dual energy).
• MR imaging (CINE cardiac imaging, myocardial tissue characterisation, phase contrast imaging of blood flow, pulmonary perfusion and angiography, hyperpolarised gases.
• Use of imaging and its integration with other investigations including cardic catheterisation.

Review applications of imaging with respect to:
• Diagnostic role (health vs disease, and stratification of Pulmonary Vascular Disease).
• Outcome studies (prognostic role and risk stratification).
• Longitudinal follow-up (therapy response and failure).
• Understanding disease mechanisms (animal models, human studies, virtual physiological human, multi-scale measurements).

Make recommendations on the use of imaging modalities including:
• Summary statements using graded evidence to include (diagnostics, prognostics, therapy response and unmet need).
• Evidenced based diagnostic algorithms (exploring different approaches using various modalities also reflecting imaging availability).
• Clear guidance on how to implement specific imaging protocols.

Goals for 2016-2018
• January 2016:
  Meeting of Task Force in Rome to establish work-streams and broaden membership.
• February 2016:
  Submit Editorial to Pulmonary Circulation: “Imaging and the pulmonary hypertension: navigating the hidden river”.
• January 2016-November 2016:
  Work-streams to commence and complete sections (with work-stream meetings held as appropriate)
• January 2017:
  Lead of each work-stream to present core findings at PVRI Imaging Symposium and further meeting of Task Force to refine /finalise scope of document.
• June 2017-December 2017:
  Initial draught of guidelines and recommendations completed / voting on recommendations and refinements prior to submission to Pulmonary Circulation.
• January 2018:
  Submission of final guidelines with Imaging Symposium at PVRI meeting to launch.
Committee for Young Clinicians & Scientists

Annual Report 2015
PVRI Committee for Young Clinicians & Scientists (CYCS) Djuro Kosanovic

PVRI CYCS (PVRI Committee for Young Clinicians & Scientists) represents the future main aim of the PVRI society to spread the word across the world about Pulmonary Vascular Disease (PVD). Our committee is a platform for young, but also experienced, clinicians and scientists to actively contribute to the development of the PVRI.

Mission statement of the CYCS

Our particular mission is to leave a trace of today for future generations of scientists and clinicians in the field of PVD, by means of the creation and maintenance of the PVRI Chronicle journal and educational/historical content of our e-learning webpage. Moreover, the CYCS actively supports the other PVRI committees to facilitate and improve the PVRI overall, leading to the nickname of our committee (Active Support Committee (ASC)).

Current leaders

- Chair: Djuro Kosanovic, MSc PhD
- Co-Chair: Michael Seimetz, MSc PhD
- Secretary: Michiel Alexander de Raaf, MSc BAsC
- Chief Editor PVRI Chronicle: Sachindra Joshi, PhD
- Co-Chief Editor: Eileen Bauer, PhD
- Skype Meeting Administrator: Ewa Kolosionek, MSc PhD

Task Force members (including the Central Asian Group)

- Djuro Kosanovic
- Michael Seimetz
- Michiel de Raaf
- Sachindra Joshi
- Eileen Bauer
- Ewa Kolosionek
- Zeenat Safdar
- Stelios Orfanos
- Salina Gairhe
- Kizito Biwre
- Mamotabo Matshela
- Rebecca Vanderpool
- Thenappan Thenappan
- Mariella Velez-Martinez
- Aigerim Toibayeva
- Xiaohui Li
- Mirjenda Bastola
- Ekaterina Legchenko
- Himal Luitel
- Natascha Sommer
- Oleg Pak
- Marco Boehm
- Bahram Neupane
- Aleksandar Petrovic
- Argen Mamazhakypov
- H. James Ford
- Zahara Ali
- Mariola Bednorz
- Sharliyn Almodovar
- Yerik Otarbayev
- Alexey Goncharov
- Sovetbek Abdurashev
- Adilet Omuralieva
- Asel Moldalieva
- Saltanat Mukaeva
- Aysul Dzekisheva

Central Asian Group

- Batyr Osmanov
- Aigerim Yeshtau
- Aigerim Tolbaeva
- Aisuluu Eshimbetova
- IBRAIml Mirzaev
- Darkhan Telcubaev
- Chyngyzbek Asanbaev

Highlights of 2015

- As a committee we have issued one PVRI Chronicle journal and are in the process of publishing the second volume at the end of this year. In addition, we have regularly submitted content to the Pulmonary Circulation newsletter.
- All educational content on the PVRI website has been evaluated for its scientific, educational and technical quality. Improvement, if needed, was performed. In addition, all educational content on the PVRI website, keywords are currently being allocated, which will increase accessibility to the content.
- The committee has been active ‘backstage’ at two important PVRI congresses, namely the PVRI Annual Meeting in Guangzhou and the Drug Discovery meeting in London. At these conferences, members of the committee substantially helped to manage the recruitment of the people who gave lectures, interviews and poster presentations. The interviews were then actively carried out by the committee members. The lectures and presentations were recorded.

In regard to activity, the PVRI CYCS has launched the Annual Point system by which one point is being collected for every hour of dedicated (and voluntary) work for the PVRI. This system was started as a pilot for quarters (Q) 3-4 in 2014 and was officially launched on 1st January 2015. The Annual Point system preserves the efficacy and efficiency of the committee as members are rewarded when they are performing essential tasks for the PVRI (which are the responsibility of the PVRI CYCS), balances the amount of work among the members and recognises reward to the most active members.

In comparison to the year 2014, the committee increased its efficacy and efficiency by 64% in the first six months of 2015. The increase means that more hours/month of dedicated work for each member on average (2014: 3.03 hrs/month/member vs. 2015 Q1-2: 4.95 hrs/month/member). This increase is fueled by increased motivation and efficiency by 64% in the first six months of 2015. The increase means that more hours/month of dedicated work for each member on average (2014: 3.03 hrs/month/member vs. 2015 Q1-2: 4.95 hrs/month/member). This increase is fueled by increased motivation amongst members, a greater number of tasks being accomplished and the restructuring of the committee as a result of deeper insight (by this Annual Point system), that members are low in activity and should be motivated in a different way.

Goals for 2016

The main goals for the next year are as follows:

1: To publish two planned PVRI Chronicle issues to deadline and with equal (or better) quality compared to the previous issues/volumes.
2: To continue increasing the activity by augmenting the efficacy and efficiency of our committee.
3: To support the other committees according to the required action during the year.
4: To create more, high-quality, lectures/interviews based on theoretical, conceptual, historical and ‘active original research’.
5: To continue increasing the activity by augmenting the efficacy and efficiency of our committee.
Welcome

It is with a deep sense of responsibility, humility and pleasure that I take over the baton from Glennis in accepting the role of President of PVRI. Glennis has been an absolute bundle of efficient energy and her two years of office has overseen a major transformation of PVRI from a club to a fully established scientific society. PVRI has grown from its childhood and teenage years into young adulthood and transition from pediatric to adult care now necessary! The British relay teams have recently shown an annoying habit of dropping the baton in athletic finals, but I can assure all that I have no intention of dropping the PVRI baton.

In Rome we launch our fantastic new website which has been built with the collaboration of the PVRI Head Office team, a specialist web-design agency and the energetic members of our Committee for Young Clinicians & Scientists.

The considerable investment in time and resources this has required will provide a highly functioning platform for all our members and will greatly enhance the work of PVRI.

On that topic, 2016 sees a major launch of a web based education programme and a focus on Pulmonary Circulation.

I plan to review the structure of the various Task Forces - in February!

Seriously though, I have a tough act to follow but rest assured I will be working hard to maintain impetus and ensure that the PVRI’s adulthood continues in the right direction.

Many thanks to Glennis for her competent captaincy and commitment and if you think I employ too much alliteration in my writing, absolutely correct!