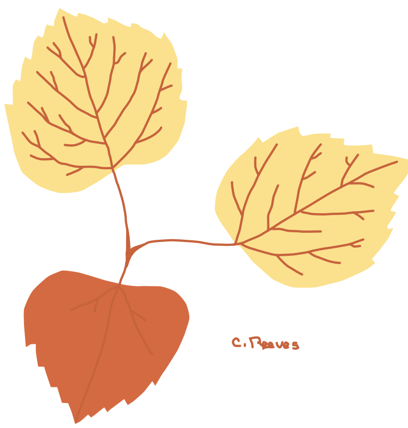
GROVER CONFERENCE

2013



September 4-8, 2013

Lost Valley Conference Center
Sedalia, CO

The **AMERICAN THORACIC SOCIETY** and the conference organizing committee gratefully acknowledge the educational grants provided for the support of this conference by:

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PROGRAM COMMITTEE

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THE PROGRAM

Since its inauguration in 1984, the 2013 Grover Conference will be the 16th in this series, representing the longest-standing conference on Pulmonary Circulation. Today it remains the principal conference for pulmonary vascular function, directly related to the interests of the ATS. Relatively small groups of attendees and highly focused topics facilitate maximal contact for scientific discourse. The seclusion of the Conference Center in Sedalia, CO provides the best opportunity for undisturbed exchange of ideas at both formal sessions and informal meetings at the conference center. The meeting is open to all interested scientists and clinician-scientists. As with past Conferences, this Conference will consist of a productive mix of young and senior scientists. Although the total number of participants is limited, we anticipate that the overall conference participants, including speakers and attendees, will be diverse and involve participants drawn from many ATS Assemblies.

Program Objectives

This four-day conference includes lectures, discussions, and poster presentations to develop a better understanding of the interaction between the right ventricle and the pulmonary circulation as it occurs during development, in normal physiology and in disease states, notably pulmonary hypertension and congenital heart disease. The aim of the Grover Conference is to integrate state-of-the-art bench research with clinical management and drug development strategies for pulmonary hypertension.

Learning Objectives

At the conclusion of this program, participants should be able to:

1. Understand the embryologic differences in the development of the right and left ventricles and understand the normal and disordered transition from fetal to adult RV and pulmonary circulation.
2. Be cognizant of the intrinsic coupling between the RV and pulmonary circulation in health and in diseases, such as pulmonary hypertension and congenital heart disease.
3. Have an understanding of the state of the art in terms of the causes of and treatments for RV failure in congenital heart disease and pulmonary hypertension while also understanding the latest imaging techniques and biomarkers to evaluate the function of the RV-PA unit.
4. Differentiate adaptive and maladaptive RV hypertrophy in human diseases and animal models.

Who Should Attend

The target audience includes researchers (both MD and PhD) and research-oriented clinicians (mostly Pulmonologists, Cardiologists, Cardio-thoracic surgeons, congenital heart specialists) who are interested in pulmonary hypertension, right heart failure, congenital heart disease, developmental biology and/or cardiopulmonary imaging. The conference will also be of great interest to student and young investigators who are early in their careers and have an interest in pulmonary hypertension, heart failure or congenital heart disease.

Speakers and Session Chairs

Kohtaro Abe, MD, PhD. Kyushu University. Fukuoka, Japan

Steven H. Abman, MD. University of Colorado Denver. Denver, Co

Stephen L. Archer, MD. University of Chicago. Chicago, IL

Brian Black, PhD. University of California at San Francisco. San Francisco, CA

Harm Bogaard, MD, PhD. VU University Medical Center. Amsterdam, Netherlands

Sebastien Bonnet, PhD. Laval University Quebec. Quebec, Canada

Michael Bristow, MD, PhD. University of Colorado Denver. Denver, CO

Ghazwan Butrous, MD, PhD. Kent University. Canterbury, United Kingdom

Hunter Champion, MD, PhD. University of Pittsburgh Medical Center. Pittsburgh, PA

Linda Demer, MD, PhD. University of California at Los Angeles. Los Angeles, CA

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

Robert F. Grover, MD, PhD. University of Colorado School of Medicine. Arroyo Grande, CA

Andre La Gerche, PhD. University of Melbourne. Melbourne, Australia

Brian Graham, MD. University of Colorado Denver. Aurora, CO

Paul M. Hassoun, MD. Johns Hopkins. Baltimore, MD

Arnoud van der Laarse, PhD. Leiden University. Leiden, Netherlands

Irene Lang, MD. Medical University of Vienna. Vienna, Austria

Jane Leopold, MD. Brigham and Women's Hospital. Boston, MA

Gregory D. Lewis, MD. Massachusetts General Hospital. Boston, MA

Gary Lopaschuk, PhD. University of Alberta. Edmonton, Canada

Antonio Augusto B. Lopes, MD. Heart Institute - University of Sao Paulo. Sao Paulo, Brazil

Joseph Loscalzo, MD, PhD. Brigham and Women's Hospital. Boston, MA

Timothy Mckinsey, PhD. University of Colorado Denver. Denver, CO

Ana Olga Mocumbi, MD, PhD. National Health Institute. Maputo,Mozambique

Lorna Moore, PhD. University of Colorado Denver. Denver, CO

Robert Naeije, MD. Universite Libre de Bruxelles. Brussels, Belgium

Anton Vonk Nordegraaf, MD, PhD. VU Medical Center. Amsterdam, Netherlands

Amit Patel, MD. University of Chicago. Chicago, IL

Andrew Redington, MD. Hospital for Sick Children. Toronto, Canada

Jalees Rehman, MD. University of Illinois at Chicago. Chicago, IL

John Ryan, MD. University of Utah. Salt Lake City, UT

Julio Sandoval, MD. National Institute of Cardiology. Mexico City, Mexico

Sanjiv Shah, MD. Northwestern Memorial Hospital. Chicago, IL

Robin Steinhorn, MD. University of California at Davis. Sacremento, CA

Kurt R. Stenmark, MD. University of Colorado Denver. Aurora, CO

Martin Strueber, MD. Heart Center Leipzig, University of Leipzig. Leipzig, Germany

David Systrom, MD. Brigham & Women's Hospital. Boston, MA

Ryan J. Tedford, MD. Johns Hopkins. Baltimore, MD

Thenappan Thenappan, MD. University of Chicago. Chicago, IL

Thomas Thum, MD, PhD. Hannover Medical School. Hannover, Germany

Norbert Voelkel, MD. Virginia Commonwealth University. Richmond, VA

E. Kenneth Weir, MD. University of Minnesota. Minneapolis, MN

James West, Ph.D. Vanderbilt University. Nashville, TN

Martin Wilkins, MD. Imperial College. London, United Kingdom

2013 Grover Conference on Coupling of the Right Ventricle and Pulmonary Circulation

COURSE SCHEDULE

Wednesday, September 4, 2013

12:00 pm **Arrivals**

6:00 pm **Welcome Reception and Dinner**

Thursday, September 5, 2013

Session I: Developmental Biology of the Right Ventricle and Pulmonary Circulation

Moderator: Robin Steinhorn, MD

6:55-7:55 am Breakfast

8:00 am Welcome and Introduction

8:10 am State of the Art: The Importance of viewing the Right Ventricle and Pulmonary Circulation as an Integrated, Functional Unit
Norbert Voelkel, MD. Richmond, VA (Virginia Commonwealth University)

8:45 am Development of the Right Ventricle and Septum: a transcriptional blue print revealed
Brian Black, PhD. San Francisco, CA (UCSF)

9:20 am Skeletal Muscle in PAH- the 'other' Forgotten Muscle
David Systrom, MD. Boston, MA (Massachusetts General Hospital)

9:55 am Break (10 min)

10:05 am Robyn Barst Lecture
Differences Between the Fetal, Newborn and Adult Pulmonary Circulation: Relevance for Age-Specific Therapy
Steven H. Abman, MD. Denver, CO (University of Colorado-Denver)

10:55 am miRNAs in the Pulmonary Vasculature
Sebastien Bonnet, PhD. Quebec, Canada (Laval University Quebec)

11:30 am The Debate: Be it Resolved: HDAC Inhibitors are Promising Therapeutic Targets for PAH Patients
Pro: Tim McKinsey, PhD. Denver, CO (University of Colorado – Denver)
Con: Harm Bogaard, MD, PhD. Amsterdam, Netherlands (VU University Medical Center)

12:40 pm Lunch

Session II: PVRI Global Health Perspective: Diseases of the RV-PA Unit

Moderator: Ghazwan Butrous, MD, PhD

3:00 pm If Pharma were to Develop One Drug for PH in Africa it would Target the RV
Ghazwan Butrous, MD, PhD. Canterbury, UK (Pulmonary Vascular Research Institute)

3:45 pm Endomyocardial Fibroelastosis
Ana Olga Mocumbi, MD, PhD. Mozambique

4:20 pm Congenital Heart Disease in South America
Antonio Augusto B.Lopes, MD. Sao Paulo, Brazil (University of Sao Paulo)

COURSE SCHEDULE

4:55 pm Schistosomiasis and the Pulmonary Vasculature
Brian Graham, MD. Denver, CO (University of Colorado – Denver)

5:30 pm Rheumatic Disease Affecting the RV and Pulmonary Vasculature in Mexico
Julio Sandoval, MD. Mexico City, Mexico (National Institute of Cardiology)

6:30 pm Dinner

Friday, September 6, 2013

Session III: Diseases Affecting the RV and Pulmonary Vasculature
Moderator: Thenappan Thenappan, MD

6:55-7:55 am Breakfast

8:05 am State of the Art: The Right Ventricle in Scleroderma
Paul Hassoun, MD. Baltimore, MD (Johns Hopkins)

8:55 am RV in Acute and Chronic Pulmonary Embolism
Irene Lang, MD. Vienna, Austria (Medical University of Vienna)

9:30 am HFpEF: Group 2 PH and the RV
Sanjiv Shah, MD. Chicago, IL (Northwestern Memorial Hospital)

10:05 am Break (10 min)

10:15 am The Response of the Pulmonary Circulation and RV to Exercise: Exercise-induced Right Ventricular Dysfunction and Structural Remodeling in Endurance Athletes
Andre La Gerche, PhD. Melbourne, Australia (University of Melbourne)

10:50 am Debate: Be it Resolved: Poor Early Outcomes Following Lung Transplantation in PAH Patients Reflect Unique RV Dysfunction
Pro: Robert Frantz, MD. Rochester, MN (Mayo Clinic)
Con: Martin Strueber, MD. Leipzig, Germany (University Heart Center Leipzig)

12:00 pm The Adrenergic System in Pulmonary Hypertension: Bench to Bedside
Michael Bristow, MD. Denver, CO (University of Colorado – Denver)

12:35 pm Lunch

Session IV: Therapeutic Targets Common to the RV and Pulmonary Vasculature
Moderator: John Ryan, MD

4:05 pm Announcement of Grover Biography
Right Heart Function at Altitude…Lessons from Leadville
Norma Elise Wäälen
Robert F. Grover, MD, PhD. Arroyo Grande, CA (University of Colorado School of Medicine)

4:40 pm Reactivation of the Fetal Gene Package in RVH and Pulmonary Hypertension: Role of MicroRNAs in the Human Heart
Thomas Thum, MD, PhD. Hannover, Germany (Hannover Medical School)

5:10 pm (Stem) Cell Therapy for PAH: Effects on the Right Ventricle
Arnoud van der Laarse, PhD. Leiden, Netherlands (Leiden University)

5:45pm BMP Signaing in the Vasculature…Bone and Beyond
Linda Demer, MD. PhD. Los Angeles, CA (UCLA)

COURSE SCHEDULE

6:30 pm Dinner

8:00 pm After Dinner Talk: Estelle Grover Lecture
High Altitude Physiology in Neonates and the Impact of High Altitude Pulmonary Hypertension on Evolutionary Patterns
Lorna Moore, PhD. Denver, CO (University of Colorado – Denver)

Saturday, September 7, 2013

Session V: Imaging in Assessing the RV, PA and Coupling
Moderator: Amit Patel, MD

6:55-7:55 Breakfast

8:05 am State of the Art: Advanced Imaging of the RV and Pulmonary Circulation in Humans
Anton Vonk Nordegraaf, MD, PhD. Amsterdam, Netherlands (VU Medical Center)

8:50 am Assessing Activity of the Adrenergic System Using MIBG
Kohtaro Abe, MD, PhD. Fukuoka, Japan (Kyushu University)

9:35 am Debate: Be it Resolved: The Right Ventricle in Pulmonary Hypertension is best imaged using advanced modalities such as MRI and PET-not Echocardiography
Pro: Hunter Champion, MD, PhD. Pittsburgh, PA (University of Pittsburgh Medical Center)
Con: John Ryan, MD. Salt Lake City, UT (University of Utah)

10:35am Break (10 mins)

Session VI: Hemodynamics and Biomechanics of the RV and Pulmonary Circulation
Moderator: Kenneth Weir, MD

10:45 AM Jack Reeves Lecture
Biomechanics of the RV in Health and Disease
Robert Naeije, MD, PhD. Anderlecht, Belgium (Erasme University Hospital)

11:20 am Evaluation and Treatment of Low Cardiac Output due to Right Ventricular Dysfunction and Cardiopulmonary Interactions in Congenital Heart Disease
Andrew Redington, MD, Toronto, Canada (Hospital for Sick Children)

11:55 am The Debate: Be it Resolved: The Resistance PAs are the Major Determinant of RV Afterload in Pulmonary Hypertension
Pro: Kurt Stenmark, MD. Denver, CO (University of Colorado – Denver)
Con: Ryan J. Tedford, MD. Baltimore, MD (Johns Hopkins)

12:45 pm Lunch

Session VI: Afternoon Session
Moderator: John Ryan, MD

3:00 pm Terry Wagner Lecture
State of the Art: Epigenetic Modifications, Basic Mechanisms and Role in Cardiovascular Disease
Joseph Loscalzo, MD, PhD. Boston, MA (Brigham and Women's Hospital)

4:00 pm Abstracts/Poster Review Session
Moderated poster session with selection from oral presentation of top scoring posters; Commemorative prizes for best abstracts

COURSE SCHEDULE

5:45 pm	Young Investigator Award Inhaled Iloprost Reverses Established Fibrosis in Maladaptive Right Ventricular Hypertrophy Secondary to Pulmonary Arterial Hypertension Jose Gomez-Arroyo, MD. Richmond, VA (Virginia Commonwealth University)
6:05 pm	Young Investigator Award Impaired Autophagy in Right Ventricular Failure (RVF) Anthony Cucci, MD. Indianapolis, IN (Indiana University)
6:25 pm	Young Investigator Award Metabolic Response to Hypoxia in Human Pulmonary Vascular Cells William M. Oldham, MD, PhD. Boston, MA (Brigham & Women's Hospital, HMS)
6:45 pm	Young Investigator Award Angiomir-126 Expression Decreased in Pulmonary Arterial Hypertension Right Ventricle Failure François Potus, MSc. Quebec, Canada (Laval University)
7:00 pm	Dinner

Sunday, September 8, 2013

Session VII: Metabolism in Progenitor Cells, the Plasma, RV and Vasculature

Moderator: Stephen L. Archer, MD

7:00-8:00 am	Breakfast
8:00 am	State of the Art: A Review of Cardiac Metabolism: Warburg, Randle and Krebs for the Nonbiochemist Gary Lopaschuk, PhD. Edmonton, Canada (University of Alberta)
8:35 am	The Renin-Angiotensin System as a Therapeutic Target in PAH Jane Leopold, MD. Boston, MA (Brigham and Women's Hospital)
9:05 am	Metabolomics in WHO 2 PH: Can Cardiac Metabolism be Inferred from the Plasma? Gregory D. Lewis, MD. Boston, MA (Massachusetts General Hospital)
9:40 am	Break (10 min)
9:50 am	Oxidative Stress and Metabolic Changes Caused by Bmpr2 Mutations James West, PhD. Nashville, TN (Vanderbilt University)
10:25 am	Metabolism in Stem Cells Jalees Rehman, MD. Chicago, IL (University of Illinois – Chicago)
11:00 am	Closing summary (10 min)
12:10	Lunch

The conference will adjourn after lunch.

ABSTRACT PRESENTATIONS

Faculty Abstracts

Assessment of Cardiac Adrenergic System Activity Using 123I-MIBG in Patients with Pulmonary Hypertension

Kohtaro Abe[1], Michinobu Nagao[2], Yoshitaka Hirooka[1] and Kenji Sunagawa[1]

Departments of Cardiovascular Medicine[1] and Clinical Radiology[2], Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

Most patients with pulmonary hypertension (PH) die from right ventricular (RV) heart failure. Recent studies demonstrated that adrenergic nervous activity, reflected by muscle sympathetic nerve activity and plasma norepinephrine levels, was significantly increased in patients with advanced PH. These adrenergic activations significantly correlated with the severity and poor prognosis of PH. In addition, the impairment of myocardial adrenergic system partly contributed to the development of RV dysfunction in rodent models of PAH. However, it has been never investigated about myocardial adrenergic system in the failing RV in PH patients. The purposes of this study were the followings; (1) to investigate RV adrenergic system in PH patients, and (2) if the impairment of myocardial adrenergic system predicts the severity of RV dysfunction. To assess RV adrenergic system activity, we used 123I-metaiodobenzylguanidine (123I- MIBG, an analog of norepinephrine) myocardial imaging. All PH patients underwent right heart catheterization and echocardiography to determine RV function. SPECT was performed in the resting state 15 min (early imaging) and 4 hr (delayed imaging) after the injection of 123I-MIBG. The patients with severe RV dysfunction showed higher washout rates and the more extent of the scintigraphic defects in the RV free walls compared with those with moderate RV dysfunction. The washout rate of 123I-MIBG in RV free wall significantly correlated with the plasma level of BNP. In conclusion, our results suggested that the impairment of RV adrenergic system assessed by 123I- MIBG imaging might predict the severity of RV dysfunction in PH patients. In a future, a larger study is still needed to be investigated whether 123I- MIBG imaging will be also useful to determine severity and prognosis in PH patients.

The Adrenergic System in Pulmonary Hypertension: Bench to Bedside

Michael R. Bristow, MD, PhD, University of Colorado Cardiovascular Institute

In heart failure with reduced left ventricular ejection fraction (“HFREF”) increased adrenergic activity and the resulting quantitative and qualitative changes in□□-adrenergic signal transduction play a major role in the development and progression of left and right ventricular adverse chamber remodeling. The chamber remodeling, typically measured by the ejection fraction that incorporates both contractility (stroke volume in the numerator) and size (end diastolic volume in the denominator) into the measurement is at least in part the result of changes in myocardial gene expression. Agents that block □1-adrenergic signal transduction (□-blocking agents) partially reverse both the remodeling phenotype and the gene expression changes, and markedly lower heart failure associated major event rates including mortality.

Despite the obvious clinical and developmental differences between the RV in PAH and the LV in HFREF, in humans the two chambers appear to behave similarly with respect to 1) the remodeling phenotypic response to pressure overload, 2) adrenergic activation, 3) □-AR signal transduction changes and 4) gene expression responses. In addition, multiple animal studies in experimental PAH have demonstrated RV benefits of □-or □/ □1-adrenergic receptor (AR) blockade. The presentation will highlight the similarities between the failing RV in PAH and the failing LV or RV in HFREF, discuss some subtle differences that appear to exist, and comment on whether there are strategies whereby anti-adrenergic agents could be safely administered to human subjects with PAH.

The Right Ventricle in Scleroderma-Associated Pulmonary Arterial Hypertension.

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

Pulmonary arterial hypertension (PAH) results from severe remodeling of the distal lung vessels leading irremediably to death through right ventricular (RV) failure. PAH (Group 1 of the World Classification of pulmonary hypertension) can be idiopathic (IPAH) or associated with other disorders such as connective tissue diseases. Prominent among the latter is systemic sclerosis (SSc), a heterogeneous disorder characterized by endothelium dysfunction, dysregulation of fibroblasts resulting in excessive collagen production, and immune abnormalities. For as yet unknown reasons, SSc-associated PAH (SSc-PAH) carries a significantly worse prognosis compared to any other form of PAH in Group 1 including IPAH.

We have previously shown that patients with SSc-PAH have a median survival of only 3 years, compared to 8 years for IPAH, despite modern PAH therapy. As death is principally due to RV failure, we speculated that RV adaptation to PAH differs between the two entities due to disparate pulmonary artery (PA) loading, perhaps from vessel stiffening, or intrinsic RV myocardial disease that limits function and adaptation to high afterload. In SSc, RV function may also be impaired by inflammatory processes, excess fibrosis of the myocardium,or altered angiogenesis, which may all contribute to impaired contractile reserve exacerbating cardio-pulmonary impedance mismatch. This is now suggested by recent findings that demonstrate that while pulmonary vascular load may be similar between IPAH and SSc-PAH patients, the latter display reduced myocardial contractility as assessed by pressure-volume loop measurements.

This presentation will focus on fundamental hemodynamic, structural, and functional differences in RV from patients with SSc-PAH compared to IPAH, which may explain survival discrepancies between these two populations. Possible underlying basic mechanisms will be discussed.

A Review of Cardiac Energy Metabolism: Warburg, Randle and Krebs for the Non-Biochemist

Gary D. Lopaschuk, Mazankowski Alberta Heart Institute University of Alberta, Edmonton, Canada

The heart has a very high energy demand and must continuously generate large amounts of adenosine triphosphate (ATP) in order to sustain contractile function. Mitochondrial oxidative phosphorylation is the primary source of ATP production by the heart, with glycolysis providing a smaller, but important, amount of ATP. Fatty acids and carbohydrates (glucose and lactate) are the main sources of acetyl-CoA for the mitochondrial Krebs Cycle, with the heart being able to quickly adapt to changes in workload, nutritional status, and hormonal status in order to match acetyl-CoA supply to acetyl-CoA demand. Unfortunately, stresses such as right ventricular pressure overload due to pulmonary hypertension can dramatically alter the source of acetyl-CoA for the Krebs Cycle, resulting in a decrease in the contribution of carbohydrates to acetyl-CoA production, and an increase in the relative contribution of fatty acid oxidation to acetyl-CoA production (i.e. the Randle Cycle). The increase in glycolysis that accompanies the decrease in carbohydrate oxidation results in a Warburg like phenomena, in which glycolysis is uncoupled from the subsequent mitochondrial oxidation of the pyruvate generated from glycolysis. The resultant production of lactate and H+'s due to this uncoupling of glucose metabolism decreases cardiac efficiency and can contribute to contractile dysfunction. As a result, strategies that improve the coupling of myocardial glycolysis to glucose oxidation are potential therapeutic approaches to treat heart failure that occurs secondary to pulmonary hypertension. One such strategy is to stimulate pyruvate dehydrogenase (PDH), the rate-limiting enzyme involved in carbohydrate oxidation. Direct activation of PDH, or activation of PDH secondary to inhibition of fatty acid oxidation, can lessen the Warburg effect, thereby decreasing lactate and H+ production and improving cardiac efficiency and function.

PVRI Global Health Perspective: Diseases of the RV-PA Unit Endomyocardial Fibrosis

Ana Olga Mocumbi, MD PhD FESC

Instituto Nacional de Saúde, Mozambique

Endomyocardial Fibrosis (EMF) affects mainly children and adolescents of certain poor regions of Sub Saharan Africa, where it is an important cause of heart failure and premature mortality. This cardiomyopathy of unknown origin has a predilection for the right ventricle. Pulmonary hypertension can be found in both left and right EMF.

On the right side pulmonary hypertension is usually related to thromboembolism due to thrombi on the right atrium cavities, more commonly the right atrium. Pulmonary hypertension related to left EMF is due to retrograde increase of pulmonary pressure caused by diastolic dysfunction.

The clinical course depends on the side affected. The echocardiographic assessment of pulmonary hypertension in EMF patients depends on the severity and extension of ventricular endocardial fibrosis, the quality of the right atrioventricular valve and presence of intracardiac thrombi. The management of pulmonary hypertension in EMF is difficult because in endemic areas. In endemic areas, affected patients reside in rural remote areas without adequate service provision. Therefore, the patients are detected with severe and advanced disease and, even when the health infrastructure is available, surgery cannot be performed without a very high risk of death and complications. The drugs used for control of symptoms and reduction of the progression of irreversible changes in the pulmonary vessels are unavailable and/or unaffordable.

Current research into the pathophysiological mechanisms and improvement in health systems in endemic areas will probably improve outcomes and alter the natural history of the disease.

Keywords: Pulmonary Hypertension, Endomyocardial Fibrosis, Sub-Saharan Africa

Metabolism in Stem Cells

Jalees Rehman

Department of Medicine, Section of Cardiology, Department of Pharmacology and University of Illinois Cancer Center, University of Illinois at Chicago, College of Medicine, Chicago, IL, 60612, USA

The two defining characteristics of stem cells are their multi-lineage differentiation potential (pluripotency) and their capacity for self-renewal. The role of growth factors as regulators of stem cell differentiation or self-renewal is well established, but less is known about the influence of metabolic pathways on stem cell function. We therefore investigated mitochondrial biogenesis, mitochondrial respiration and the mitochondrial membrane potential during the differentiation of adult human mesenchymal stem cells (MSCs) and human embryonic stem cells (ESCs).

Our data show that mitochondrial biogenesis and oxygen consumption increase markedly during MSC differentiation, and that reducing mitochondrial respiration by hypoxia or by inhibition of the mitochondrial electron transport chain significantly suppresses differentiation. Furthermore, we used a novel approach to suppress mitochondrial activity using a specific siRNA-based knockdown of the mitochondrial transcription factor A (TFAM), which also resulted in an inhibition of MSC differentiation.

In embryonic stem cells, we also observed a marked metabolic shift during cell differentiation. Undifferentiated cells exhibited high levels of glycolytic activity, whereas differentiating cells displayed increased glucose oxidation. The change in metabolic activity was also associated with expression changes of AMP-Kinase (AMPK) and suppression of selected AMPK isoforms was able to modulate ESC differentiation.

These findings suggest that metabolic modulation of adult stem cells or embryonic stem cells is not just a marker of their differentiation state, but can direct stem cell differentiation.

(Stem) Cell Therapy for PAH: Effects on the Right Ventricle.

Arnoud van der Laarse[1,2], PhD, Christa M. Cobbaert[2], PhD, and Soban Umar[3], MD, PhD.

[1]Department of Cardiology, [2]Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center, Leiden, the Netherlands, and [3]Department of Anesthesiology, Division of Molecular Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA.

Abstract

The conditions by which a state of "compensated" RV hypertrophy switches to a state of RV failure are partially known: development of (1) fibrosis, (2) ischemia, (3) proteolytic degradation of intracellular troponins, (4) impairment of presynaptic sympathetic function; (5) "fetal" gene expression, including metabolic switch from fatty acid oxidation to glycolysis, (6) up-regulation of mitochondrial uncoupling proteins leading to decreased mechanical efficiency, (7) apoptosis in cardiomyocytes, and (8) slowed conduction due to gap junction loss may determine whether the RV starts failing. We believe that these changes are potentially reversible given (1) the many reports about successful therapy of MCT-induced PAH, hypoxia-induced PAH, and high flow-induced (by shunting) PAH in experimental animals, and (2) the reports about reversed RV remodelling after lung transplantation in patients with end-stage PAH. The therapeutic effects of (stem) cell therapy are considered to be (1) paracrine effects from (stem) cells that had engrafted in the myocardium (or elsewhere) by compounds that have anti-inflammatory, anti-apoptotic, and pro-angiogenic actions, and (2) unloading effects on the RV due to (stem) cell-induced decrease of pulmonary vascular resistance and decrease of pulmonary artery pressure.

The Importance of Viewing the Right Ventricle and Pulmonary Circulation as an Integrated Functional Unit

Norbert F. Voelkel, M.D.

Pulmonary and Critical Care Medicine Division and Victoria Johnson Laboratory for Lung Research

Historically, the right ventricle (RV) which is driving the blood through the "lesser circulation" was for some time "the forgotten" ventricle. Because it has now been generally accepted that patients suffering from severe forms of PAH very frequently die from RVF, it has also been recognized that the mechanistic underpinnings of RVF must be investigated. The highly variable natural history of PAH patients is also variable in the susceptibility to develop RVF. This raises the question which arethe factors, in addition the RV afterload, that contribute to the development of RVF and which of these are potentially reversible? Again, historically remarkable, the Cardiovascular Pulmonary Research (CVP) lab was built on the concept of an integrated lung vessel-heart function and the participation of other organs in the setting of pulmonary hypertension – in particular under conditions of chronic hypoxia and high altitude. While inflammation and modified actions of the innate and adaptive immune system participate in pulmonary vascular remodeling without clearly identified consequences for RV function, one hypothesis is that neuroendocrine overdrive may transition the RV from compensated RVH to overt RVF. The novel concept of a "sick lung circulation affects the heart" can now be framed in the context of information flow from the activated and phenotypically altered lung vascular cells and their interactions with circulating cells, to the coronary and microcirculation of the heart. Mediators generated within sick lung vessels, cell fragments and microRNA-containing microparticles, which can be taken up by myocardial capillary EC, are postulated to play a role in the development of heart failure in severe PAH. Myocardial mitochondropathy, capillary rarefaction and dysfunction of their EC may all be affected by the information received from the sick lung vessels.

Non-Faculty Abstracts

Inhaled Iloprost Reverses Established Fibrosis in Maladaptive Right Ventricular Hypertrophy Secondary to Pulmonary Arterial Hypertension

Jose Gomez-Arroyo[1], Aamer A. Syed[1], Lazslo Farkas[1], Donatas Kraskauskas[1], Masahiro Sakagami[1], Peter Byron[1] and Norbert F. Voelkel[1]

[1]Virginia Commonwealth University, Richmond, Virginia, United States of America.

Rationale: Prostacyclin analogues, such as Iloprost, are used to treat pulmonary arterial hypertension (PAH). Prostacyclin treatment improves cardiac output and functional capacity in PAH patients, however the underlying mechanism is not fully understood. Objective:We sought to evaluate whether iloprost improves right ventricular (RV) function by reversing capillary rarefaction in maladaptive RV tissue. Methods and Results: Angioobliterative-PAH and RV failure were induced in rats with a single injection of SU5416 followed by four weeks of 10% hypoxia. Upon confirmation of RV dysfunction and PAH, rats were randomized to 0.1 μg/kg nebulized Iloprost or drug-free vehicle, three times daily for two weeks. RV function and exercise capacity were evaluated pre-and-post Iloprost/vehicle treatment for paired-analysis. Inhaled iloprost significantly improved RV longitudinal contraction and increased exercise capacity, whereas RV systolic pressure and plexiform-like lesions remained unchanged. Unexpectedly, the expression VEGFA and capillary density remained unchanged after iloprost treatment. In contrast, we found a striking reduction in RV collagen deposition and collagen mRNA levels in the iloprost treated group. Moreover, RV tissue from iloprost treated rats had a 20-fold decrease in connective tissue growth factor expression(CTGF). RV tissue from iloprost treated rats also exhibited increased MMP-9 activity. In-vitro, cardiac fibroblasts treated with iloprost showed a reduction of TGFβ1-induced CTGF, in a protein kinase A-dependent manner. Moreover, iloprost decreased TGFβ1-induced cardiac fibroblast activation and migration.

Conclusions: Inhaled iloprost improves RV function and reverses established RV fibrosis partially by preventing collagen synthesis and by increasing collagen turnover.

Right Ventriculo-arterial coupling determined by cardiac MRI in patients treated for pulmonary hypertension: prognosis and outcome

Brewis MJ,[1] Naeije R,[2] Peacock AJ.[1]

[1]Scottish Pulmonary Vascular Unit, Glasgow, UK. [2]Hôpital Erasme, Brussels, Belgium.

It is possible to estimate right ventriculo-arterial (VA) coupling non invasively using cardiac MRI (CMR) derived stroke volume (SV) end systolic volume (ESV) ratio (SV/ESV). Uncoupling has been shown in patients with pulmonary hypertension(PH) using this method [1] and correlated negatively with increasing pulmonary vascular resistance. We hypothesized that SV/ESV may predict outcome in patients with PH, and may be improved by pulmonary vasodilator treatment.

Methods: 88 treatment naive group I PH patients underwent CMR and right heart catheterisation at baseline. 43 patients subsequent underwent follow up CMR after minimum of 3 months of therapy.

Results: SV/ESV negatively correlated with PVR (R^2 -0.51, $p<0.0001$) in agreement with previous literature [1] A value of 1.5 had a 92% sensitivity 84.6% specificity for detection a PVR ≥ 3 (AUC 0.922). SV/ESV was a predictor of survival on Univariate analysis (P=0.028 HR 0.561 CI 0.336-0.938) in comparison to right ventricular ejection fraction (RVEF) p=0.011 HR 0.321 (0.134-0.768). Only left ventricular end diastolic volume (LVEDVI) remained an independent predictor on multivariate cox (p=0.047). A trend towards improvement in SV/ESV was observed with treatment [figure 1] but this did not reach statistical significance.

Conclusion: Early reduction in VA coupling (as determined by SV/ESV) occurs in patients with PH. SV/ESV may prove useful tool for non-invasive screening of patients at risk of PH. Vasodilator treatment shows a trend towards improved SV/ESV, which may be elucidated by a larger cohort.

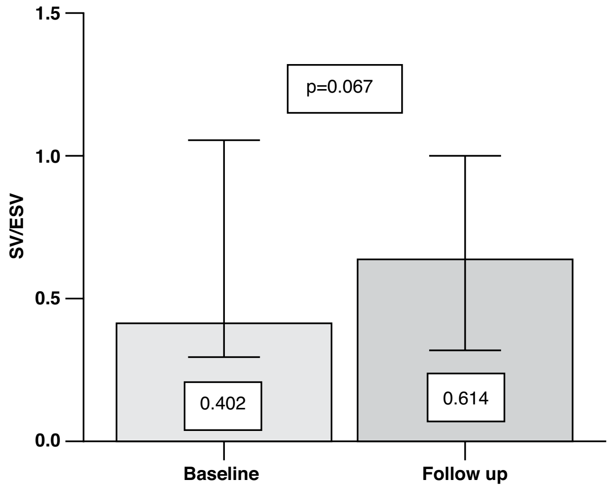

Figure 1: SV/ESV obtained at baseline and following minimum of 3months of therapy. Data displayed is median with range at each time point. Wilcoxon matched pairs t test showed a trend towards significant increase in SV/ESV.

References:

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Right Ventricular Function Predicts Mortality in Complex Co-Morbid Pulmonary Hypertension

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Objective: Elevated pulmonary artery pressures are a clinical feature of several cardiopulmonary diseases that are prevalent among elderly veterans. However, reports of echocardiographic characteristics pertaining to biventricular heart structure and function, pulmonary vasculature, as well as prognostic impact of these echocardiographically derived parameters in a "real-world" PH cohort with high cardiopulmonary co-morbidities are lacking.

Methods: In this retrospective study, we identified152patients with pulmonary artery systolic pressure (PASP)> 60mmHg over a five year period. The clinical characteristics and biventricular function were further characterized, and ultimately compared by Student's t-test or Chi-square analysis for deceased and surviving cohorts. Mortality hazard ratios adjusted for age as well as for comorbidities were established for all relevant echo parameters.

Results: Overall, 152 individuals (age 78.8 ± 10.2 years) were identified with significant PH. Overall mortality was high (69.7%), median survivalwas 129 days (Range: 0-1,985 days)with a high prevalence of underlying cardiopulmonary comorbidities. Inpatient status at time of echocardiogram and increased heart rate correlated with higher mortality. Left ventricular systolic function, diastolic function (E/A, E/e', estimated left atrial pressures), PASP, or echo derived pulmonary vascular resistance were not related to increase in hazard of death. In contrast, right ventricular systolic function (as assessed by TAPSE and tissue Doppler systolic velocity, RVS') significantly increased hazard of death after adjusting for age and underlying clinical confounders.

Conclusion:PH in the elderly veteran population is associated with a high mortality. Independent of the underlying etiology of elevated PA pressures TAPSE and RVS' are significantly associated with increased mortality in patients with advanced pulmonary hypertension.

PKC Regulation in Right Ventricular Fibrosis

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Pulmonary hypertension (PH) is associated with significant morbidity and mortality related to right ventricular (RV) failure. In PH, persistent afterload eventually leads to an increase in RV fibrosis and RV dysfunction. The molecular mechanisms underlying

RV fibrosis are currently not well characterized. The PKC family of serine/threonine kinases (notably PKC isoforms , , and) has been identified to play an important role in cardiac function. However, alteration of PKC expression in response to PH in RV cellular compartments, or the downstream signaling is unknown. We hypothesized that RV fibrosis in hypoxic PH is associated with differential PKC isoform expression and signaling. We exposed adult Sprague-Dawley rats to normoxia or hypoxia (10% FiO2) for 3 weeks. Cardiac fibroblasts (CF) were isolated from the ventricular compartments. Immunoblot analyses were performed to study the expression of PKC isoforms and p38 phosphorylation. We observed that hypoxia-induced RV hypertrophy and fibrosis caused an increase in PKC-II and expression in CF from both the left and right ventricle. Concomitantly, we noted that p38 phosphorylation decreased in RV CF but was unchanged in the LV. Next, in vitro studies were performed with isolated CF either transiently transfected with dominant negative PKCII or PKC cDNA, or pre-incubated with PKC inhibitors, LY333531 (PKCII) and rottlerin (PKC). CF were then exposed to angiotensin II for 48 hours. Angiotensin II increased cell proliferation and decreased p38 phosphorylation, however these changes were attenuated by inhibition of PKC. Thus we conclude that right ventricular fibrosis may occur through PKC-dependent inactivation of p38; a mechanism which may be important in the pathophysiology of RV fibrosis in PH.

Impaired Autophagy in Right Ventricular Failure (RVF)

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Indiana University

Rationale: Left ventricular injury models link dysregulated autophagy to maladaptive remodeling. However, the role of autophagy in RVF is unknown. We investigated autophagic flux, as well as markers of mitophagy, cardiomyocyte survival and apoptosis in models of adaptive and maladaptive RV remodeling.

Methods: Hemodynamic, morphologic and echocardiographic parameters of RV function were measured in rats with Sugen/hypoxia (SuHx)-induced RVF (n=9). Additional animals were treated with the autophagy inducer rapamycin (3mg/kg/d; n=4) or the lysosome inhibitor chloroquine (60mg/kg 16h prior to sacrifice; n=4). Selected endpoints were investigated in RVs of rats with hypoxia-induced PH (HPH; n=5). $p<0.05$ was considered statistically significant.

Results: SuHx-RVs exhibited increased autophagic proteins LC3-II and p62 ($p<0.05$ vs. untreated control), but no increase in the autolysosome marker LAMP-2, indicating impaired autophagic flux. These findings were associated with RV fibrosis, decreased bcl-2/bax ratio and increased caspase-3 activity (all $p<0.05$ vs. untreated). Impaired autophagic flux was confirmed by lack of LC3-II or p62 increase with chloroquine. Concomitant mitophagy was demonstrated by a significant increase in BNIP3 expression. Increases in LC3-II and p62 strongly correlated with alterations in RV mass, bcl-2/bax, and echocardiographic parameters. Neither LC3-II, p62, bcl-2/bax or caspase-3 were significantly altered in HPH-RVs. Rapamycin treatment in SuHx decreased p62 and attenuated SuHx-induced increases in RVSP and RV mass, but also increased mitophagy and worsened RV function.

Conclusion: Maladaptive (SuHx) but not adaptive (HPH) RV remodeling is characterized by impaired autophagic flux and mitophagy. In particular, autophagy is initiated but not completed, and a block exists at the autolysosomal fusion/degradation level. Enhancing autophagy with rapamycin in this context is insufficient to restore autophagic flux, and may even be detrimental for RV function.

Vasoreactivity and Persistent Vascular Remodeling in Experimental Pulmonary Hypertension

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Abstract:

During the last decade, a rat model of angio-obliterative pulmonary arterial hypertension based on the combination of a VEGF receptor blocker (Sugen/SU5416) and chronic hypoxia was introduced and described. However, a comprehensive hemodynamic characterization in conscious animals has not been reported.The aim of this study is to characterize hemodynamic responses in the Suhx-model and associate these with serial histology.Pulmonary hypertension was induced in rats with a single injection of SU5416 followed by four weeks of hypoxic exposure. Using a transdiaphragmatic approach, a telemetry blood pressure catheter was placed in the right ventricle

to continuously measure Right Ventricular Systolic Pressure (RVSP).RVSP increased in response to chronic hypoxia and remained elevated upon return to normoxia, with a plateau RVSP 30% below the maximum RVSP during hypoxia. Rats exposed to hypoxia-only showed a similar initial increase in RVSP, but a lower maximum RVSP and near-normalization of RVSP upon return to normoxia. Short periods of hyperoxia in order to test for the contribution of hypoxic pulmonary vasoconstriction demonstrated in SU5416/hypoxia rats a dramatic reduction in RVSP during the first three weeks after SU5416 administration. Progressive vascular remodeling consisted of a ~4 times increase in intima thickness, while little changes in media thickness were found.In SU5416/hypoxia rats, an initial vasoreactive stage is followed by non-vasoreactive pulmonary vascular remodeling, in particular intima remodeling. Pharmacotherapy administration should be carefully timed when using the SU5416/hypoxia rat model for pre-clinical studies.

Apples and Oranges; Fruitfulness of HDAC Inhibitors in Experimental Pulmonary Hypertension

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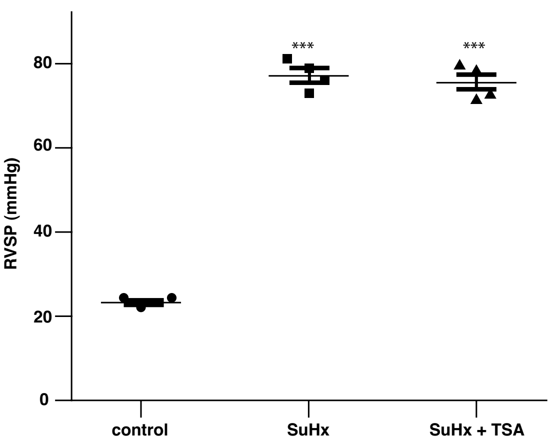
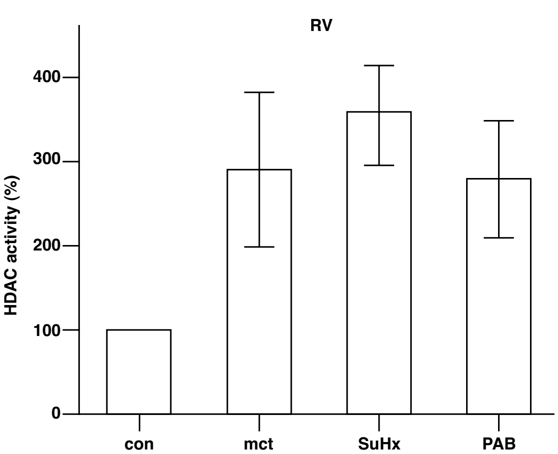
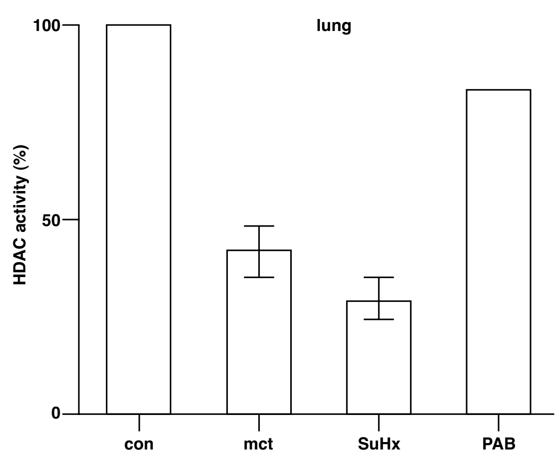
Pulmonary Arterial Hypertension (PAH) is a rapidly progressive and devastating disease described by remodeling of the lung vessels, which increases pulmonary vascular resistance and eventually results in right ventricular dysfunction. Histone deacetylase inhibitors (HDAC) have been very beneficial to hamper tumor growth and are therefore associated with therapeutic potential for pulmonary arterial hypertension. However, different HDAC's have different responses regarding cardiac hypertrophy and preclinical outcomes are controversial. In this study HDAC-inhibitor trichostatin A was administered in the sugen hypoxia model (SuHx) which induces experimental pulmonary hypertension by a combined exposure of the vascular endothelial growth factor receptor inhibitor SU5416 and chronic hypoxia. Also, general HDAC activity was tested in several experimental pulmonary hypertension (expPH) models, control, mct, SuHx and PA-banding; to assess the potential yield to gain therapeutically. Sugen hypoxia induced pulmonary hypertension was not hampered by trichostatin A. In different experimental pulmonary hypertension models HDAC activity was decreased in lung tissue, whereas it was increased in cardiac tissue. This study concludes that in SuHx-lungs, HDAC activity is decreased and further inhibition is of no benefit. The increased right ventricular HDAC activity might be due to adaptive responses which will deteriorate cardiac function when hampered. To keep the progress of HDAC inhibitors for PAH constructive,cautious care should be taken to push clinical tests forward in regard to PAH.







Role of Oxidized Lipids in Pulmonary Hypertension

Salil Sharma, Soban Umar, David Ross, Srinivasa T Reddy and Mansoureh Eghbali, UCLA, Los Angeles,CA

Pulmonary hypertension (PH) is characterized by increase in pulmonary arterial pressure and is associated with severe pulmonary vascular disorders. Biological oxidation products of arachidonic acid and linoleic acid, including hydroxyeicosatetraenoic acids (HETEs) and hydroxyoctadecadienoic acids (HODEs) play an important role in the pathogenesis of vascular disorders including atherosclerosis; however, their role in PH has not been investigated. Here we examined whether the circulating levels of oxidized lipids are elevated in PH and explored the therapeutic role of 4F, a HDL mimetic peptide, in rescuing PH. We found that plasma levels of HETEs and HODEs are significantly elevated in PH both in patients and animals. More importantly, we discovered that 4F peptide (50mg/kg/day) reduces oxidized fatty acid levels and rescues pre-existing PH in two experimental models induced by MCT (60mg/kg) in rats or by hypoxia in mice. MicroRNA analysis revealed that miR193 is downregulated ~3 fold in PH and 4F therapy fully restored miR193 to control levels. Overexpression of miR193 in the lungs of PH animals (20nM, intratracheal instillation at days 16, 21 and 26 in MCT model or at days 14 and 18 in hypoxic mice) rescued pre-existing PH and resulted in downregulation of the transcript levels of lipoxygenases including ALOX5, ALOX12 and ALOX15, the enzymes responsible for the production of oxidized fatty acids. In vitro treatment of human pulmonary artery smooth muscle cells (hPASMC) with HETEs and HODEs suppressed miR193 levels in the absence of 4F. Lastly, miR193 overexpression decreased serum or 12-HETE-induced proliferation of hPASMCs whereas miR193-kockdown increased proliferation. In conclusion, 4F rescues preexisting PH by reducing the elevated levels of oxidized lipids in PH via inducing miR193 and targeting lipoxygenases.

Glutamine Addiction Characterizes the Metabolic Shift in Pulmonary Arterial Hypertension

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The pathogenesis of pulmonary arterial hypertension (PAH) is characterized by a change in cellular metabolism that mirrors that of cancer. Based on preliminary studies from our lab and others, we investigated glutamine metabolism in pulmonary microvascular endothelial cells (PMVECs) from murine and human models of PAH, as glutaminolysis has been shown to be upregulated in malignant cells as well as in some models of PAH. We have demonstrated that PMVECs from BMPR2 mutant mice take up more glutamine than wild-type cells. Using stable isotope tracer quantification by mass spectrometry, we have shown that the intracellular fate of glutamine is different in mutant PMVECs, suggesting altered Krebs cycle carbon flow. Using quantitative twophoton autofluorescence of NADH and FAD, we have shown that the intracellular redox state of BMPR2 mutant PMVECs is more significantly affected by glutamine deprivation than in wild-type cells. We have shown that BMPR2 mutant PMVECs have an increased glutamine requirement to support proliferation and survival compared to wild-type, and that this “glutamine addiction” associates with normoxic HIF stabilization. Finally, we have shown that systemic glutamine levels are increased in patients with pulmonary arteriopathies, but that the transpulmonary uptake of glutamine in these same patients is profoundly increased compared to controls and substantially exceeds the uptake of glucose. Taken together, these studies point to a significant role for glutaminolysis in PAH and may allow for the rapid development of novel diagnostics and therapeutics.

Does Postnatal Hyperoxic Lung Injury Predispose to Development of Hypoxic Pulmonary Hypertension (PH) Later in Life?

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Introduction: PH development frequently requires multiple pulmonary vascular insults. The role of early hyperoxic lung injury as a potential first hit remains unknown. We tested whether early hyperoxia (O2) exposure is a predisposing factor for the development of hypoxia-induced PH (HPH) following exposure to hypobaric hypoxia (HH).

Methods: Male and female Sprague-Dawley pups were exposed to >90% O2 or room air (RA) from postnatal day 0-4. All pups were allowed to mature in room air. At 10 weeks of age, rats were exposed to 2 weeks of HH (Patm=362 mmHg; RA-HH [n=7] and O2-HH [n=8]). At 12 weeks, exercise capacity (VO2max via treadmill testing), right ventricular (RV) form and function (echocardiography), lung function (diffusing capacity), hypoxia-induced erythrocytosis (hematocrit), hemodynamics (RV systolic pressure), and RV hypertrophy (RV/LV+S) were assessed.

Results: Hypoxia exposure led to a robust HPH phenotype with increased RVSP, RV/LV+S, and hematocrit, and decreased RV stroke volume. While there were no differences in VO2max, diffusing capacity, RVSP or hematocrit between O2-HH and RA-HH rats, there was a trend toward higher RV/LV+S and better cardiac index and RV stroke volume in O2-HH rats. Despite these improvements in RV function, 25% hypoxia-induced mortality was noted amongst O2-HPH rats, compared to 0% mortality amongst RA-HH (p=0.09).

Conclusion: Early hyperoxia exposure appears to predispose to more profound RV hypertrophy following later hypoxia, and may allow for better RV function. Despite these favorable changes, postnatal hyperoxic lung injury also seems to represent a risk factor for mortality upon PH development. Whether the increased RV hypertrophy in O2-HH rats is adaptive or maladaptive is under investigation.

Aberrant Expression of EC-SOD in IPAH: Possible Regulation by Epigenetic Mechanisms

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New evidence indicates that epigenetic mechanisms regulate expression of key genes in pulmonary arterial hypertension (PAH). In animal models,loss of the vascular antioxidant enzyme extracellular superoxide dismutase (EC-SOD) worsens pulmonary hypertension. We hypothesized that epigenetic mechanisms will lowerEC-SOD expression in PAH. We tested RNA isolated from lungs obtained at transplantation through the Pulmonary Hypertension Breakthrough Initiative from 23 subjects with idiopathic PAH (IPAH) and 16 failed donors (FD). Lung EC-SOD mRNA expression was decreased in IPAH (0.34 ± 0.06 IPAH vs 0.55 ± 0.07 FD relative to ▯2microglobulin, p<0.05).DNA methylation of the EC-SODpromoter can decrease EC-SODexpression.Therefore, we performed bisulfite conversion followed by bisulfite sequencing of genomic lung DNA to test %methylationat18 CpG sites in the EC-SOD promoter. The methylation status of the EC-SODpromoter was highly variable, likelydue to baselinedifferencesbetweenlung cell types. We then tested primary PASMC derived from 3 individuals with IPAH and 3 FD. EC-SODmRNA was decreased in 2 of the IPAH PASMC (33% ± 0.08 of FD SOD3 expression). In IPAH PASMC, EC-SODexpression did not increase after a 5-day treatment with 5-azaC, suggesting DNA methylation was not responsible for low EC-SOD. In contrast, treatment with TSA, a histone deacetylase inhibitor, did not increase EC-SODexpression in FD PASMC, but increased EC-SODexpression over 2-fold in IPAH PASMC.These data suggestthat the decrease in EC-SOD gene expression in PAH could be regulated by epigenetic mechanisms, eg.histone acetylation. Further studies will confirm these findings and interrogatehow loss of EC-SOD contributes to PAH.

Il-6 Deficient Bone Marrow Enhances Susceptibility to Schistosoma-Induced Ph

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Background: Schistosomiasis-associated pulmonary arterial hypertension (PAH) affects over 200 million individuals worldwide. Recent evidence supports the role of inflammation as a fundamental driver of many causes of PAH, and studies in rodent models have revealed the role of IL-6 in hypoxic and monocrotaline induced PAH.However, the precise role of IL-6inPAH remains unclear. We hypothesized that bone marrow-derived IL-6 was implicated in Schistosoma-induced Th2 inflammation and vascular remodeling.

Methods: Wild type mice with and without bone marrow transplant (BMT)from IL6-/- mice(C57BL6/J background; N=4-5 per group) were first intraperitoneally (IP) sensitized to S. mansoni150eggs/gram body weight, and then intravenously (IV) challenged via tail vein with the same dose of S. mansoni eggs. One week after injection, right ventricular catheterization was performed, followed by quantitative analysis of the lung tissue for degree of vascular remodeling.

Results: Mice with IL6-/- bone marrow showed increased right ventricular systolic pressure as compared to control mice (mean pressures: 26.2 mmHg vs 20.7 mmHg; P=0.083). Mice with IL6-/- bone marrow also developed significant RV hypertrophy, as measured by the Fulton index (P=0.034). In addition, quantitative analysis of the vascular remodeling revealed a trend towards increased intima thickness and decreased media thickness for mice with IL6-/- bone marrow compared to control mice (P=0.310 and P=0.516, respectively).

Conclusion: IL-6 deficient bone marrow results in more severe PH.

Molecular Mechanisms Underlying17beta-Estradiol (E2)-Mediated Improvement In Right Ventricular (RV) Function In Su5416/Hypoxia-Induced PH (SuHx-PH)

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Rationale:E2 improves RV function and exercise capacity inmale rats with SuHx-PH.However, the underlying molecular mechanisms and the contribution of the two estrogen receptors, ER□ and ER□, are unknown.

Methods:RV systolic pressure (RVSP), cardiac output (CO), and PA and RV remodeling were measured in male SuHx-PH rats treated with E2; complemented by echocardiographic assessment and measurement of exercise capacity (VO2max via treadmill testing). In addition, we assessed E2 effects on RV free wall and interventricular septum (IVS) proliferative and cell fate signaling, as well as mitochondrial function and neurohormonal activation.Subgroups of animals were treated with the selective ER□-agonist DPN.

Results:SuHx caused robust PH (□RVSP, RV mass, PA remodeling; □PA acceleration time), RV dysfunction (□CO), exercise intolerance (□VO2max), and RV apoptosis (□bcl-2/bax; □caspase-3 activity). E2 did not decrease RVSP, but reduced RV thickness, improved RV stroke volume, and increased VO2max ($p<0.05$ vs. SuHx). This was accompanied by beneficial effects on RV tissue, where E2 increased the bcl2/bax ratio, and attenuated SuHx-induced increases in caspase-3 activity, GLUT1 expression and ANP mRNA ($p<0.05$). DPN did not recapitulate E2's effects. Neither SuHx nor E2 elucidated significant biochemical changes in the IVS.

Conclusions:In male SuHx-PH rats, E2 favorably affectsRV function and exercise capacity,as well asRV survival signaling, mitochondrial function and neurohormonal activation. These effects do not appear to be ER□-mediated. The role of ER□ and the effect of E2 in female rats are currently under investigation. E2's RV effects may allow for better adaptation to increased afterload, providing a potential explanation for the female survival benefit observed in PAH.

Histamine H2-Receptor Antagonists and the Right Ventricle: The Mesa Right Ventricle Study

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Introduction:

Histamine is a potential therapeutic target in pulmonary hypertension and heart failure. Histamine is abundant in the myocardium and H2 receptors are the predominant histamine receptor subtype in human hearts. The relationship between H2 receptor antagonists (H2RA) and right ventricular (RV) structure and function is not known.

Methods:

The Multi-Ethnic Study of Atherosclerosis enrolled 6,814 men and women without clinical cardiovascular disease. RV parameters were interpreted from cardiac MRI in 4,204 participants all of whom had detailed medication use ascertained by interview. Linear regression models estimated the independent association of baseline H2RA use with RV mass, RV end diastolic volume (RVEDV), and RV ejection fraction (RVEF). Analyses were adjusted for demographics, anthropometrics, smoking, pack years, diabetes mellitus, hypertension, and the corresponding left ventricular (LV) parameter. Confounding by co-medication and indication were considered.

Results:

The study sample included 4,124 participants with complete assessment of the RV and all covariables. Participants were 61.5±10.1 (mean±SD) years old, 52.6 % female and 39.3 % white. H2RA users tended to be older, with a higher BMI and more likely to be white. H2RA use was associated with less RV mass and a smaller RVEDV (Table 1). Adjustment for concurrent medication use did not alter these associations. Adjustment for LVEDV attenuated the relationship between H2RA use and RVEDV. Restricting the sample to the 419 participants using either H2RA or proton pump inhibitors as a proxy for acid reflux did not change the qualitative relationship between H2RA use and RV mass (Table 2).

Conclusion:

H2RA use is associated with less RV mass and smaller LV and RVEDV in individuals without known cardiovascular disease. This may reflect antagonism of myocardial H2 receptors or influence histamine-mediated pulmonary vascular remodeling. Further study is needed to determine whether H2RA may have a role in diseases complicated by RV failure.

Table 1. Difference in right ventricular structure and function in groups differing by H2 receptor antagonist use (n=4,124)

Model	Use of H2 Receptor Antagonist		
	RV	95% CI	p-value
Mass, g (Full Model)	-0.7	(-1.2, -0.2)	0.003
Mass, g (Full Model + co-medications)	-0.7	(-1.2, -0.2)	0.004
Mass, g (Full Model + LV Mass)	-0.6	(-1.0, -0.2)	0.008
EDV, mL (Full Model)	-4.3	(-7.3, -1.3)	0.005
EDV, mL (Full Model + co-medications)	-4.4	(-7.5, -1.3)	0.006
EDV, mL (Full Model + LVEDV)	-0.8	(-3.0, 1.5)	0.50
EF, % (Full Model)	-0.1	(-0.9, 0.8)	0.87
EF, % (Full Model + co medications)	-0.1	(-1.0, 0.8)	0.77
EF, % (Full Model + LVEF)	-0.3	(-1.1, 0.5)	0.53

Full model: age, gender, race/ethnicity, height, weight, city, education, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance

Co-medications: beta-blockers, ace-inhibitors, leukotriene receptor antagonist, non-steroidal anti-inflammatory medications including aspirin, and oral steroids

Table 2. Difference in right ventricular structure and function in groups differing by H2 receptor antagonist use, restricted to individuals on either PPI or H2 antagonists (n=419)

Model	Use of H2 Receptor Antagonist		
	RV	95% CI	p-value
Mass, g (Full Model)	-0.7	(-1.3, 0.0)	0.06
Mass, g (Full Model + co-medications)	-0.7	(-1.4, 0.0)	0.05
Mass, g (Full Model + LV mass)	-0.7	(-1.3, 0.0)	0.04
EDV, mL (Full Model)	-3.4	(-7.6, 0.9)	0.12
EDV, mL (Full Model + co-medications)	-3.4	(-7.9, 1.1)	0.14
EDV, mL (Full Model + LVEDV)	-2.2	(-5.2, 0.9)	0.16
EF, % (Full Model)	0.0	(-1.2, 1.2)	0.99
EF, % (Full Model + co-medications)	-0.2	(-1.4, 1.0)	0.74
EF, % (Full Model + LVEF)	-0.1	(-1.2, 1.0)	0.82

Full model: age, gender, race/ethnicity, height, weight, city, education, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance

Co-medications: beta-blockers, ace-inhibitors, leukotriene receptor antagonist, non-steroidal anti-inflammatory medications including aspirin, and oral steroids

Hypoxia Stimulates Extra-Adrenal Aldosterone Synthesis in Pulmonary Endothelial Cells to Modulate Pulmonary Vascular Fibrosis and Pulmonary Arterial Hypertension

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Hyperaldosteronism is associated with vascular fibrosis in pulmonary arterial hypertension (PAH) accompanied by hypoxia; however, the contribution of aldosterone to the pulmonary vasculopathy of hypoxia is unknown. We hypothesized that hypoxia modulates extra-adrenal aldosterone synthesis in human pulmonary artery endothelial cells (HPAECs) to promote vascular fibrosisin PAH. To test this hypothesis, HPAECs were exposed to normoxia or hypoxia (2% FiO2) for 24 hr. Compared to normoxia, hypoxia upregulatedexpressionof steroidogenic acute regulatory protein (StAR)(28.1 ± 0.1 vs. 41.6 ± 0.1 a.u., p<0.01), which facilitates the rate-limiting step in steroidogenesis, to induce a 2.1-fold (p=0.02) increase in aldosterone levels in the culture medium of HPAECs assessed by immunoassay andmass spectrometry. We nextinvestigated the relevance of StARto PAH in vivo. Compared to controls, StAR was increased in remodeled pulmonary arterioles in Sugen/Hypoxia-PAHrats, mice exposedtochronic hypoxia, and PAH patientsby57% (p<0.001), 66% (p<0.02), and 40% (p<0.01), respectively. Sugen/Hypoxia-PAH rats expressed increased pulmonary arteriolar levels of the fibrogenic protein connective tissue growth factor (CTGF)by 1.9-fold (p<0.01) and collagen III by 2.1-fold (p<0.01), which wasattenuated bythealdosterone antagonist eplerenone (0.6 mg/g chow) by 81% (p<0.01) and 38% (p<0.01), respectively, effects accompanied by significant improvement in pulmonary hypertension. These data demonstrate that StARupregulation by hypoxiainducesa hyperaldosterone state in HPAECsin vitro, which increases CTGF to promote vascular fibrosis in PAH in vivo. Identifying StAR and/or CTGF as novel treatment target(s) to attenuate pulmonary vascular fibrosis has potential therapeutic implications for PAH patients.

Metabolic Response to Hypoxia in Human Pulmonary Vascular Cells

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Hypoxia is a potent stimulus of pulmonary vascular remodeling. We sought to characterize the metabolic responses of normal pulmonary vascular cells to hypoxia. Metabolic profiling of human pulmonary artery endothelial (EC) and smooth muscle (SMC) cell extracts after 24 h exposure to 0.2% oxygen was performed with liquid chromatography-mass spectrometry (LCMS). Hypoxia had a significant impact on pathways associated with energy metabolism (the tricarboxylic acid cycle, glycolysis, and the pentose phosphate shunt) and amino acid biosynthesis. Surprisingly, α-ketoglutarate (αKG) and its reduced metabolite, 2-hydroxyglutarate (2HG), were among the most robustly increased metabolites by hypoxia in both cell types. This finding was confirmed by targeted LCMS demonstrating a 2.7 ± 0.3, 1.7 ± 0.2, and 2.3 ± 0.1-fold increase in αKG in EC, SMC, and human lung fibroblasts (LF) (mean ± SEM, p < 0.0001, n = 8-25), with a 2.0 ± 0.2, 1.6 ± 0.2, and 4.4 ± 0.3-fold increase in 2HG (p < 0.01, n = 8-25). Hypoxia-inducible factor (HIF) stabilization with desferrioxamine and CoCl2 did not increase αKG or 2HG under normoxic conditions in EC, but did increase 2HG and αKG in LF in normoxia (2.3 ± 0.5 and 3.0 ± 0.5 fold, n = 2, 5), while the HIF inhibitor daunorubicin inhibited the 2HG increase due to hypoxia in LF. Cell extracts derivatized with diacetyl-L-tartaric anhydride to enabled chiral separation of the R and S enantiomers of 2HG by LCMS. Baseline levels of R2HG and S2HG were similar, but S2HG demonstrated a greater hypoxia-mediated increase (R v. S: 1.6 v. 0.8-fold, p = 0.02, n = 3 in EC, 1.2 v. 1.4-fold, p = 0.37, n = 4 in SMC, 0.8 ± 0.1 v. 2.5 ± 0.3 fold, p = 0.003, n = 4 in LF). Knockdown of S2HG dehydrogenase potentiated the hypoxia-mediated increase in 2HG, while knockdown of R2HG dehydrogenase had no effect. Interestingly, TNFα in EC and LF or TGFβ1 in LF under normoxic conditions also leads to 2HG accumulation. S2HG is a competitive antagonist of αKG-dependent dioxygenases involved in histone demethylation, DNA hydroxylation, and prolyl hydroxylation, the latter leading to HIF stabilization. These data identify a novel metabolic response to hypoxia in pulmonary vascular cells, and suggest a mechanism by which these changes can potentiate other adaptive features of the hypoxia response.

Angiomir-126 Expression Decreasedin Pulmonary Arterial Hypertension Right Ventricle Failure

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Introduction: Right Ventricular Failure (RVF) is the majorpredictor ofmorbidity and mortality in pulmonary arterial hypertension (PAH). Left and right ventricle (LV; RV) differ in many aspects. Thus knowledge on cannot be extrapolated to the other and the reason for which the RV fails faster than the LV remains unknown.In PAH patients, hypertrophied RV is relatively ischemic, potentially because of suppressedangiogenesis. Inhibited angiogenesis explain hypertrophied RV muscle's increased O2 requirements and subsequent failure at a point in which an imbalance between O2 demand and delivery occurs. The MicroRNA (miRNA) angio-miR-126 promotes angiogenesisby inhibiting SPRED-1 and therefore triggering VEGF pathways. We hypothesized that specific miR-126downregulationpromotes RV ischemia and the transition from compensated (CRV) to decompensated (DRV) RVin PAH.

Methods/results: We studied free RV wall tissue from humans with normal RV function(n=5), CRV (n=3) and PAH (DRV) (n=2), and rats with normal RV function, CRV and DRV (n=5). miR-126 expression (qRT-PCR) and RV microcirculation (CD31 immunofluorescence and lectin perfusion) were studied. As expected, compared tocontrol and CRV, DRV had lower miR-126and microvessel density (n=5; $p<0.05$) creating an imbalance between O2 demand and delivery (note that miR-126 expression did not fall in LV).miR-126 downregulation in DRV increases SPRED-1 thereby decreasing VEGF pathway activation ($p<0.05$). Finally, in endothelial cellsisolated from human RV, miR-126 up-regulation (mimic) increased angiogenesis in PAH (matrigel assay) while downregulation of miR-126 (antagomir) in control or CRV mimickedPAH phenotype by decreasing angiogenesis.

Conclusion: We demonstratedthat the specific RV downregulation of miR-126 contributes to ischemic status of the DRV. Targeting miR-126 represents a new avenue of investigation in preventing and reversing failing RV.

β-arrestins RegulateBMPR-II Signaling and the Development of Pulmonary Arterial Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a disease associated with elevated pulmonary vascular resistance that leads to right ventricular (RV) hypertrophy, dilation and ultimately failure. PAH is often associated with decreased signaling by the type II bone morphogenetic protein receptor (BMPR-II), a member of the TGF-β receptor (TβR) superfamily. Consequently, gene mutations and signaling events that decrease BMPR-II activity are thought to increase susceptibility to PAH. In this work, we find that the β-arrestins (βarrs), versatile adapter proteins known to regulate signaling by a myriad of seven transmembrane receptors (7TMRs), bind to and regulate signaling by BMPR-II. BMPR-II signals are tranduced through the phosphorylation of downstream effector Smads. Downstream of BMPR-II activation, siRNA-mediated knockdown ofβarr1decreasesSmad phosphorylation while knockdown of βarr2 increases Smad phosphorylation significantly. Mirroring these biochemical phenotypes, βarr knockout mice display altered development of pulmonary arterial hypertension in response to hypoxia. βarr1 KO mice, which display decreased BMPR-II signaling, develop significantly worse hypoxia-induced pulmonary hypertensionand RV function compared to βarr2 KO, which are protected from RV failure compared to WT mice. These results demonstrate that βarrs reciprocallyregulate BMPR-II signaling and the development of PAH, suggesting that pulmonary β-arrs may be an attractive therapeutic target in PAH.

Targeted delivery of protease-resistant EC-SOD to the pulmonary artery

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Extracellular superoxide dismutase (EC-SOD), the major form of SOD in vessels, protects against O2- mediated oxidative stress and development of pulmonary hypertension (PH). SOD replacement has shown promise in different lung disease models, but with major limitations due to proteolytic degradation, lack of vascular targeting, and short tissue half life. We propose that site-specific and stable SOD activity is required in order to be an optimally effective therapy. Advancements in targeted drug delivery research, especially nanoparticle mediated gene delivery, have shown great potential and can be applied to vascular diseases such as PH. The central hypothesis is that the use of genetically modified expression plasmids via nanoparticles coated with homing peptides will improve the ability to target delivery of stable EC-SOD to the PA. EC-SOD variant expression plasmids were generated by site directed mutagenesis and were tested in pulmonary artery smooth muscle cells (PASMC). To quantify expression of intact EC-SOD, culture media from transfected PASMC was collected, then incubated on heparin coated plates or on PASMC with or without trypsin protease. Protease resistant EC-SOD (EC-SOD – E209Δ) had increased production (~40%) and binding to heparin (~80%) and cell surfaces (~60%) due to decreased susceptibility of proteolytic cleavage between E209 and R210. Wild type EC-SOD (EC-SOD – WT) was naturally susceptible to proteolysis. EC-SOD plasmids were encapsulated in RGD-functionalized or non-functionalized PLGA nanoparticles. RGD binds with high affinity to vB3 integrins, which are upregulated in hypoxic PA endothelial cells (PAEC). RGD-PGLA increased uptake in the PA and in PAEC. These studies provide a strong rationale to test this targeted EC-SOD expression system in rodent models of PH.

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