Pulmonary Hypertension and Right Ventricular Failure: New Insights into an Old Problem

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Content Collaborator
Session 3: Pulmonary Hypertension and Right Ventricular Failure:
New Insights into an Old Problem

Learning Objectives
1. Distinguish the Diagnostic Classification of the various forms of pulmonary hypertension (PH).
2. Explain the physiology behind right sided heart failure.
3. Apply a systematic approach to working up patients with suspected PH.
4. Identify the limitations of available treatments for PH, and their evidence based indications.
5. Recognize when to refer PH patients for advanced care.

Faculty

Ronald J. Oudiz, MD
Associate Professor of Medicine
Division of Cardiology
University of Texas Southwestern Medical Center
Dallas, Texas

Dr Ronald J. Oudiz is the professor of medicine at the David Geffen School of Medicine at UCLA, director of the Pulmonary Hypertension Center, and is a faculty cardiologist at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center in Southern California. He received his Medical School training at the University of Southern California in Los Angeles, CA, his Internal Medicine training at the University of California, San Diego, and his training in cardiovascular diseases at Harbor-UCLA Medical Center in Torrance. Dr Oudiz is board certified in Internal Medicine and Cardiovascular Diseases. He is a past holder of scientific research awards from the American Heart Association and the National Institutes of Health. In 2011, Dr Oudiz received the Pulmonary Hypertension Association Award of Excellence in Pulmonary Arterial Hypertension Care. He has authored several papers in pulmonary hypertension and has presented his research at national and international seminars. Dr Oudiz has been on task forces for the past three World Symposia on Pulmonary Hypertension; covering clinical endpoints, diagnostic testing right ventricular function, and physiology. He is a past editor in chief of the scientific publication Advances in Pulmonary Hypertension and has participated in several trials of innovative medical treatments for pulmonary hypertension, many of which are still ongoing. Dr Oudiz’s research focuses are describing the physiologic abnormalities that are caused by pulmonary hypertension using measurements of lung gas exchange during exercise and exercise rehabilitation as a treatment modality for patients with pulmonary hypertension.

Peter Libby, MD, FACC
Chief, Cardiovascular Medicine
Brigham and Women’s Hospital
Mallinckrodt Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Dr Peter Libby is chief of cardiovascular medicine at the Brigham and Women’s Hospital (BWH) in Boston. He also serves as the Mallinckrodt Professor of Medicine at Harvard Medical School, where he directs the DW Reynolds Cardiovascular Clinical Research Center. His current research focus is the role inflammation plays in vascular diseases such as atherosclerosis. His areas of clinical expertise include general and preventive cardiology.
Dr Libby earned his medical degree at the University of California, San Diego, and completed his training in internal medicine and cardiology at the Peter Bent Brigham Hospital (now the BWH). He has received recognition and numerous awards for his research accomplishments, including the 2006 Distinguished Scientist Award of the American College of Cardiology. He also holds an honorary Master of Arts from Harvard University.

An author and lecturer on cardiovascular medicine and atherosclerosis, Dr Libby has published extensively in medical journals, including Circulation, the Journal of Clinical Investigation, Proceedings of the National Academy of Sciences, the New England Journal of Medicine, and Nature. He is editor in chief of the new ninth edition of Braunwald's Heart Disease. Dr Libby has also contributed chapters on the pathogenesis, treatment, and prevention of atherosclerosis to Harrison's Principles of Internal Medicine. He has frequently served as a consultant to the National Heart, Lung, and Blood Institute; including a 5 year term on its Board of Scientific Councillors and was the recipient of the organization's MERIT Award. Dr Libby has held numerous visiting professorships and has been selected to deliver over fifty named or keynote lectures throughout the world.

Dr Libby's professional memberships include the Association of American Physicians, the American Society for Clinical Investigation, and honorary membership in the British Atherosclerosis Society. The current president of the Association of University Cardiologists, Dr Libby has served in many roles as a volunteer for the American Heart Association, including chairman of several research committees and member of executive committee councils on arteriosclerosis, circulation, and basic science.

Faculty Financial Disclosure Statements

The presenting faculty reports the following:

Dr Oudiz receives grant funds and/or honoraria for providing research support and/or consulting services from Actelion; Bayer; Gilead; Ikaria; Lung LLC; Medtronics; Pfizer Inc.; and United Therapeutics.

Dr Libby is a scientific advisory board member for Athera Biotechnologies, BIND Biosciences, Carolus Therapeutics, and Interleukin Genetics. He also serves as an unpaid consultant and/or is involved in clinical trials with Amgen; AstraZeneca Pharmaceuticals LP; Boehringer Ingelheim; Bristol-Myers Squibb; Genzyme; GlaxoSmithKline; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Pronova BioPharma; and Sigma-Tau Pharmaceuticals, Inc.

Suggested Reading List


Pulmonary Hypertension and Right Ventricular Failure: New Insights into an Old Problem

SPEAKERS
Ronald J. Oudiz, MD
Peter Libby, MD, FACC

Presenter Disclosure Information

The following relationships exist related to this presentation:
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Off-Label/Investigational Discussion

• In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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Pulmonary Hypertension and Right Ventricular Failure: New Insights into an Old Problem

Ronald J. Oudiz, MD, FACC
Professor of Medicine,
The David Geffen School of Medicine at UCLA
Director, Liu Center for Pulmonary Hypertension
Los Angeles Biomedical Research Institute
at Harbor-UCLA Medical Center
Torrance, CA, USA

Approximately how many patients do you see each week with Pulmonary HTN?

1. None
2. 1 to 10
3. 11 to 20
4. 21 to 30
5. 31 to 40
6. 41 to 50
7. 51 to 60
8. >60
Outcomes Question 1

A 65-year-old female with dyspnea and pulmonary hypertension, normal LV function and mild RV dilation on echocardiogram has the following findings:

Vitals signs: BP: 144/82, HR: 72, SpO2 96% (R)
PA catheterization: RA 8 mmHg, RV 62/8 mmHg, PA 60/24 mmHg (mean 36 mmHg), PCW 22 mmHg, CO 5.2 L/min.

Which of the following diagnoses is likely?

1. Idiopathic pulmonary arterial hypertension
2. Non-restrictive ventricular septal defect
3. Pulmonic stenosis
4. Diastolic LV dysfunction

Outcomes Question 2

A 70-year-old male patient with non-ischemic cardiomyopathy and known history of pulmonary hypertension presents to the Emergency Department in the evening with 2 days of increasing dyspnea and lower extremity edema. Exam is consistent with volume overload and mild pulmonary edema. Telemetry shows sinus tachycardia. BNP is elevated, and bedside echocardiogram shows moderate LV and RV dilation with LV EF 35-40% and moderately-reduced RV function. Estimated RV systolic pressure is 70 mmHg. Serum creatinine is elevated at 1.8 mg/dL. Blood pressure is 94/60 mmHg, HR 105 bpm, SpO2 is 92 % (RA). The patient took his afternoon medications, which include lisinopril, carvedilol, and spironolactone. In addition to continuing his outpatient medications, which of the following should be administered in the Emergency Department?

1. Furosemide 40 mg IV
2. Diltiazem SR 120 mg po
3. Atenolol 100 mg po
4. Hydralazine 10 mg IV
5. Amiodarone 400 mg IV

Outcomes Question 3

Which of the following drugs has been shown to improve mortality in WHO Group II pulmonary hypertension patients?

1. Sildenafil
2. Tadalafil
3. Bosentan
4. Epoprostenol
5. None of the above

Case:

66 yo Obese Man with Dyspnea, DM, HTN, Hyperlipidemia, RVSP est. 56 mm Hg

Pt admitted for further management (Friday)

What would you do for further management?

What is the most likely cause of this patient’s PH?

Pulmonary Hypertension (PH) – Definition

mPAP >25 mm Hg at rest

Pulmonary Hypertension (PAH) - Definition

mPAP >25 mm Hg at rest
+ PCWP (or LVEDP) ≤15 mm Hg
+ PVR >3 Wood units
**Pulmonary Hypertension: Diagnostic classification**

1. **Pulmonary arterial hypertension (PAH)**
   1.1. Idiopathic PAH (IPAH)
   1.2. Heritable
      1.2.1. BMPR2
      1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
      1.2.3. Unknown
   1.3. Drug- and toxin-induced
   1.4. Associated with
      1.4.1. Connective tissue diseases
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart diseases
      1.4.5. Schistosomiasis
      1.4.6. Chronic hemolytic anemia
   1.5 Persistent pulmonary hypertension of the newborn

2. **Pulmonary hypertension owing to left heart disease**
   2.1. Systolic dysfunction
   2.2. Diastolic dysfunction
   2.3. Valvular disease

3. **PH due to Lung Diseases and/or Hypoxemia**
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4. Sleep-disordered breathing
   3.5. Alveolar hypoventilation disorders
   3.6. Chronic exposure to high altitude
   3.7. Developmental abnormalities

4. **Chronic thromboembolic pulmonary hypertension (CTEPH)**

5. **Pulmonary hypertension with unclear multifactorial mechanisms**
   5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

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**Pulmonary Circulation – Normal physiology:**

Higher pulmonary venous (or pulmonary arterial wedge) pressures are required for adequate filling of the left ventricle during the high cardiac outputs of intense exercise.

Pulmonary Vascular Resistance (PVR) falls during exercise, because the increased capillary pressures cause recruitment and distention of capillaries.

The pulmonary arterial pressure therefore passively rises in response to the increase in venous pressure.

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**Pulmonary Circulation – Abnormal physiology:**

**CASCADE OF EVENTS**

Increased LA/PV pressure

↑ PAP is independent of degree of systolic LV dysfunction and degree of MR

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**A Quick Word on Chronic Thromboembolic Pulmonary Hypertension (CTEPH; Group IV)**

Do Not Miss It. It is Curable!
Pulmonary Circulation – Abnormal physiology:

CASSEDE OF EVENTS

- Increased LA/PV pressure
- Diastolic LV dysfunction
- Diastolic and systolic LA dysfunction
- Pulmonary venous (PCW) hypertension
- Increase in pulmonary microvascular pressure
- Damaged alveolocapillary barrier
- Rupture of barrier
- Pore stretching
- Leak of lung epithelium-specific proteins across the alveolocapillary barrier
- Surfactant-specific proteins (SP-A, B, C, D)

Effects on the Right Ventricle

1. Circumferential tension (Ttmp) = (Pcap - Palv) x r
2. Alveolar surface tension (Tst)
3. Longitudinal tension (Tel) (associated with lung inflation)


Casade of Events

Pulmonary Circulation – Abnormal physiology:

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Representative photomicrograph of marked thickening of the basement membrane of a pulmonary capillary in a patient with chronic increase in pulmonary capillary pressure caused by heart failure.

Lee S. Electron microscopic studies of the alveolar-capillary barrier in the patients of chronic pulmonary edema. Jpn Circ J. 1979;43:945-954

Electron micrographs showing stress failure in pulmonary capillaries

- Capillary endothelium is disrupted; alveolar epithelium basement membranes are continuous
- Disruption of all layers of the capillary wall with a red cell passing through the opening
- Alveolar epithelial layer (right) and capillary endothelial layer (left) are disrupted

Increased LA/PV pressure
Diastolic LV dysfunction
Diastolic and systolic LA dysfunction
Pulmonary venous (PCW) hypertension

Increase in pulmonary microvascular pressure

Damaged alveolocapillary barrier
rupture of barrier 1,2
pore stretching 3

Leak of lung epithelium-specific proteins across the alveolocapillary barrier
Surfactant-specific proteins (SP-A, B (1), C, D)

Endothelial dysfunction

Effects on the Right Ventricle

“Passive” PH with LV Dysfunction

- transpulmonary gradient <12

- The elevated hydrostatic pressure in the pulmonary veins leads to passive elevation of pulmonary arterial pressure (PAP).

“Reactive” PH with LV Dysfunction

- transpulmonary gradient >25

- Pulmonary vascular remodeling leads to irreversible pulmonary vascular disease.

- a result of changes* in the elastic fibers of the pulmonary arterial wall, intimal fibrosis and medial hypertrophy

* changes similar to those seen in idiopathic pulmonary arterial hypertension (IPAH)

What is the effect of the increased PVR on the Right Ventricle?

- The RV must generate higher pressure to maintain pulmonary blood flow
  - RVH
  - RV dilation
  - RV failure
- Reduced blood flow through the lungs
- Decreased cardiac output
- Decreased oxygen to the tissues
- Decreased ATP production

RV failure—end-stages of PH

Back to the Case:

66 yo Obese Man with Dyspnea, DM, HTN, HL, RVSP est. 56 mm Hg

Pt admitted for further management (Friday)

What would you do for further management?

What is the most likely cause of this patient’s PH?

Epidemiology of PH by Echo

- Single ECHO lab / Australian community of 160,000
- Etiology of PH noted on echocardiogram

- PAH, 2.3%
- Unknown, 6.8%
- CTEPH, 0.6%
- Lung disease, 9.7%
- Sleep-related hypventilation, 1.9%
- Congenital heart disease, 78.7%

AHA/ACC Guidelines 2009

Doppler Echocardiographic Estimates of Pulmonary Artery Pressure and Right-heart Catheterization Measurements
Case 2a: 66 yo Obese Man with Dyspnea, DM, HTN, HL, RVSP est. 56 mm Hg

Would you do an RHC in this patient?

Even if you do an RHC…

BE CAREFUL IN INTERPRETING RESULTS

Case: 66 yo Obese Man with Dyspnea, DM, HTN, Hyperlipidemia, RVSP est. 56 mm Hg

Pt diuresed over the weekend

RHC done Monday

RHC: RAP 9 mm Hg, PCW 12 mm Hg, PAP 58/25 mm Hg (mean = 36), CO 5.2 L/min

What is the diagnosis?
Pre-referral Diagnoses Compared With Diagnoses Obtained at PAH Tertiary Care Centers

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-referral Diagnosis</th>
<th>Post Referral Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>41 (73%)</td>
<td>39 (18%)</td>
</tr>
<tr>
<td>Group 2</td>
<td>0</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Group 3</td>
<td>4 (7%)</td>
<td>13 (66%)</td>
</tr>
<tr>
<td>No PH</td>
<td>7 (12%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Unk.</td>
<td>1 (18%)</td>
<td>0</td>
</tr>
</tbody>
</table>

39% of patients initiated on PAH-specific medication prior to referral did not have Group I PAH.

Evolution of HF with Preserved EF and PH/RV Failure

Exertional dyspnea

Pulmonary Vascular Stress

PH with HfEF

PVR ↑

LV stiffens

Systemic HTN


Treatment of PH with Left Heart Disease

Drugs that lower PAP in LHD

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Hypertension Drugs Studied in LHD</td>
<td>epoprostenol (FIRST)</td>
<td>prostacyclin analogue not stated trial terminated early</td>
</tr>
<tr>
<td>iloprost</td>
<td>prostacyclin analogue</td>
<td>myocardial ischemia induced trial terminated early</td>
</tr>
<tr>
<td>nitric oxide</td>
<td>Vasodilator</td>
<td>vasoreactivity safe to use given by inhalation</td>
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Soluble Guanylate Cyclase: Mechanism

GTP

sGC

cGMP

PDE-5 inhibitor

NOS

Nitric Oxide Synthase

cGMP is the intracellular messenger (pulmonary vasodilator) for NO

Treatment of PH/LHD

Soluble Guanylate Cyclase: Mechanism

NOS

Arg → NO + cit → sGC → GTP → cGMP

PDE-5 inhibitor

riociguat, an sGC analogue

cGMP is the intracellular messenger (pulmonary vasodilator) for NO

LEPHT: Riociguat vs. Placebo for HFrEF and PH

- placebo-corr Δ mPAP: p=NS
- PVR decreased 28% vs placebo p<0.05
- SVR decreased 21% vs placebo p<0.05
- "Balanced Vasodilator Effect"

When Should I Refer a PH Patient for Advanced Care?

a. PAH – always
b. Group II - diagnosis is uncertain and/or treatment response inadequate
c. Group III – pulmonary specialist
d. Group IV – always
e. Group V – probably always

Summary

- Increases in pulmonary venous pressure leads to passive increases in pulmonary arterial pressure.
- When transmural pulmonary capillary pressure exceeds 24 mmHg, pulmonary capillary structure is distorted; when the pressure exceeds 39 mmHg, structure is disrupted ("stress failure").
- Chronic pulmonary venous hypertension can result in abnormal pulmonary vascular structure and abnormal pulmonary vascular endothelial function (with vasoconstriction because of slow blood flow, due to increased EFT, decreased NO, etc) which may be irreversible.
- How the balance of forces that causes permanent pulmonary vascular dysfunction is modulated, resulting in permanent pulmonary vascular disease in some patients, remains to be elucidated.
- The cascade of events in heart failure that leads to pulmonary vascular disease ultimately affects right ventricular load and function, and leads to right ventricular failure, systemic circulatory impairment, and death.

Outcomes Question 1

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Question & Answer