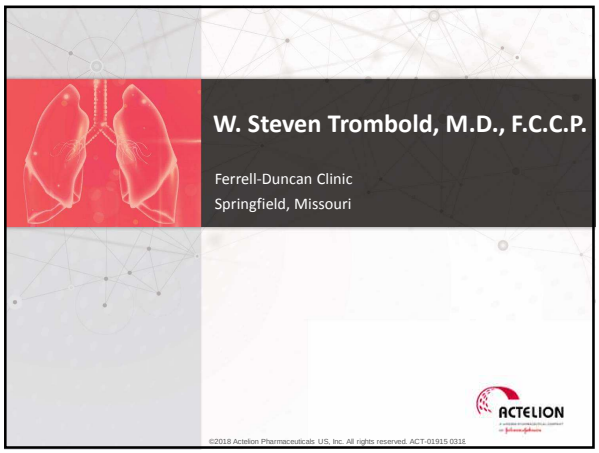
W. Steven Trombold, M.D., F.C.C.P.
Ferrell-Duncan Clinic
Springfield, Missouri
ACTELION
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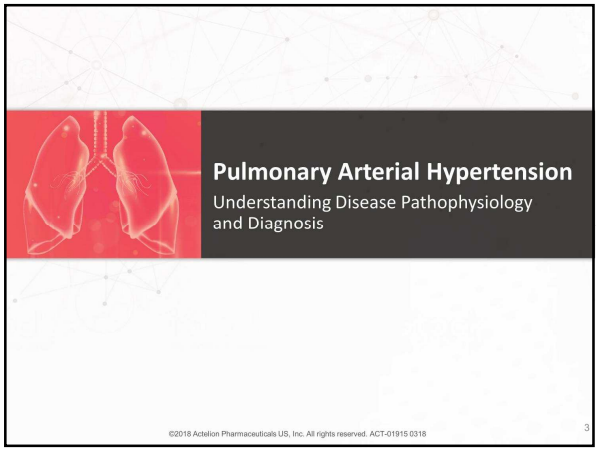
Pulmonary Arterial Hypertension
Understanding Disease Pathophysiology and Diagnosis
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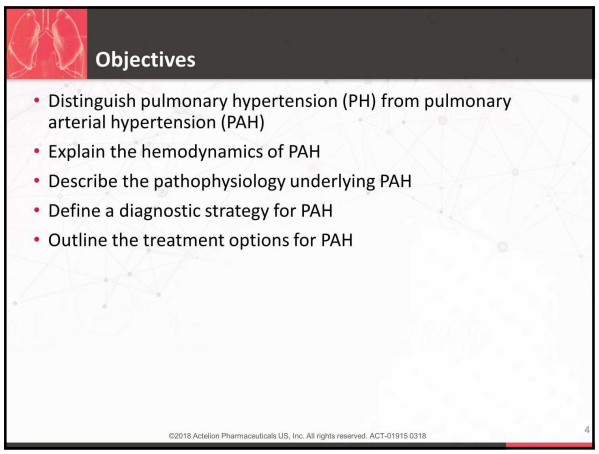
3


Objectives
• Distinguish pulmonary hypertension (PH) from pulmonary arterial hypertension (PAH)
• Explain the hemodynamics of PAH
• Describe the pathophysiology underlying PAH
• Define a diagnostic strategy for PAH
• Outline the treatment options for PAH
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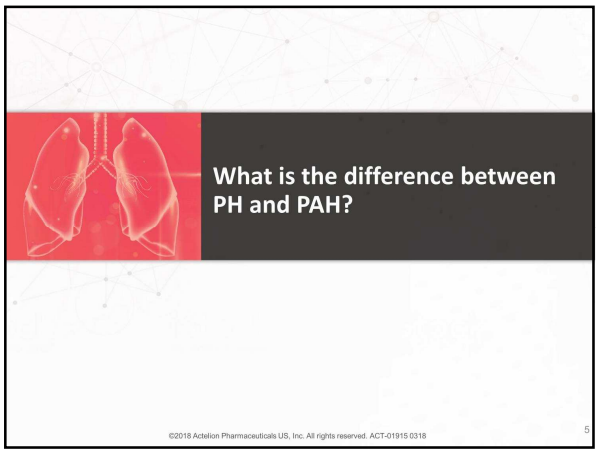
What is the difference between PH and PAH?
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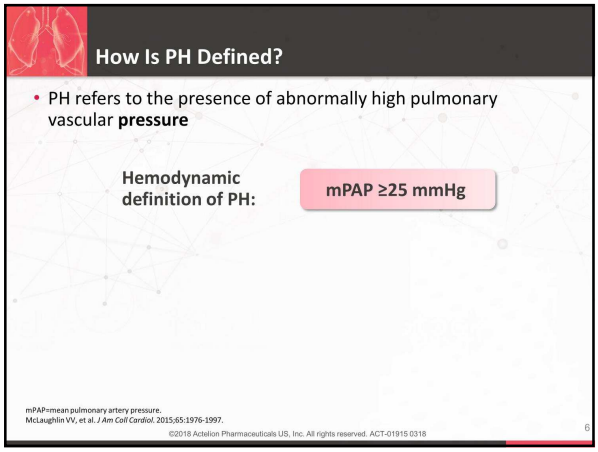
How Is PH Defined?
• PH refers to the presence of abnormally high pulmonary vascular **pressure**
Hemodynamic definition of PH:
mPAP ≥25 mmHg
mPAP=mean pulmonary artery pressure.
McLaughlin VV, et al. *J Am Coll Cardiol.* 2015;65:1976-1997.
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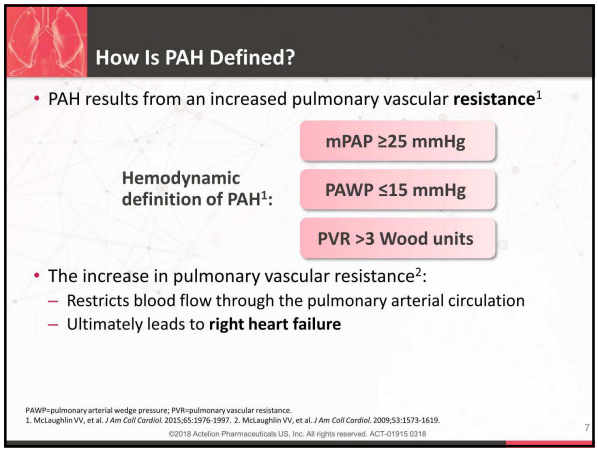
How Is PAH Defined?
• PAH results from an increased pulmonary vascular **resistance**[1]
Hemodynamic definition of PAH[1]:
mPAP ≥25 mmHg
PAWP ≤15 mmHg
PVR >3 Wood units
• The increase in pulmonary vascular resistance[2]:
– Restricts blood flow through the pulmonary arterial circulation
– Ultimately leads to **right heart failure**
PAWP=pulmonary arterial wedge pressure; PVR=pulmonary vascular resistance.
1. McLaughlin VV, et al. *J Am Coll Cardiol.* 2015;65:1976-1997. 2. McLaughlin VV, et al. *J Am Coll Cardiol.* 2009;53:1573-1619.
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Clinical Classification of Pulmonary Hypertension (Nice, 2013)

1. Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic PAH (IPAH)
- 1.2 Heritable PAH
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
  - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced PAH
- 1.4 Associated PAH
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis

1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension (PH) due to left heart disease
- 2.1 LV systolic dysfunction
- 2.2 LV diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to lung diseases and/or hypoxia
- 3.1 COPD
- 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 lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. PH with unclear multifactorial mechanisms
- 5.1 Hematologic disorders
- 5.2 Systemic disorders
- 5.3 Metabolic disorders
- 5.4 Others

ALK1=activin receptor-like kinase type 1; BMPR2=bone morphogenetic protein receptor type 2; CAV1=caveolin-1; COPD=chronic obstructive pulmonary disease; ENG=endoglin; HIV=human immunodeficiency virus; LV=left ventricle/ventricular; SMAD9=mothers against decapentaplegic 9.
Simonneau G, et al. *J Am Coll Cardiol*. 2013;62(25 suppl):D34-D41.

8

Functional Assessment of PAH

WHO Functional Classification	
Class I	Patients with [PAH] but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with [PAH] resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with [PAH] resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with [PAH] with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

NYHA Functional Classification	
Class I	No symptoms with ordinary physical activity.
Class II	Symptoms with ordinary activity. Slight limitation of activity.
Class III	Symptoms with less than ordinary activity. Marked limitation of activity.
Class IV	Symptoms with any activity or even at rest.

NYHA=New York Heart Association; WHO=World Health Organization.
Adapted from: Rubin LJ. *Chest*. 2004;126(1 suppl):7S-10S.

9

What are the pathophysiological changes in PAH?

10

Identifying Causes of PH Anatomically: Where Is the Triggering Lesion in PAH?

1. Pulmonary arterial hypertension (PAH)[1]

- 1.1 Idiopathic PAH (IPAH)
- 1.2 Heritable PAH
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
  - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced PAH
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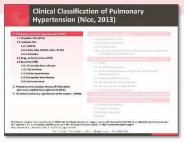
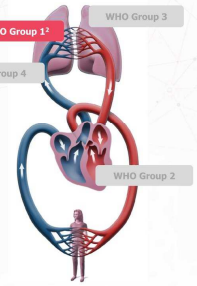
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis

Clinical Classification of Pulmonary Hypertension (Nice, 2013)

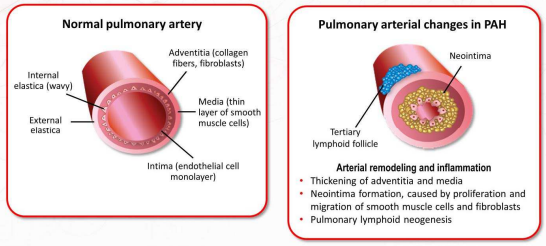




1. Simonneau G, et al. *J Am Coll Cardiol*. 2013;62(25 suppl):D34-D41. 2. McLaughlin VV, et al. *J Am Coll Cardiol*. 2015;65:1976-1997.

11

Pathophysiologic Changes in PAH: Pulmonary Vascular Remodeling



Adapted from: McLaughlin VV, et al. *J Am Coll Cardiol*. 2015;65:1976-1997.

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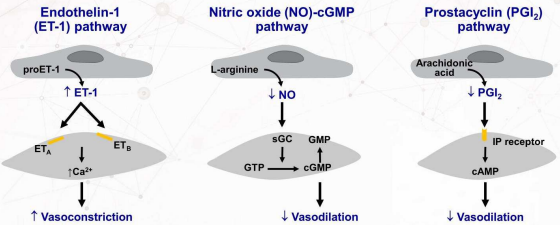
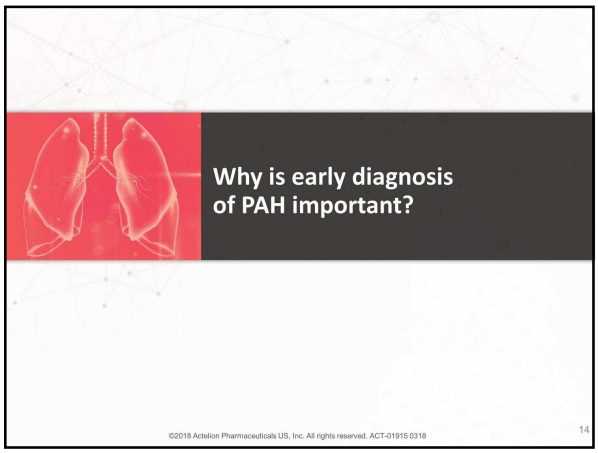
Pathogenesis of PAH: Vasoconstriction[1,2]



cAMP=cyclic adenosine monophosphate; cGMP=cyclic guanosine monophosphate; ERA=endothelin receptor antagonist; ET_A=endothelin receptor type A; ET_B=endothelin receptor type B; GMP=guanosine monophosphate; GTP=guanosine triphosphate; IP=prostacyclin receptor; PDE-5i=phosphodiesterase type 5 inhibitor; sGC=soluble guanylate cyclase.

Adapted from: 1. Humbert M, et al. *Circulation*. 2014;130:2189-2208. 2. McLaughlin VV ,et al. *J Am Coll Cardiol*. 2015;65:1976-1997.

13


Why is early diagnosis of PAH important?
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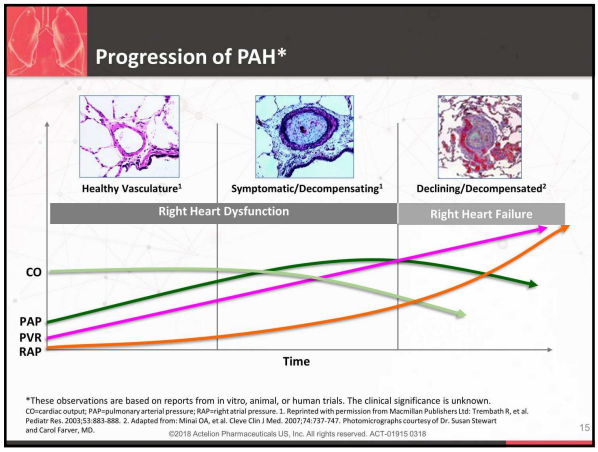
Progression of PAH*
Healthy Vasculature[1]
Symptomatic/Decompensating[1]
Declining/Decompensated[2]
Right Heart Dysfunction
Right Heart Failure
CO
PAP
PVR
RAP
Time
*These observations are based on reports from in vitro, animal, or human trials. The clinical significance is unknown.
CO=cardiac output; PAP=pulmonary arterial pressure; RAP=right atrial pressure. 1. Reprinted with permission from Macmillan Publishers Ltd: Trembath R, et al. Pediatr Res. 2003;53:883-888. 2. Adapted from: Minai OA, et al. Cleve Clin J Med. 2007;74:737-747. Photomicrographs courtesy of Dr. Susan Stewart and Carol Farver, MD.
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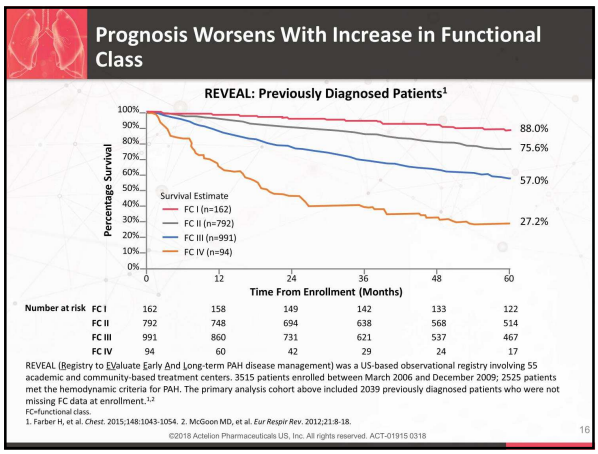
Prognosis Worsens With Increase in Functional Class
REVEAL: Previously Diagnosed Patients[1]
Percentage Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Survival Estimate
FC I (n=162)
FC II (n=792)
FC III (n=991)
FC IV (n=94)
88.0%
75.6%
57.0%
27.2%
0
12
24
36
48
60
Time From Enrollment (Months)
Number at risk FC I 162 158 149 142 133 122
FC II 792 748 694 638 568 514
FC III 991 860 731 621 537 467
FC IV 94 60 42 29 24 17
REVEAL (Registry to EValuate Early And Long-term PAH disease management) was a US-based observational registry involving 55 academic and community-based treatment centers. 3515 patients enrolled between March 2006 and December 2009; 2525 patients met the hemodynamic criteria for PAH. The primary analysis cohort above included 2039 previously diagnosed patients who were not missing FC data at enrollment.[1,2]
FC=functional class.
1. Farber H, et al. Chest. 2015;148:1043-1054. 2. McGoon MD, et al. Eur Respir Rev. 2012;21:8-18.
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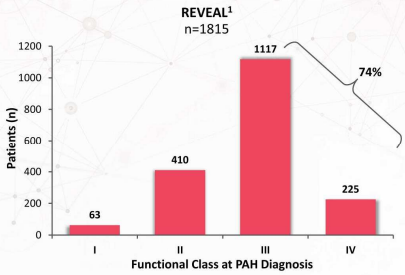
Diagnosis of PAH Is Often Late



REVEAL was a US-based observational registry involving 55 academic and community-based treatment centers. 3515 patients enrolled between March 2006 and December 2009; 2525 patients met the hemodynamic criteria for PAH. The study population consisted of 2493 patients, of whom 526 (21.1%) had recognition of PAH >2 years after the onset of symptoms and 1967 (78.9%) had recognition ≤2 years. Data presented above do not sum to the total study population due to missing data.[1,2]

1. Adapted from: Brown LM, et al. *Chest*. 2011;140:19-26. 2. McGoon MD, et al. *Eur Respir Rev*. 2012;21:8-18.

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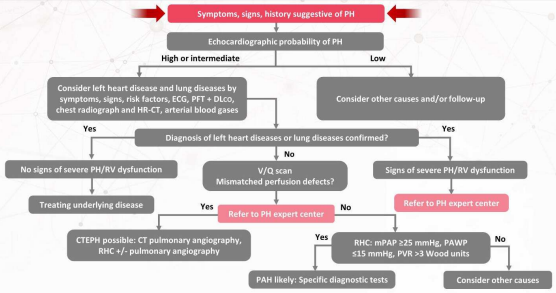
How is PAH diagnosed?

18

PAH: A Diagnosis of Exclusion



DLco=diffusion capacity of the lung for carbon monoxide; ECG=electrocardiogram; HR-CT=high resolution computed tomography; PFT=pulmonary function test; RHC=right heart catheterization; RV=right ventricle/ventricular; V/Q=ventilation/perfusion.

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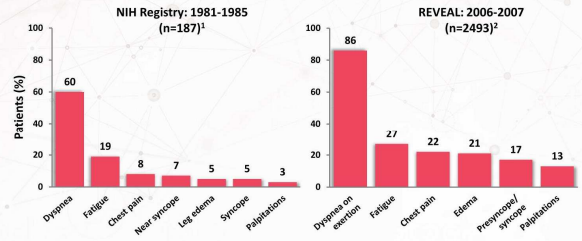
Medical History: Most Common Symptoms



REVEAL was a US-based observational registry involving 55 academic and community-based treatment centers. 3515 patients enrolled between March 2006 and December 2009; 2525 patients met the hemodynamic criteria for PAH. The study population above consisted of 2493 patients, of whom 526 (21.1%) had recognition of PAH >2 years after the onset of symptoms.[2,3]

NIH=National Institutes of Health.

1. Rich S, et al. *Ann Intern Med*. 1987;107:216-223. 2. Brown LM, et al. *Chest*. 2011;140:19-26. 3. McGoon MD, et al. *Eur Respir Rev*. 2012;21:8-18.

20

Medical History: Drugs and Toxins Associated With PAH

Definite
- Aminorex
- Fenfluramine
- Dexfenfluramine
- Toxic rapeseed oil
- Benfluorex
- SSRIs*

Possible
- Cocaine
- Phenylpropanolamine
- St. John's Wort
- Chemotherapeutic agents
- Interferon α and β
- Amphetamine-like drugs

Likely
- Amphetamines
- L-tryptophan
- Methamphetamines
- Dasatinib

Unlikely
- Oral contraceptives
- Estrogen
- Cigarette smoking

*SSRIs have been demonstrated as a risk factor for the development of persistent pulmonary hypertension in the newborn (PPHN) in pregnant women exposed to SSRIs (especially after 20 weeks of gestation). PPHN does not strictly belong to Group 1 (PAH) but to a separated Group 1.

SSRI=selective-serotonin reuptake inhibitor.

Simonneau G, et al. *J Am Coll Cardiol*. 2013;62(25 suppl):D34-D41.

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Medical History: Risk Factors for PAH

Risk Factor	Estimated Prevalence of PAH
HIV infection	≈0.5%[1]
Schistosomiasis infection	4.6%[2]
Portal hypertension	2% to 6%[3,4,*]
Connective tissue disease	3% to 13%[5,†]

*In hemodynamic studies of patients with portal hypertension.

†PAH confirmed by RHC.

1. Sitbon O, et al. *Am J Respir Crit Care Med*. 2008;177:108-113. 2. Lapa M, et al. *Circulation*. 2009;119:1518-1523. 3. Hadengue A et al. *Gastroenterology*. 1991;100:520-528. 4. Colle IO et al. *Hepatology*. 2003;37:401-409. 5. Chung L, et al. *Chest*. 2010;138:1383-1394.

22

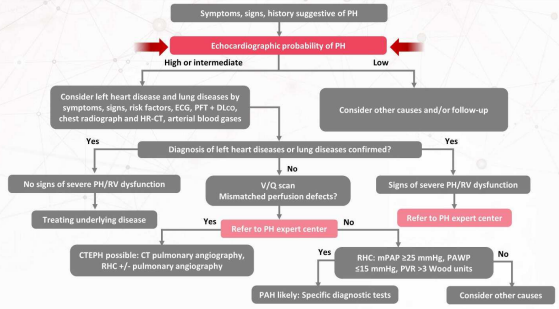
Diagnosis of PAH: Role of Physical Examination

Sign	Implication
Accentuated pulmonary component of S_2 (audible at apex in over 90%)	High pulmonary pressure increases force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of pulmonary valve into high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Left parasternal lift	High right ventricular pressure and hypertrophy present
Right ventricular S_4 (in 38%)	High right ventricular pressure and hypertrophy present
Increased jugular *a* wave	Poor right ventricular compliance

S_2=second heart sound; S_4=right ventricular (RV) third heart sound; S_4=RV fourth heart sound.
Adapted from: McLaughlin VV, et al. *Circulation*. 2009;119:2250-2294.

23

Diagnosis of PAH: Role of Echocardiography



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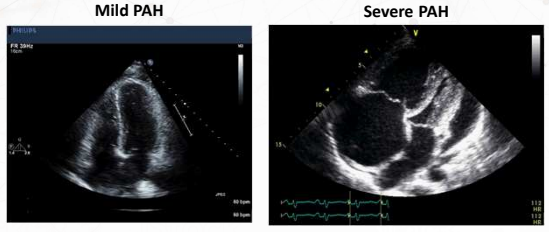
Echocardiograms From Patients With Mild Versus Severe PAH



Apical 4-chamber view

Videos courtesy of Sharon Howell.

24

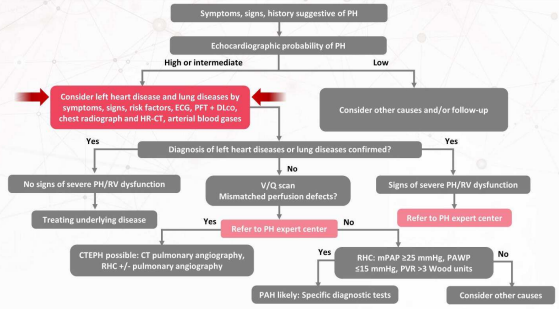
Reference Limits for Recommended Measures of Right Heart Structure and Function

Variable	Abnormal
Chamber dimensions	
RV basal diameter	>4.2 cm
RV subcostal wall thickness	>0.5 cm
RVOT (PSAX/PLAX)	>2.7 cm/>3.3 cm
RA major/minor dimension	>5.3 cm/>4.4 cm
RA end-diastolic area	>18 cm^2
Systolic function	
TAPSE	<1.6 cm
Pulsed/tissue Doppler MPI	>0.40/>0.55
FAC	<35%
Diastolic function	
E/A ratio	<0.8 or >2.1
E/E′ ratio	>6
Deceleration time	<120 ms

FAC=fractional area change; MPI=myocardial performance index; PLAX=parasternal long-axis; PSAT=parasternal short-axis; RA=right atrial; RVOT=right ventricular outflow tract; TAPSE=tricuspid annular plane systolic excursion.
Adapted from: Rudski LG, et al. *J Am Soc Echocardiogr*. 2010;23:685-713.

26

Diagnosis of PAH: Role of ECG, PFTs, and X-ray



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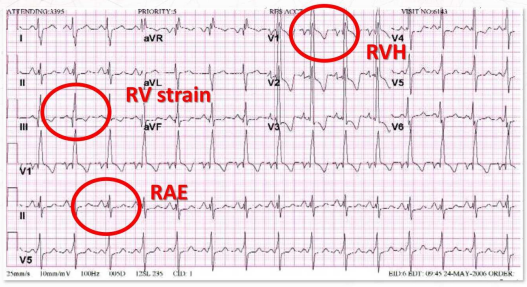
Diagnosis of PAH: Role of ECG



RAE=right atrial enlargement; RVH=right ventricular hypertrophy.
Image courtesy of Pulmonary Hypertension Association.

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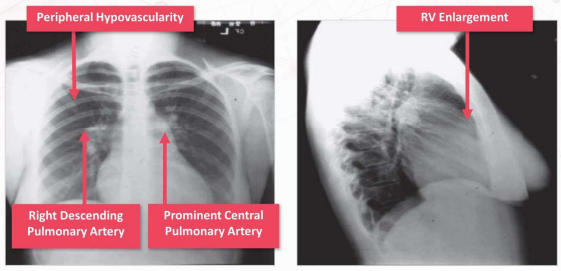
Diagnosis of PAH: Role of PFTs

- Important component of diagnostic workup to identify the contribution of underlying airway or parenchymal disease[1]
- Decreased DLCO and mild-to-moderate reduction in lung volumes usually seen in PAH[1]
- In patients with systemic sclerosis:
  - Reduced DLCO and normal lung volumes is suggestive of PAH[2]
  - DLCO correlates inversely (r=0.60) with invasively measured sPAP[2]
  - Annual PFTs and echocardiogram recommended[3]

sPAP=systolic pulmonary arterial pressure.
1. Galiè N, et al. *Eur Respir J*. 2015;46:903-975. .2 McGoon M, et al. *Chest*. 2004;126(1 suppl):14S-34S.
3. Hoeper MM, et al. *J Am Coll Cardiol*. 2013;62(25 suppl):D42-D50.

29

Diagnosis of PAH: Role of Chest X-ray



McLaughlin VV, et al. *Circulation*. 2009;119:2250-2294.

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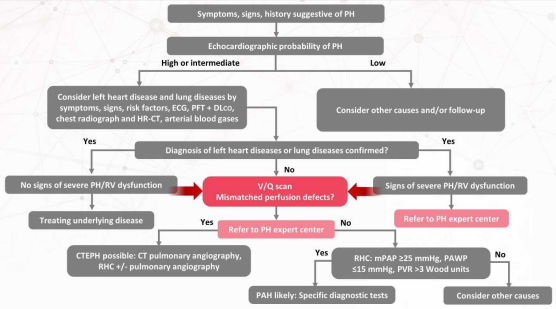
Diagnosis of PAH: Role of V/Q Scan



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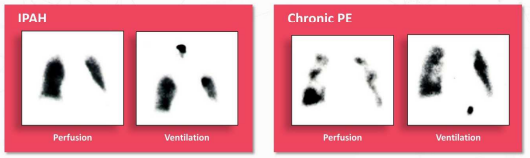
V/Q Scan to Exclude CTEPH

- V/Q scan should be performed to exclude diagnosis of CTEPH[1]
- >1 segmental-sized or larger mismatched perfusion defects seen with CTEPH[2]
- Normal V/Q scan makes CTEPH diagnosis unlikely[1]



PE=pulmonary embolism.
Images courtesy of Richard N. Channick, MD.
1. Galiè N, et al. *Eur Respir J*. 2015;46:903-975. 2. McGoon M, et al. *Chest*. 2004;126(1 suppl):14S-34S.

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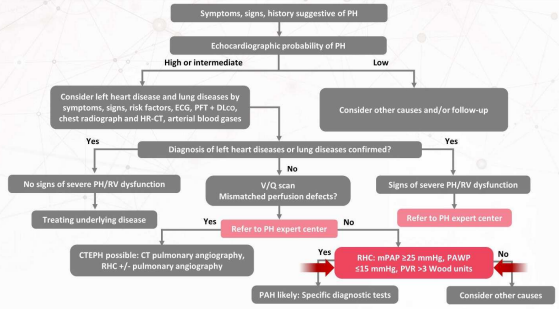
Diagnosis of PAH: Role of RHC



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Diagnosis of PAH Requires RHC

RHC[1]

- Required to confirm diagnosis, calculate resistance, and guide therapy for PAH[1]
- Distinguishes between PAH and other types of PH[1]
  - With fluid challenge, differentiate from HFpEF in patients with volume-depletion
- Measures degree of right heart dysfunction[2]
  - RA pressure
  - CO

Essential Components of Invasive Hemodynamic Assessment[3]

- mPAP
- PAWP
- PVR
- RA/RV pressure
- CO/CI
- O_2 saturations (SVC, IVC, RV, PA, SA)
- Negative/positive response to acute vasodilator challenge

CI=cardiac index; HFpEF=heart failure with preserved ejection fraction; IVC=inferior vena cava; O_2=oxygen; PA=pulmonary artery; SA=systemic artery; SVC=superior vena cava.
1. Rosenkranz S, et al. *Eur Respir Rev*. 2015;24:642-652. 2. McGoon M, et al. *Chest*. 2004;126(1 suppl):14S-34S. 3. McLaughlin VV, et al. *Circulation*. 2009;119:2250-2294.

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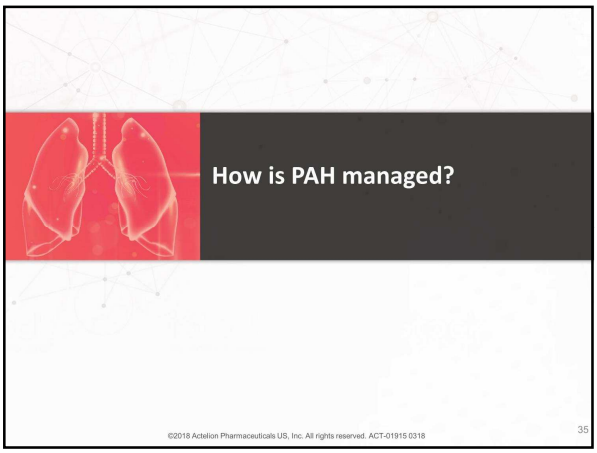

PAH Treatment Goals

- Improve FC[1,2]
- Improve hemodynamic and echocardiographic parameters[2,3]
- Improve exercise capacity[2,3]
- Prevent disease progression[3]
- Improve quality of life[3]
- Improve survival[3]

1. Barst RJ, et al. *J Am Coll Cardiol*. 2009;54(1 suppl):S78-S84. 2. McLaughlin VV, et al. *J Am Coll Cardiol*. 2013;62(25 suppl):D73-D81.
3. McLaughlin VV, et al. *Circulation*. 2009;119:2250-2294.

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PAH General Care

Anticoagulation	• Anticoagulant treatment may be considered in patients with IPAH, HPAH, PAH due to use of anorexigens, and PAH associated with CTD[1]
Oxygen	• Continuous long-term O_2 therapy is recommended in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[1]
Fluid/ volume control	• Diuretics[1,2] • Low salt diet[2]

HPAH=heritable pulmonary arterial hypertension.
1. Galiè N, et al. *Eur Respir J*. 2015;46:903-975. 2. McLaughlin VV, et al. *J Am Coll Cardiol*. 2015;65:1976-1997.

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Drug Therapies for PAH[1,2]

Therapeutic Options	Route of Administration
Calcium channel blocker (if vasodilator positive)	• Oral
ERA	• Oral
PDE-5i	• Oral • Intravenous*
Prostacyclin and analogs; IP receptor agonist†	• Oral • Inhaled • Subcutaneous • Intravenous
sGC	• Oral

*Sildenafil only.
†Oral route of administration only.
1. Galiè N, et al. *Eur Respir J.* 2015;46:903-975. 2. McLaughlin VV, et al. *J Am Coll Cardiol.* 2015;65:1976-1997.

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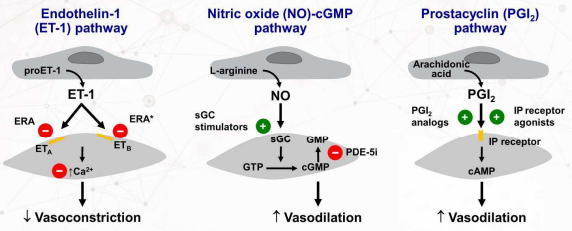
Drug Therapies for PAH[1,2] (continued)



*Not all ERAs antagonize the ET$_B$ receptor.
Adapted from: 1. Humbert M, et al. *Circulation.* 2014;130:2189-2208. 2. Galiè N, et al. *Eur Respir J.* 2015;46:903-975.

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Guidelines on Initiating PAH-specific Therapy

- Current treatment paradigm emphasizes early disease intervention and the use of combination therapy[1]
- Patients with low or intermediate risk who are non-responsive to acute vasoreactivity testing can be treated with either initial monotherapy or initial oral combination therapy[2]
- For patients who are non-vasoreactive and at high risk, initial combination therapy including intravenous prostacyclin analogs should be considered[2]

1. Humbert M, et al. *Circulation.* 2014;130:2189-2208. 2. Galiè N, et al. *Eur Respir J.* 2015;46:903-975.

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Summary

- Patients with PAH are often diagnosed late in disease course[1]; screening of patients who are at risk is critical to establish early diagnosis[2]
- Symptoms of PAH can be non-specific; a thorough workup is required[3]
  - Diagnosis requires confirmation with RHC[3]
- Pathogenesis of PAH involves mediators from the endothelin, prostacyclin, and nitric oxide pathways, resulting in vascular proliferation, inflammation, fibrosis, and hypertrophy[4]
- Treatment of PAH has evolved to incorporate combination therapy targeting multiple signaling pathways[3]

1. Badesch DB, et al. *Chest*. 2010;137:376-387. 2. Hoeper MM, et al. *J Am Coll Cardiol*. 2013;62(25 suppl):D42-D50. 3. Galiè N, et al. *Eur Respir J*. 2015;46:903-975. 4. McLaughlin VV, et al. *J Am Coll Cardiol*. 2015;65:1976-1997.

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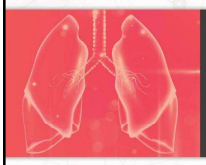

Backup slides

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Exercise Capacity: 6-Minute Walk Test

- Helps to determine baseline prognosis and assess response to treatment and/or disease progression[1]
- Simple, inexpensive, reproducible, and well standardized[2]
- Measures distance patient can walk on a flat, hard surface in 6 minutes (also known as 6-minute walk distance [6MWD])[2]
  - Patient chooses level of intensity and can stop/rest during test
- Results are influenced by—but not corrected for—factors such as patient height, weight, age, and sex[2]

1. McGoon M, et al. *Chest*. 2004;126(1 suppl):14S-34S. 2. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. *Am J Respir Crit Care Med*. 2002;166:111-117.

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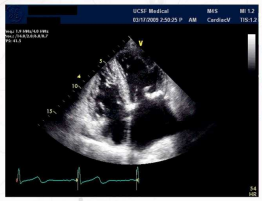
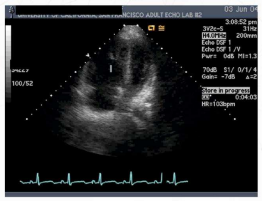
Echocardiography: PVH Versus PAH

PVH



PAH



PVH=pulmonary venous hypertension.
Images courtesy of Dana McGlothlin, MD.