The Circle of New Life for Pulmonary Hypertension Patients:

Where does Palliative Care have a role in the new treatment era?

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Director, PHA Comprehensive Pulmonary Hypertension Care Center.
Medical Director , Lung Transplant Program.
Froedtert and the Medical College of Wisconsin

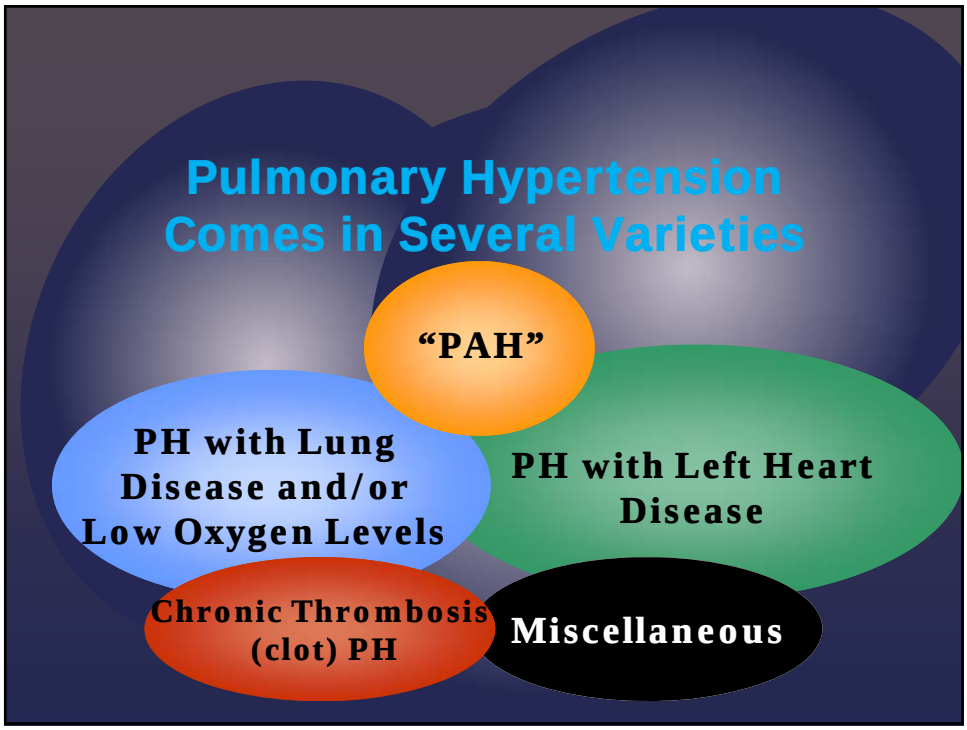
- Review the DEFINITION of pulmonary hypertension (PH)
- Discuss the different GROUPS of PH Patients
- Examine the PROGNOSIS of PH patients in the different GROUPS
- Differentiate the BENEFITS and SIDE EFFECTS of different treatments for PH patients.
- List CHRONIC CARE and END OF LIFE challenges for the different PH groups.
- Discuss the SPECIALTY PALLIATIVE CARE availability and role in the care of PH patients.

Objectives:

Introductory Questions:

- Is Pulmonary HTN common?
  - If so, Which Group?
- Is Pulmonary HTN rare, an "orphan" disease
  - If yes, which Group?
- Can Pulmonary HTN be cured?
- Are there effective treatments?

- Yes, Many patients with left sided heart failure have Group II Pulmonary HTN.
- Yes, Group I PAH Pulmonary HTN remains an uncommon disease.
- Chronic PE patients who have a successful surgery return to near normal: OSA patients on CPAP.
- Yes, particularly for Group I PAH patients now.



5th World Symposium on PH: Hemodynamic Profile of PH/PAH.

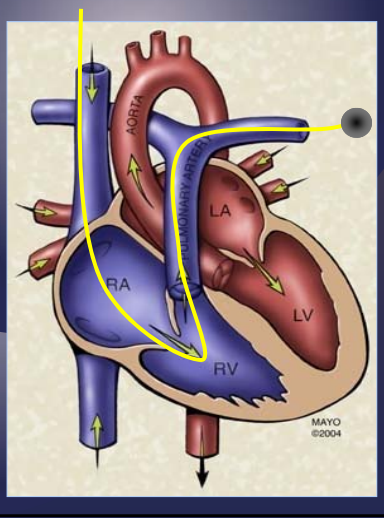
(Normal PA Pressure Mean 20, 30/15 mmHg)

PH	Mean PAP ≥25 mm Hg at rest during RHC
Precapillary PAH	Mean PAP ≥25 mm Hg *plus* PAWP ≤15 mm Hg *OR*
Postcapillary	PAWP > 15 mmHg (Left Heart Disease)

PAP = Pulmonary Artery Pressure. PAWP = Pulmonary arterial wedge pressure, mimics left atrial pressure.

Hoeper MM et al. *J Am Coll Cardiol*. 2013;62:D42-D50.

Right Heart Catheterization: The Definitive Diagnosis



Is There a Reason to Suspect PH? *Clinical Presentation*

History	Nonspecific Complaints	
• Dyspnea (86%) • Fatigue (27%) • Chest pain (22%) • Edema (22%) • ***Syncope (17%)*** • Dizziness (15%) • Cough (14%) • Palpitations(13%)		

REVEAL. Brown LM et al. *Chest.* 2011;140:19-26.
Adapted from McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Pulmonary Hypertension Diagnosis

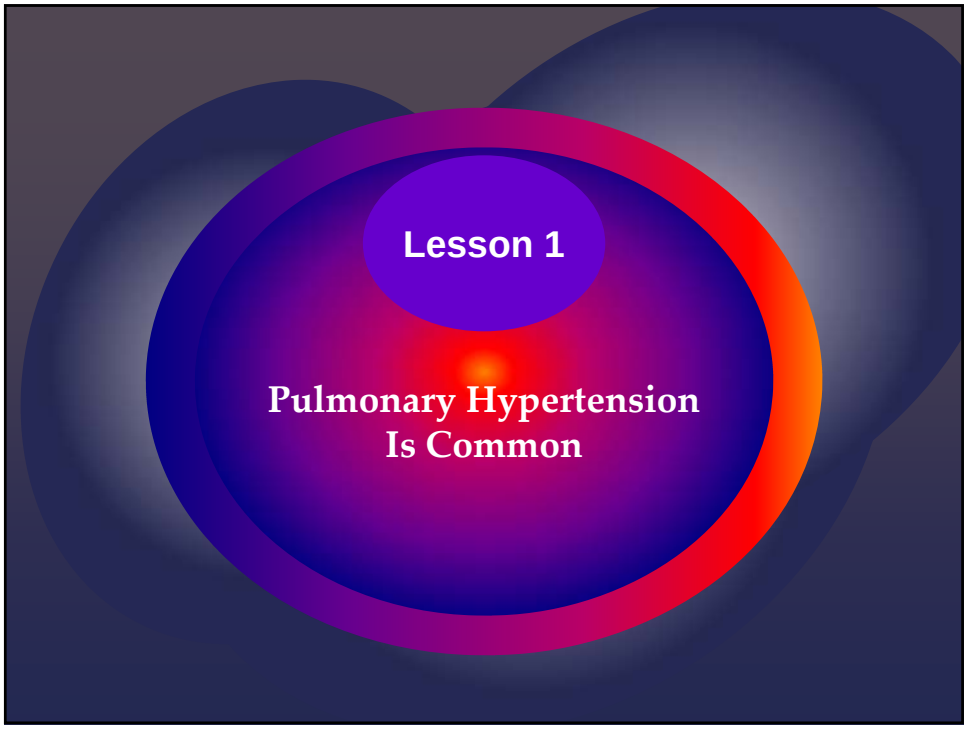
REVEAL. Brown LM et al. *Chest.* 2011;140:19-26.
Adapted from McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

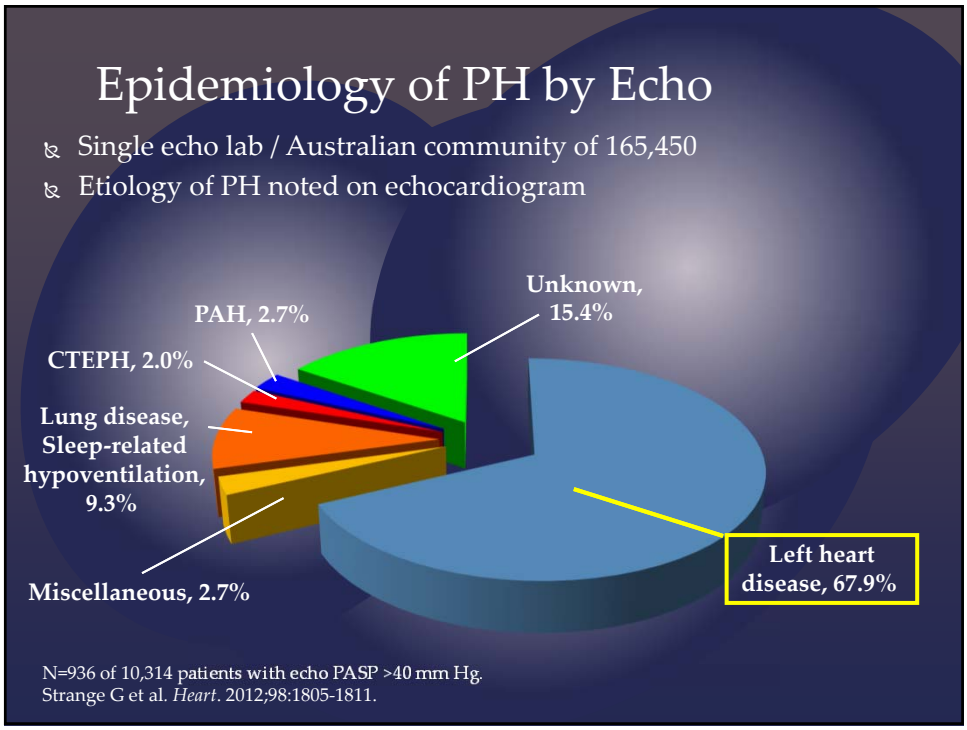
Presence of PH

- **Loud second heart sound**
- **RV heave**
- **Heart murmur**
- **RV gallop**

Presence of RV Failure

- **Distended neck veins**
- **Enlarged liver**
- **Swollen feet and ankles**
- **Swollen abdomen**


Lesson 1
Pulmonary Hypertension
Is Common


Epidemiology of PH by Echo
Single echo lab / Australian community of 165,450
Etiology of PH noted on echocardiogram
Unknown, 15.4%
PAH, 2.7%
CTEPH, 2.0%
Lung disease, Sleep-related hypoventilation, 9.3%
Miscellaneous, 2.7%
Left heart disease, 67.9%
N=936 of 10,314 patients with echo PASP >40 mm Hg.
Strange G et al. Heart. 2012;98:1805-1811.

PH Patient Chronic Care Needs:
Heart Failure Overlap (Group II),
Chronic Lung Disease Overlap (Group III),
Specialty Pulmonary Hypertension Care (Group I, IV, V)

MCW-FMLH: Among first 26 PHA CC Centers in USA

PH Care Centers
Providing excellence in pulmonary hypertension care

KEY POINTS

- Patients with PAH may benefit from a palliative care approach as part of standard care.
- Palliative care can exist in parallel with aggressive PAH disease-targeted therapies.
- There is a need for more education of both clinicians and patients about the benefits of palliative care.
- The access to specialist palliative care provision needs to be improved to ensure that this is available to all patients with PAH when appropriate.

Palliative care and Pulmonary Arterial Hypertension.

12

Gin-Sing, W. Palliative care in pulmonary arterial hypertension. Current Opinion in Supportive and Palliative Care. 11 (1): March 2017, 7-11.

4/23/2018

5th World Symposium on PH: Classification GROUPS

1. Pulmonary arterial hypertension

1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK1, ENG, Smad 9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases (update)
1.4.5 Schistosomiasis

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″.

2. 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

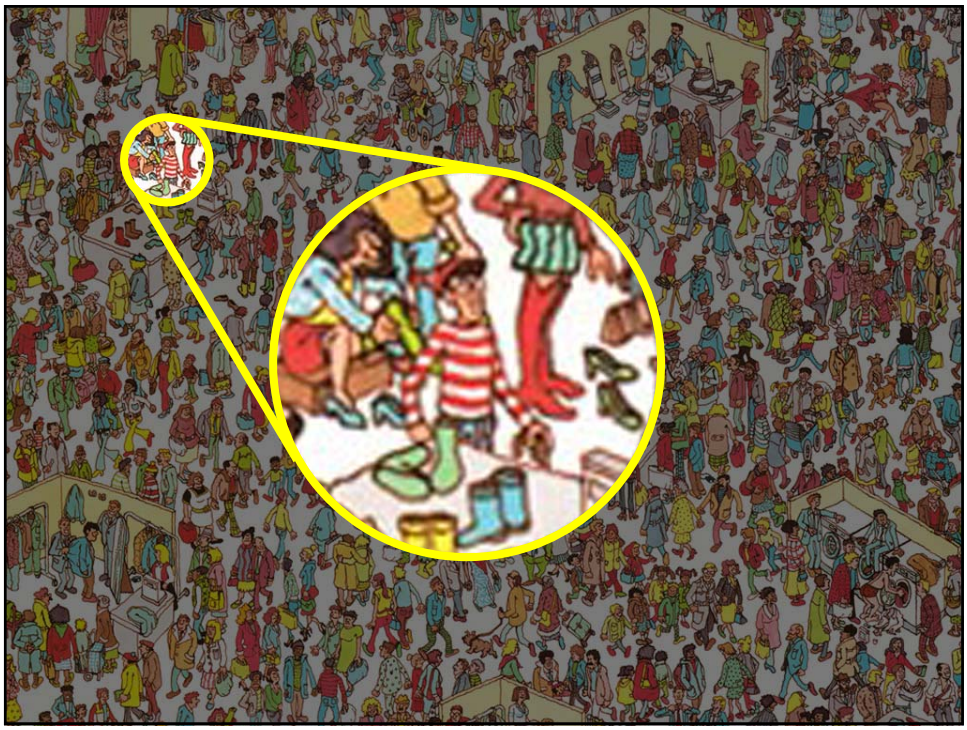
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (update)

4. Chronic thromboembolic PH

5. PH with unclear multifactorial mechanisms

5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis,
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

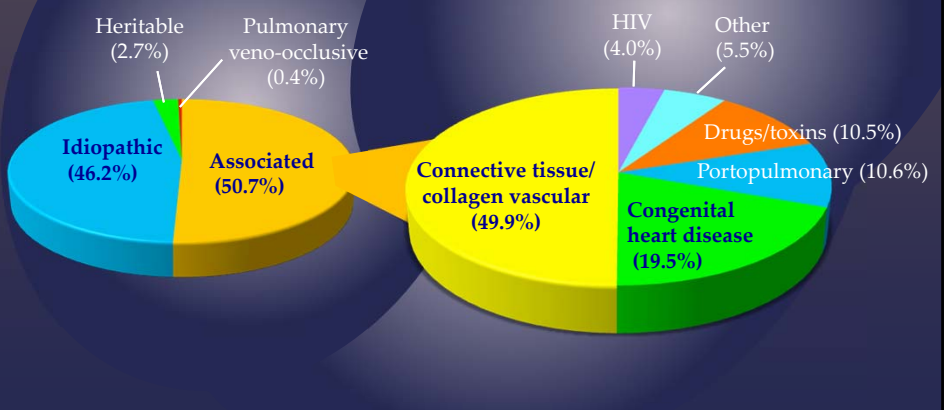
Simonneau G et al. *J Am Coll Cardiol*. 2013;62:D34-D41.



Lesson 2

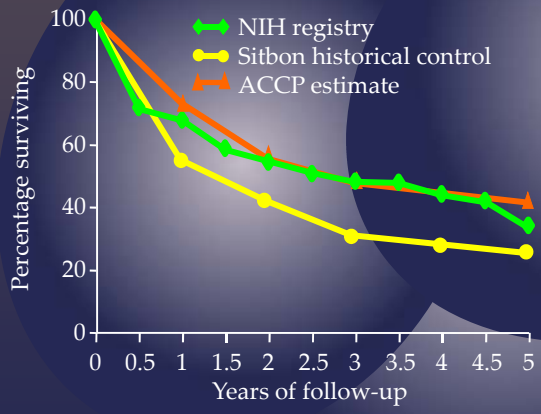
WHO Group I PAH Is Rare but Deadly—
Make the Diagnosis Early

Group I PAH Distributions in the US: REVEAL Registry



Based on Venice Clinical Classification (2003); 2967 patients.
Adapted from Badesch DB et al. *Chest*. 2010;137:376-387.

Idiopathic PAH: Survival

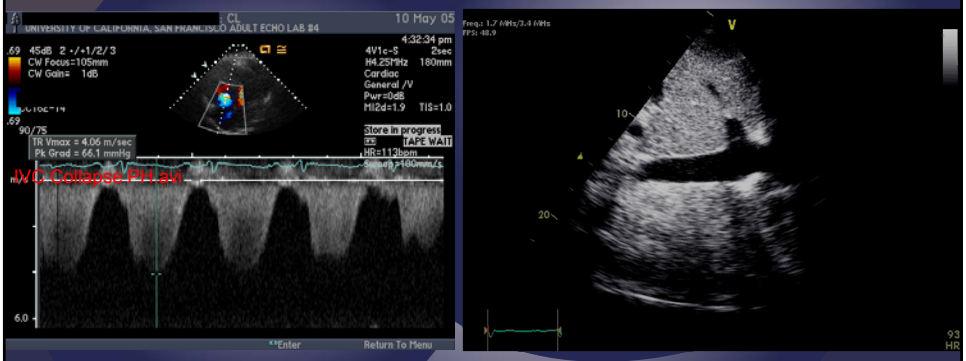


- Incidence: 2-6 cases per million in US
- Poor prognosis in an era lacking therapy 50% - 3 year survival.
- Therapeutic options and research efforts now offer more HOPE !

➢ ***REVEAL Registry 2012,*** PAH treatment era: 50% - 7 year survival.

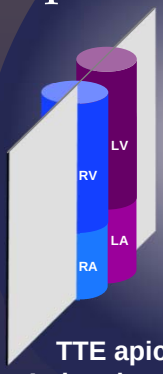
Adapted from: Sitbon O et al. *J Am Coll Cardiol*. 2002;40:780-788. D'Alonzo GE et al. *Ann Intern Med*. 1991;115:343-349. McLaughlin VV et al. *Chest*. 2004;126:78S-91S. Benza RL et al, *Chest* 2012; 142: 448-456.

Echo: *Estimation* of RV Systolic Pressure (RVSP) = PA systolic pressure. Accuracy? Over and under diagnosis.



RVSP = 4(velocity of TR jet)^2 + RA pressure
= 4(4)^2 + 20
= ~84 mm Hg

PAH: RV Changes: Apical 4 chamber view on Echo

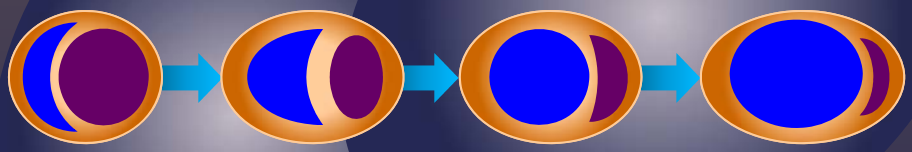


TTE apical 4-chamber view

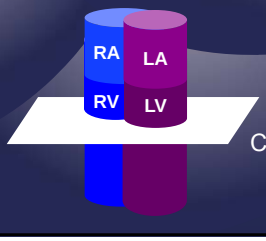
Normal

PH

The Right Ventricle in PAH (parasternal axis view on Echo)



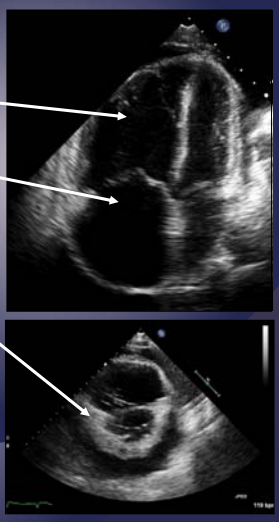
Progressive structural changes in the RV due to poor adaptation to increasing PVR

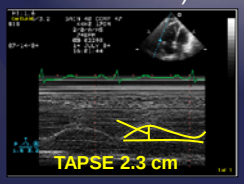


Cross section

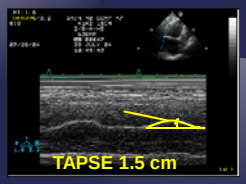
Is There a Reason to Suspect PH? *Echo:*
It is not just the pressure ! Look at the right heart.

- RV enlargement
- RA enlargement
- Septal straightening
- Loss of IVC inspiratory collapse
- Tricuspid regurgitation
- **Pericardial effusion**
- Decreased RV systolic dysfunction
  - TAPSE (tricuspid annular plane systolic excursion)





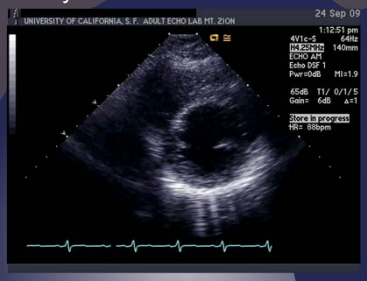
Relatively preserved RV function



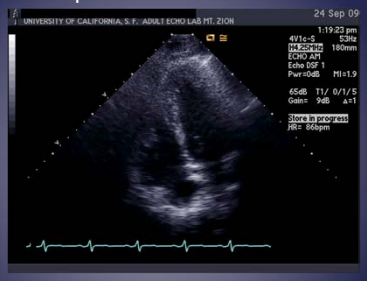
RV dysfunction

McLaughlin VV et al. *J Am Coll Cardiol.* 2009;53:1573-1619.

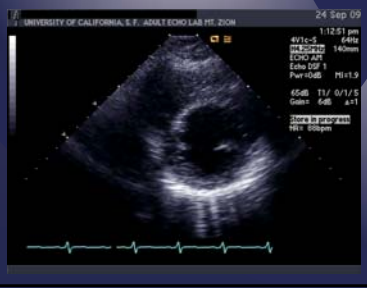
Systole in short-axis view



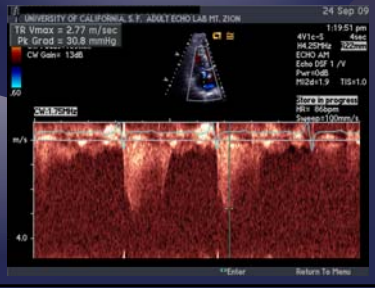
Apical 4-chamber view

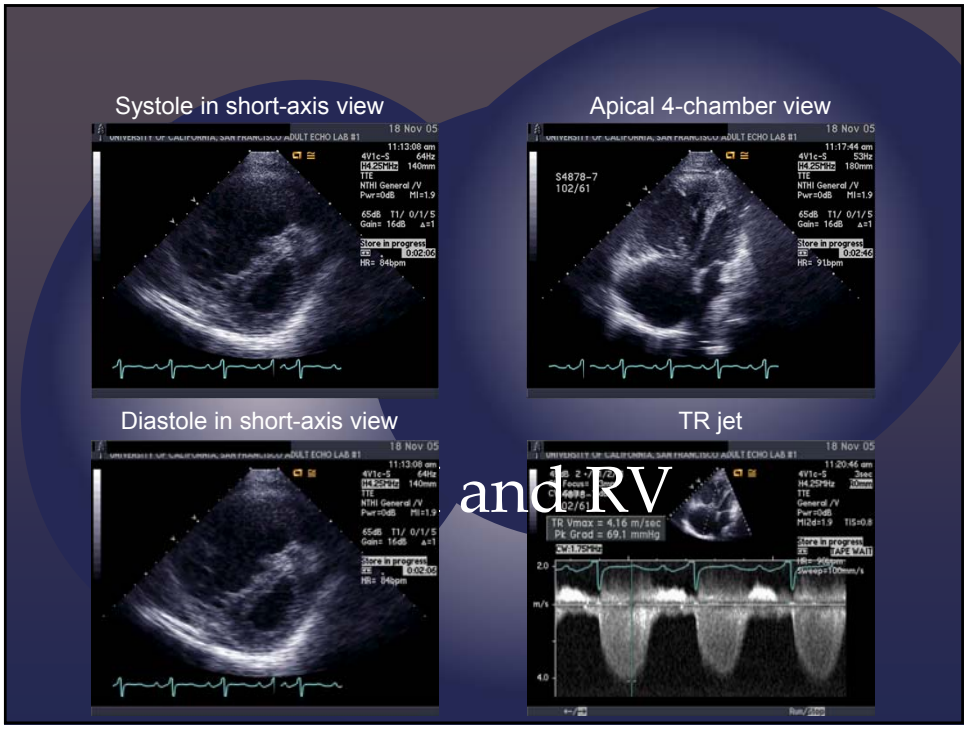


Diastole in short-axis view



TR jet





Group I PAH: Pulmonary Arterial Hypertension:

- Symptoms often nonspecific; average 14-month delay from initial presentation to diagnosis
- Poor prognosis without therapy and close follow-up
- Evaluation must be methodical and include right heart catheterization (RHC)
- Prognosis improves with therapy, but PAH remains a progressive fatal disease
- Therapies and management strategies continue to evolve

5th World Symposium on PH: Classification

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  - 1.4.5 Schistosomiasis

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent PH of the newborn

2. PH due to left heart disease
- 2.1 LV systolic dysfunction
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Simonneau G et al. *J Am Coll Cardiol.* 2013;62:D34-D41.

Most Common Cause of Elevated PA Pressures by Echo: Left Heart Disease (Group II PH).

"Complication" of Heart Failure NOT a new disease.

Symptoms
- paroxysmal nocturnal dyspnea
- orthopnea

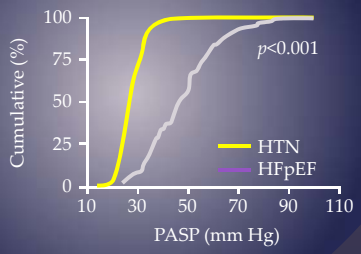
History
- diabetes
- hypertension
- obesity
- coronary artery disease
- metabolic syndrome

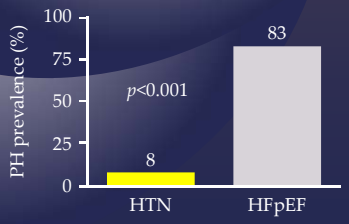
ECG
- atrial fibrillation
- absence of right axis deviation

Echo
- left atrial enlargement
- left ventricular hypertrophy
- normal RA, RV with elevated PA pressure
- Abnormal diastolic filling
- Abnormal systolic function ease to differentiate
- mitral or aortic disease

Common Causes of PH: In Older Patients, Consider Diastolic Heart Failure

- PH by echo in a community-based sample:
  - heart failure with preserved EF: 83% with PH
  - HTN but no CHF (control): 8% with PH
- Patients with PH:
  - older
  - higher systolic BP
  - larger LA size
  - higher E/e' ratio





Lam CS et al. *J Am Coll Cardiol*. 2009;53:1119-1126.

Pulmonary Venous Hypertension –Left Heart: A Simplified View

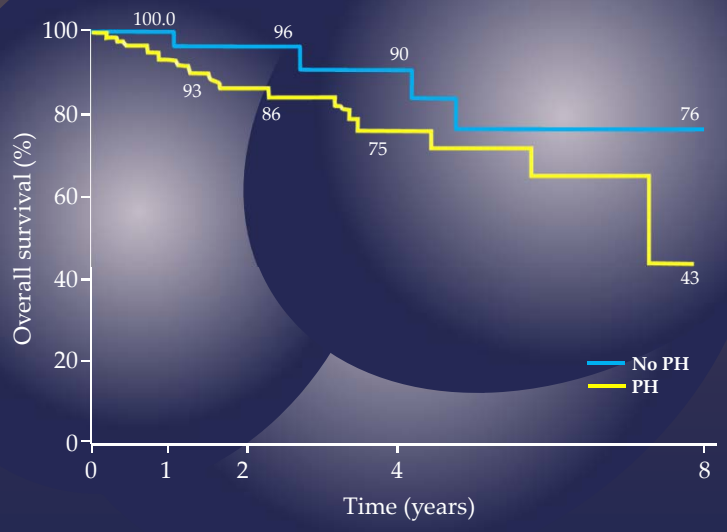
- Normal, or mildly elevated transpulmonary pressure gradient with readily apparent cause
  - treat underlying cause for improvement.
- Substantially elevated transpulmonary pressure gradient (PH "out of proportion" to LHD)
  - treat cardiovascular risk factors (including BP, aggressive volume control) as best you can;
  - Sleep Problem too? (*"Common Bed Partners"*)
  - improvement in PH , symptoms may be slow
  - *No FDA-approved therapies for diastolic dysfunction yet*

Sleep-disordered Breathing and PH: Group III Lung Disorders

- Nocturnal hypoxemia results in pulmonary arterial constriction, and remodelling
- PH can occur with either obstructive sleep apnea (OSA) or central sleep apnea
- PH is usually only mild to moderate
- Treatment of Sleep Apnea can improve the PH in these patients (2-3 months)

Sajkov D et al. *Am J Respir Crit Care Med*. 1994;149:416-422.

Impact of PH on Outcomes in Obstructive Sleep Apnea

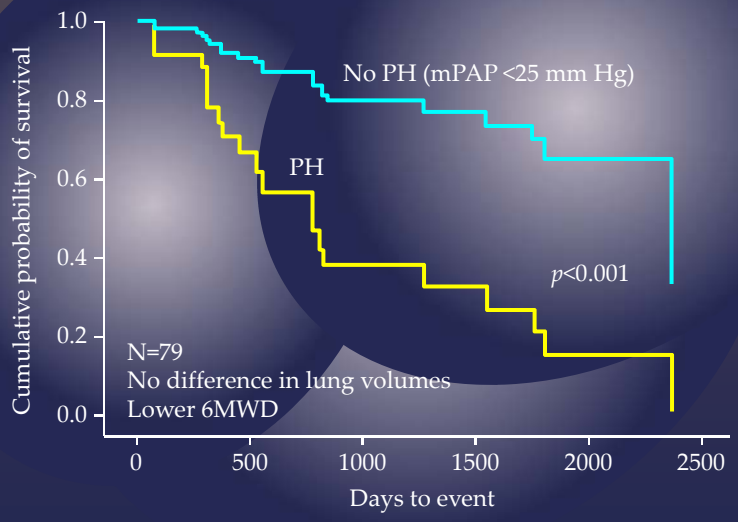


Minai O et al. *Am J Cardiol*. 2009;104:1300-1306.

Group III Pulmonary Hypertension in Parenchymal Lung Disease Pts.

- May explain worsening symptoms in patient with stable lung function, PFTs, otherwise. *Sign of worse prognosis in most lung diseases.*
- Contributes to exercise limitation: cardiovascular limitation versus respiratory limitation
- Disproportionately low DLCO (capillary blood volume) may suggest pulmonary vascular disease
- Correlates better with low oxygen levels than PFTs
- **Treatment:** Oxygen, Disease specific, Lung Transplant?
- *Pilot study with sildenafil in COPD PH patients encouraging;*
- *Pulmonary Fibrosis (IPF) patients WORSE with ambrisentan, Riociguat. Sildenafil?, Inhaled Prostaglandin trials ?*

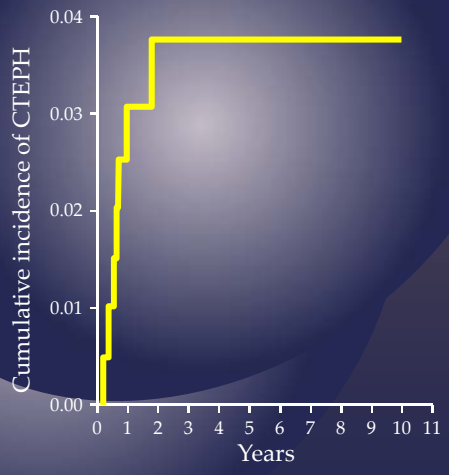
PH as a Predictor of Survival in Patients With IPF - Pulmonary Fibrosis



Lettieri CJ et al. *Chest.* 2006;129:746-752.

Incidence of Group IV CTEPH : (chronic thromboembolic PH)

- USA: 600,000 cases of acute PE each year
- Approximately 3% to 4% 1-2 yr after acute PE
- Only 40% to 50% - history of previous episodes of acute PE
- VQ scan: identifies *old* PE better than CTA PE study.



McLaughlin VV et al. J *Am Coll Cardiol*. 2009;53:1573-1619.
Pengo V et al. *N Engl J Med*. 2004;350:2257-2264.
Tapson VF, Humbert M. *Proc Am Thorac Soc*. 2006;3:564-567.

Group IV CTPEPH Treatment 2018.

Functional Class IV: Definite Benefit to surgery; Poor 1-2 yr Survival without surgery.

Mean PA pressure > 50mmHg, < 50% survival.

Others can be long term Medical Survivors – accept limitations.

- ❑ Pulmonary thromboendarterectomy "Near cure" (*Torre Pines Stress Test*); 2- 10% mortality with surgery.
- Lifelong Anticoagulation in ALL patients.

- Oxygen, anticoagulation, ? IVC filter, and now medical therapies for patients who are not surgical candidates.
- *Riociguat approved for CTEPH,*
- *Macitentan pending approval.*

PH Treatment Goals

- Fewer/less severe symptoms
- Improved exercise capacity
- Improved "hemodynamics"
- Prevention of clinical worsening (heart failure, admissions, increased SOB)
- Improved quality of life (benefits versus side effects)
- Improved survival ?

Chronic Adjuvant Therapies in PH

Digoxin: Usually NOT

- Variable inotropic effect and use
- No long-term data; need to balance unproven benefits with known risks

Oxygen: YES! (QOL usually better?)

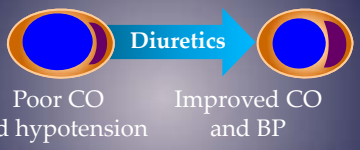
- Use to prevent hypoxic vasoconstriction
- Consider exercise, sleep, altitude
- Aim for target saturation >90%
- May not correct hypoxia with shunt

Adapted from: Badesch DB et al. *Chest. 2004;126:35S-62S.* Badesch DB et al. *Chest*. 2007;131:1917-1928. McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Chronic Adjuvant Treatment

Diuretics

- **Most patients need this Rx.**
- Monitor renal function
- *Quality of Life, Compliance*



Anticoagulation

- **Recommended in CTEPH, and IPAH only**
- Observational data, one limited prospective study; small prospective study.
- *Balance limited benefits - known risks*

Usually acceptable to stop except in CTEPH, recurrent PE Patients.

Fuster V et al. *Circulation.* 1984;70:580-587.
Badesch DB et al. *Chest.* 2004;126:35S-62S. Preston 2016.

Selection of Appropriate Therapy:

Group I PAH Patients:

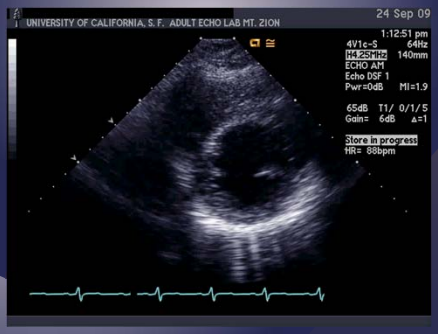
Chronology

1980s: Calcium Channel Blockers, Diuretics, Oxygen.
1996: IV Epoprostenol (Flolan) - "PPH" only; 1998 Group I PAH.
2001: Bosentan, first oral drug. Group I PAH
2018: 12 Drugs Group I PAH, 1 Drug Group IV CTEPH.

Case: TD

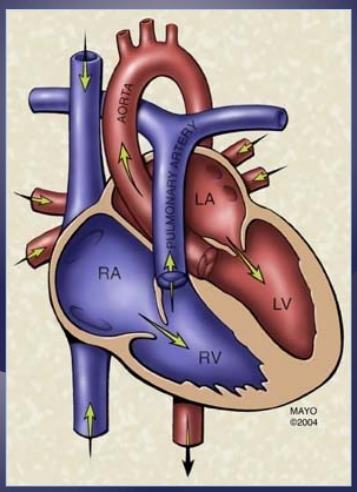
- 60 yo female
- Alcohol Abuse, Osteopenia
- Fall and Pelvic fracture with severe left femur fracture.
- Pre-op evaluation done.
- Referred 2013 for evaluation of abnormal echo with RV enlargement and PH suggested by echo.
- Normal VQ scan, US no cirrhosis.

Echo: Mild RV enlargement, Mild RV systolic Dysfunction, Mild elevation in PASP.



Case TN (2)

- Right Heart Catheterization done. RA pressure 4, PA pressure mean 26, PAWP 9 (all mmHg). CI 2.8 L/min m2.
- Mild PAH , Idiopathic with preserved RV function.
- Recommended to complete surgery and then return promptly for treatment.
- Lost to fu for period of time.



Group I PAH Therapy

(+) Vasodilator Response to inhaled NO (ONLY 10%)

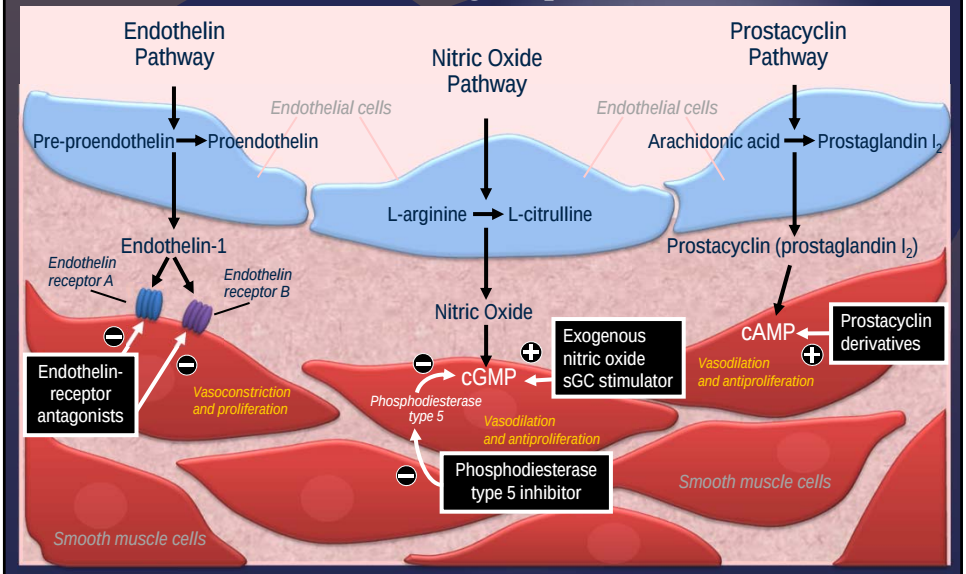
- *Calcium channel blockers ONLY in select PAH pt!*

(–) Vasodilator Response or Non-sustained Vasodilator Response.. Other therapies !

- Endothelin receptor antagonists
- Phosphodiesterase-5 inhibitors
- Prostanoids
- ***(Do NOT use CCB in this nonresponder PAH group; do not treat like Left heart failure)***

McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Mechanisms of Action of Approved Therapies for GROUP I PAH (not other groups)

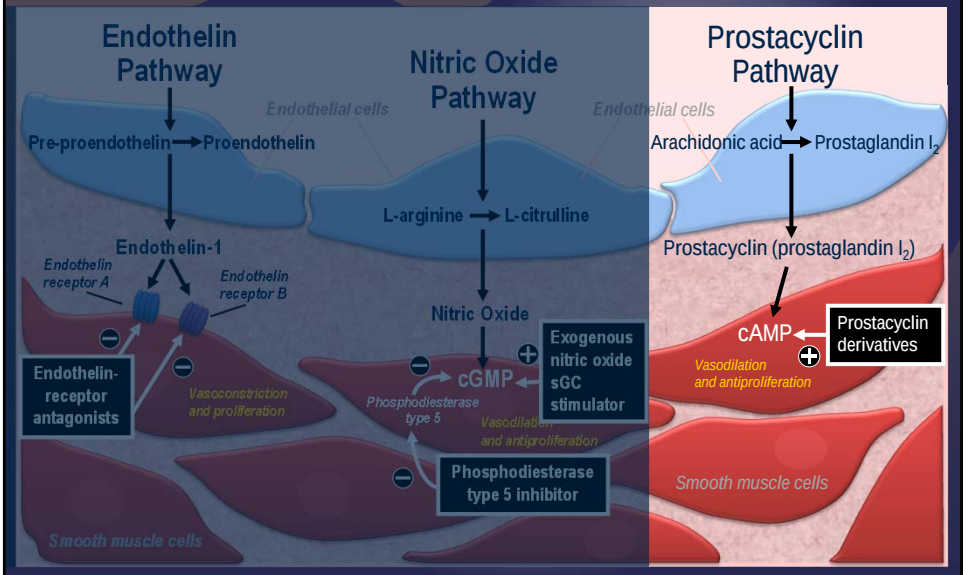


Adapted from Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

5th World Symposium on PH Goals of Therapy: Setting the Bar Higher; Add on therapy……

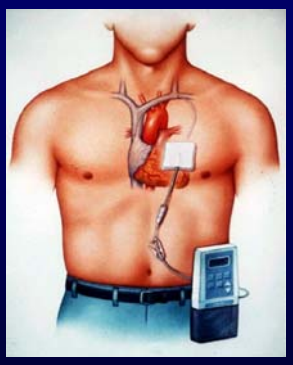
Functional Class	• I or II
Hemodynamics	• Normalization of RV function (RAP <8 mm Hg and CI >2.5-3.0 L/min/m^2)
Echocardiography/ MRI	• Normal/near normal RV size and function
BNP level	• 'Normal'
6MWD	• 380-440 m, may not be aggressive enough
CPET	• Peak VO_2 >15 mL/kg/min • VE/VCO_2 @ AT <45

McLaughlin VV et al. *J Am Coll Cardiol 2013*.:62:D73-81.



Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

Prostacyclin Analogues: Intravenous, Subcutaneous, Inhaled, or Oral



Epoprostenol (Flolan® or Veletri®)
Treprostinil (Remodulin®)

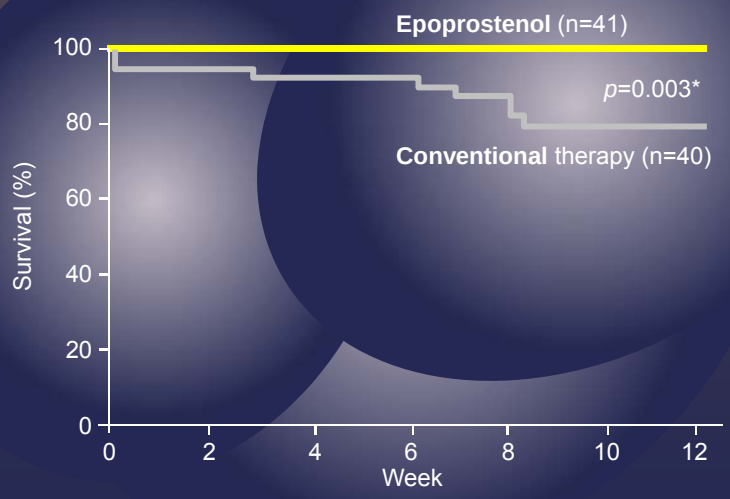
Treprostinil (Remodulin®)

Treprostinil (Orenitram®)
Selexipag (Uptravi®)

Iloprost (Ventavis®)
Treprostinil (Tyvaso®)

Epoprostenol IV: FC III-IV, 2 ng/kg/min titrated to desired clinical response in 1-2 ng/kg/min increments.
Treprostinil IV / SC: FC II-IV, 1.25-2.5 ng/kg/min/wk. IV=diluted. Inhaled: FC III, to 54 mcg, 4 inh/d. Oral: FC II-III, starting at 0.25 mg bid and titrated in 0.25 mg increments as tolerated.
Iloprost Inhaled: FC III-IV, 2.5-5 mcg, 6-9 inh/d.

Survival Among Patients With IPAH: Epoprostenol (Flolan) vs Conventional Therapy. 12 week study.

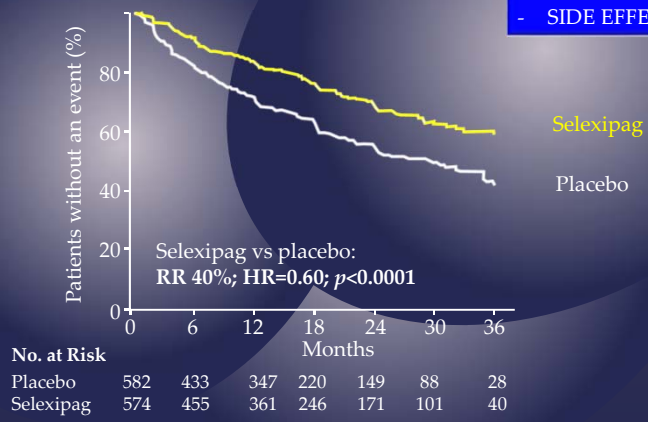


*Two-sided, by log-rank test.
Barst RJ et al for the PPH Study Group. *N Engl J Med*. 1996;334:296-301.

Oral Prostacylin Therapy: Time to First Morbidity or Mortality Event—GRIPHON

80% on background therapy:

- SIDE EFFECTS STILL



No. at Risk

Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

Sitbon O et al. *N Engl J Med*. 2015;373:2522-33.

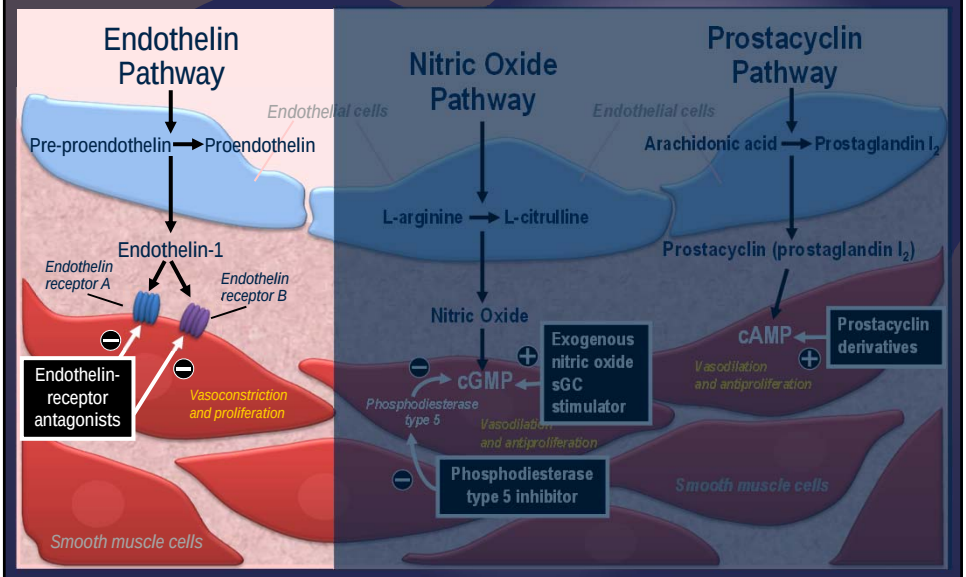
Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension

- Dizziness
- Syncope
- Rebound PH if interruption of epoprostenol delivery (due to short half-life)
- Delivery site complications (pain, infection, cough, thrombosis, infusion)

Vary according to drug and route of delivery (Po, Inhaled, SQ, IV)

Approved Therapeutic Targets



Adapted from Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

Endothelin Receptor Antagonists: Pivotal Trials: *Bosentan, Ambrisentan, Macitentan.*

Study Name Drug	N Etiology Class	Design	Positive Results
BREATHE-1 Oral bosentan* vs placebo	213 PAH III, IV	Double-blind 16-week	• 6MWD • Delay clinical worsening • Symptoms
EARLY Oral bosentan vs placebo	185 PAH II	Double-blind 6-month	• Delay clinical worsening • Hemodynamics
ARIES-1&2 Oral ambrisentan § vs placebo	394 PAH II, III	Double-blind 12-week	• 6MWD • Delay clinical worsening
SERAPHIN Oral macitentan† vs placebo	742 PAH II,III	Double-blind Event-driven morbidity/mortality	• Delay disease progression • 6MWD • Symptoms

***Bosentan = Tracleer®. Approved for FC II-IV. 62.5-125 mg po bid.**
§ Ambrisentan = Letairis®. Approved for FC II-III. 5-10 mg po qd
† Macitentan = Opsumit®. Approved for FC II-III. 10 mg po qd.

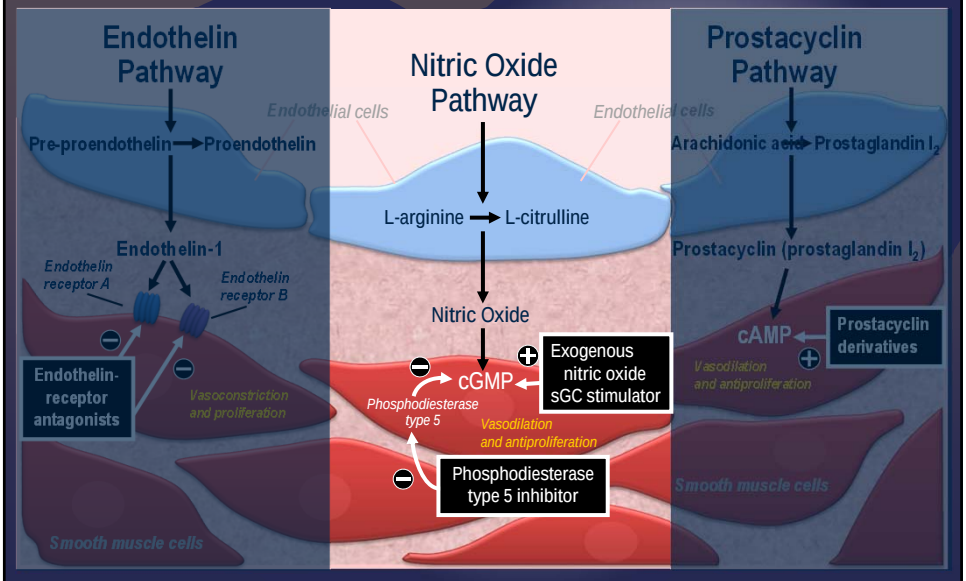
Rubin L et al. *N Engl J Med.* 2002;346:896-903. Channick RN et al. *Lancet.* 2001;358:1119-1123. Galiè N et al. *Lancet.* 2008;371:2093-2100. Galiè N et al. *Circulation.* 2008;117:3010-3019. Pulido T et al. *N Engl J Med*. 2013;369:809-818.

Endothelin Receptor Antagonists: Side Effects

- Nasal congestion
- Abnormal hepatic function*
  - monthly LFTs required for bosentan
- Anemia
  - monitor CBC quarterly
- Edema
  - lower extremity edema may require diuretic adjustment
- Teratogenic
  - Avoid pregnancy !

*PHA Scientific Leadership Council recommends LFT testing at onset of all treatments for PAH and periodically thereafter, *at prescriber's discretion*.

Approved Therapeutic Targets



Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

PDE-5 Inhibitor Pivotal Trials: *Sildenafil, Tadalafil*

Study Name Drug	N Etiol Class	Design	Positive Results
SUPER-1 Oral sildenafil* vs placebo	278 PAH I-IV	Double-blind 12-week	• 6MWD • Symptoms • Hemodynamics
PHIRST-1 Oral tadalafil § vs placebo	405 PAH I-IV	Double-blind 16-week	• 6MWD • Delay clinical worsening • Hemodynamics • HRQoL

***Sildenafil = Revatio®. Approved for FC II-III. 20 mg po tid.**
§ Tadalafil = Adcirca®. Approved for FC I-IV. 40 mg po qd.

Galiè N et al. *N Engl J Med*. 2005:353:2148-2157.
Galiè N et al. *Circulation*. 2009;119;2894-2903.

PDE-5 Inhibitor Side Effects

- Nose bleed, congestion
- Headache
- Dyspepsia
- Flushing
- Diarrhea
- Visual changes
- *Contraindicated with use of nitrates*

sGC Stimulator Pivotal Trials: Group I, IV
Riociguat

Study Name Drug	N Etiol Class	Design	Positive Results
PATENT-1 Oral riociguat* vs placebo	278 PAH I-IV	Double-blind 12-week	• 6MWD • Symptoms • Hemodynamics • Delay clinical worsening
CHEST-1 *Oral riociguat* *vs placebo*	*261* *CTEPH* *I-IV*	*Double-blind* *16-week*	• *6MWD* • *Symptoms* • *Hemodynamics*

***Riociguat = Adempas®. Approved for WHO Group 1; persistent CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH; titrated to maximum 2.5 mg po tid.**

Ghofrani HA et al. *N Engl J Med*. 2013;369:319-329.
Ghofrani HA et al. *N Engl J Med*. 2013;369:330-340.

sGC Stimulator Side Effects

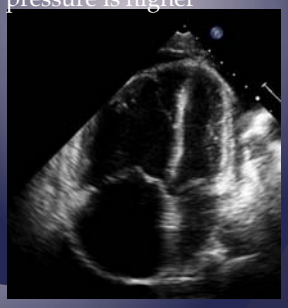
- Headache
- Dizziness
- Dyspepsia/gastritis
- Nausea
- Diarrhea
- Hypotension
- Vomiting
- Anemia
- Gastroesophageal reflux
- Constipation
- Some bleeding risk

- *Contraindicated in pregnancy, with use of nitrates or NO donors in any form, or with use of PDE inhibitors*

Case TN (3)

- Returned and started on sildenafil TID monotherapy for PAH in 2014. (less side effects, monitoring and less LFT effects)
- Changed to tadalafil once daily for compliance.
- Erratic FU but compensated initially on therapy and better exercise tolerance. ETOH use.
- HOWEVER……
- Returned one year later 2015 with increased edema, DOE, consistent with early RV failure.
- Unable to get in for repeat Right Heart Catheterization.
- Diuretics added to Tadalafil.

Echo shows worsening RV size and Worsening function. Estimated PASP Is > 60 mmHg. Estimated RA pressure is higher



Candidate for additional combination Therapy?

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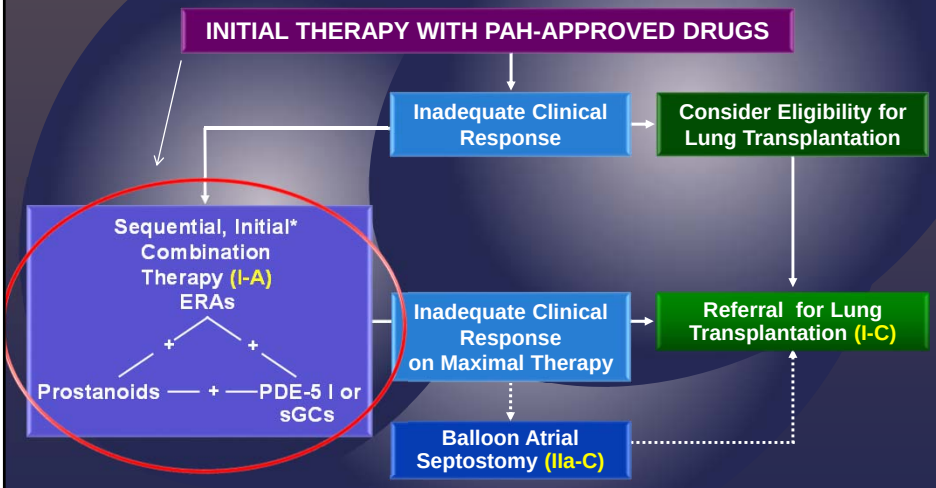
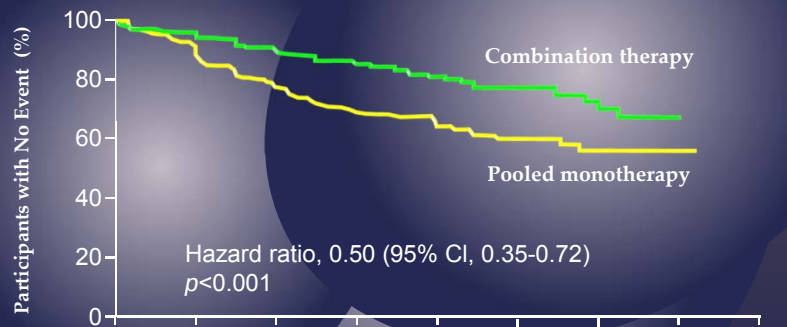
5th World Symposium on PH: 2013 Treatment Algorithm



Galiè N et al. *J Am Coll Cardiol*. 2013;62:D60-D72.
AMBITION study, N Engl J Med, 2015

AMBITION: Effect of *UPFRONT* Ambrisentan Plus Tadalafil Versus Monotherapy on Clinical Worsening*



No. at risk:								
Combination therapy	253	229	186	145	106	71	36	4
Pooled monotherapy	247	209	155	108	77	49	25	5

* Death, hospitalization for worsening PAH, disease progression, unsatisfactory long-term clinical response. Galiè N et al. *N Engl J Med*. 2015;373:834-44.

Case TN (4)

- Worsening RV function on Echo.
- Continued signs of RV failure
- Unable to come in for Repeat Right Heart Catheterization.
- Too Unreliable for most potent therapies of infusion prostaglandins.
- Oral Selexipag BID added to Tadalafil daily. Some benefit, limited side effects, erratic fu.

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Summary

- PAH-specific therapies promote vasodilation, leading to reduction in pulmonary vascular resistance and improved RV function
- Selection of initial therapy largely depends upon severity of disease at diagnosis
  - low-risk patients can be treated with oral agents
  - high-risk patients require parenteral prostacyclins
  - sequential combination therapy to follow
- Upfront Combination ERA/PDE5I therapy was recently shown to reduce risks of disease progression and hospitalization for worsening PAH, and to improve exercise capacity (AMBITION)

Pulmonary Hypertension

Mary Furbee: Spiral. (Used with permission)

- PH Physicians are open to Palliative Care (90% consulted Palliative Care in last year)
- Palliative care consult – minimum standard?
  - for short term acute problems beyond PH team expertise (?)
  - For end of life care (59% consulted when pt. actively dying)
- Only 2% of PAH patients acknowledged Palliative care specialist involved; only 14% at time of death.
- PH MD: 43% worried about "pt. losing hope, giving up" if palliative care consulted; 20% about limitations on aggressive care if involved.

Palliative care and Pulmonary Arterial Hypertension.

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Footer TeGin-Sing, W. Palliative care in pulmonary arterial hypertension. Current Opinion in Supportive and Palliative Care. 11 (1): March 2017, 7-11.
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4/23/2018

- PAH symptoms negatively impact QOL
- PH patients symptoms:
  - Dyspnea and fatigue – 70%
  - Drowsiness – 39%
  - Pain – 34%
- Depression can be present in up to 40% of patients
- Partial symptom care provided by PH specialists.

Palliative care and Pulmonary Arterial Hypertension.

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FooGin-Sing, W. Palliative care in pulmonary arterial hypertension. Current Opinion in Supportive and Palliative Care. 11 (1): March 2017, 7-11.
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Pulmonary Venous Hypertension –Left Heart: A Simplified View

- Normal, or mildly elevated transpulmonary pressure gradient with readily apparent cause
  - treat underlying cause for improvement.
  - spironolactone added to diuretics. Nitrates?
- Substantially elevated transpulmonary pressure gradient (PH "out of proportion" to LHD)
  - treat cardiovascular risk factors (including BP, aggressive volume control) as best you can;
  - Sleep Problem too? (*"Common Bed Partners"*)
  - improvement in PH , symptoms may be slow
  - *No FDA-approved therapies for diastolic dysfunction yet*

- Co-morbidities lead to difficult ongoing symptom management.
- Poor mobility, obesity, pain. Vicious cycle.
- Volume control: Hospitalizations;
- Devices - adjust therapy
- Sleep Apnea also common. ?compliance with Devices
- Oxygen needs develop.
- Lifestyle modifications are difficult. Salt, Fluid, Calories, Activity.
- Heart failure symptoms common when severe PH present. "something must be able to be done!"
- Dependent on others; Long term care needs, Placement.
- Side effects of drugs: *"nurses must hate me when I need to go to the bathroom"*

Group II PH: Left Heart Disease. Treatment and End of Life Challenges.

Group III Pulmonary Hypertension in Parenchymal Lung Disease Pts.

- May explain worsening symptoms in patient with stable lung function, PFTs, otherwise. *Sign of worse prognosis in most lung diseases.*
- Contributes to exercise limitation: cardiovascular limitation versus respiratory limitation

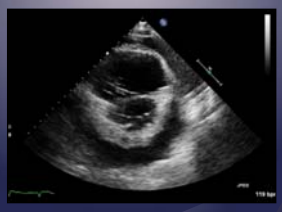
- **Treatment:** Oxygen, Disease specific, Lung Transplant?
- *Pilot study with sildenafil in COPD PH patients encouraging;*
- *Pulmonary Fibrosis (IPF) patients WORSE with ambrisentan, Riociguat. Sildenafil?, Inhaled Prostaglandin trials ?*

Group III PH: Lung Disease. Challenges at end of life

- No approved therapies for PH in parenchymal lung disease patients;
- No survival benefit to be offered. *"DO NO HARM"*
- Compliance with oxygen, diuretics and lung treatments are mainstay.
- Lung transplant not an option for many patients especially if > 70 yo, BMI >32-34.
- Sildenafil and other PH vasodilators can WORSEN oxygenation.
- Often develop escalating oxygen needs particularly with exertion. (high flow concentrators, pulse oximetry monitors)
- SOB management at end of life with titrated oxygen. (nasal side effects, device restrictions), and medications.

Case TN (5)

- Admitted 2018. Decompensated RV failure, Stasis dermatitis, MSSA bacteremia.
- ICU management of respiratory failure and RV failure.
- Repeat Right Heart Cath:
- RA pressure 11, PA mean 40, PAWP 11, CI 2.0 L /min m2.
- SVT treated, PT, OT.
- Discharged 5 weeks later: Combination therapy continued with diuretics, Family support.
- Goals of care. Optimistic Outlook with family support.
- SNF not feasible due to cost of Medications.



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Case TN (6)

- Readmitted in 3 weeks.
- Right heart failure; Hypoxemia.
- Medication problems.
- Visiting RN not let in.
- Family visit daily but not 24/7.
- *WHAT NEXT?*
- To go back to Monotherapy sildenafil for cost. Careful Diuresis.
- Try for placement at Rehab/ SNF
- Outlook? DNR status?
- Goals of Care. *Wedding in family "Up North"*

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Case TN (7)

- Palliative Care Consult:
- DNR status: more insight; 3rd party opinion helpful. Made DNR.
- POA: Revised with local daughter now as main POA
- No commitment to fu as OP.
- Hopeful to survive and make wedding and other life events
- What could have been done better?

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- Complicated therapies, Combination therapy is now the trend.
- Expensive medications; Total > $75K /year common.
- Funding Stress!
- Side effect management is essential
- Hypoxemia often complicates course when treatment starts to fail. Veno-occlusive disease component?
- Inpatient or residential hospice terminal care common.
- Need to be able to manage medications; Some are not candidates for *BEST* therapy.
- Expense limits rehab, placement options.
- Prostaglandin drugs have the most side effects but are the most potent.
- Pace of Decline when drugs are withdrawn is variable; Can be very fast with some prostaglandin infusion patients.

Group I PAH: Long term care and End of Life Challenges.

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Summary

- Classification: five major groups
- Group I PAH: uncommon, but serious and progressive
- *Prognosis is improving with treatments for Group I PAH patients but complicated.*
- Group IV Chronic PE patients: Surgery is complicated but can be a "near cure"; and now medication therapies exist

- Treating only ?"The Tip of the PH Ice Berg"
  - *No approved PH specific therapies for Group II Left Heart Disease,*
  - *Or for Group III Lung disease patients with complication of pulmonary hypertension*

- Also varies by different PH group
- Group II PH left heart disease patients with many co morbidities, recurrent heart failure admissions.
- Group III Lung disease patients: escalating SOB, and oxygen needs present key challenges.
- Group I PAH patients. Complicated medications, expense and other barriers limits some options especially with placement and hospice, careful end of life symptom management very helpful
- Palliative care collaboration is key part of PH patient care.

Chronic Care and End of Life Challenges

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Footer Text 4/23/2018

KEY POINTS

- Patients with PAH may benefit from a palliative care approach as part of standard care.
- Palliative care can exist in parallel with aggressive PAH disease-targeted therapies.
- There is a need for more education of both clinicians and patients about the benefits of palliative care.
- The access to specialist palliative care provision needs to be improved to ensure that this is available to all patients with PAH when appropriate.

Palliative care and Pulmonary Arterial Hypertension.

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Gin-Sing, W. Palliative care in pulmonary arterial hypertension. Current Opinion in Supportive and Palliative Care. 11 (1): March 2017, 7-11.

4/23/2018

Photograph of the Patient's Tattoo Entered into the Medical Record to Document His Perceived End-of-Life Wishes.

DNR bracelets on Amazon?

Holt GE et al. N Engl J Med 2017;377:2192-2193.

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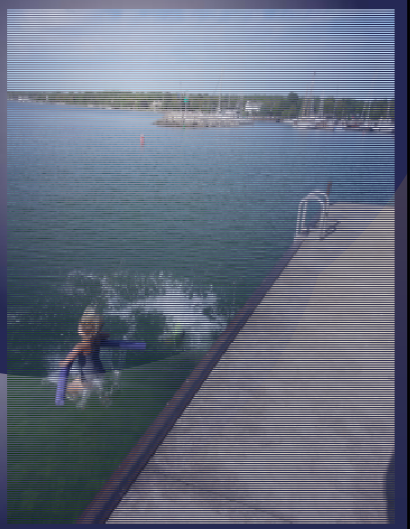
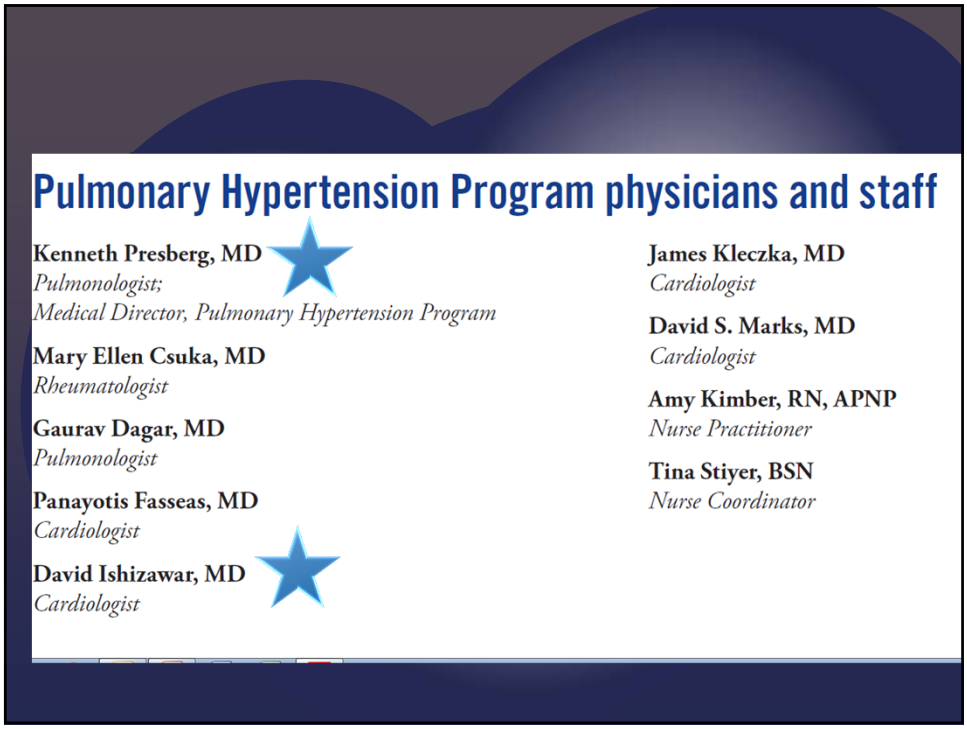
Correct Diagnosis, Best Plan, Partner before you jump in……

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Medical Director, Pulmonary Hypertension Program
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Rheumatologist
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David Ishizawar, MD
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