Pulmonary Hypertension: An Update

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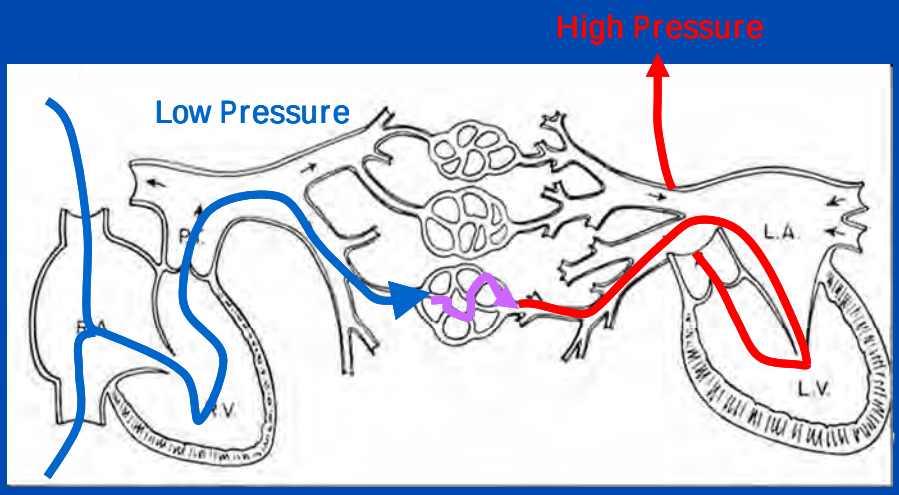
Normal Physiology

Pulmonary Perfusion 101



Pulmonary Artery Catheter (Swan-Ganz Catheter)

Normal Pulmonary Hemodynamics

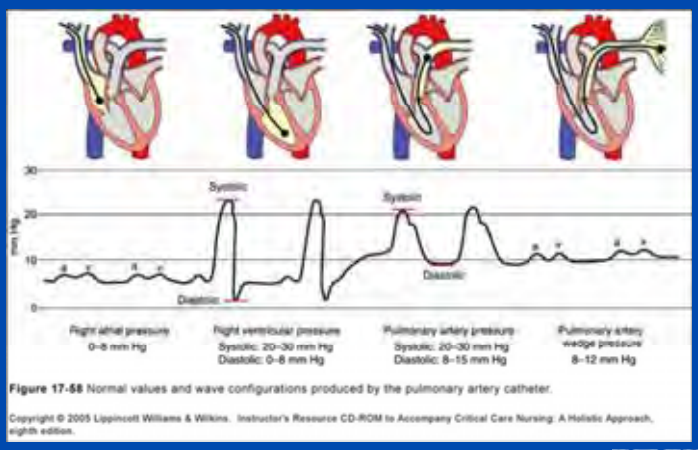


Figure 17-58 Normal values and wave configurations produced by the pulmonary artery catheter.

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PAH Classification: Venice, 2003

- 1. Pulmonary Artery Hypertension
- 2. Left Heart Disease
- 3. PH with respiratory disease or hypoxia
- 4. PH secondary to embolic disease
- 5. Miscellaneous

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What is Pulmonary Arterial Hypertension (PAH)?

- Pulmonary hypertension (PH) is a group of diseases of the small vessels of pulmonary circulation
- Pulmonary arterial hypertension (PAH) is one form of PH
- PAH is defined as:
  - Sustained elevation of mean pulmonary arterial pressure of >25 mm Hg at rest or >30 mm Hg with exercise
  - Mean pulmonary capillary wedge pressure (PCWP) and/or mean left ventricular end-diastolic pressure <15 mm Hg

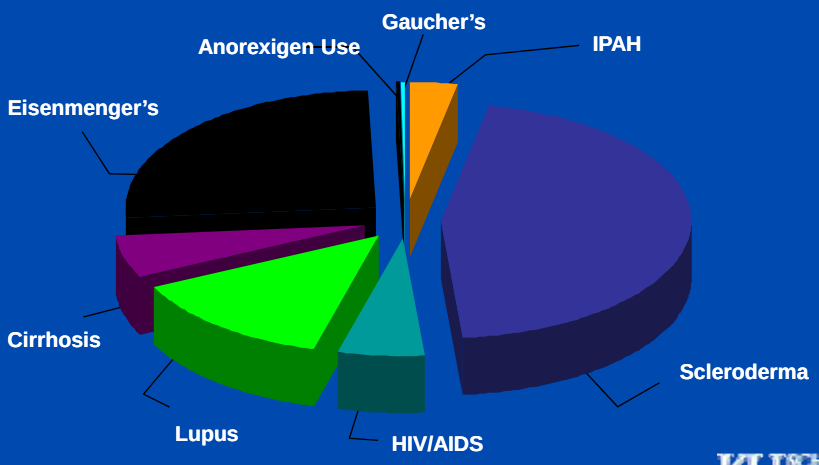
Evian Classification of Pulmonary Hypertension– Group 1

1. Pulmonary Arterial Hypertension

1.1 Idiopathic PAH (formerly PPH)
- (a) Sporadic
- (b) Familial
- (c) PVOD/PCH

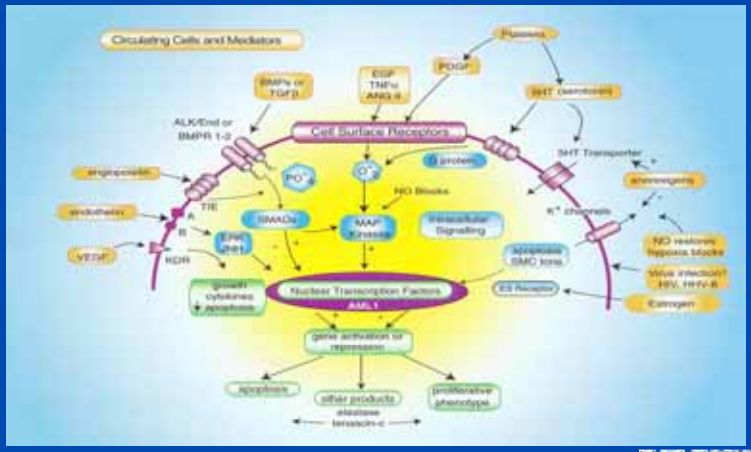
1.2 Related to:
- (a) Collagen vascular disease
- (b) Congenital systemic to pulmonary shunts
- (c) Portal hypertension
- (d) HIV infection
- (e) Drugs / toxins

Estimated Prevalence of PAH (By Condition)



Pathophysiology

The Challenge



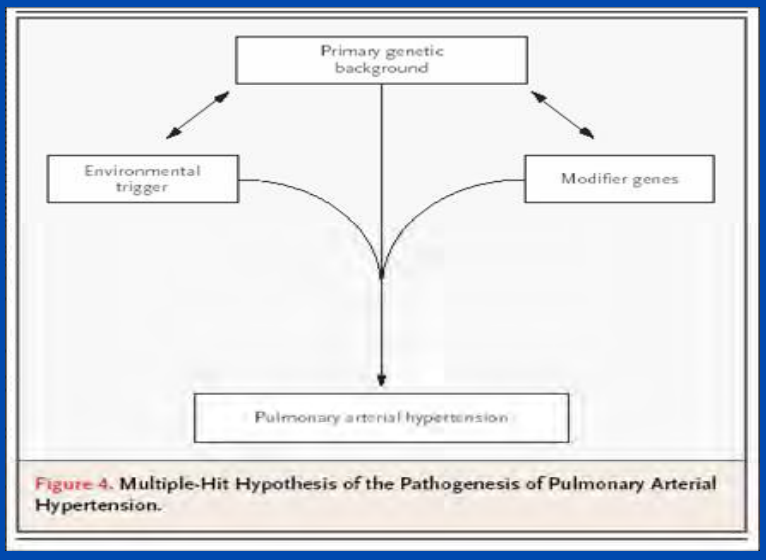
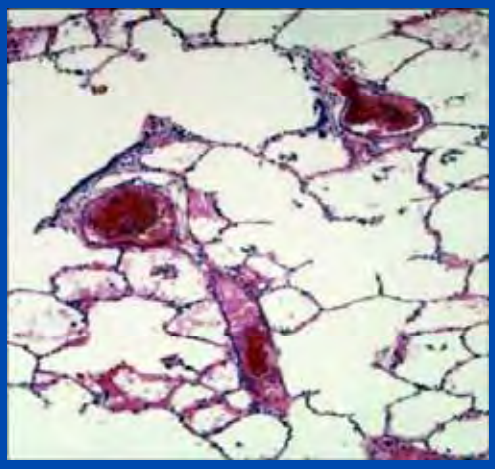


Figure 4. Multiple-Hit Hypothesis of the Pathogenesis of Pulmonary Arterial Hypertension.

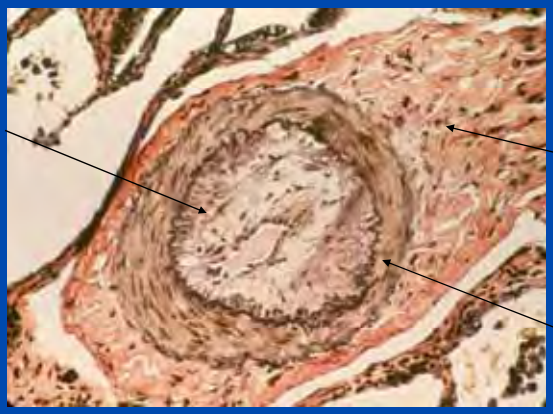
N Engl J Med 2004;351:1655-65.

- Pulmonary artery remodeling
  - Intimal fibrosis
  - Medial hypertrophy
  - Adventitial proliferation
  - Luminal obliteration
  - On occasion: vasculitis or changes in pulmonary veins

Normal Pulmonary Artery and Alveolus

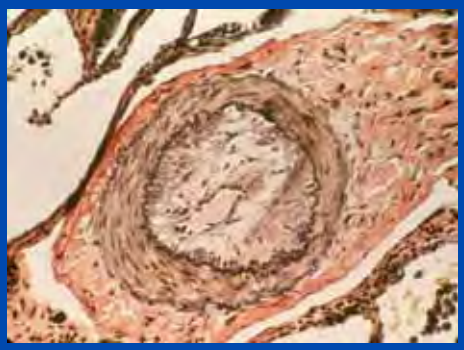


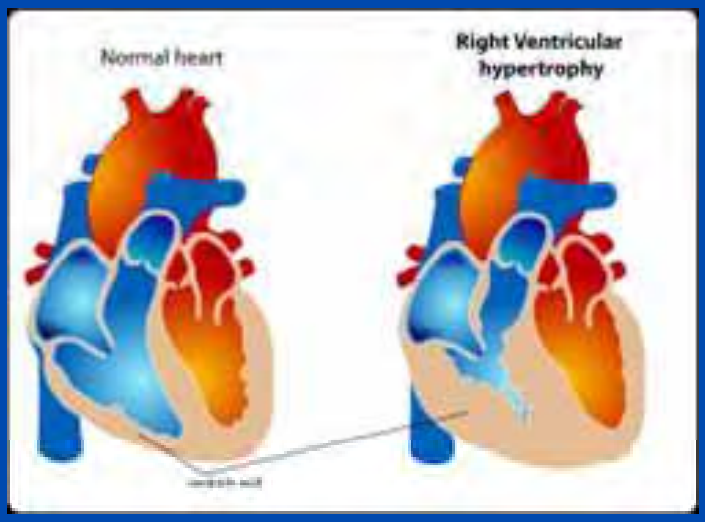
Pathology of PAH

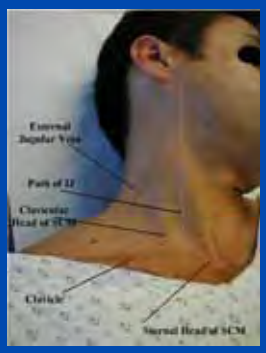


Gaine S and Rubin L: Lancet 1998; 352: 719-725

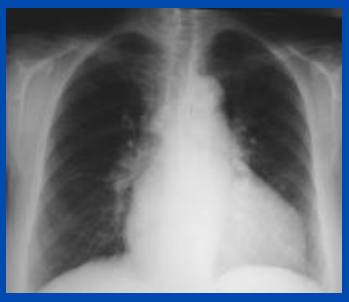
A matter of “simple” plumbing




Normal heart
Right Ventricular hypertrophy



Diagnosis



PH: Diagnosis and Evaluation

Routine

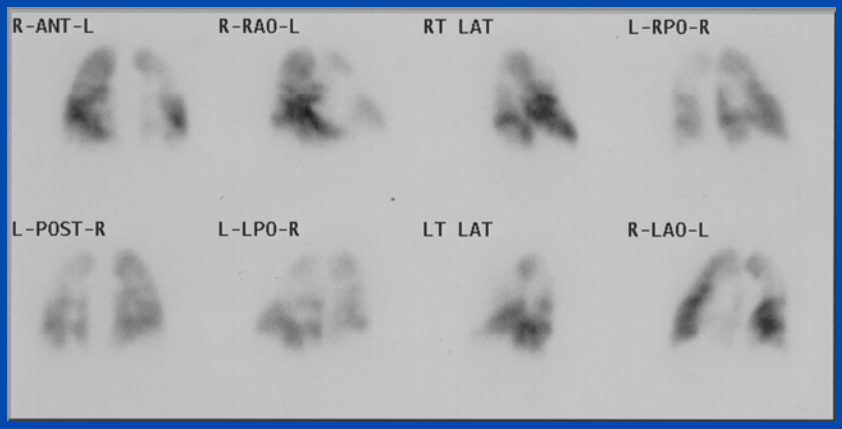
- CXR, PFTs, 6 minute walk, CT, oximetry
- EKG
- Serology and laboratory testing (esp autoimmune)?
- **V/Q vs Spiral CT**
- **ECHO vs Right Heart Catheterization**

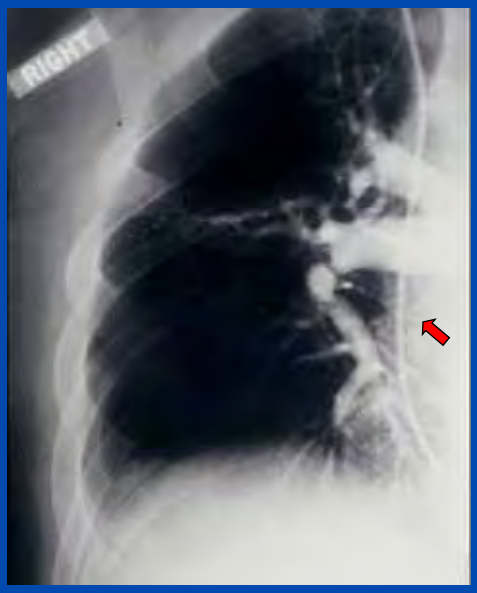
Special Circumstances

- Left Heart Cath
- Pulmonary Angiogram
- Lung Biopsy

V/Q scan in IPAH

V/Q Scan in CTEPH




RIGHT

Echocardiogram

- Screening tool?
- Mechanism to follow pulmonary pressures?
- Non-invasive
- “Cheap”

Echocardiogram utility:

- Chamber morphology
- Left ventricular systolic/ diastolic function
- Exclusion of congenital heart disease
- Intra-cardiac shunts
- Valvular function
- Estimation of PA pressure?

Cardiac Catheterization

- To exclude congenital heart disease
- To assess contribution of left heart (PAOP)
- To establish severity and prognosis
- Establish presence/absence of vasodilator response

Catheterization is required for nearly every patient with suspected pulmonary hypertension (who will be treated)

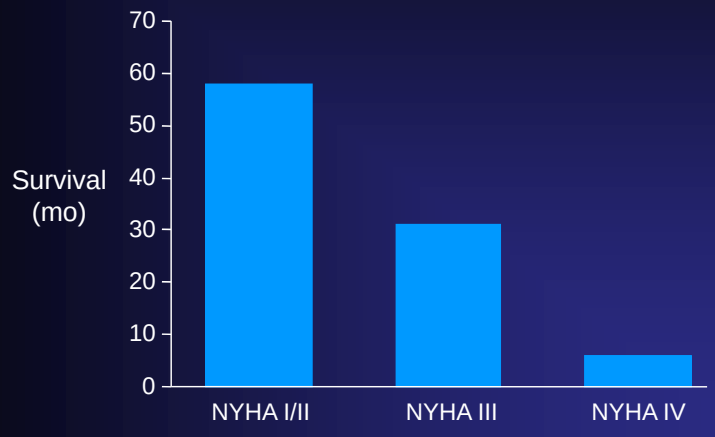
PAH Determinants of Risk

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO class	IV
Longer (>400 m)	6MW distance	Shorter (<300 m)
Minimally elevated	BNP	Very elevated
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion, significant RV dysfunction
Normal/near normal RAP and CI	Hemodynamics	High RAP, low CI

McLaughlin VV, McGoon MD. *Circulation*. 2006;114:1417-1431.

Treatment

Survival in PAH Patients According to NYHA Functional Class



D'Alonzo GE et al. *Ann Int Med.* 1991;115:343-349.

The Ultimate Goal of Treatment

- Improve symptoms
- Improve survival

With the least invasive therapy possible

First, Do No Harm

General Considerations

- Do no harm:
  - Hypotension
  - Nitrates
  - Beta-blockers
  - NSAIDs
  - Sedation
  - Vagal maneuvers (EGD, TEE)
  - Contraception/ Pregnancy

Parameters for Therapeutic Decision Making

- What is the magic PA pressure?
- Six Minute Walk
- BNP
- Right ventricular size and function
- Hemodynamics
- Functional Class
- Combination

PAH specific therapies General thoughts

- Most increase 6 minute walk, functional class, modestly improve hemodynamics
- Little data on survival impact outside of Flolan
- Choice based on availability, onset of action, drug interactions, provider experience, patient preference, lifestyle considerations
- There is no cure: these are all palliative interventions

General Considerations in PAH Management

- Consider referral to dedicated Pulmonary Vascular Center
  - Resources
  - Insurance Issues
  - Concentrates rare group of patients for studies, support groups

"Supportive Therapy"

Supportive Therapy

- Oxygen
- Coumadin
- Digoxin
- Diuretics
- Treatment of underlying/ co-existing disease

PAH Specific Therapies

Where Do We Have Data?

- 1. Pulmonary Artery Hypertension
- 2. PH owing to left heart disease
- 3. PH owing to lung disease/ hypoxia
- 4. CTEPH
- 5. Unclear multifactoial etiologies

Where Do We Have Data?

- 1. IPAH
- 2. Heritable
- 3. Drug and toxin induced
- 4. APAH
  - CTD, HIV, Portopulmonary, Congenital heart disease, schistosomiasis, chronic hemolytic anemia

Goals of Therapy

- Improved QoL
- Improved functional status
- Improved Survival
- Anti-proliferation and remodeling
- RV size and function
- Prevent in in situ thrombosis formation

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Goals of Therapy

- Feel Better!
- Live Longer!
- Breathe!

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It's a spectrum

- Nothing
- Oral Medicines
- Nebulized Medicines
- Continuously Infused Medicines
- Lung Transplant

25 years ago…

- Very Little!

Current FDA Approved Therapies

Prostacyclin (PGI_2)
- Epoprostenol (Flolan®, GlaxoSmithKline)

Prostacyclin Analogues (Prostanoids)
- Treprostinil (Remodulin®, United Therapeutics)
- Iloprost (Ventavis® Inhalation Solution, CoTherix)

Endothelin-Receptor Antagonists
- Bosentan (Tracleer®, Actelion)
- Ambrisentan (Letairis, Gilead)

Phosphodiesterase Inhibitors
- Sildenafil (Revatio, Pfizer)

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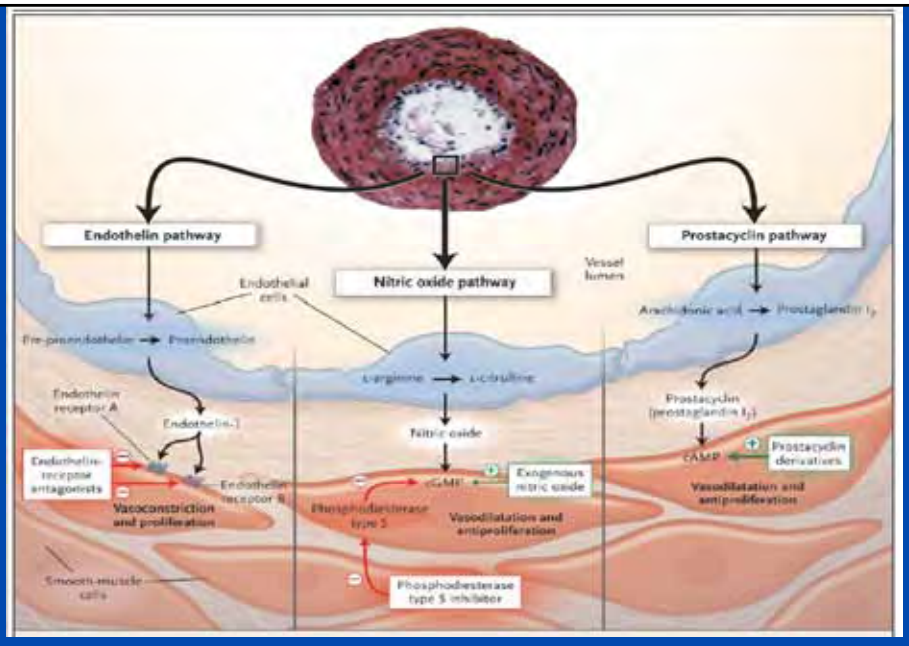


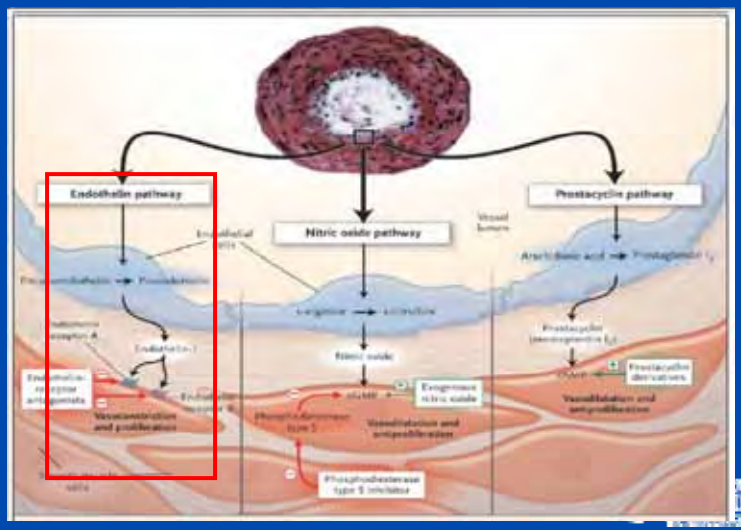
N Engl J Med 2004;351:1425-36.

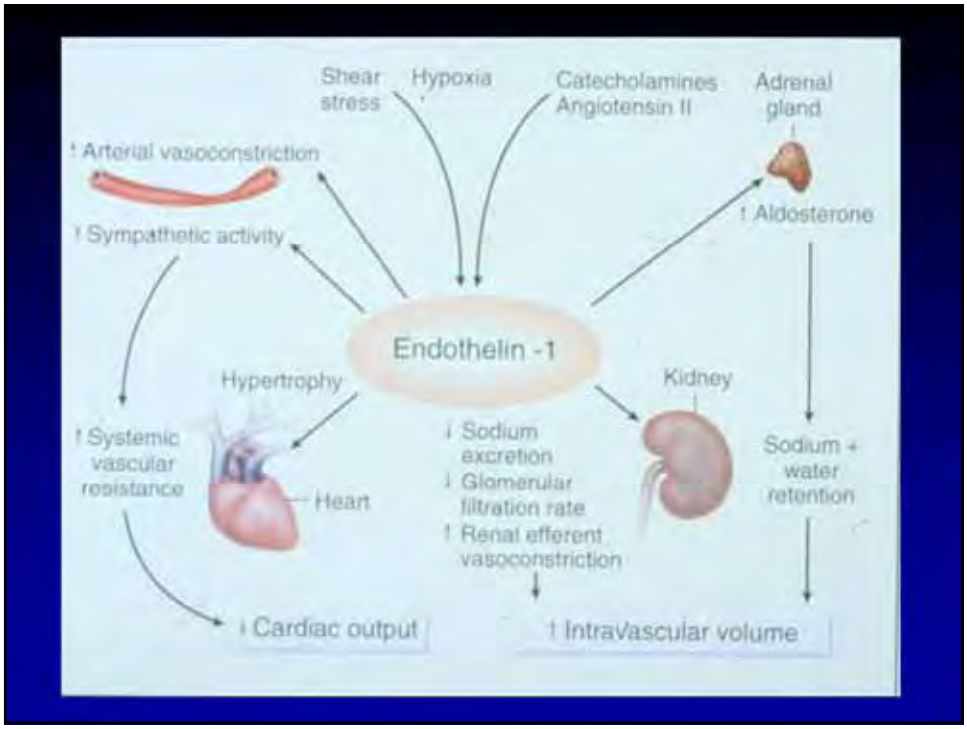
Oral Therapies

- Sildenafil (Revatio/ Viagra)
- Tadalafil (Cialis/Adcirca)

- Bosentan (Tracleer)
- Ambrisentan (Letairis)

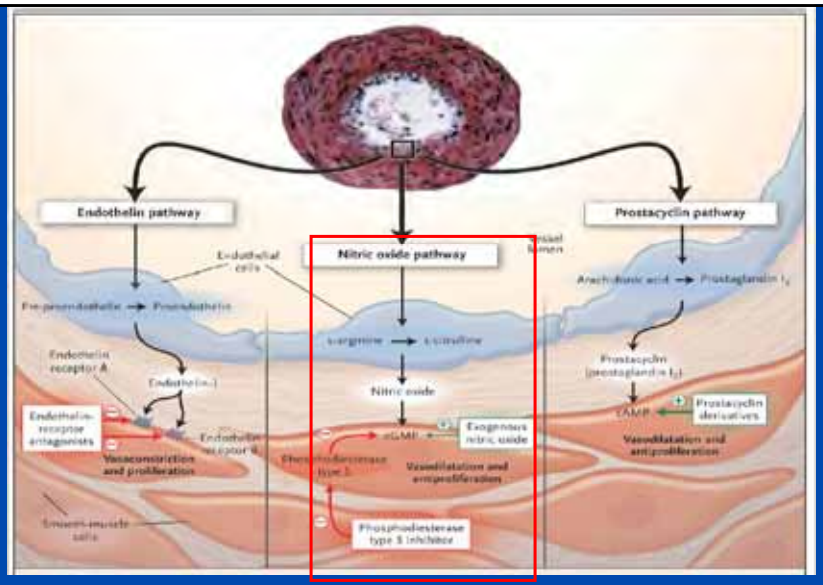
Endothelin





Some ERA issues:

- LFT abnormalities (11%)
- Takes time to work
- Avoidance of CSA and glyburide
- Use of contraception



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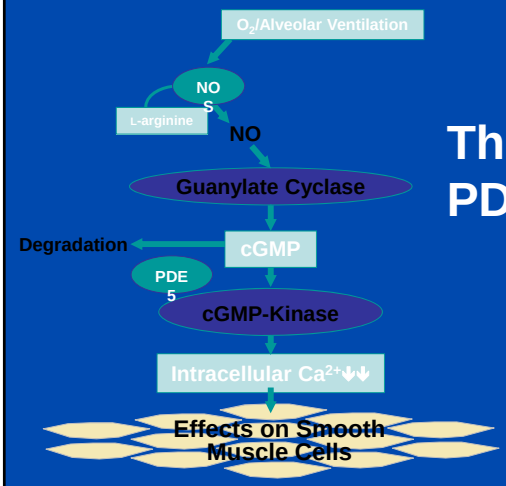


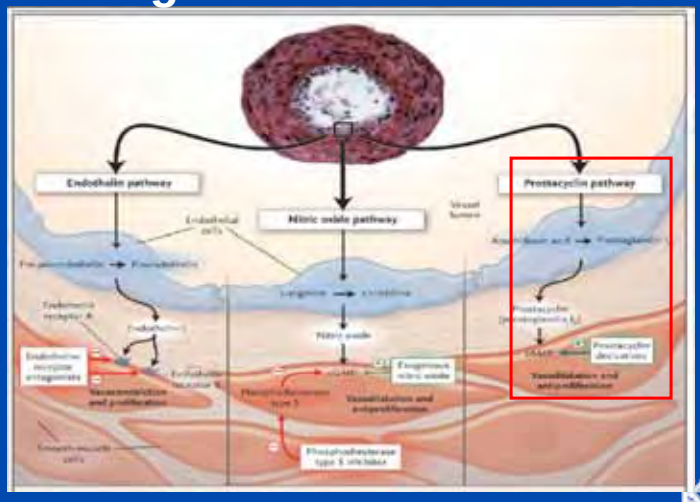
The NO Pathway—PDE5 Inhibition

Chart adapted from Ghofrani HA et al. *J Am Coll Cardiol.* 2004;43:69S.
Badesch DB et al. *CHEST.* 2004;126(suppl):48S.

Some PDE-5 issues:

- BP
- HA
- Vision changes
- Theoretical risk of priapism
- No alpha blockers/nitrates

Prostaglandins



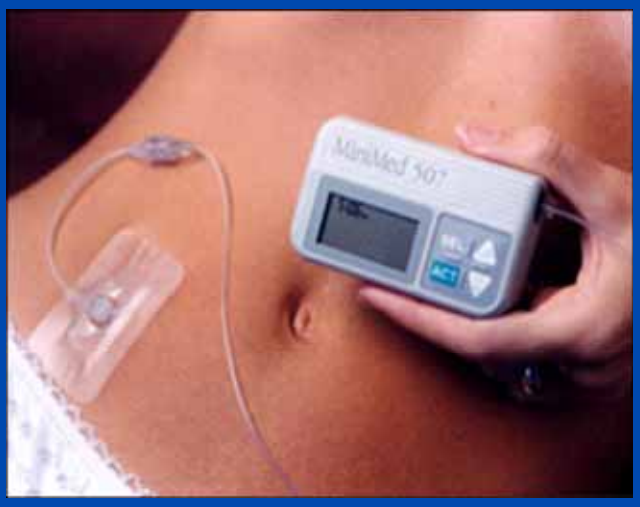
N Engl J Med 2004;351:1425-36.

Prostacyclin

- PGI2
- Activity through cAMP
- Vasodilator
- Inhibits proliferation of vascular smooth muscle
- Decreases platelet aggregation
- Decreased prostacyclin synthase in PAH

IV Epoprostenol (Flolan)

SQ Trepostinil (Remodulin)



Nebulized Prostacyclin: Iloprost (Ventavis)

Inhaled Iloprost

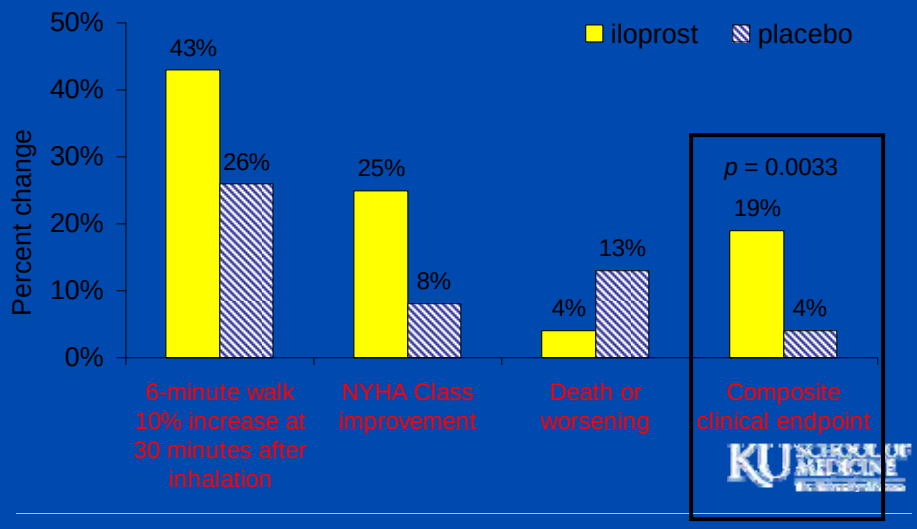
Phase III Study Design (AIR)

- Randomized, double-blind, placebo-controlled
- 12 weeks inhaled iloprost versus placebo
- 203 patients with NYHA Class III or IV PH
  - Primary pulmonary hypertension (50%)
  - Associated with connective tissue disease (17%) or anorexigen use (4.5%)
  - Chronic thromboembolic PH (28%)
- 37 European centers in 11 countries

Olschewski H, Simonneau G, Galiè N, et al, AIR Study Group. *N Engl J Med* 2002;347:322-9

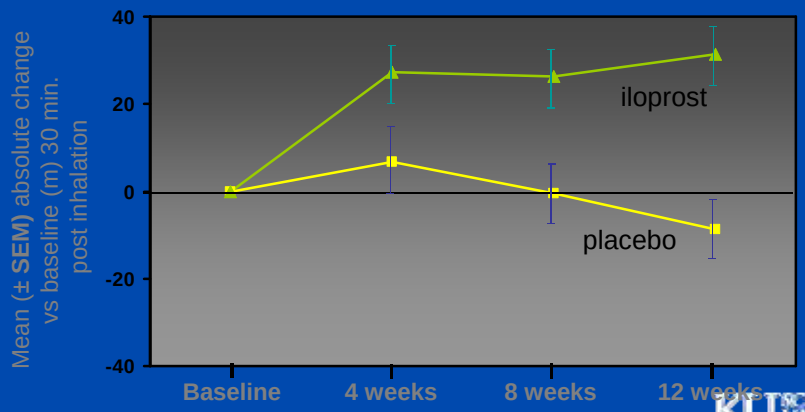
Inhaled Iloprost:

Composite Primary Endpoint for PAH Patients (WHO Group I)



Ventavis package insert

Change in 6-Minute Walk Distance in PAH Patients (WHO Group I)



Placebo corrected difference at 12 weeks = 40 meters (p<0.01)

Ventavis package insert

Inhaled Trepostinil

- Each treatment completed in less than one minute

Inhaled Trepostinil-- TRIUMPH

- Age 18-75
- Baseline 6MWD of 200-450 meters
- Stable NYHA Class III or IV
- Confirmed diagnosis of PAH
  - Idiopathic or Familial
  - Collagen vascular associated disease
  - HIV or Anorexigen associated disease
- On stable background therapy of bosentan (125 mg BID) or sildenafil for 3 months prior to enrollment

ATS, 2008

TRIUMPH 1

ATS, 2008

Lowest Quartile Walks (204-302 m)

ATS, 2008

The Temptation…..

Table 2. Change in 6MW distance in the pivotal trials of PAH.

	Epoprostenol[7]	Bosentan[13]	Sitaxsentan[16]	Ambrisentan[14]	Sildenafil[15]
Duration of Treatment	12	16	18	12	12
Dose	~9 ng/kg/min) (mean dose	125 mg†	100 mg†	10 mg†	20 mg†
Baseline 6MW Distance (m)‡	316	326	360	341	347
Δ 6MW* Distance (m)	+ 32	+ 27	+ 25	+ 43	+ 43%
% Δ 6MW Distance	+ 10%	+ 8%	+ 7%	+ 13%	+ 12%

Data were either taken directly or derived from information provided in cited references.
†Data only provided for sub-groups receiving highest *approved* dose of respective medication.
‡Differs from Table 1 data, which reported baseline distances for entire study populations.
*Reflects change in 6MW distance for active drug group in each study.

Chakinala, Advances in PH, Spring 2009

But….apples vs oranges vs carrots

Table 1. Baseline cohort characteristics of pivotal trials.

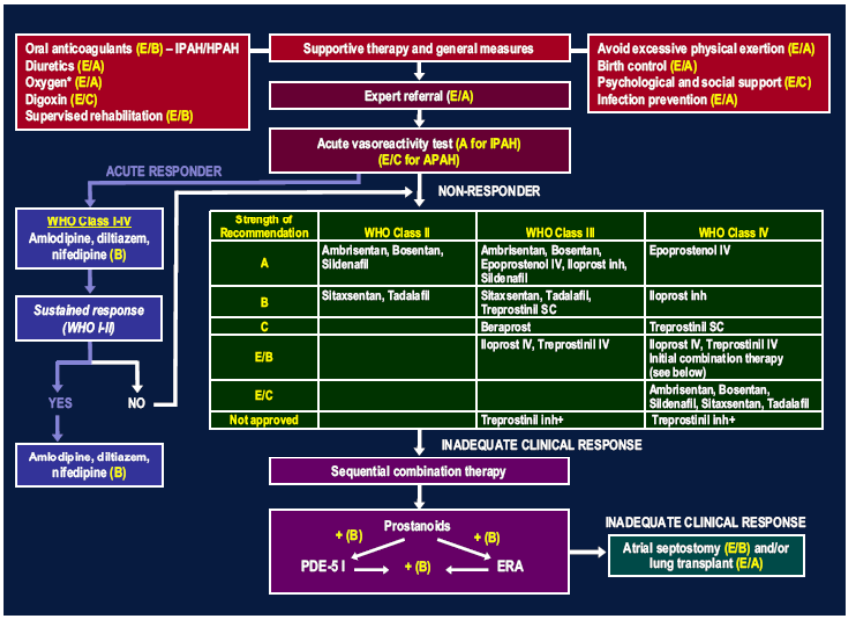
	Epoprostenol[7]	Bosentan[13]	Sitaxsentan[16]	Ambrisentan[14]	Sildenafil[15]
Number Treated	81	213	185*	393	277
Mean Age (yrs)	40	48	48	51	49
Gender (%) F / M	73 / 27	79 / 21	77 / 23	79 / 21	75 / 25
Diagnosis (%) IPAH / APAH	100 / NA	70 / 30	60 / 40	64 / 36	63 / 37
Functional Class (%) I-II / III / IV	NA / 75 / 25	NA / 76 /24	38 / 58 / 4	40 / 55 / 5	39 / 58 / 3
Mean PAP (mm)	60	54	47	49	53
Mean RAP (mm)	13	10	NR	8	9
Cardiac Index (l/min/m2)	2.1	2.4	2.5	2.5	2.4
Baseline 6MWD (m)	294	335	336	345	344

Data were either taken directly or derived from information provided in cited references.

*Excluded the sub-group of patients on open-label bosentan.

IPAH – Idiopathic PAH; APAH – Associated PAH; PAP – pulmonary artery pressure; RAP— right atrial pressure; 6MWD – 6-minute walk distance; NA – not applicable; NR – not reported

Chakinala, Advances in PH, Spring 2009

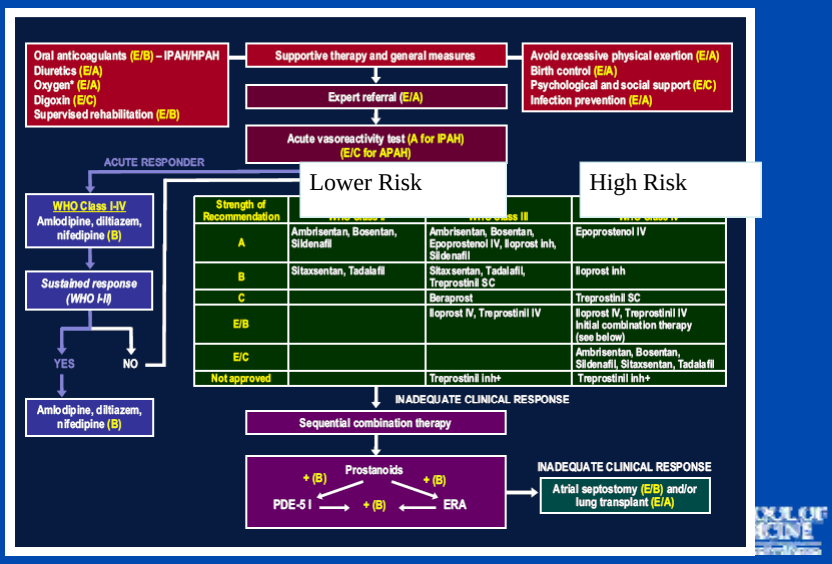


J Am Coll Cardiol 2009;54:S78–84

PAH Determinants of Risk

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO class	IV
Longer (>400 m)	6MW distance	Shorter (<300 m)
Minimally elevated	BNP	Very elevated
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion, significant RV dysfunction
Normal/near normal RAP and CI	Hemodynamics	High RAP, low CI

McLaughlin VV, McGoon MD. *Circulation*. 2006;114:1417-1431.



J Am Coll Cardiol 2009;54:S78–84

Rationale for Combination Therapy

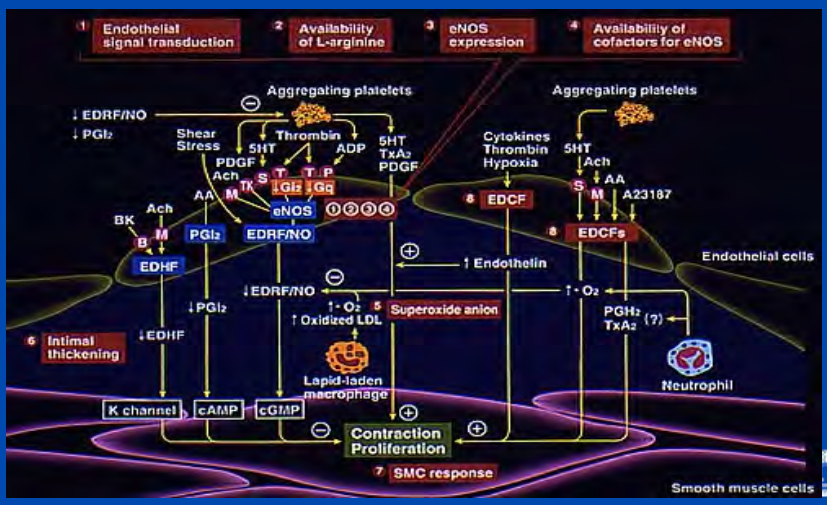


Table 1. Prostanoids Plus Endothelin Receptor Antagonist Combination Trials

Combination	Study Design	Number of Patients	Dosing	Results	*P* value
Bosentan + iloprost/beraprost[30]	OL	20	Bosentan 125 mg bid + Prostanoid, maximal tolerated dose	6MWD + 45 m Exercise testing parameters	< .05 < .05
Bosentan + epoprostenol (BREATHE-2)[31]	RCT	33	Bosentan 125 mg bid + Epoprostenol 12-16 ng/kg/min	PVR -36% vs -23% 6MWD NYHA FC	NS NS NS
Bosentan + iloprost (COMBI)[11]	RCT	40	Bosentan 125 mg bid + Iloprost 5 mcg 6 times daily	6MWD TCW Functional Class	NS NS NS
Bosentan + iloprost (STEP)[10]	RCT	67	Bosentan 125 mg bid + Iloprost 5 mcg up to 6 times daily	6MWD + 26 m Delayed TCW	.051 .022
Bosentan + prostanoids[12]	OL	16	Bosentan 125 mg bid + Iloprost intravenous or inhaled; or Beraprost	6MWD + 42 ± 66 m Tei index improved	< .001 <.001

NYHA FC = New York Heart Association functional class; OL = open label; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; 6MWD = 6-minute walk test distance; Tei index = echocardiographic index of right ventricular function; TCW = time to clinical worsening.

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Table 2. Ongoing Clinical Trials of Combination Add-on Therapies

	Initial Therapy	Added Therapy	Number of Patients	Study Duration	Primary Endpoint
FREEDOM-C	Bosentan and/or sildenafil	Treprostinil	300	16 weeks	6 MWD
TRIUMPH-1	Bosentan	Treprostinil	150	12 weeks	6 MWD
PACES (extension)	Epoprostenol	Sildenafil	264	Long-term	6 MWD
VISION	Sildenafil	Iloprost	180	16 weeks	6 MWD
PHIRST	Naïve or bosentan	Tadalafil	400	16 weeks	6 MWD
Pfizer	Bosentan	Sildenafil	106	12 weeks	6 MWD
COMPASS-2	Sildenafil	Bosentan	180	Event driven	6 MWD Morbidity/mortality events
COMPASS-3	Bosentan	Sildenafil	100	12 weeks	6 MWD

6MWD = 6-minute walk test distance.

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Novel Approaches Undergoing Evaluation for PAH

- Combination Therapies
- Novel Deliveries of Approved Therapies
- New Targets

Table 3. Novel therapeutic candidates for future clinical trials.

Soluble cyclic GMP Agonist
Nitric Oxide Synthase Coupler
Tyrosine Kinase Inhibitors
Endothelial Progenitor Cell Transplantation
(Editor's note: the above agents are covered in Dr. Langleben's accompanying article)
Tissue-tropic Endothelial Receptor Antagonist
Prostacyclin Receptor Agonist
Rho A Kinase Inhibitor
Statins
Serotonin Receptor Antagonists
Serotonin Transporter Inhibitors

Team Approach

- Nurses
- Respiratory Therapists
- Pulmonologists
- Rheumatologists
- Primary Care
- Cardiologists

Contact Info

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