Pulmonary Hypertension Diagnosis and Therapy

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37 year old female

RQ: Presented January 2007

- 37-yr-old woman, previously healthy
- Delivered second child 14 mo previously
- Limited exercise tolerance since delivery, attributed to weight gain
- Dyspnea 8/06 while playing with older child; syncope while walking up an incline

RQ: Initial Symptoms

- Currently has dyspnea with raking, walking about 1 block, walks slowly in store
- Exertional light-headedness
- Atypical chest pain
- Occasional palpitations
- Lower extremity edema

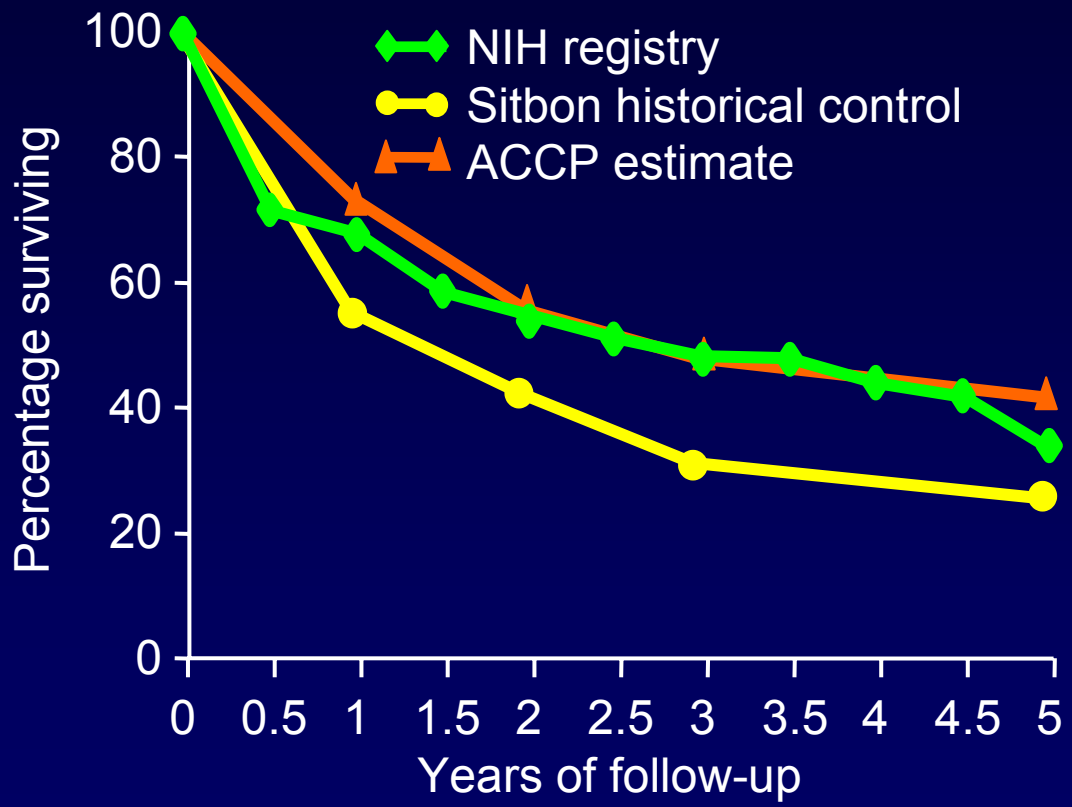
RQ: Additional History

- PMH: 2 children 4 yr and 14 mo
  - IBS: diet-controlled
- Meds: none
- All: contrast
- FH: PPH in a paternal aunt, CAD, DM, HTN
- SH: rare ETOH, o/w unremarkable

RQ: Physical Exam

- HR 90; BP 130/68; Wt 190; Ht 5'4"
- JVP ~15 cm, reduced carotid upstrokes
- Clear lungs
- Palpable RV heave, RRR, nl S, loud P_2, III/VI, TR m
- 2+ LE edema

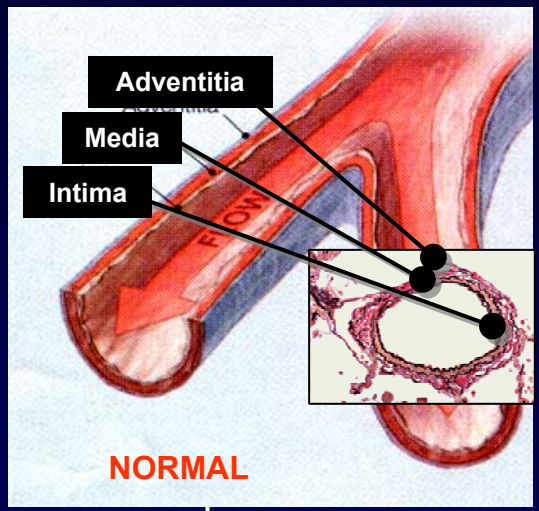
A Disease of Decline and Deterioration: IPAH Survival if Untreated

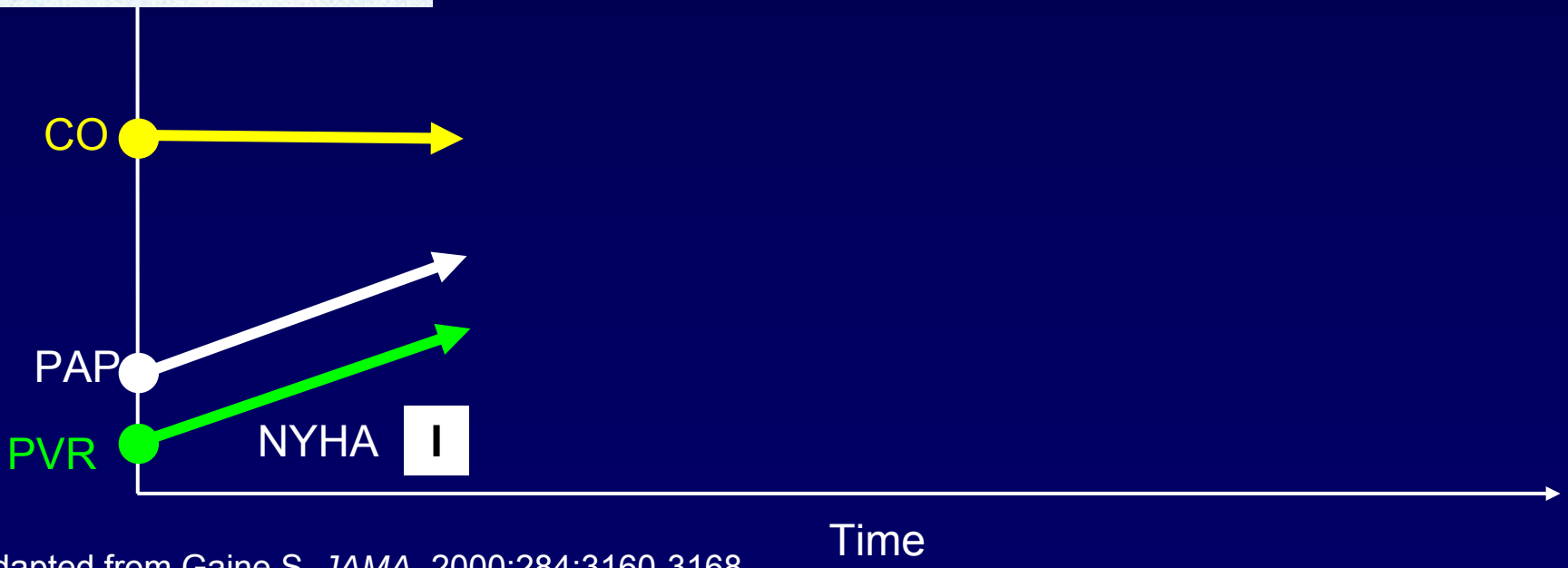


- Poor prognosis in an era lacking therapy
- Therapeutic options and research efforts now offer more hope

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

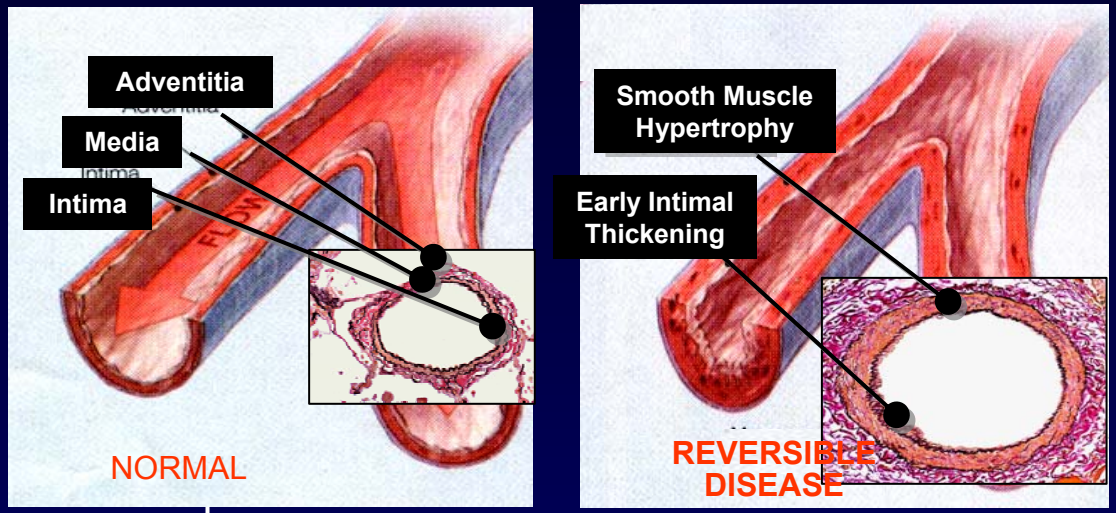
PAH: Hemodynamic and Clinical Course

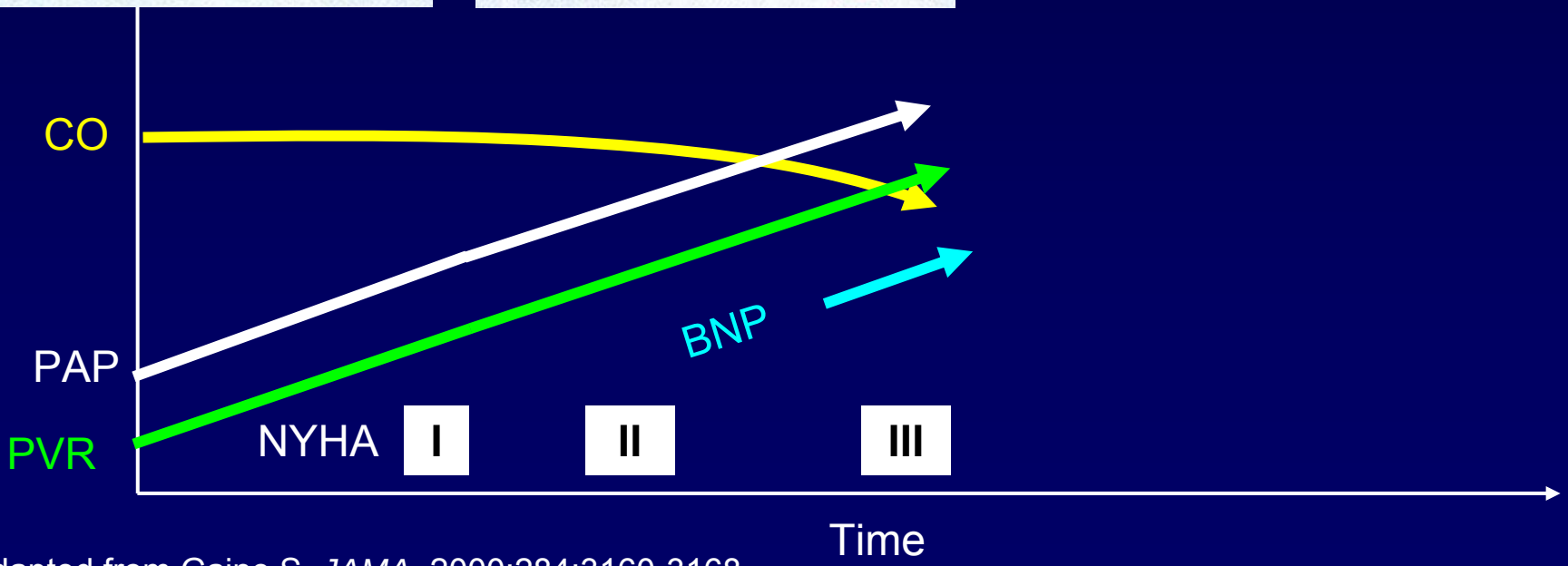




Adapted from Gaine S. *JAMA.* 2000;284:3160-3168.

PAH: Hemodynamic and Clinical Course





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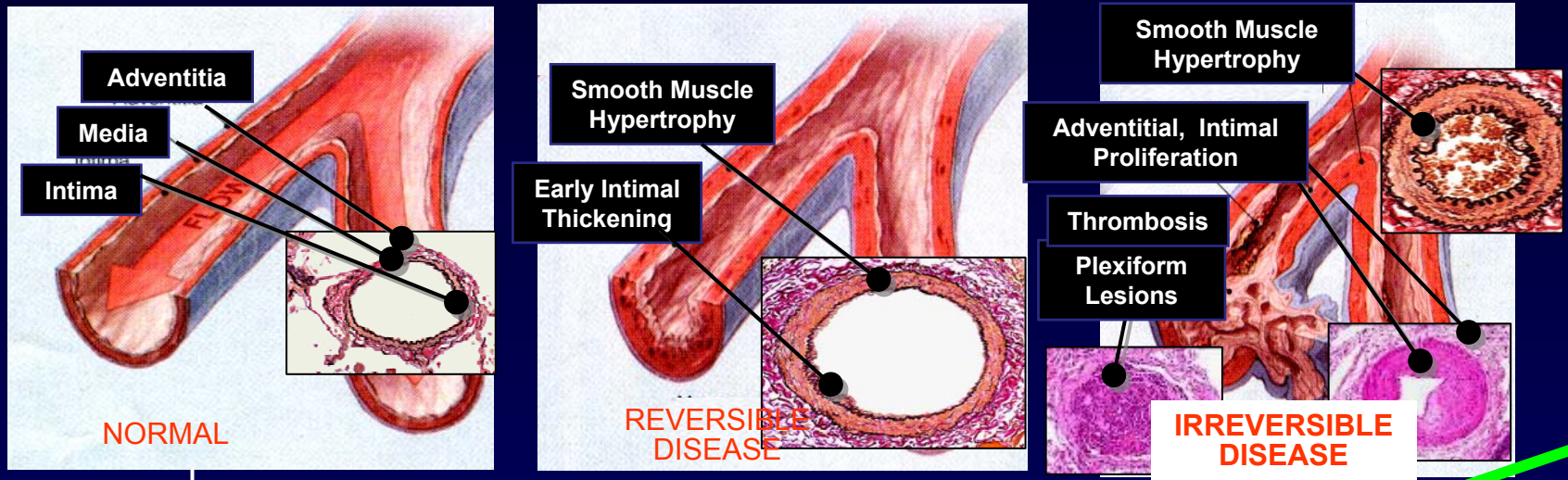
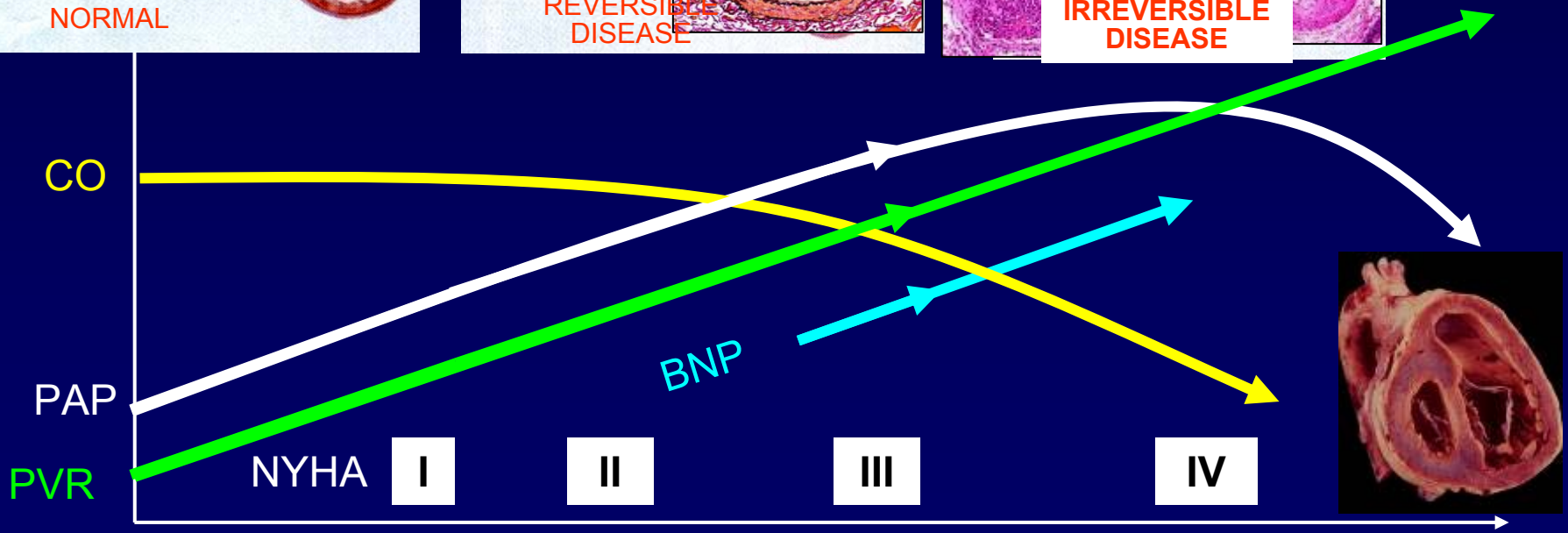
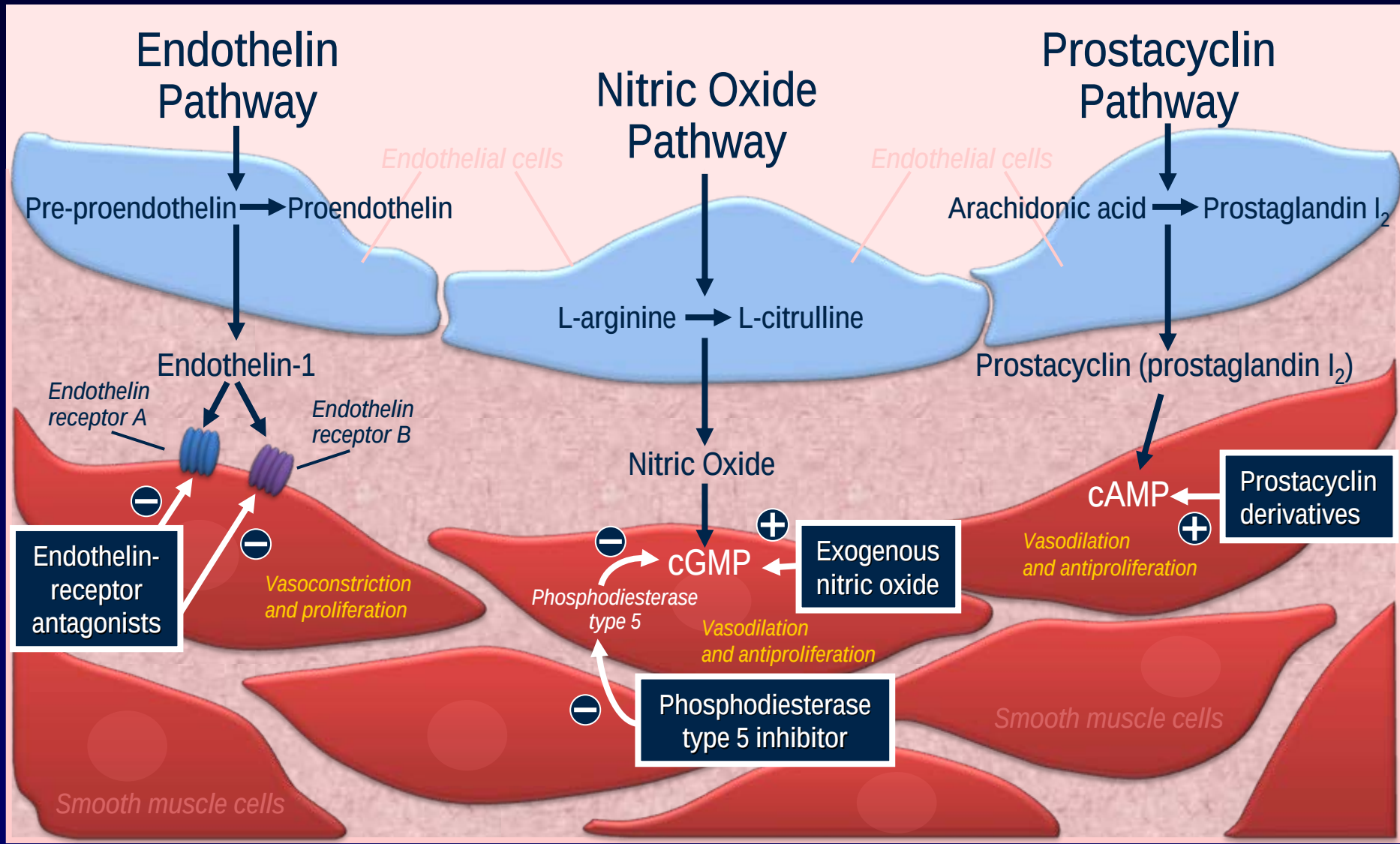
PAH: Hemodynamic and Clinical Course





Adapted from Gaine S. *JAMA.* 2000;284:3160-3168.

Mechanisms of Action of Therapies for PH



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

Clinical Classification of Pulmonary Hypertension (Dana Point)

1. PAH

- Idiopathic PAH
- Heritable
- Drug- and toxin-induced
- Persistent PH of newborn
- Associated with:
  - CTD
  - HIV infection
  - portal hypertension
  - CHD
  - schistosomiasis
  - chronic hemolytic anemia

1'. PVOD and/or PCH

2. PH Owing to Left Heart Disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

3. PH Owing to Lung Diseases and/or Hypoxia

- COPD
- ILD
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

4. CTEPH

5. PH With Unclear Multifactorial Mechanisms

- Hematologic disorders
- Systemic disorders
- Metabolic disorders
- Others

Simonneau G et al. *J Am Coll Cardiol.* 2009;54;S43-S54.

Is There a Reason to Suspect PAH?

Clinical Presentation

Common Initial Symptoms (N=187)	Patients (%)
Dyspnea	60
Fatigue	19
Syncope or near syncope	13
Chest pain	7
Palpitations	5
Leg edema	3

McGoon M et al for the American College of Chest Physicians. *Chest.* 2004;126:14S-34S.
Rich S et al. *Ann Intern Med.* 1987;107:216-223.

Is There a Reason to Suspect PAH?

Physical Exam

Presence of PH

- Loud P2
- RV lift
- Systolic murmur (TR)
- Diastolic murmur (PR)
- RV S4

Presence of RV Failure

- JVD with V wave
- RV S3
- Hepatomegaly
- Edema
- Ascites

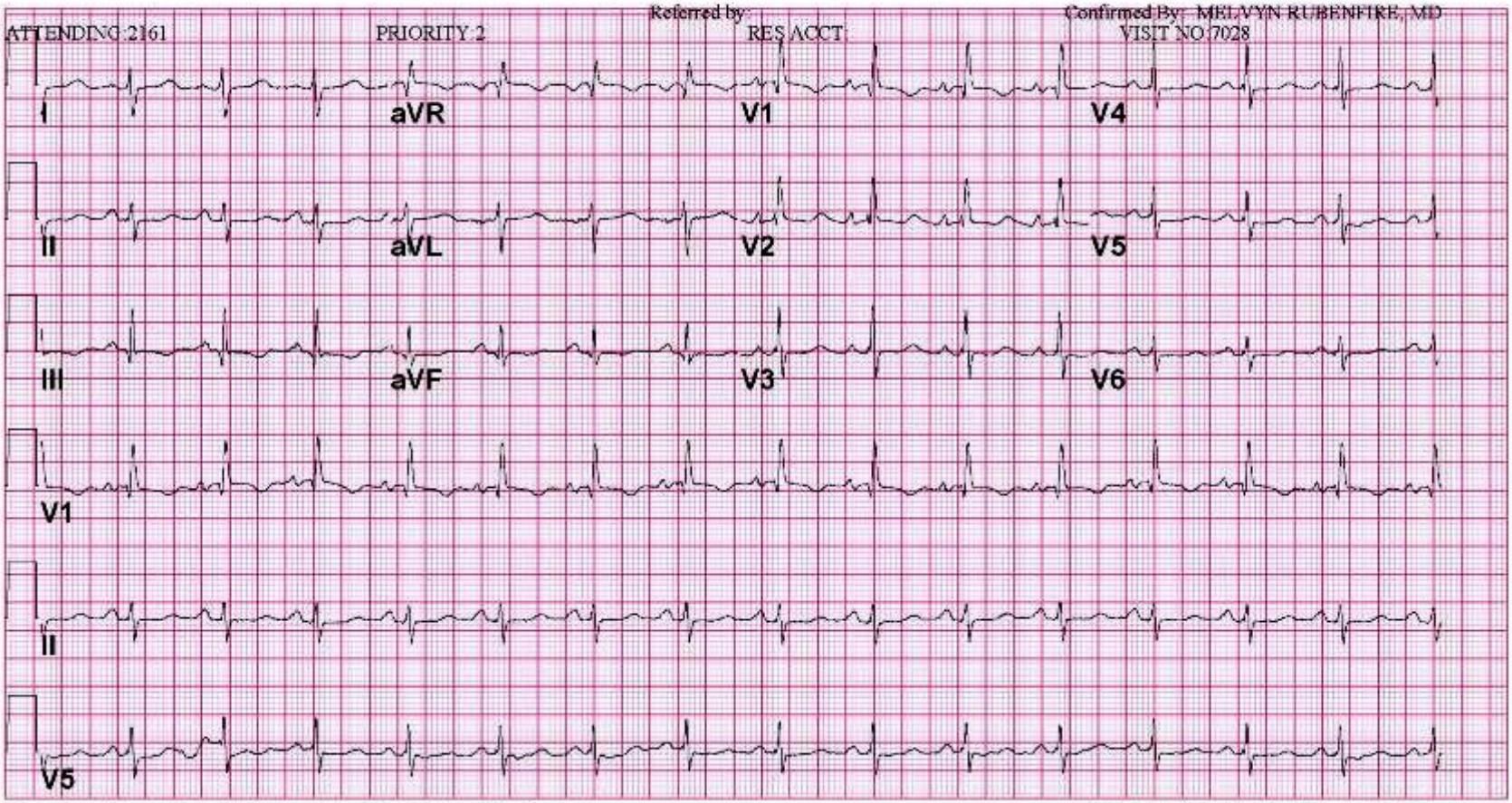
Is There a Reason to Suspect PAH?

Risk Factors

- Family history
- Connective tissue disease
- Congenital heart disease
- Portal hypertension—OLT candidate
- Environmental/drug factors
- HIV

29-JAN-2007 12:54:03 THE UNIVERSITY OF MICHIGAN

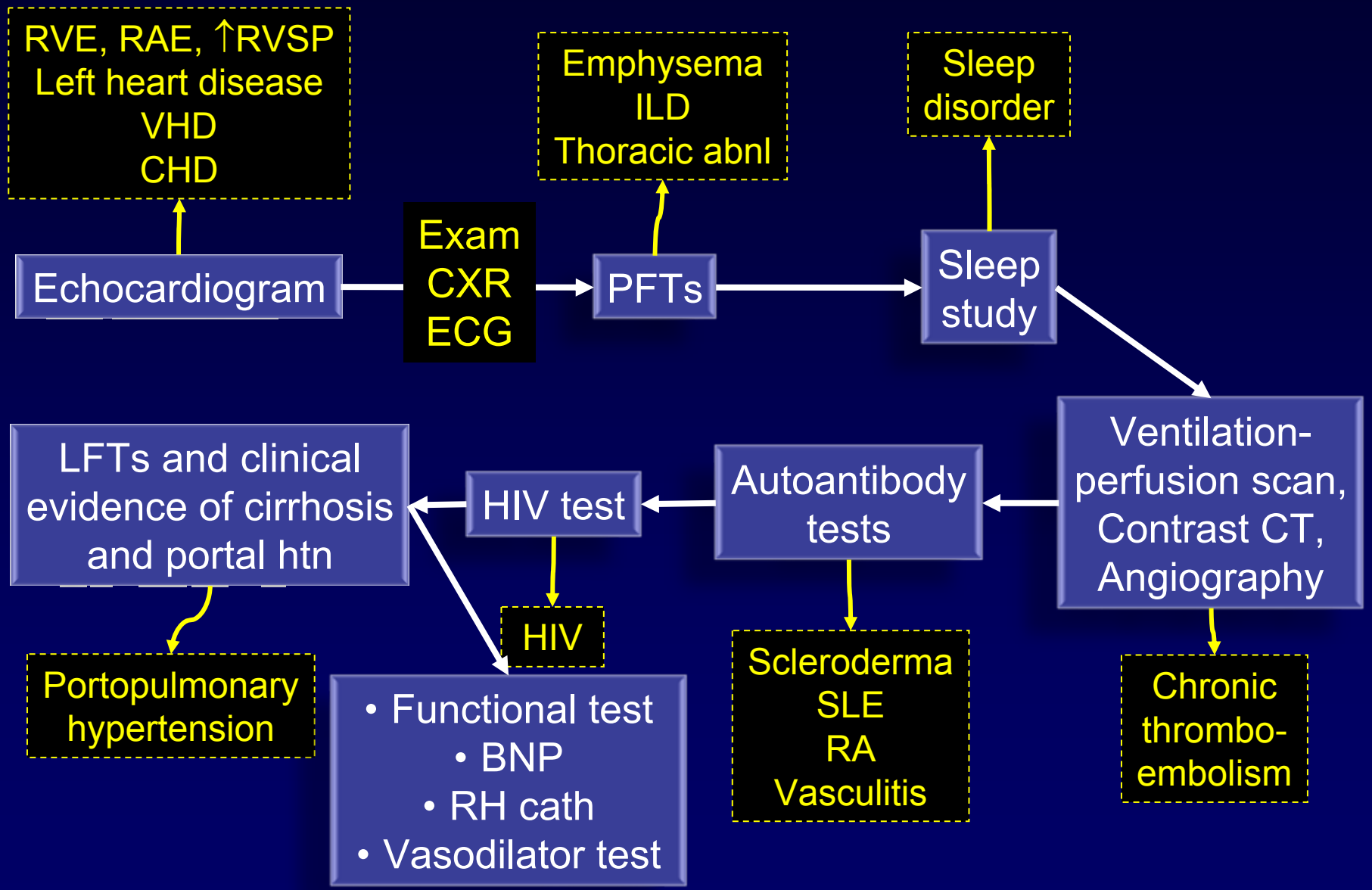
Normal sinus rhythm
Incomplete right bundle branch block
Right ventricular hypertrophy
Prolonged QT
Abnormal ECG



RQ: Labs

- ANA-negative
- Echo: nl LV Fn, RAE, RVE, RVSP 60, TEE—no shunt
- Spiral CT: no PE
- PFTs: nl volumes and flows, D2CO 81%
- 6MWD: 222 m, 99-96%

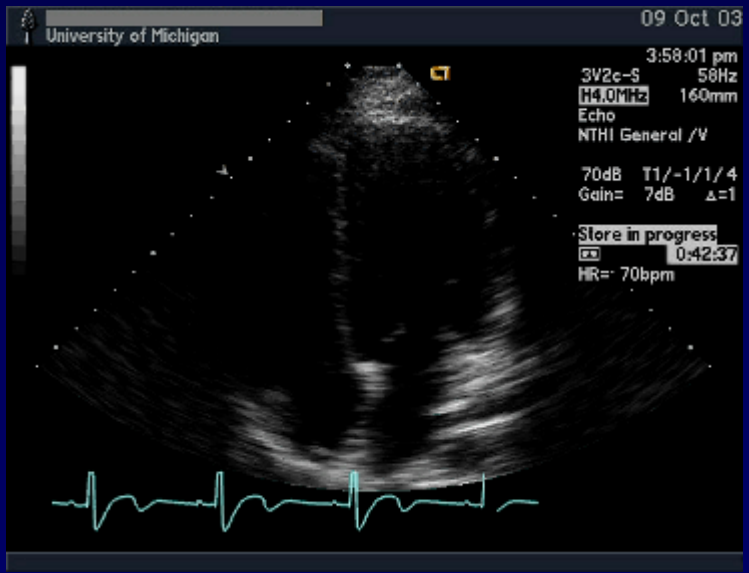
Diagnostic Approach



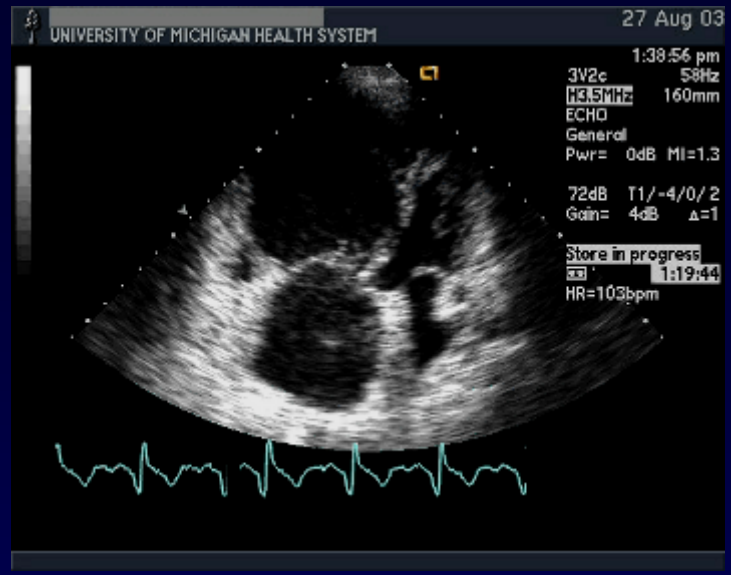
McLaughlin VV, McGoon Michael D. *Circulation.* 2006;114:1417-1431.

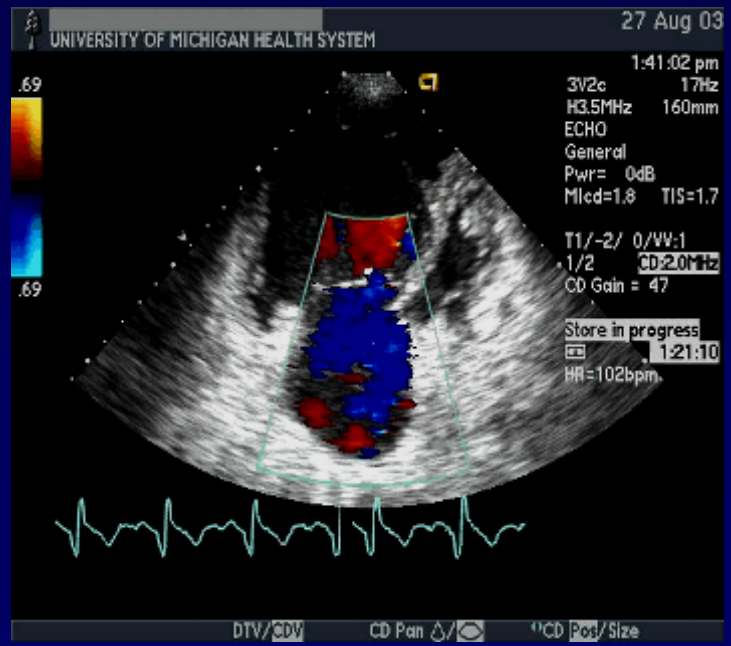
Echocardiogram

- Chamber size
- LV and RV systolic function
- LV diastolic function
- Valvular function
- TR
- Bubble study



Normal





Pulmonary Hypertension

Dana Point Definition of PH/PAH

PH

- Mean PAP ≥25 mm Hg

PAH

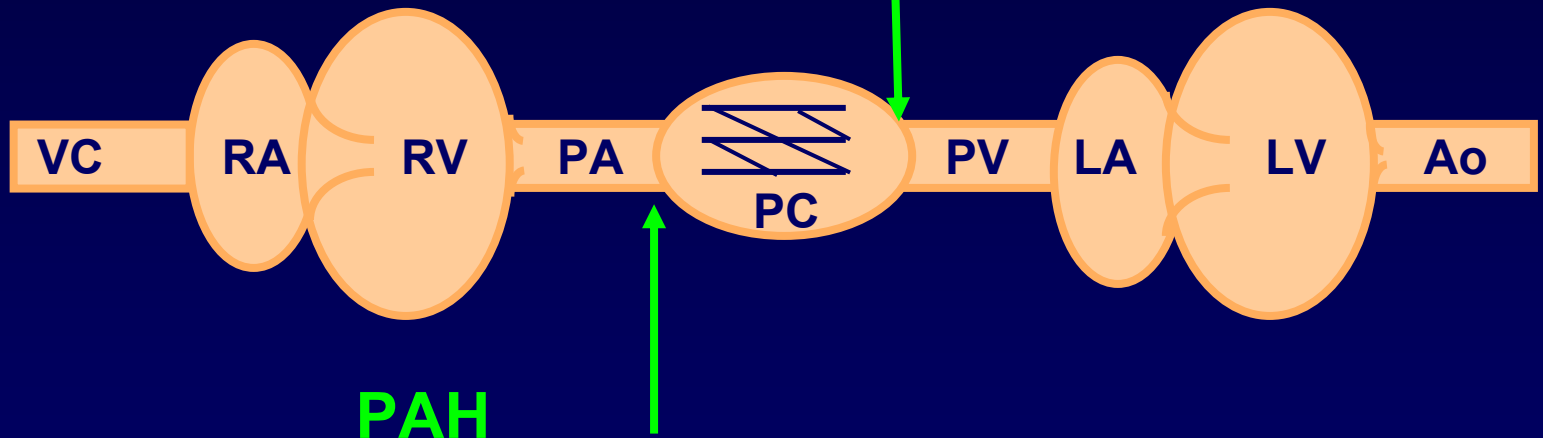
- Mean PAP ≥25 mm Hg plus PCWP/LVEDP ≤15 mm Hg

Badesch D et al. *J Am Coll Cardiol.* 2009;54:S55-S66.

PH: The Importance of Hemodynamics

Pulmonary venous hypertension

Elevated PCWP, normal PVR



PAH

PH with respiratory disease

CTEPH

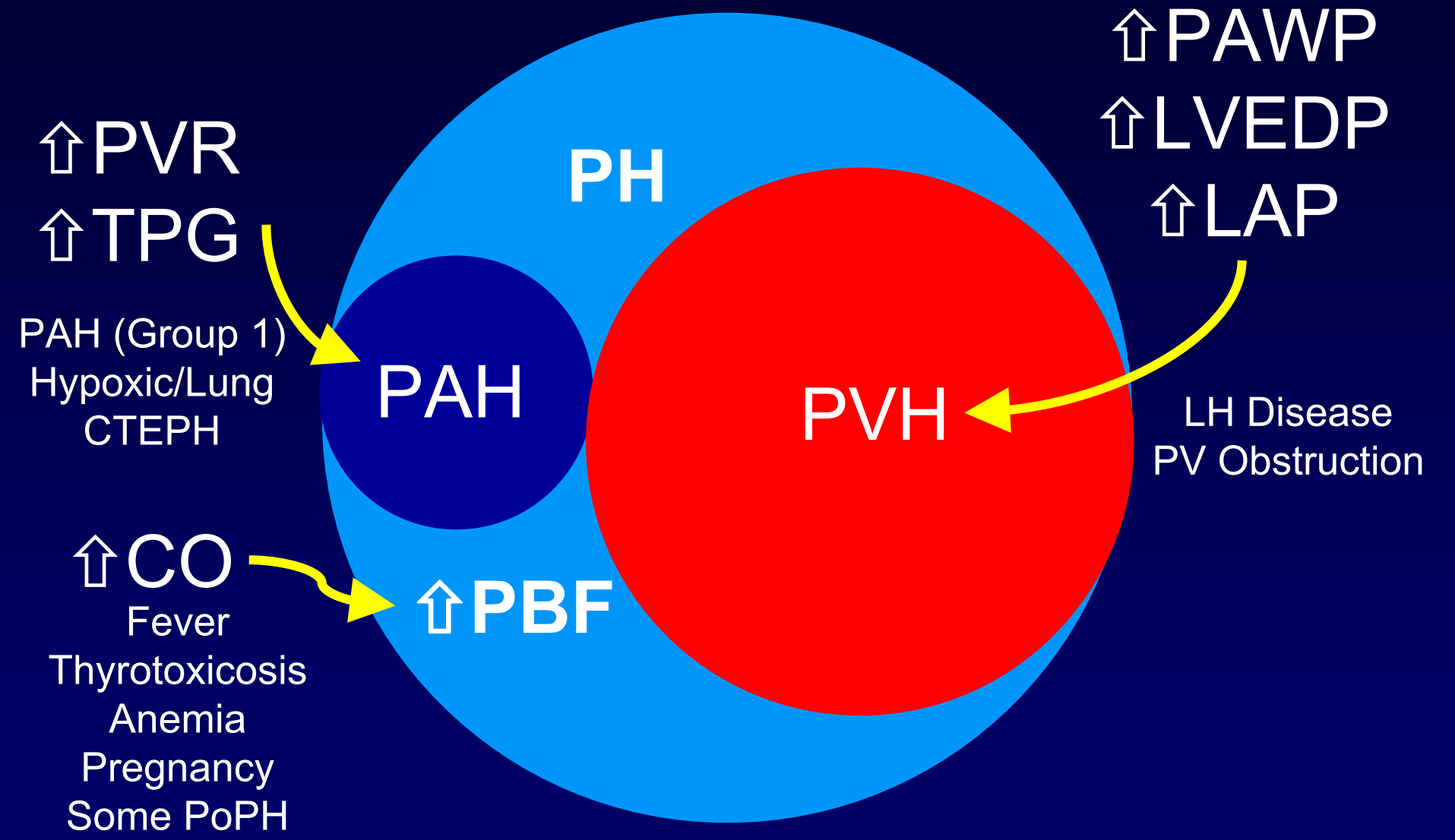
Normal PCWP, elevated PVR

Other:
High CO

RQ: Right Heart Cath

	1/29/07 Baseline	Nitric Oxide 20 ppm
RAP (mm Hg)	19	20
PAP (mm Hg)	93/40, mean 63	93/46, mean 64
Left ventricular EDP (mm Hg)	10	
Oxygen saturation (%) Pulmonary artery Femoral artery	 52.9 91.4	 58.3 91.7
Cardiac output / Cardiac index (L/min) Fick	2.5/1.3	2.88/1.52
PVR (Wood units) Fick	21.2	15.2

Importance of Right Heart Cath



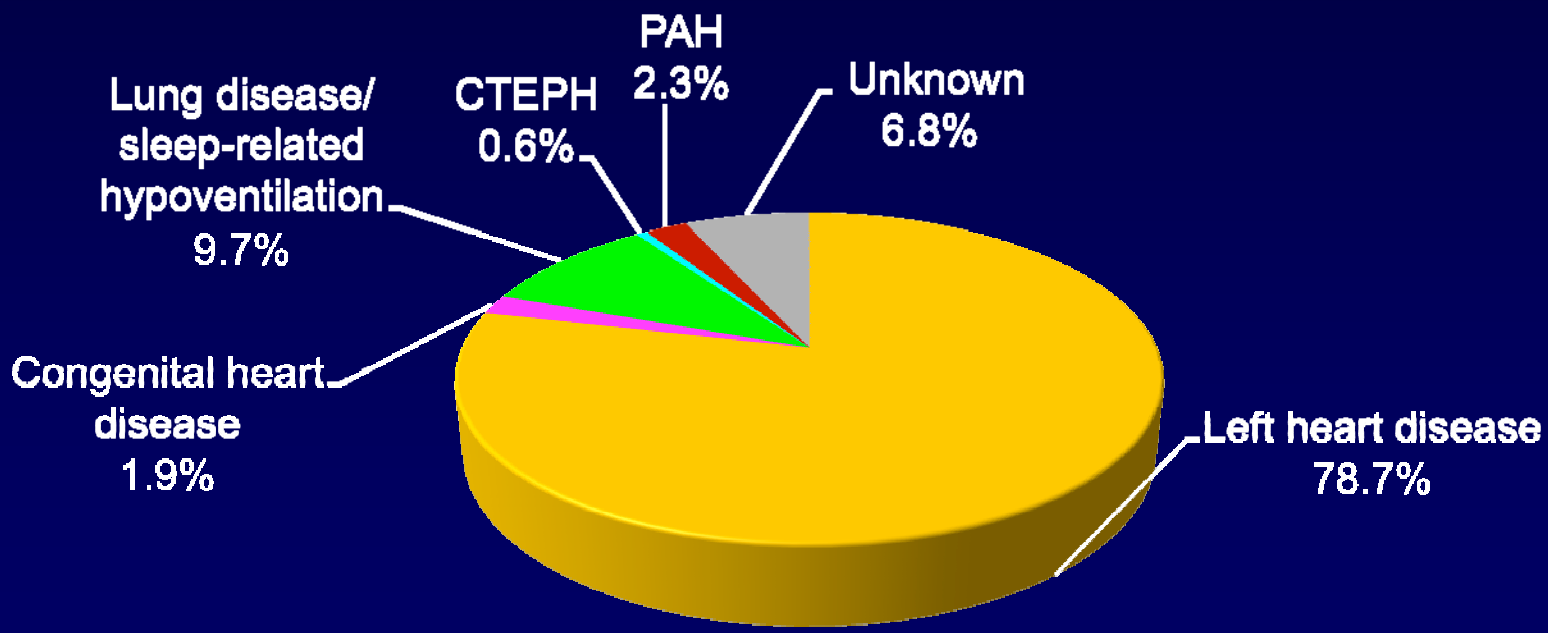
Cardiac Catheterization

- Exclude congenital heart disease
- Measure wedge pressure or LVEDP
- Establish severity and prognosis
- Test vasodilator therapy

Catheterization is required when pulmonary hypertension is suspected

PH by Echo ≠ PAH

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



N=483 of 4579 patients with echo PASP >40 mm Hg.
Gabbay E. *Am J Respir Crit Care Med*. 2007;175:A713.

Summary

- High index of suspicion
- Thorough diagnostic evaluation
- Exclude thromboembolic disease
- Evaluate potential causes/contributing issues
- Right heart catheterization required prior to initiating PAH therapy
- Baseline functional evaluation

RQ: Initial Management

- Admitted to U of M following cath
- IV diuresis
- IV epoprostenol initiation

RQ: Return Visit May 2007

- Significantly improved
- No limitations
- Functional Class I
- Meds
  - epoprostenol 30ng/kg/min
  - warfarin
  - furosemide 20 mg
  - KCL 10 mEq qd

RQ: Follow-up Physical Exam

- HR 80; BP 103/59; Wt 144.8 lb
- JVP 6, carotid upstrokes nl
- Clear lungs
- Palpable RV heave, nl S, loud P_2, II/VI TR murmur
- No LE edema

RQ: 6MWD

- 222 m: 99-96% in January 2007
- 486 m: 99-97% in May 2007

RQ: Return Visit September 2007

- Continues to do well
- No limitations
- Functional Class I
- Meds
  - epoprostenol 39 ng/kg/min
  - warfarin
  - furosemide 20 mg MWF
  - KCL 10 mEq qd MWF

RQ: Physical Exam

- HR 84; BP 108/67; Wt 140.4 lb
- JVP 6, carotid upstrokes nl
- Clear lungs
- Palpable RV heave, nl S, loud P_2, II/VI TR murmur
- No LE edema

RQ: 6MWD

- 222 m: 99-96% in January
- 486 m: 99-97% in May
- 556 m: 99-97% in September

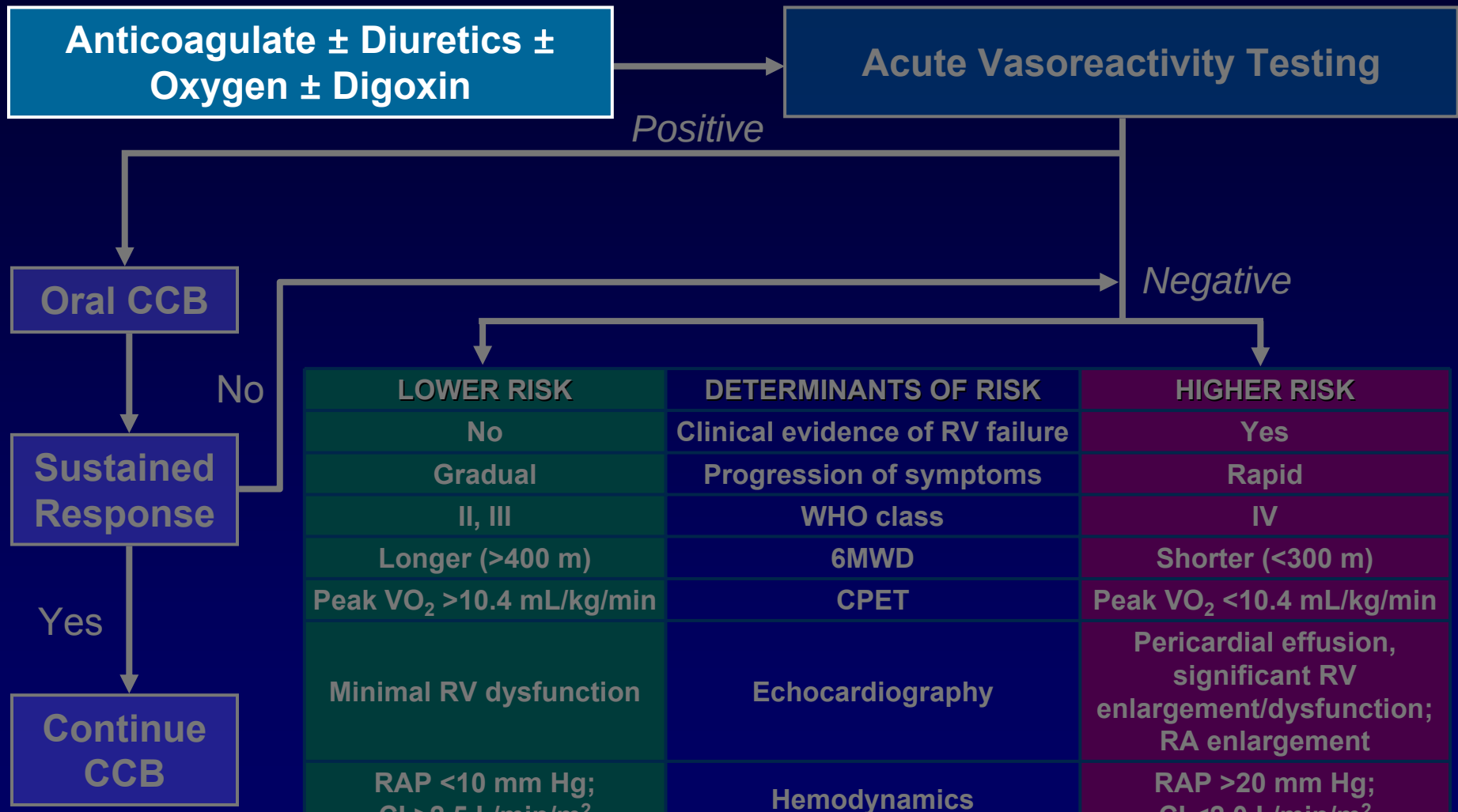
RQ: Subsequent Right Heart Cath

	1/29/07 Baseline	1/7/08 Epo 38 ng/kg/min
RAP (mm Hg)	19	2
PAP (mm Hg)	93/40, mean 63	65/24, mean 40
PCWP (mm Hg)	10	7
Oxygen saturation (%) Pulmonary artery Femoral artery	 52.9 91.4	 76.2 97
Cardiac Output / Cardiac Index (L/min) Fick	2.5/1.3	4.61/2.77
PVR (Wood Units) Fick	21.2	7.2
6MWD (m)	222	602
Functional class	IV	I

PAH Treatment Goals

- Fewer/less severe symptoms
- Improved exercise capacity
- Improved hemodynamics
- Prevention of clinical worsening
- Improved quality of life
- Improved survival

What Is the Optimal Treatment Strategy?



LOWER RISK	DETERMINANTS OF RISK	HIGHER RISK
No	Clinical evidence of RV failure	Yes
Gradual	Progression of symptoms	Rapid
II, III	WHO class	IV
Longer (>400 m)	6MWD	Shorter (<300 m)
Peak VO_2 >10.4 mL/kg/min	CPET	Peak VO_2 <10.4 mL/kg/min
Minimal RV dysfunction	Echocardiography	Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement
RAP <10 mm Hg; CI >2.5 L/min/m^2	Hemodynamics	RAP >20 mm Hg; CI <2.0 L/min/m^2
Minimally elevated	BNP	Significantly elevated

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

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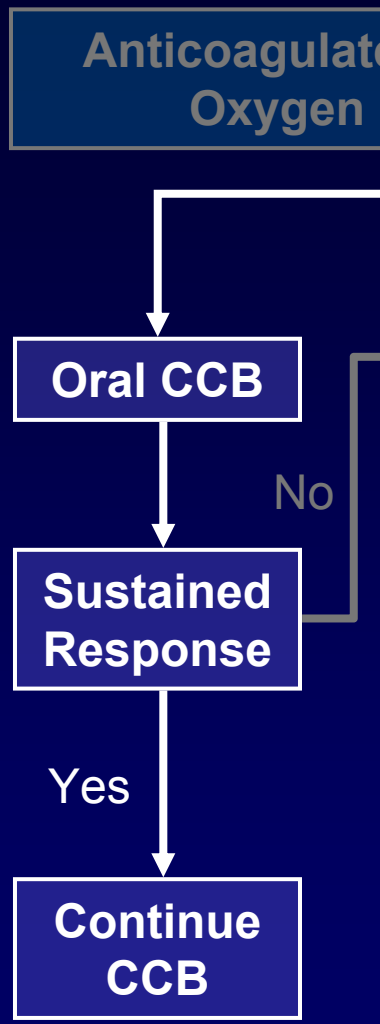

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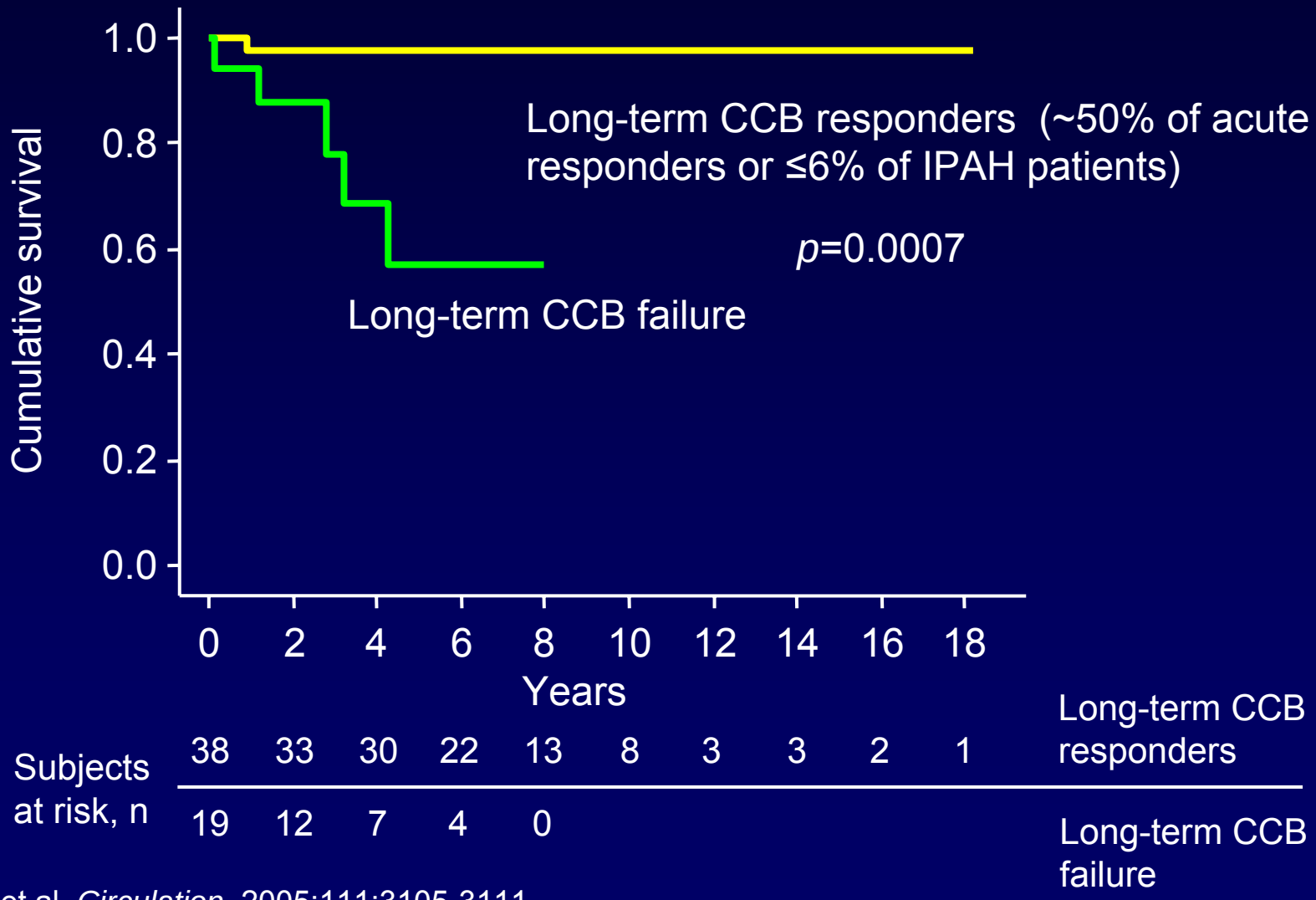
Survival in IPAH
Long-term CCB Responders



Sitbon O et al. *Circulation.* 2005;111:3105-3111.

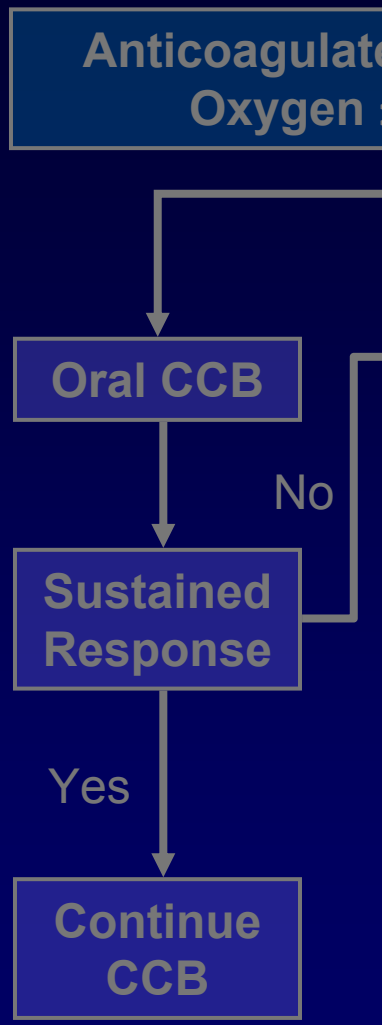
Calcium Channel Blockers Only If "Vasodilator Responsive"

"Vasodilator Response"

- Fall in mPAP ≥10 mm Hg
- + PAPm (absolute) <40 mm Hg
- + Normal CO

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

What Is the Optimal Treatment Strategy?



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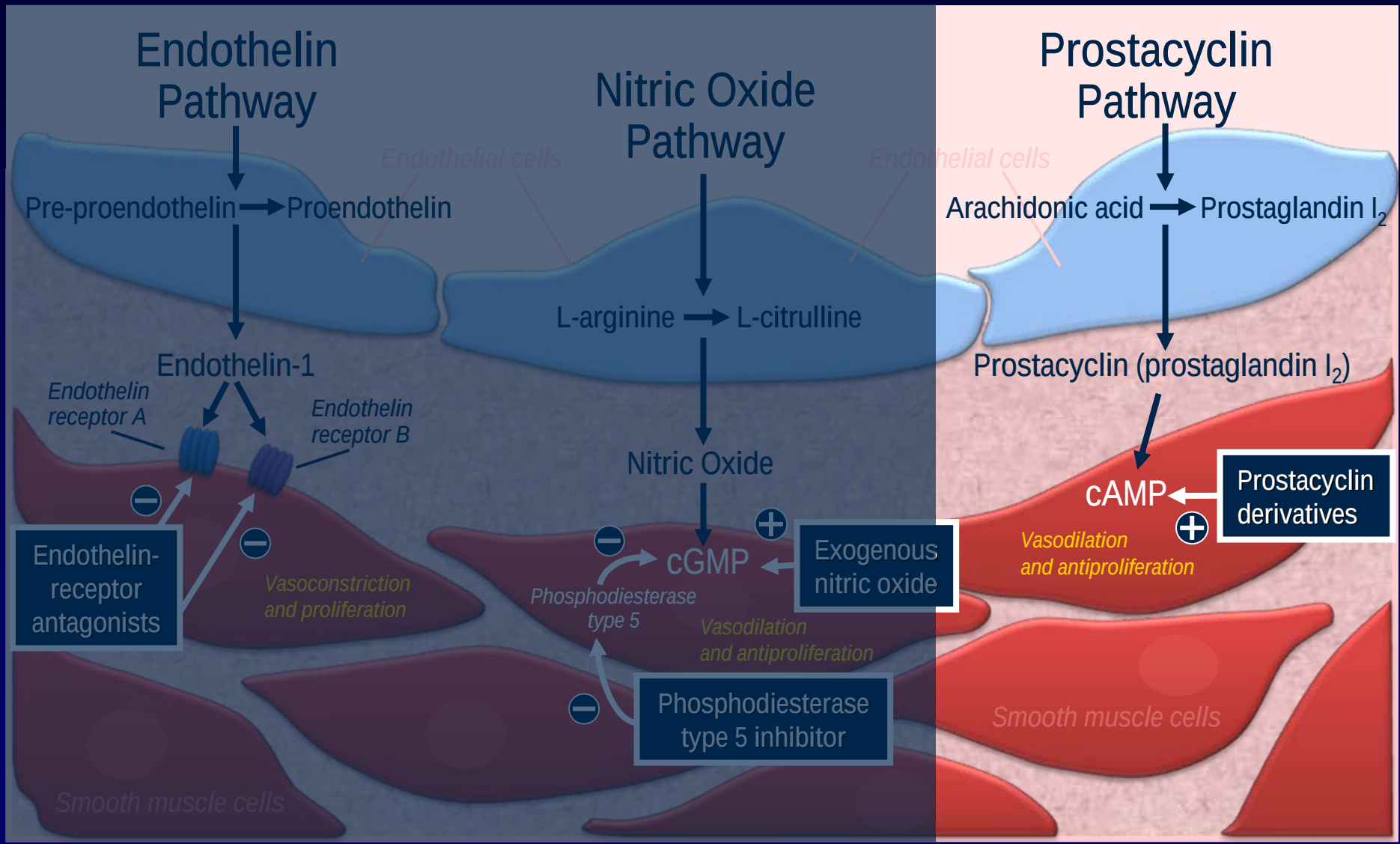
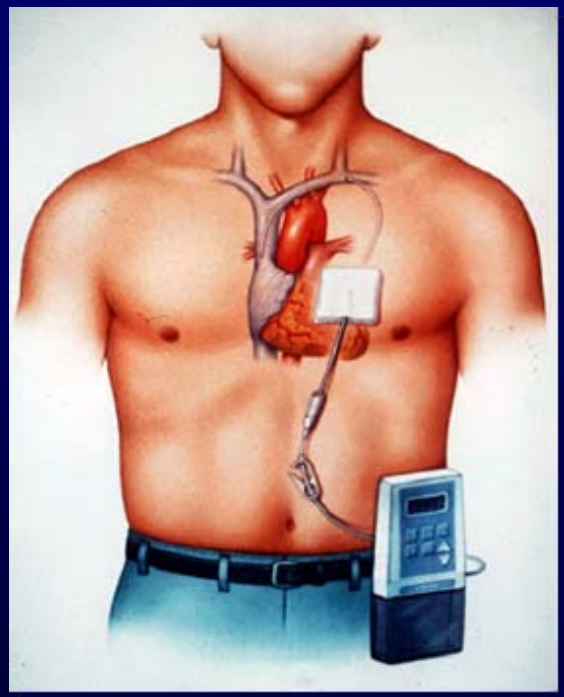
Approved Therapeutic Targets

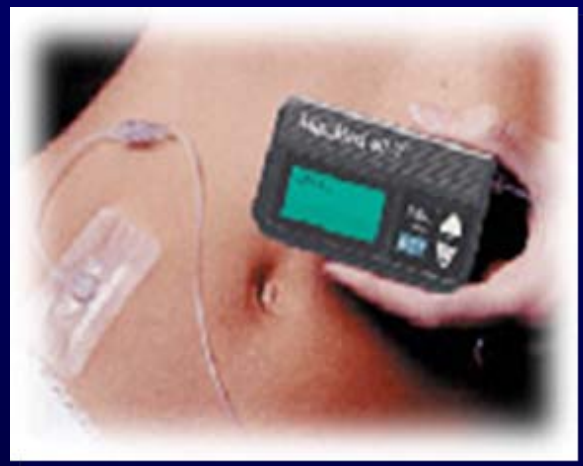


Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

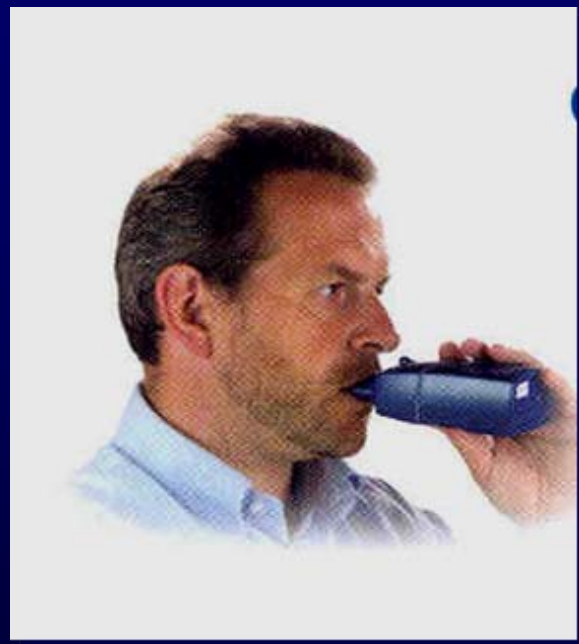
Prostacyclin Analogues: Intravenous, Subcutaneous, or Inhaled



Epoprostenol (Flolan®)
Treprostinil (Remodulin®)

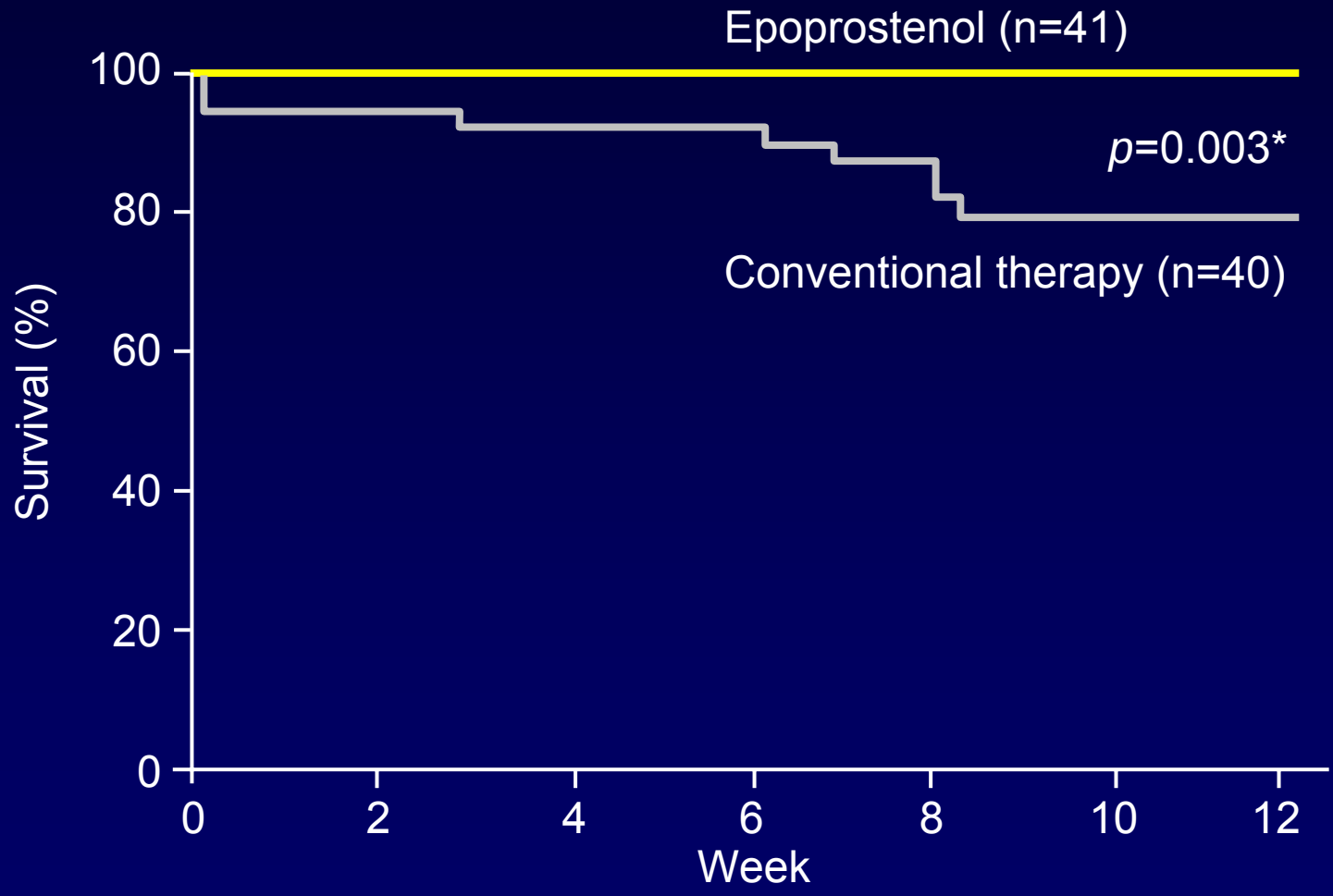


Treprostinil
(Remodulin®)



Iloprost (Ventavis®)
Treprostinil (Tyvaso®)

Survival Among Patients With IPAH: Epoprostenol vs Conventional Therapy



*Two-sided, by log-rank test.

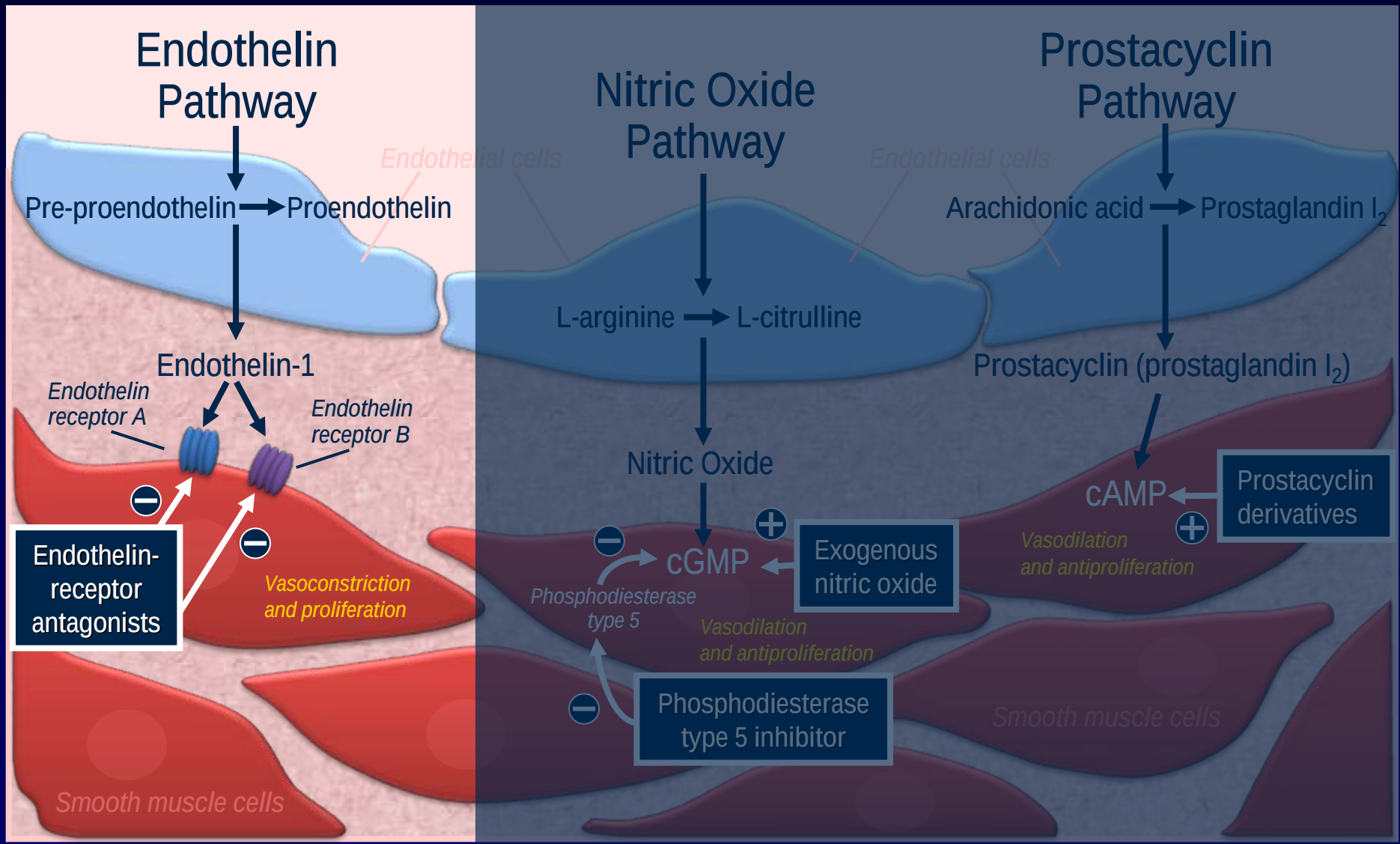
Barst RJ et al for the PPH Study Group. *N Engl J Med*. 1996;334:296-301.

Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension
- Dizziness
- Syncope
- Cough (inhaled)
- Delivery site complications

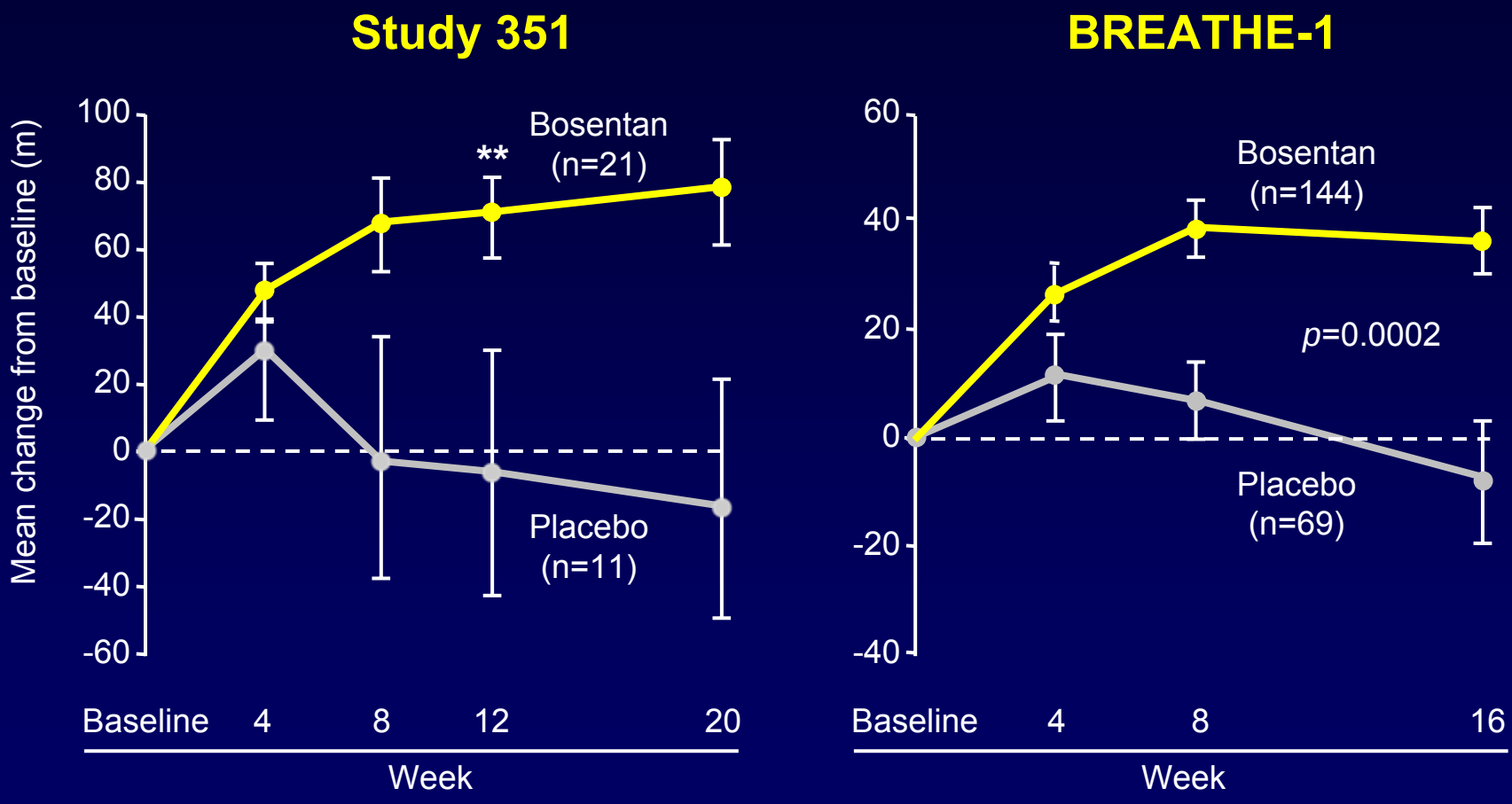
Vary according to drug and route of delivery

Approved Therapeutic Targets



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

Bosentan*: 6-MWD (351 and BREATHE-1)



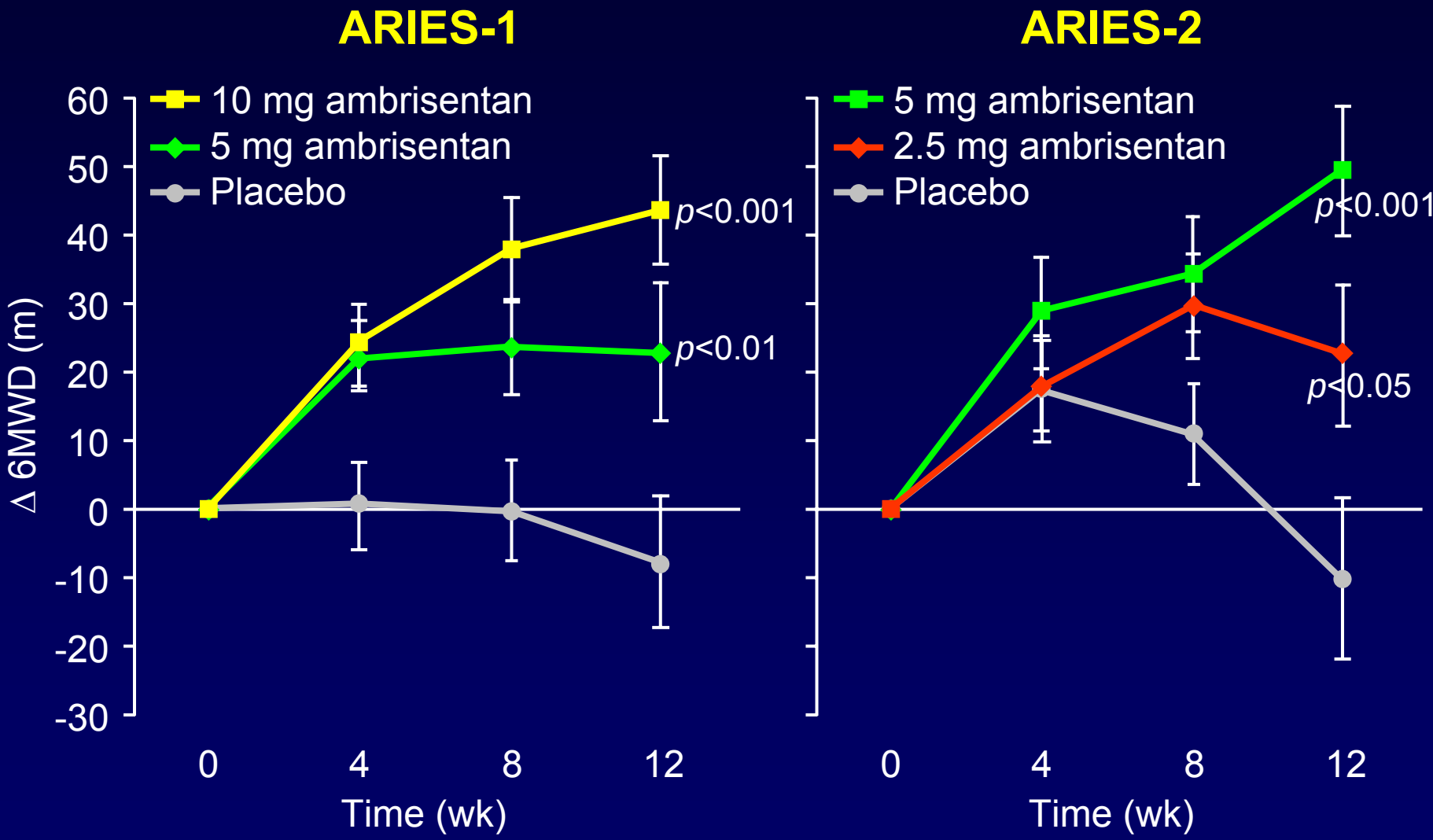
*Tracleer®

**$p<0.05$ vs baseline; $p=0.021$ vs placebo. Values are mean±SEM.

Channick RN et al. *Lancet.* 2001;358:1119-1123.

Rubin LJ et al. *N Engl J Med*. 2002;346;896-903.

Ambrisentan* in PAH: 6MWD (ARIES)



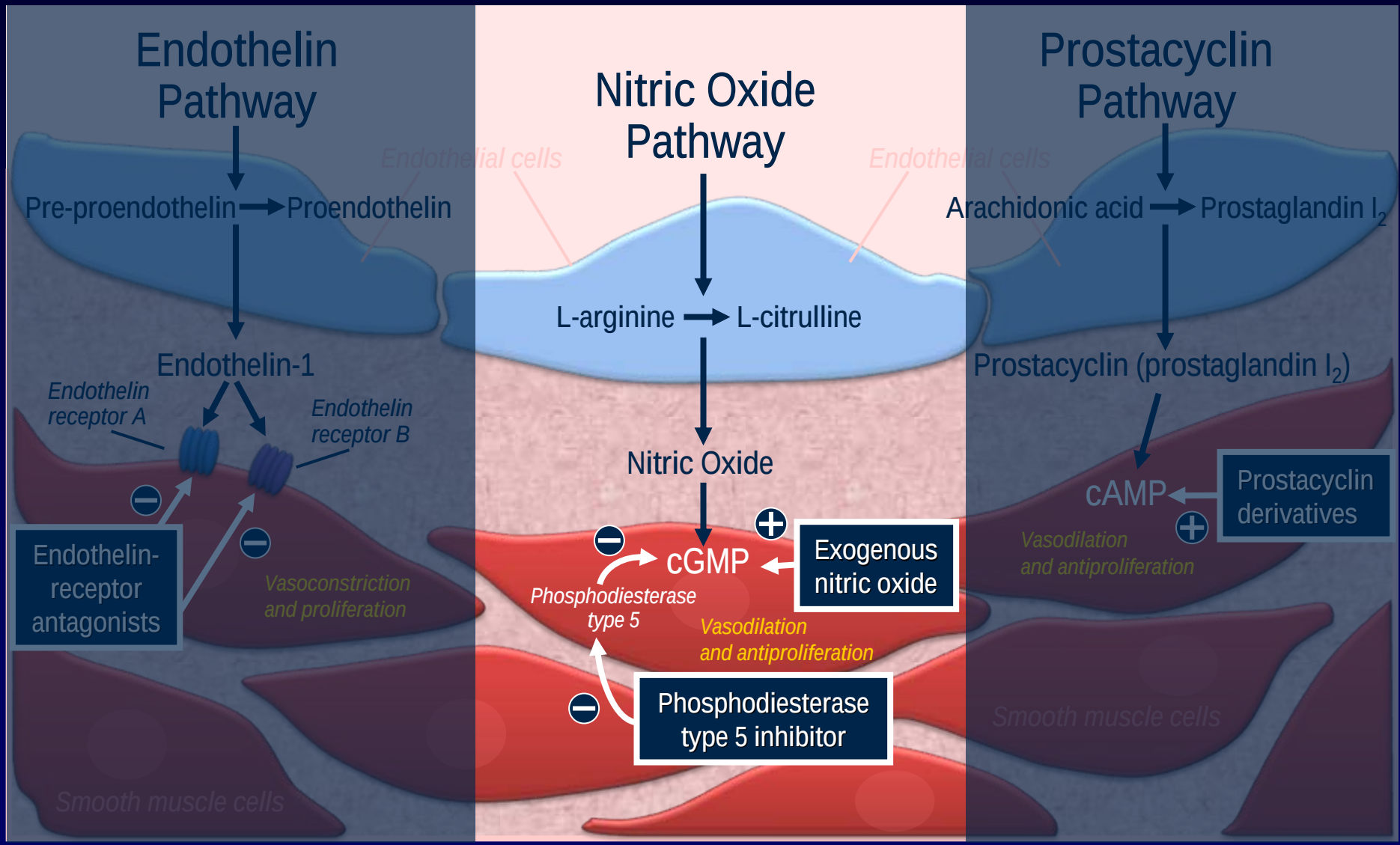
*Letairis® *p*-values are vs placebo.

Galiè N et al. *Circulation.* 2008;117:3010-3019.

Endothelin Receptor Antagonists: Side Effects

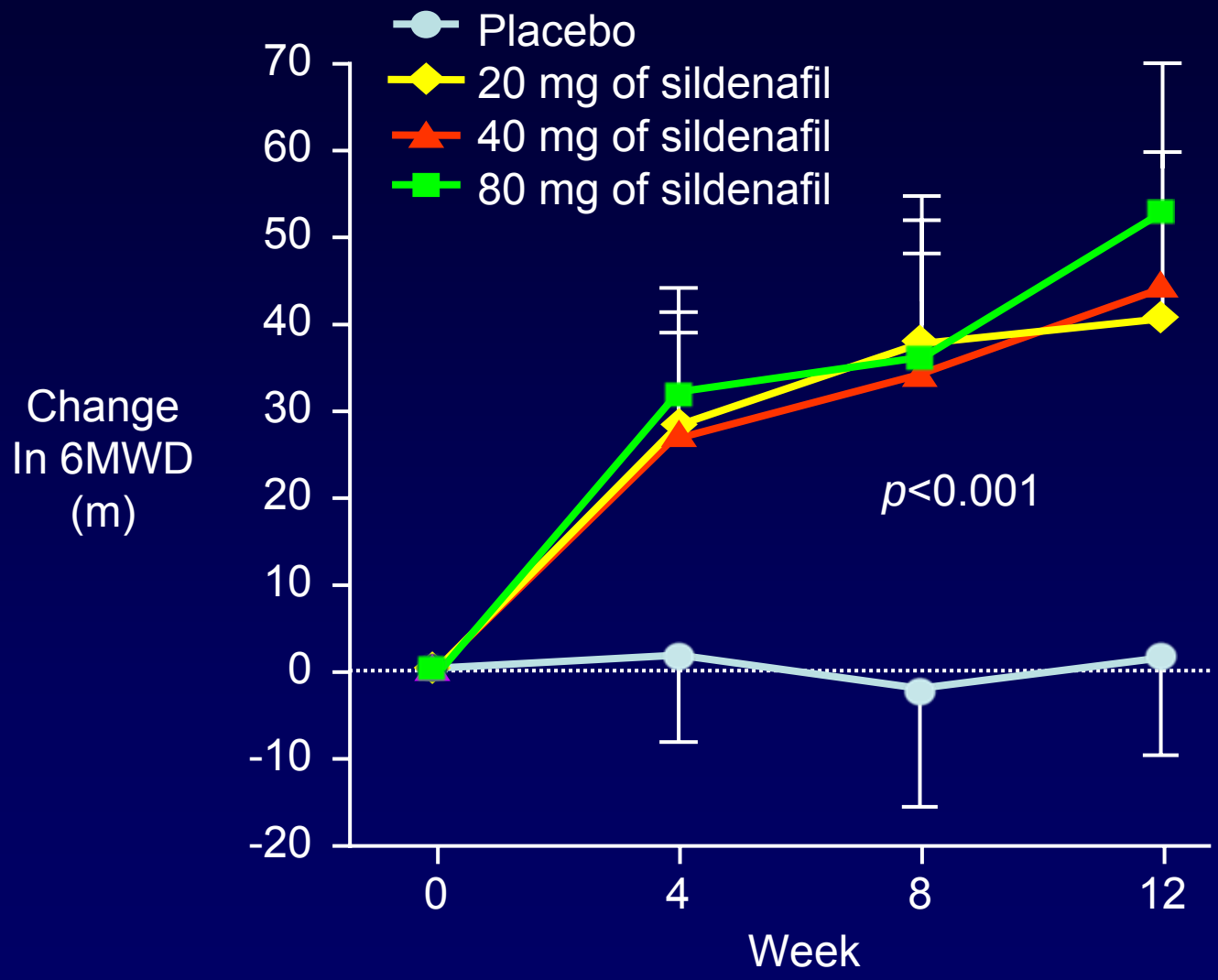
- Nasal congestion
- Abnormal hepatic function
  - reversible transaminase elevations >3X ULN
  - may require dose adjustments or discontinuations
  - monthly LFTs required
- Edema
  - lower extremity edema may require diuretic adjustment
- Use requires dual contraceptive methods (hormonal plus barrier)

Approved Therapeutic Targets



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

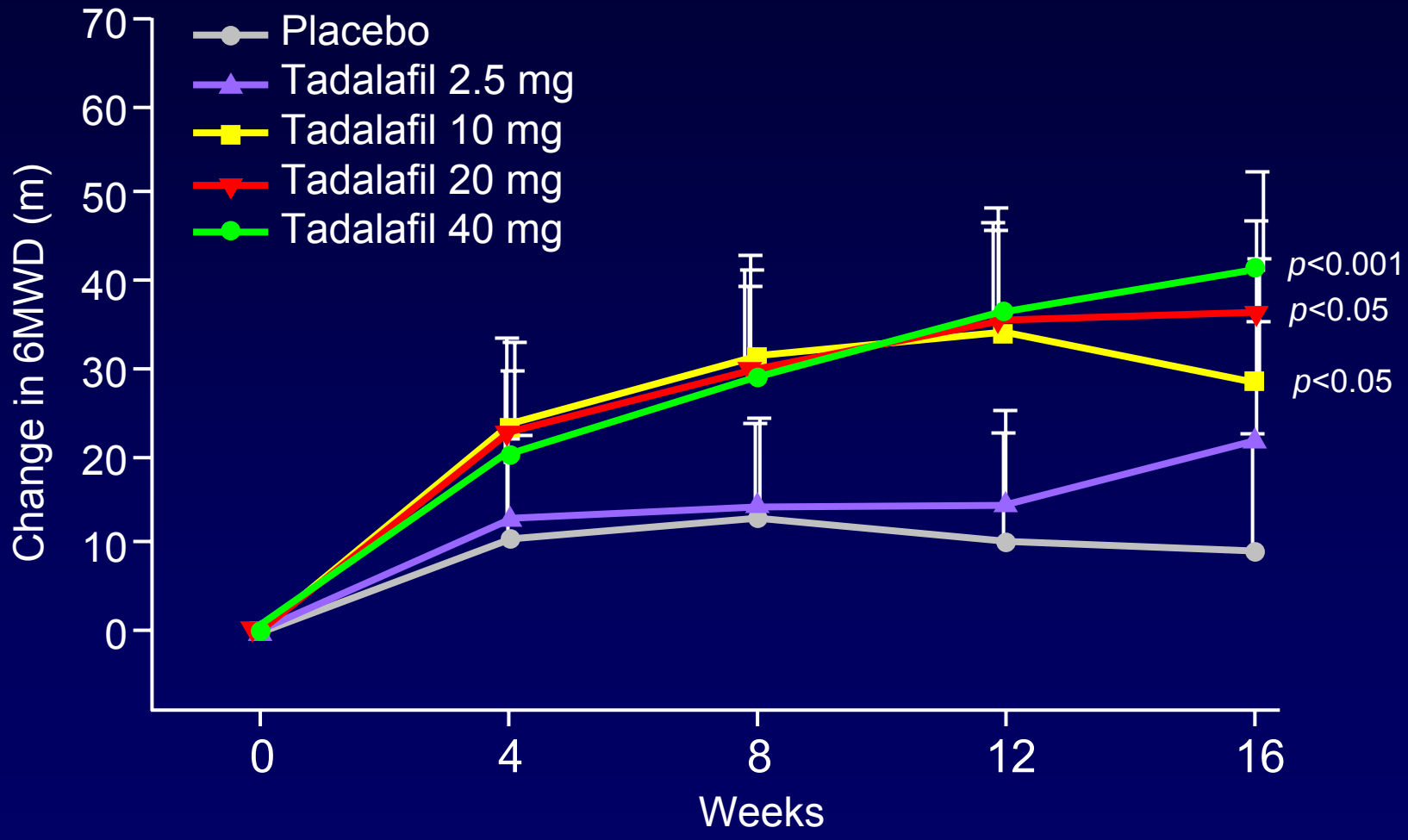
Effect of Sildenafil* on 6MWD (SUPER)



*Revatio®

Galiè N et al. *N Engl J Med*. 2005;353:2148-2157.

Effect of Tadalafil* on 6MWD (PHIRST)



*Adcirca®

Galiè N et al. *Circulation.* 2009;119;2894-2903.

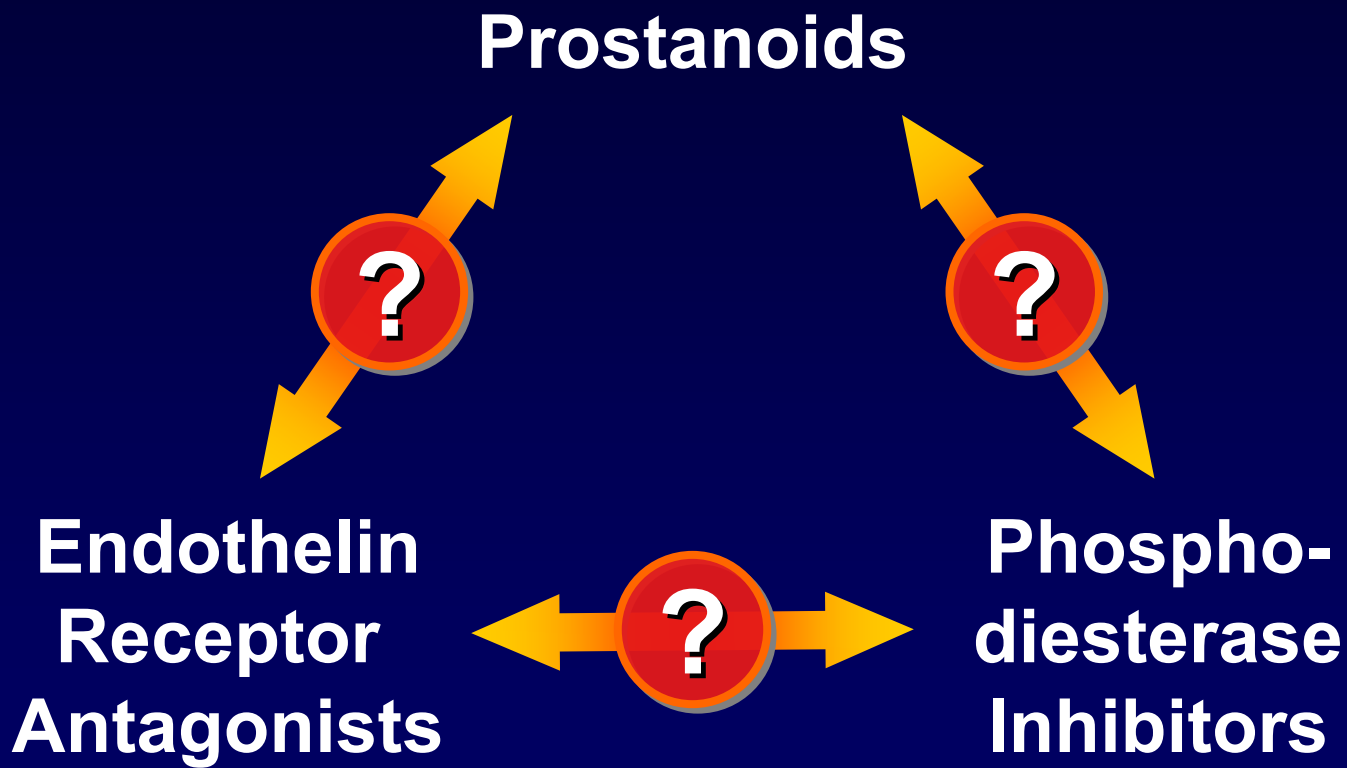
PDE-5 Side Effects

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

Treatment of PAH: Evidence-based Approach

- How is initial treatment chosen?
- When and how is treatment response assessed?
- When should treatments be changed or combined?

Combination Therapy



Combination Therapy: Other Ongoing or Recently Completed Clinical Trials

	Current therapy	Added therapy	Patients (*n*)	Study duration	Primary end point
FREEDOM-C	Bosentan and/ or sildenafil	Treprostinil oral	300	16 weeks	6MWD
AMBITION	Ambrisentan/ tadalafil/combo	Combo vs mono	300	Event-driven	Morbidity/mortality event
Pfizer	Bosentan	Sildenafil	106	12 weeks	6MWD
COMPASS-1	Bosentan	Sildenafil	45	Single dose	PVR
COMPASS-2	Sildenafil	Bosentan	250	Event-driven	Morbidity/mortality event
COMPASS-3	Bosentan	Sildenafil	100	16 weeks	6MWD
ATHENA-1	Sildenafil or tadalafil	Ambrisentan	40	24 weeks	PVR
SERAPHIN	Naïve/PDE-5/PGI/combo	Macitentan	742	Event-driven	Morbidity/mortality event
PATENT	Naïve/PGI/ERA	Riociguat	462	12 weeks	6MWD
IMPRES	≥2 current therapies	Imatinib	200	24 weeks	6MWD
ATPAHSS	Ambrisentan/ tadalafil/combo	Combo vs mono	63	36 weeks	RV mass/PVR
GRIPHON	ERA, PDE5 or both	Selexipag	670	Event-driven	Morbidity/mortality event
Novartis	Stable PAH therapy	Noilotinib	66	6 months	PVR

61-year-old Female

Presentation

- 61-yr-old female with a 3-yr history of progressively worsening dyspnea was referred because of PH noted on an echocardiogram
- She denied CP, LH, syncope, and LE edema
- Her symptoms had progressed to functional class III
  - she denied symptoms c/w OSA
- PMH: systemic hypertension and diabetes, 3 uncomplicated deliveries
- Current medications were verapamil 240 mg bid and atenolol 25 mg qd
- SH: no tobacco, alcohol, or illicits
- FH: noncontributory

Physical Exam

- Height: 5' 4"
- Weight: 180 lb
- BP: 150/90 mm Hg; normal JVP;
  normal carotid pulse
- Clear lungs
- Palpable RV tap, loud S2, RS4, II/VI TRM,
  no LE edema

Test Results

- ECG: NSR, normal axis
- V/Q: normal
- Echo: normal LV systolic function, normal RV size, ↑ PAP
- PFTs: slight restriction
- ANA and HIV-negative

What Is the Next Step?

A. Initiate therapy with an ERA
B. Initiate therapy with a PDE-5 inhibitor
C. Right heart catheterization
D. Repeat echo in 6 months

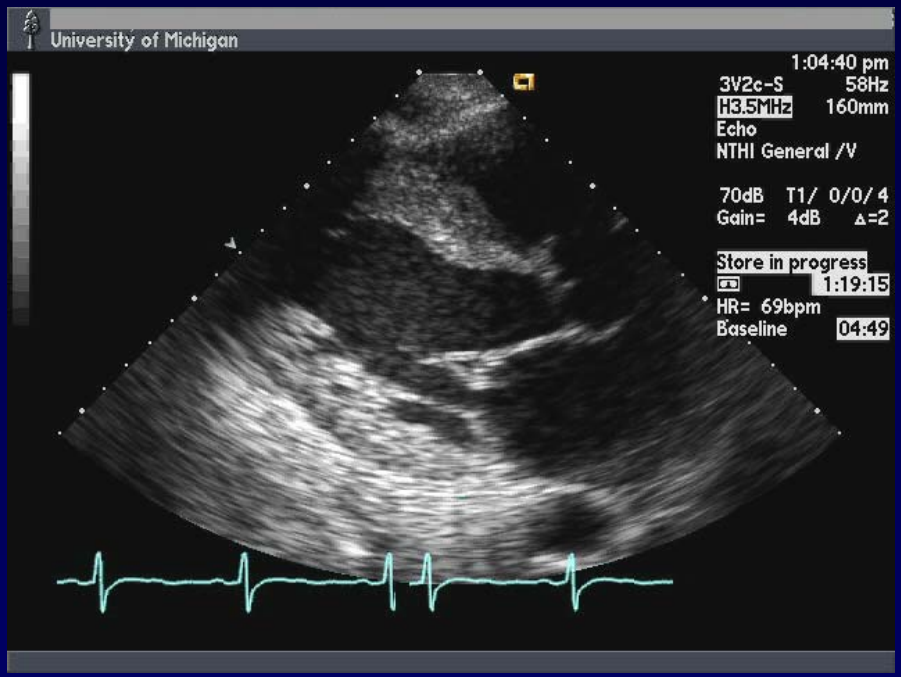
What Is Highest on Your Differential?

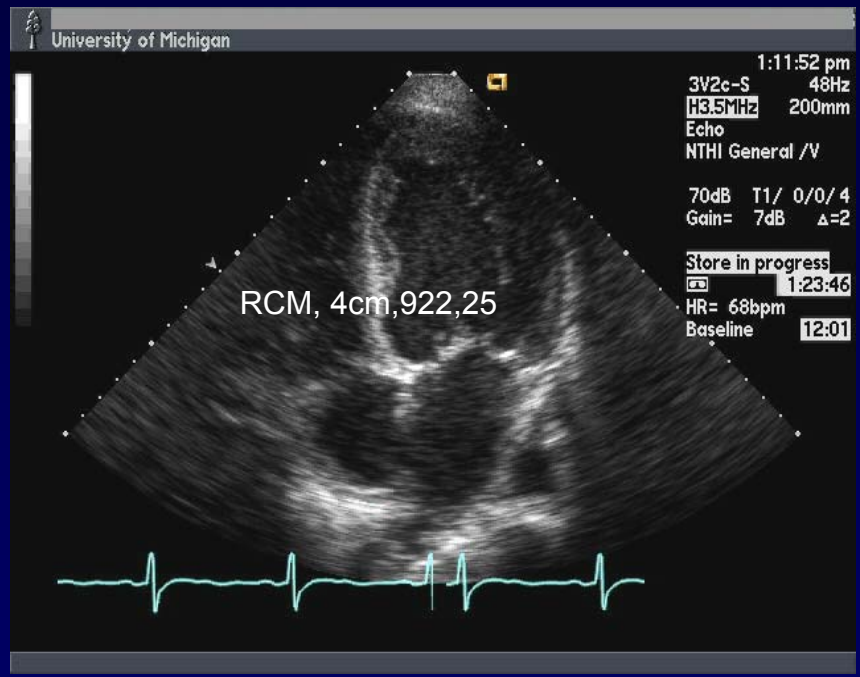
- Idiopathic PAH
- Diastolic dysfunction
- Chronic thromboembolic PH
- An ASD

Test Results

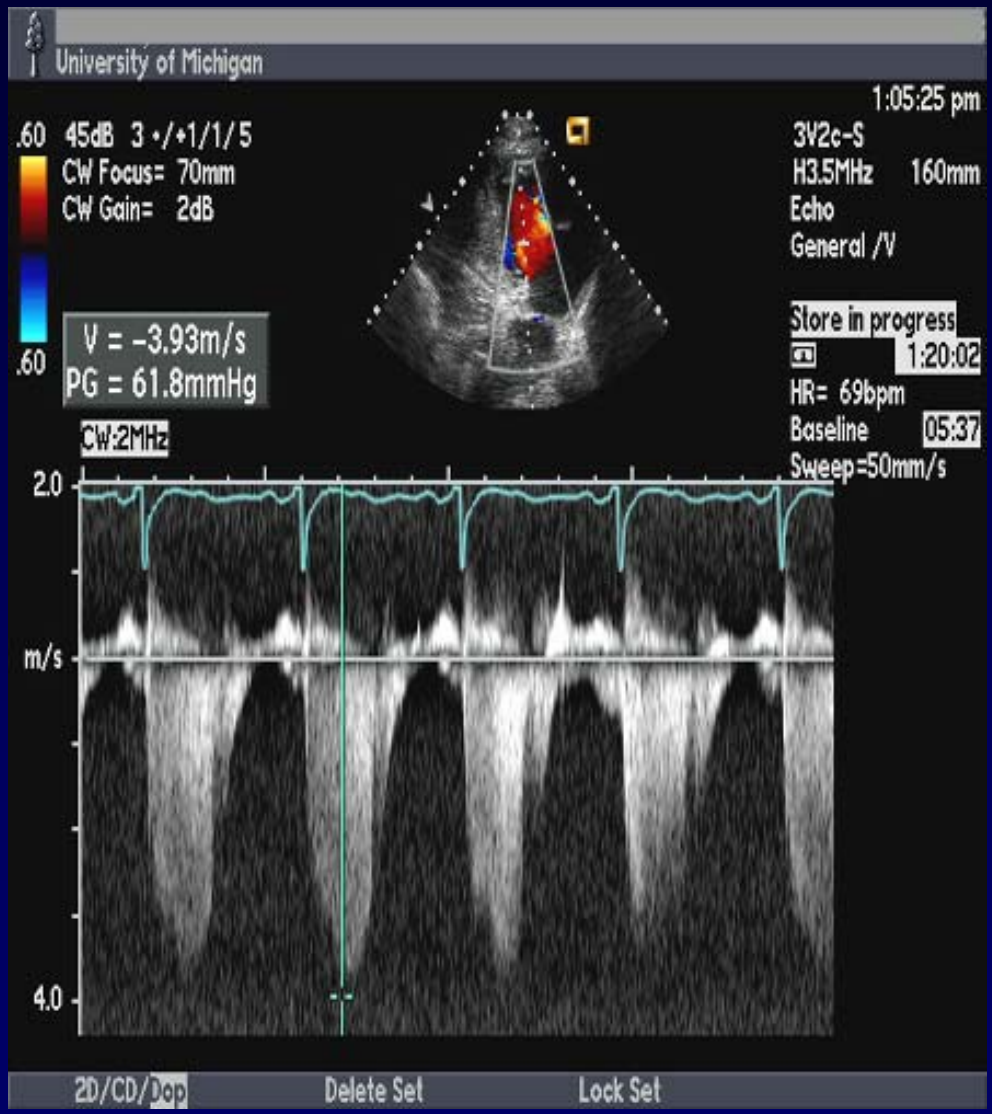
	Baseline	Nipride (2.0)
PA	80/28 50	44/15 24
Ao	205/95 138	165/72 98
RA	8	5
PCWP	28	7
LVEDP	29	—
CO	4.28	5.45
CI	2.38	3.03
Ao Sat	95	92
PA Sat	68	71
PVR	5.14	3.11

LVH/Diastolic Dysfunction

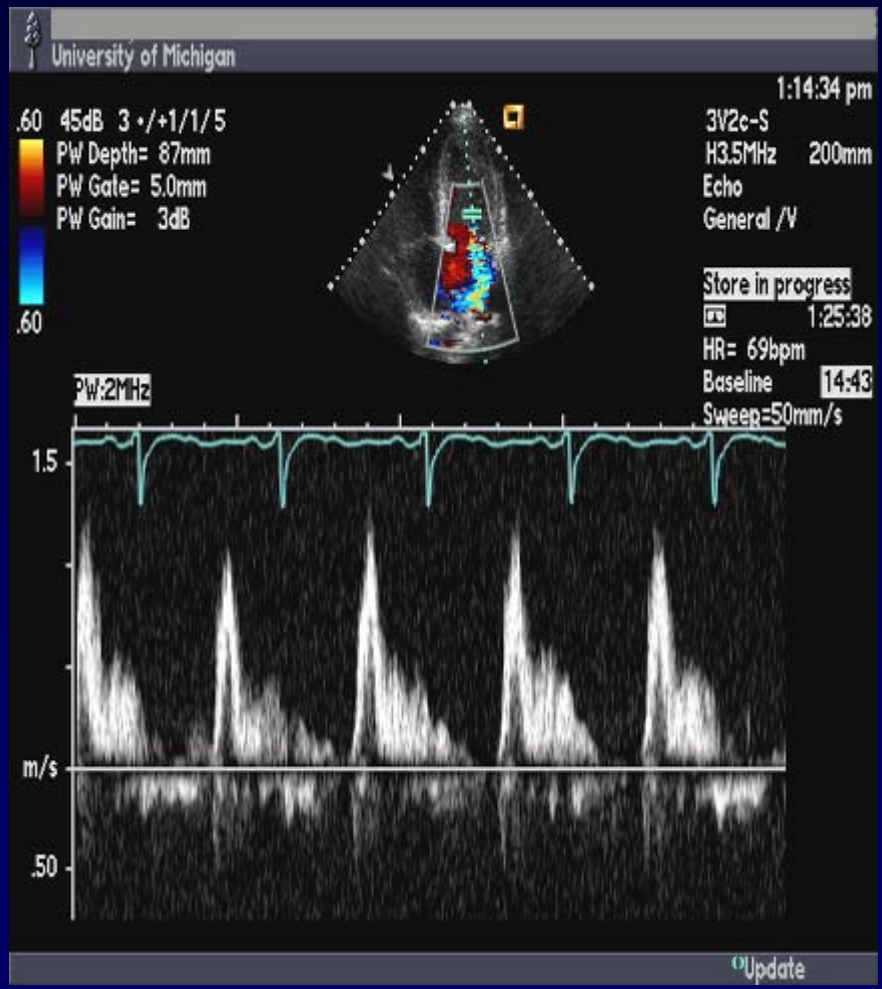


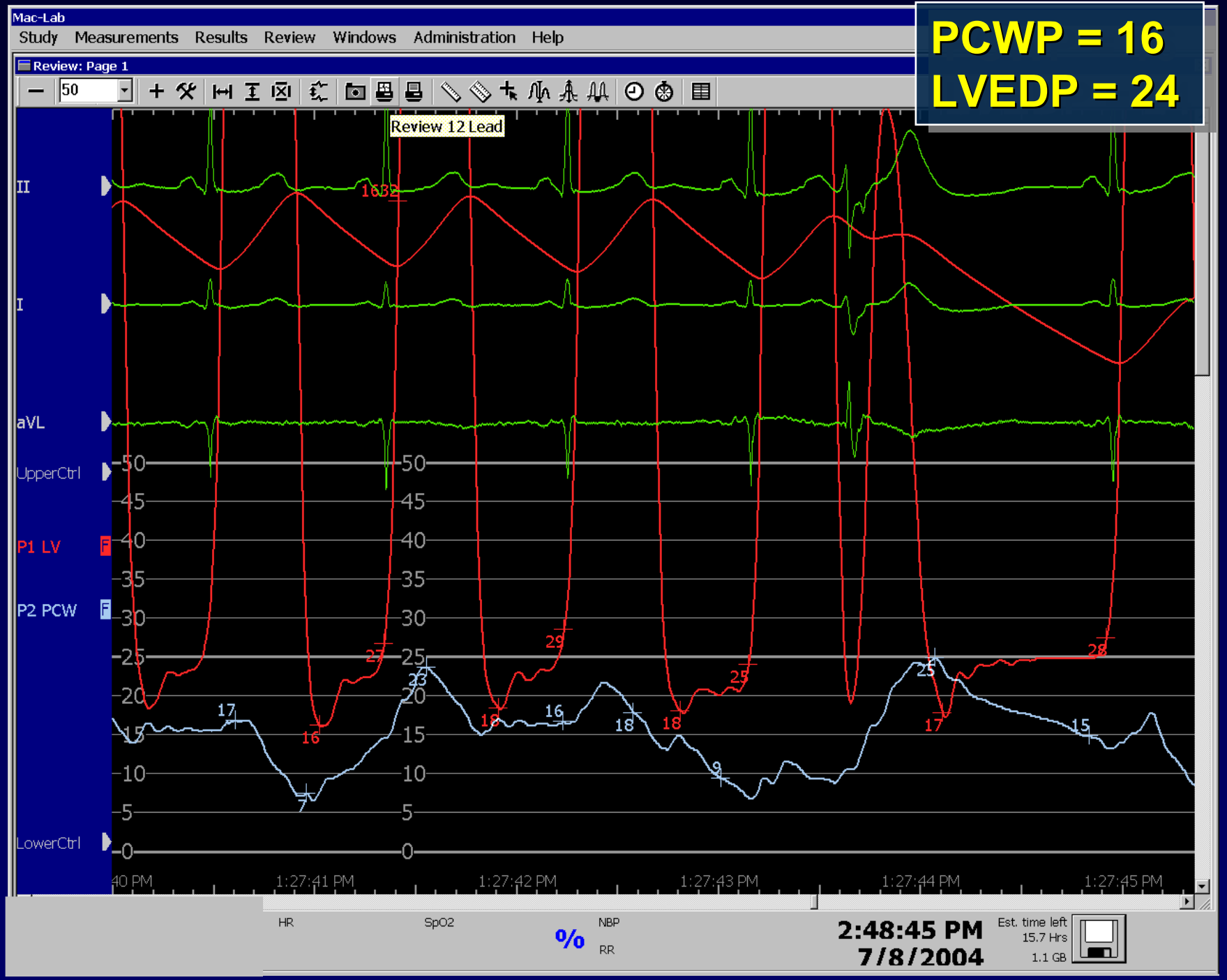


LVH/Diastolic Dysfunction



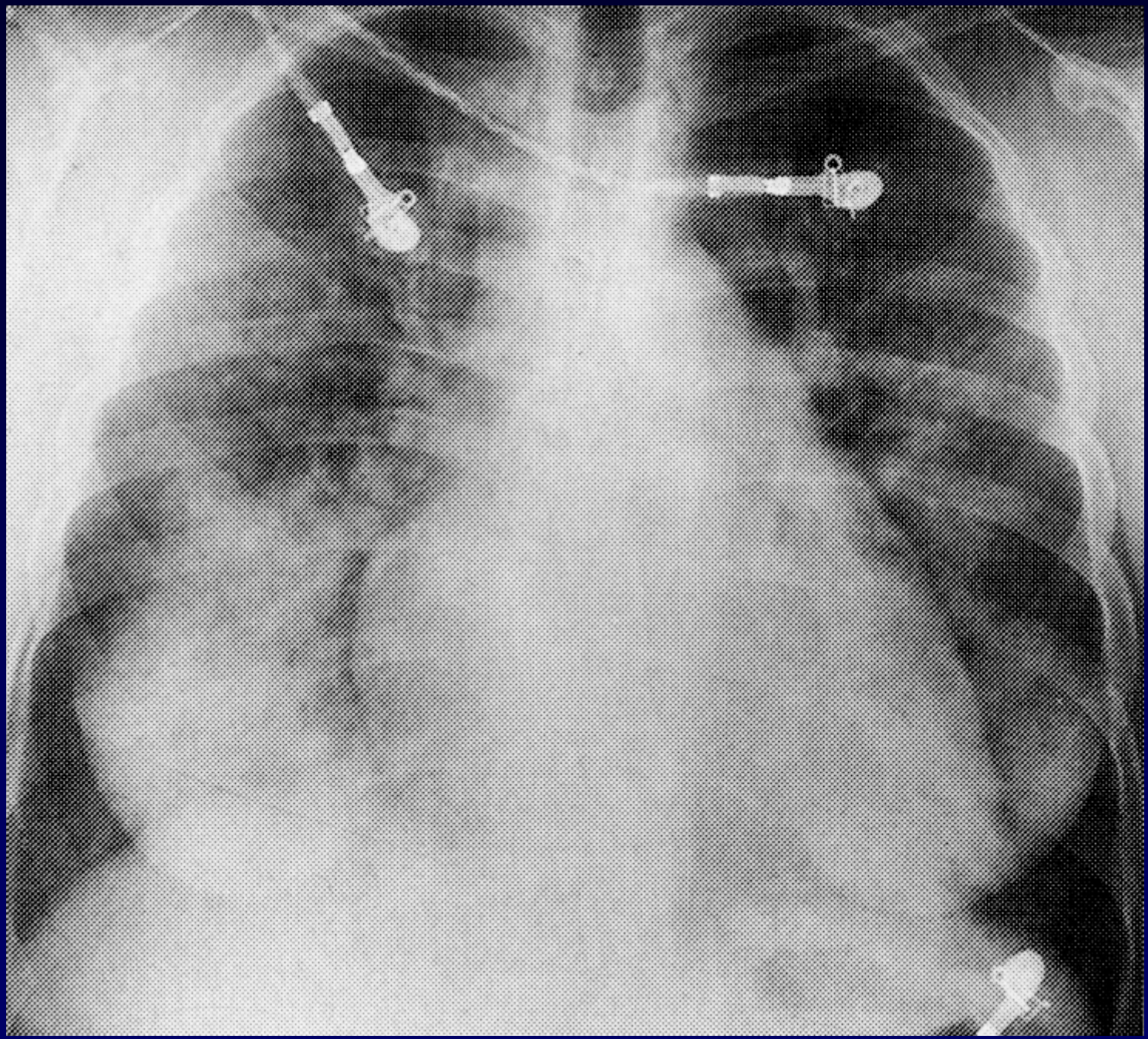
Mitral Inflow: Grade 3 Diastolic Dysfunction




Mac-Lab
Study Measurements Results Review Windows Administration Help
Review: Page 1
Review 12 Lead
PCWP = 16
LVEDP = 24
II
I
aVL
UpperCtrl
P1 LV
P2 PCW
LowerCtrl
1:27:41 PM
1:27:42 PM
1:27:43 PM
1:27:44 PM
1:27:45 PM
HR
SpO2
%
NBP
RR
2:48:45 PM
7/8/2004
Est. time left
15.7 Hrs
1.1 GB

Follow-up

- Patient was referred back to primary MD with recommendations for BP control and fluid management
- Patient remained dyspneic and primary MD initiated therapy with IV epoprostenol



Hypertensive Heart Disease

- What are clinical clues that etiology of PH is on left side of heart?
- What is “pulmonary hypertension out of proportion to left heart disease”?
- How do you treat it? What if PA pressures are still high despite optimal treatment of BP?
- Is echo adequate for assessing left heart function?
- Is wedge pressure an adequate measure of left heart function?

50-year-old Caucasian Male

Presentation

- 50-yr-old white male with past medical history of hypertension presents with shortness of breath x 3 yr, worsening; outside echo: PH
- Patient had episode of “pneumonia” a few years ago and “never seemed to get over it”
- NYHA Class III
- No history of heart disease, DVT/PE, family history, drug use, CTD, sleep apnea Sx, or lung disease

Physical Examination

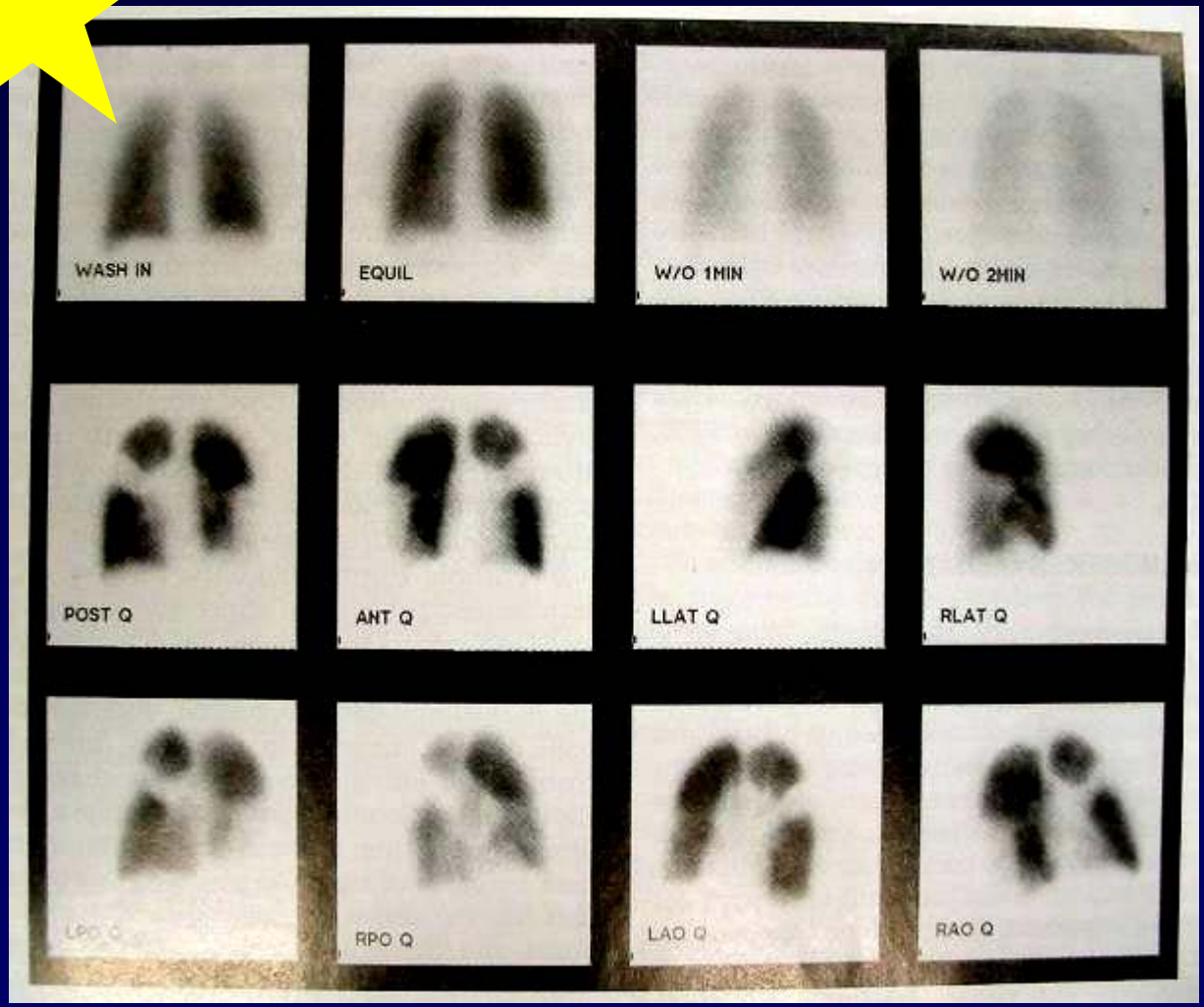
- BP 110/68; HR 86; RR 18; O_2 sat 94% on room air
- No JVD
- Lungs: no rales or wheezes
- Heart: loud P2, II/VI syst murmur LLSB
- 1-2+ edema, L > R

Initial Testing

- Echo: moderate RA/RV enlargement, PA syst 64 + CVP, neg bubble, normal LV size/function
- PFTs: mild restriction, DLCO 56% predicted
- CXR: cardiomegaly, no infiltrates

What Next?

V/Q vs CT

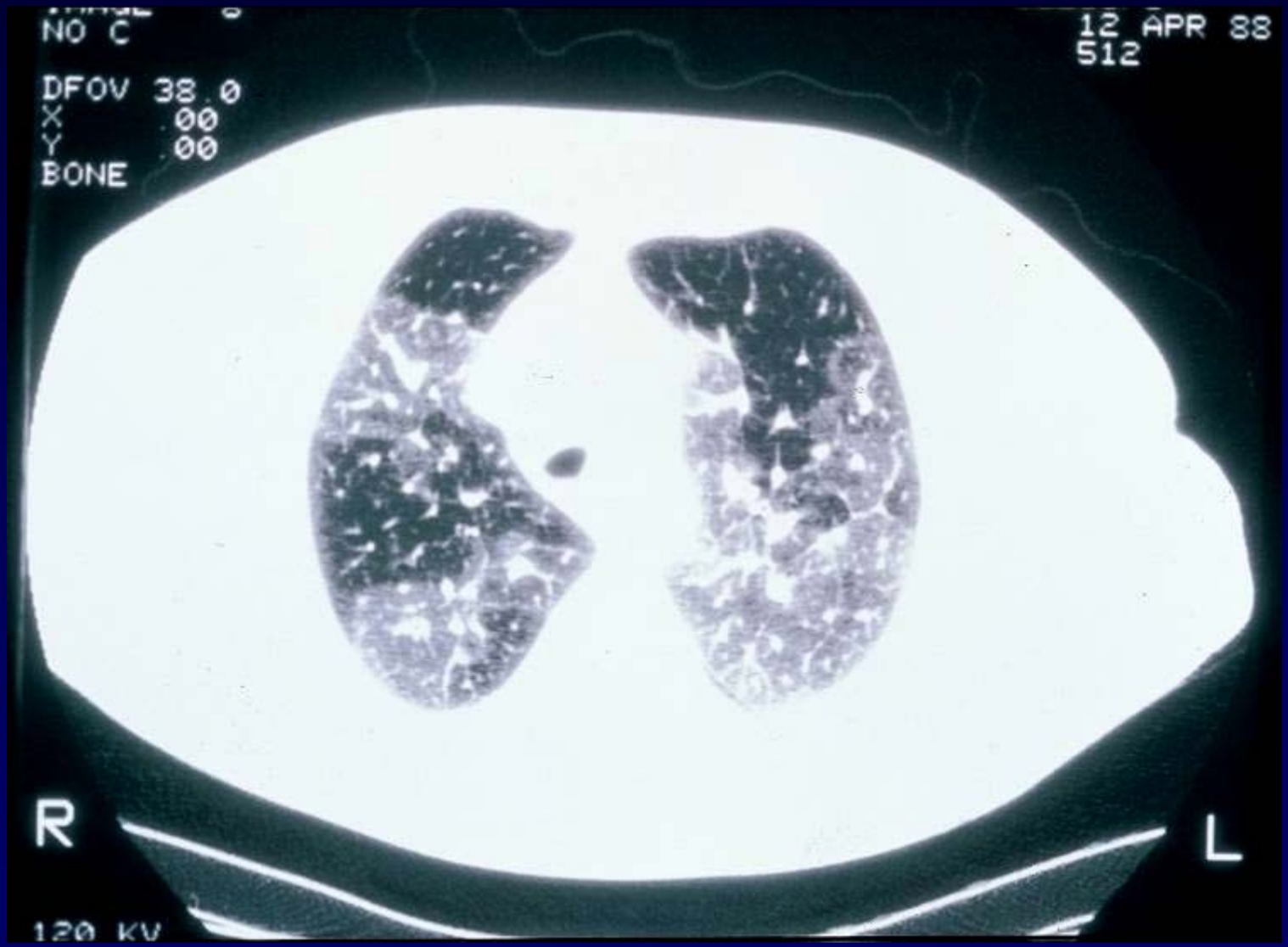


Teaching Point

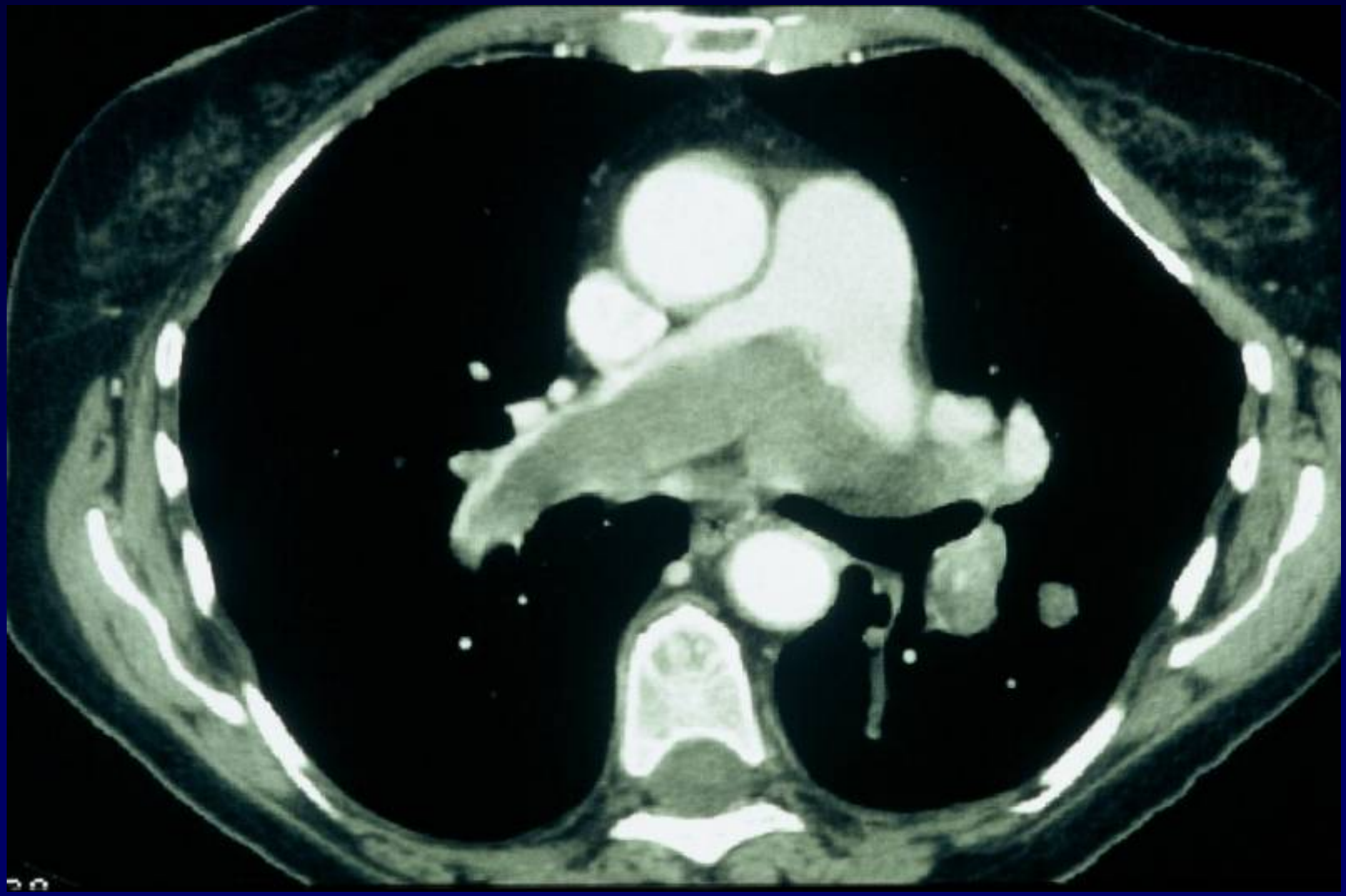
CT Scan in CTEPH

- May be useful in confirming diagnosis
- More useful in ruling out other processes
- Mosaic pattern of perfusion useful finding

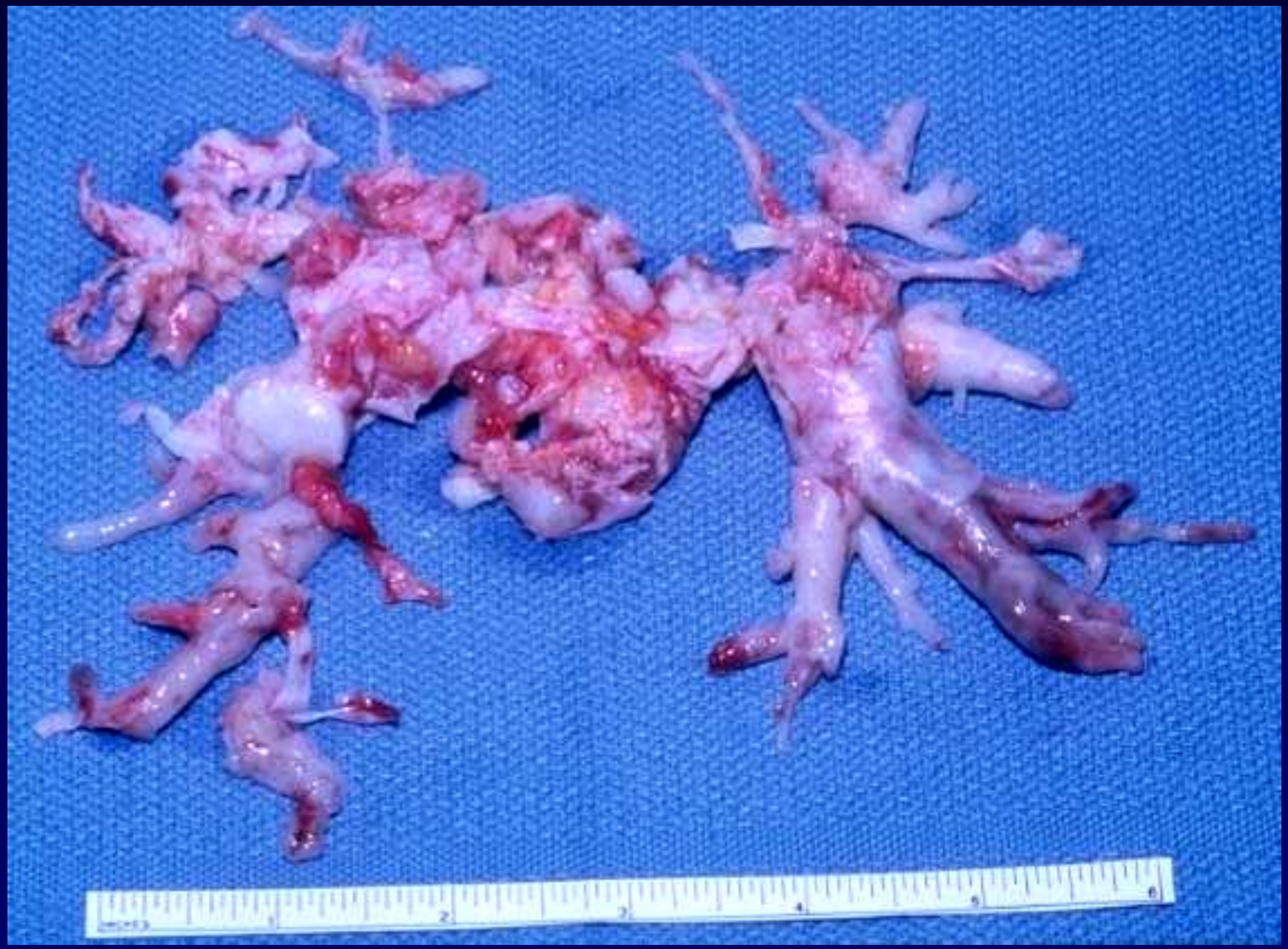
CTEPH: Mosaic Perfusion



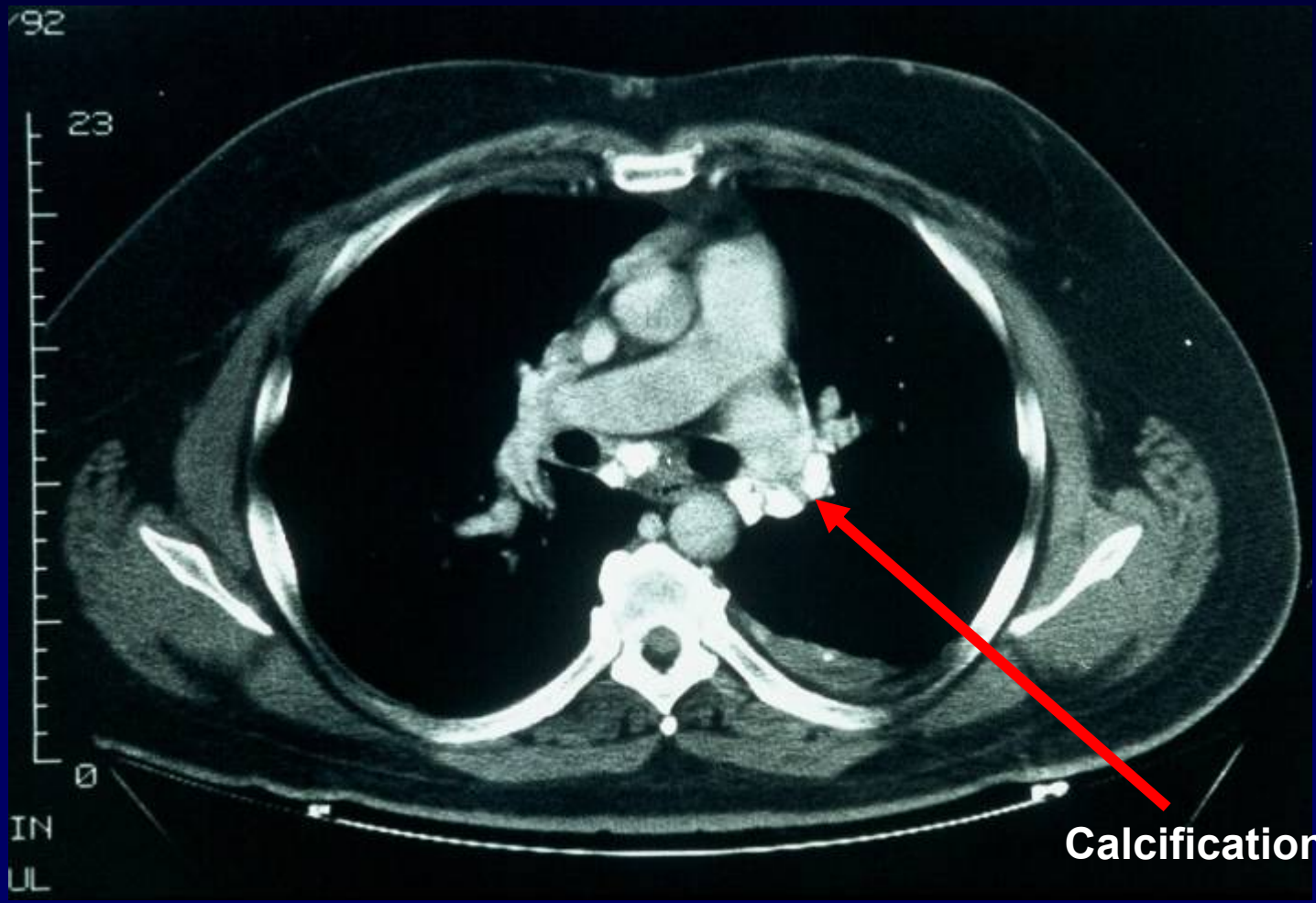
Differential Diagnosis of CTEPH: What Is It?



Pulmonary Artery Sarcoma



Differential Diagnosis of CTEPH: What Is It?

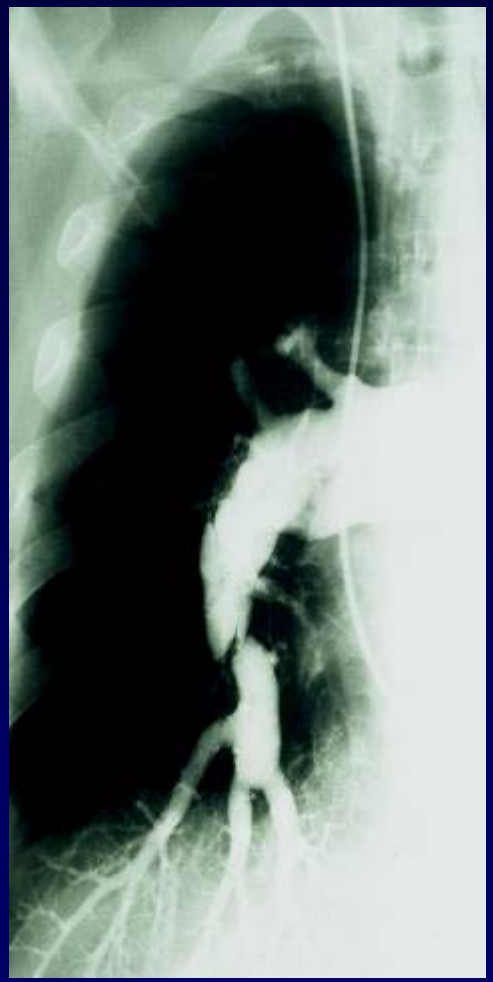


Fibrosing mediastinitis

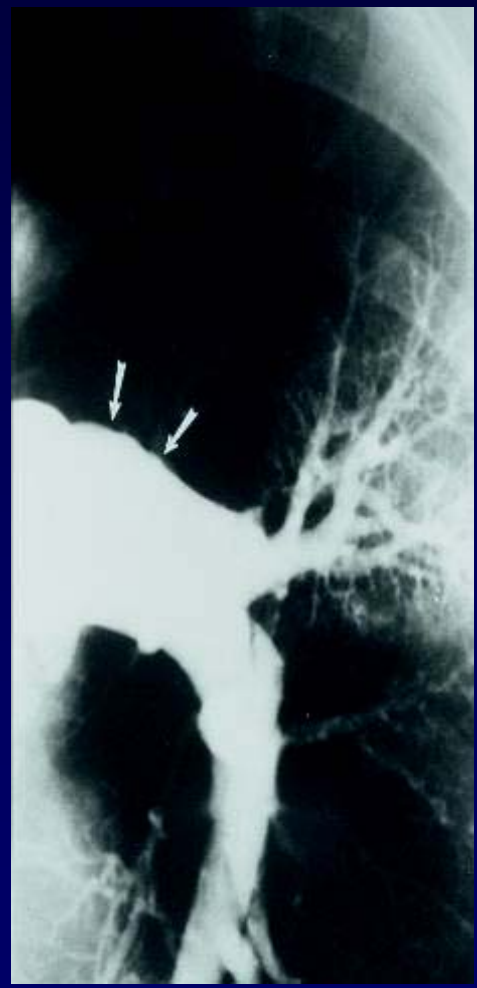
Back to our patient…

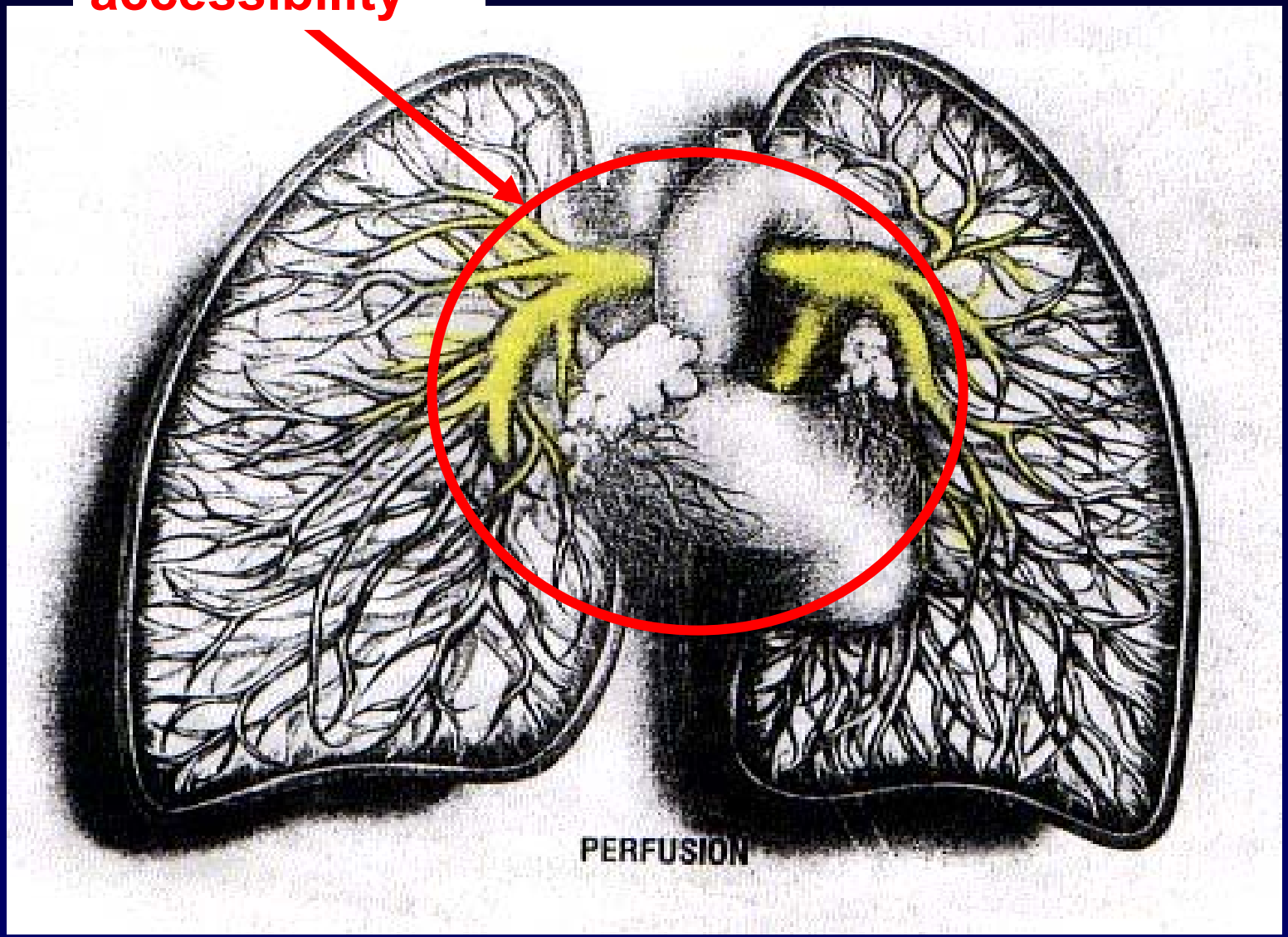
Next Step?

Right heart cath
PA GRAM

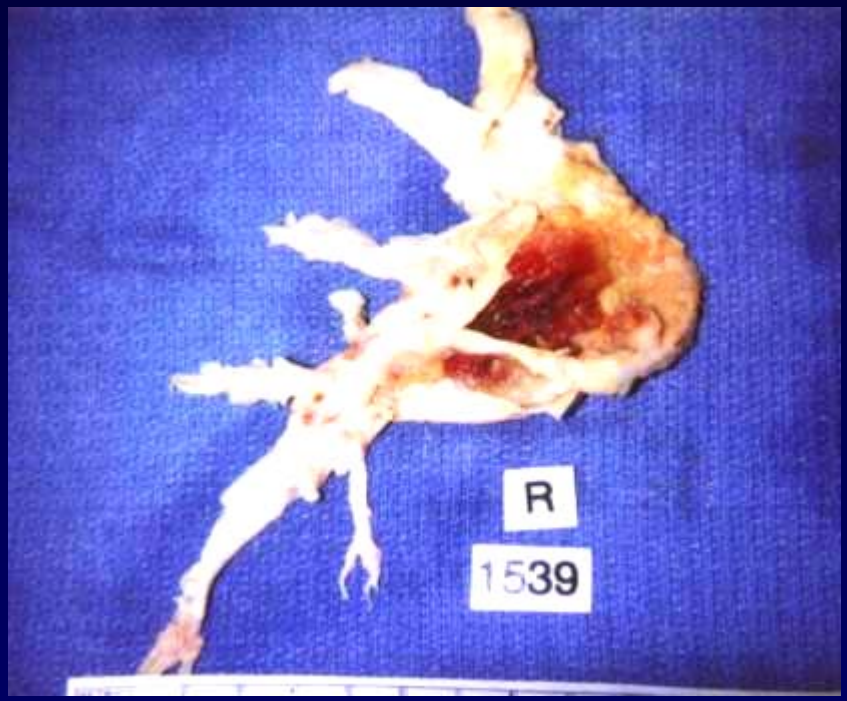


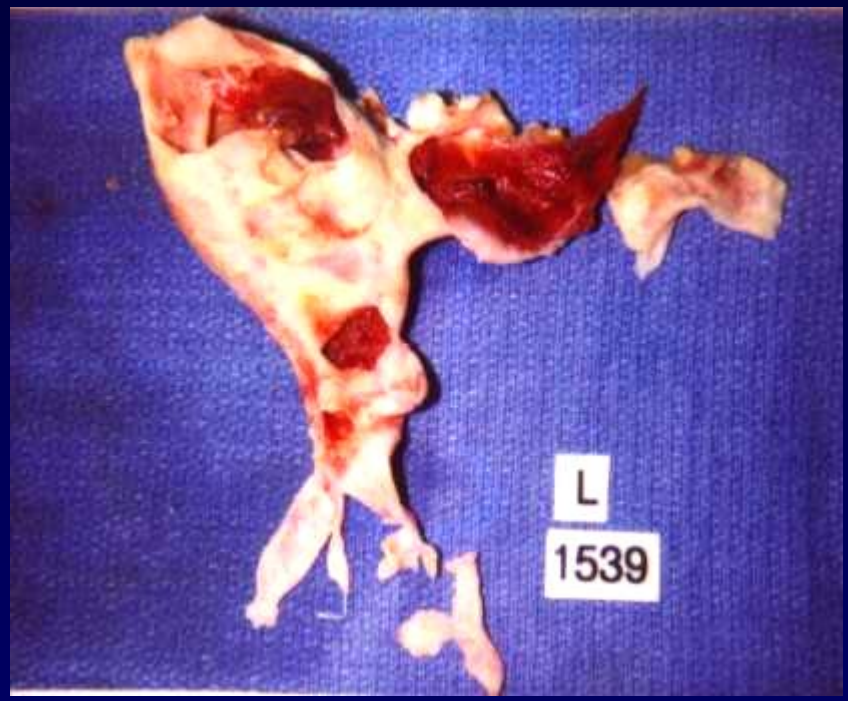
RA 9, PA 86/48(61), PCW 5,
CO 4.6, PVR 12




Zone of accessibility
PERFUSION

Case: Post-op





mPAP: 26
PVR: 3

Questions

1. What physical exam finding might have been useful if present?

   Pulmonary flow murmur

2. Does the absence of a history of DVT/PE help?

   No