Pulmonary Arterial Hypertension in Scleroderma

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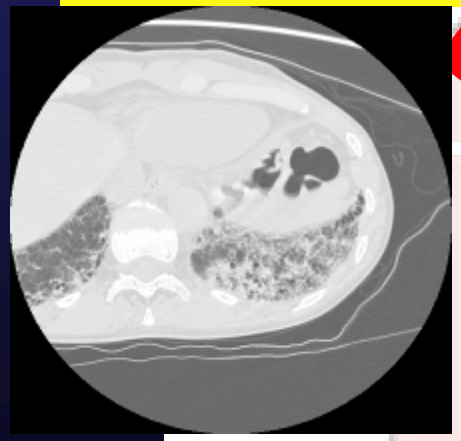
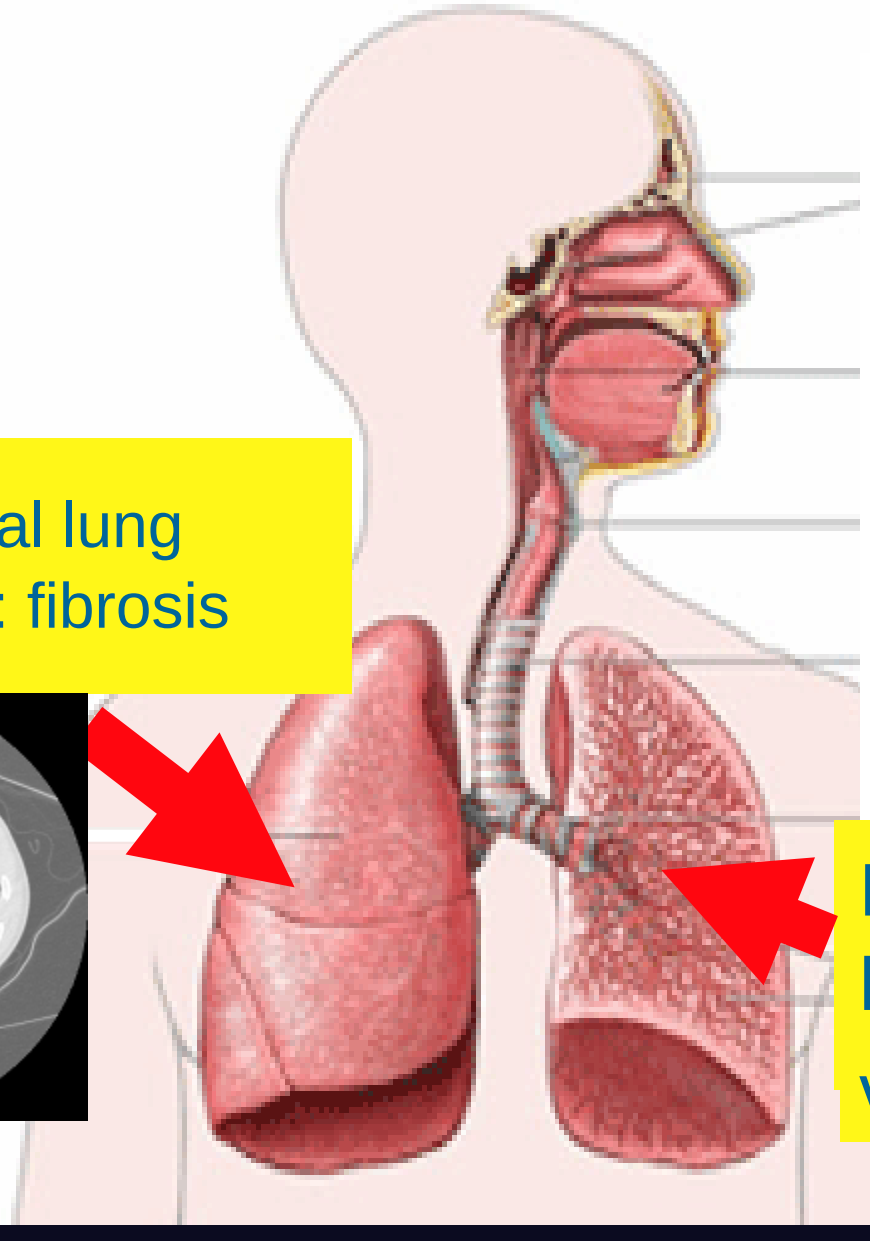
Outline: Scleroderma and PAH

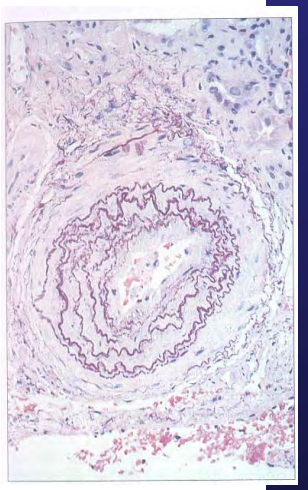
- Lung involvement in scleroderma
- PAH is a vascular complication of Scleroderma
- Manifestations of PAH
- Screening, diagnosis and evaluation of PAH
- Management of PAH
- Take-home message

Lung Involvement in Scleroderma

Interstitial lung disease: fibrosis

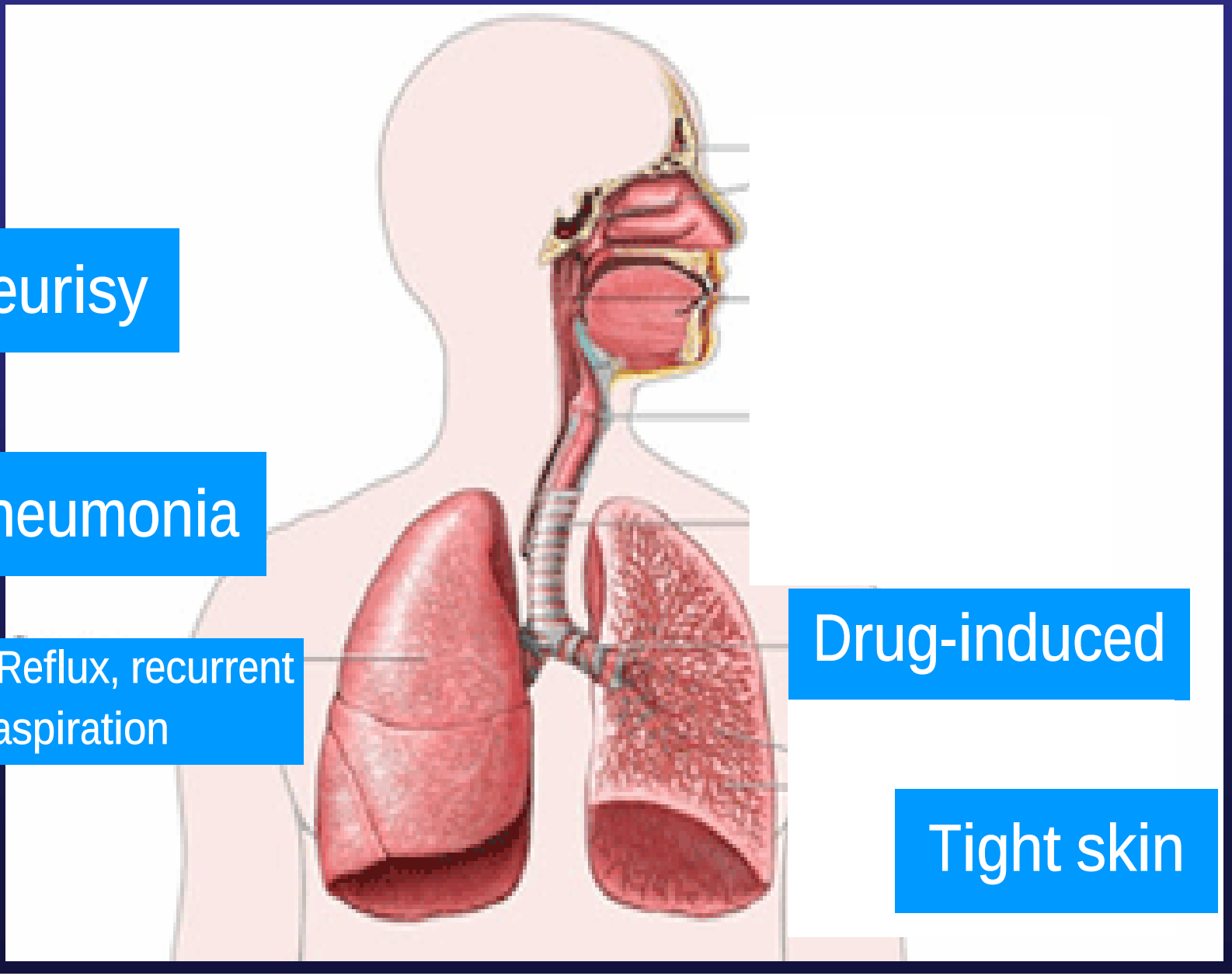






Pulmonary hypertension: vascular

Lung Involvement in Scleroderma



Pleurisy

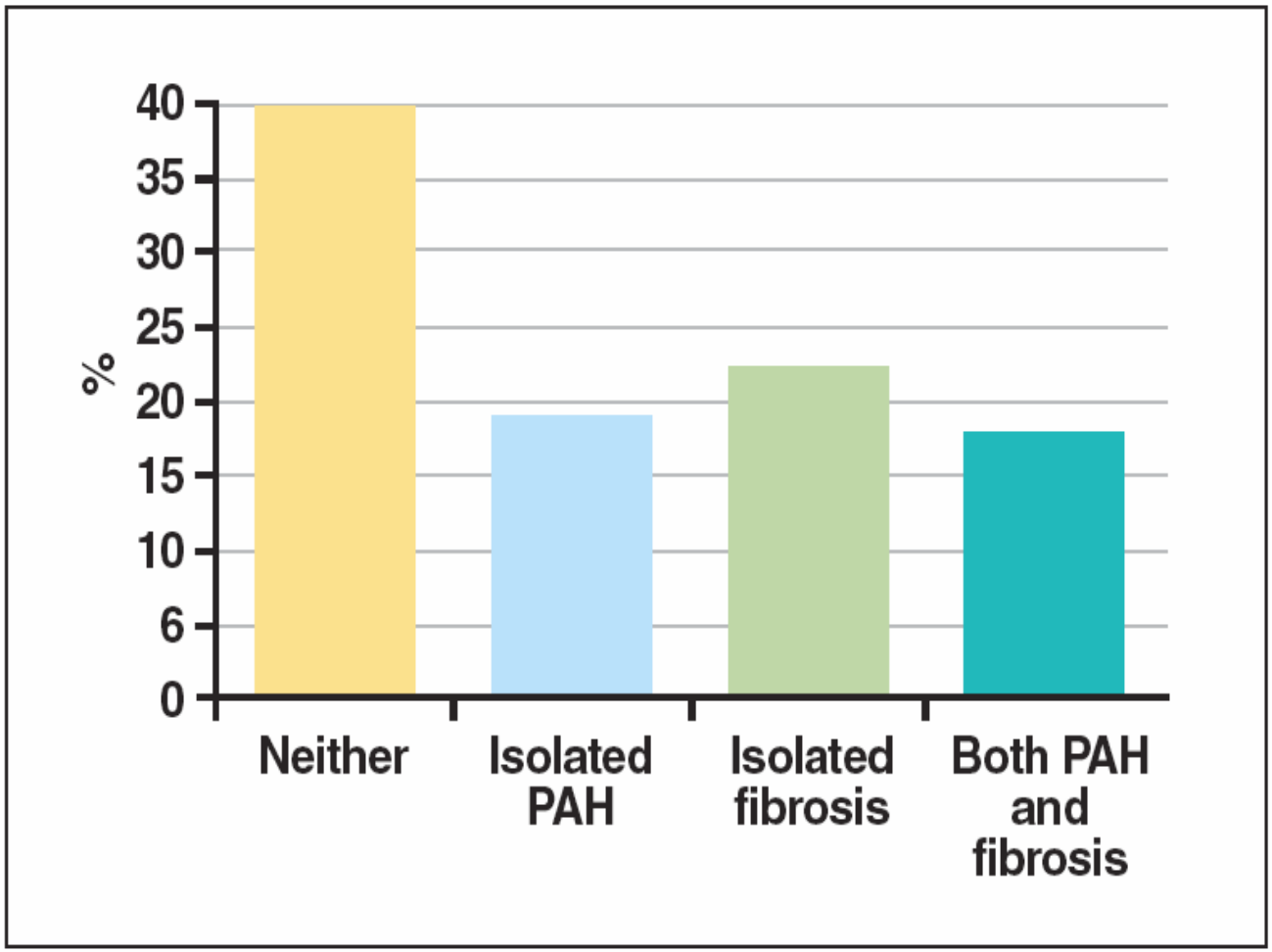
Pneumonia

Reflux, recurrent aspiration

Drug-induced

Tight skin

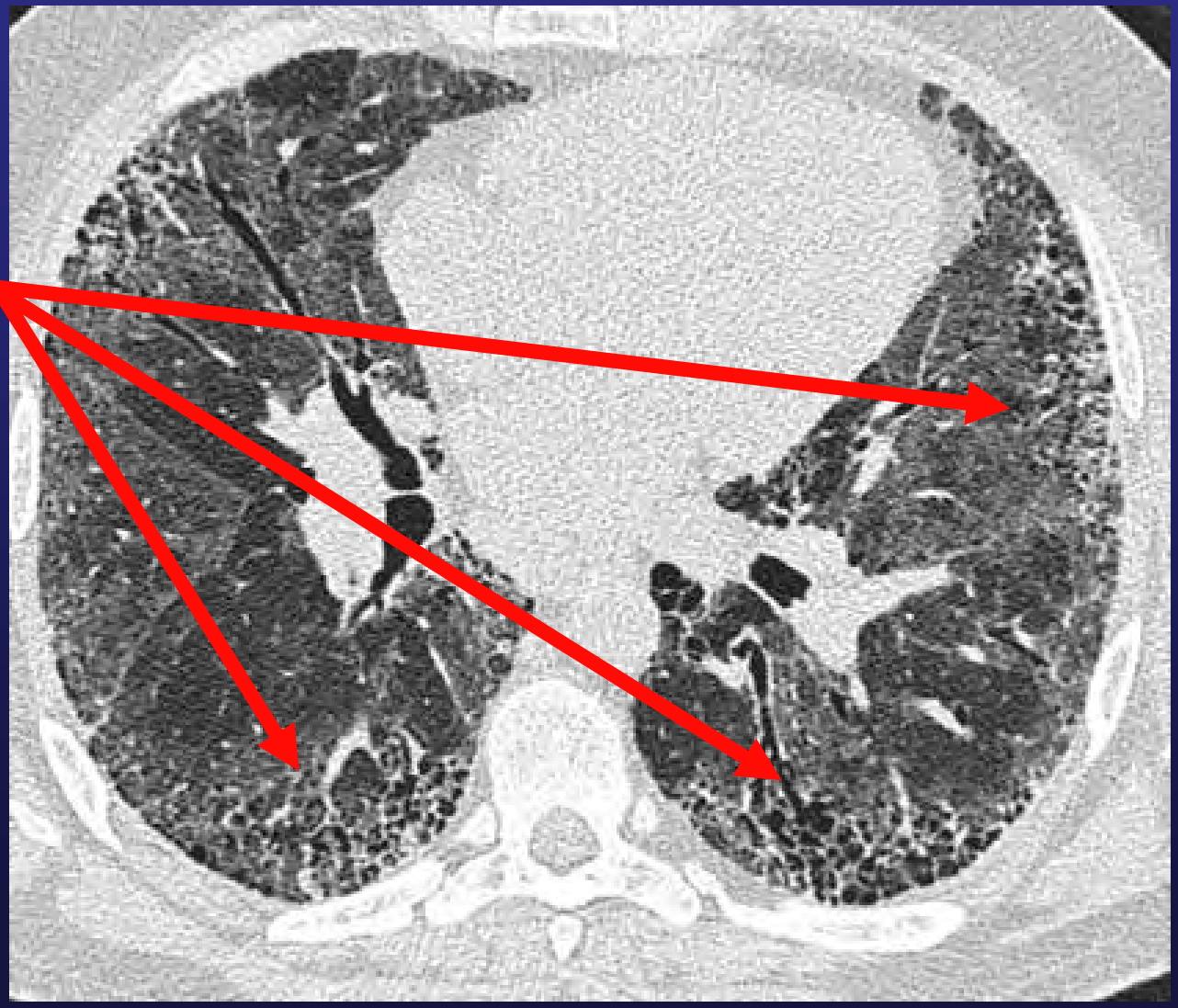
Scleroderma and the Lung



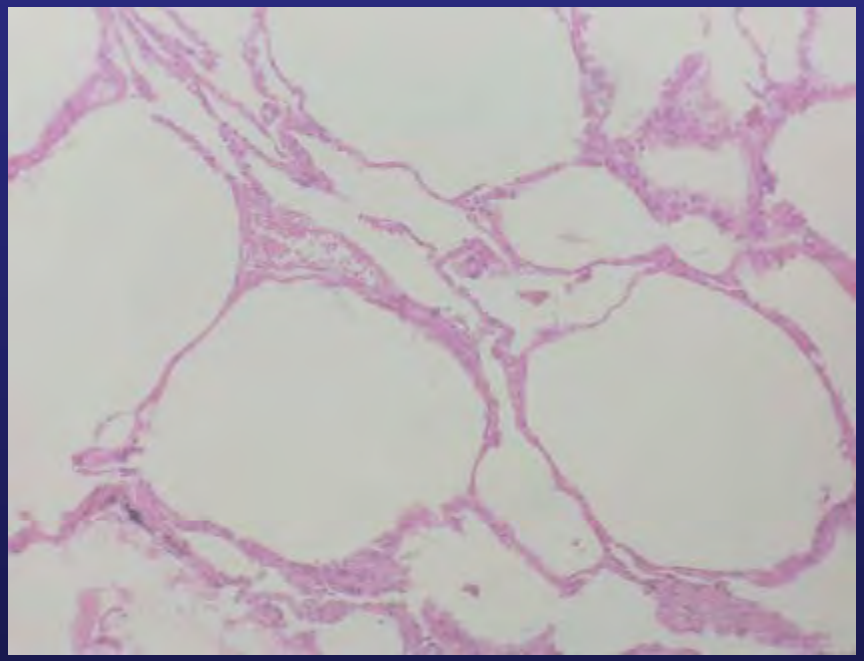
Chang B et al. Natural history of mild-moderate PAH. J Rheumatol 2006: 33: 269.

Interstitial Lung Disease (Fibrosis) in Scleroderma

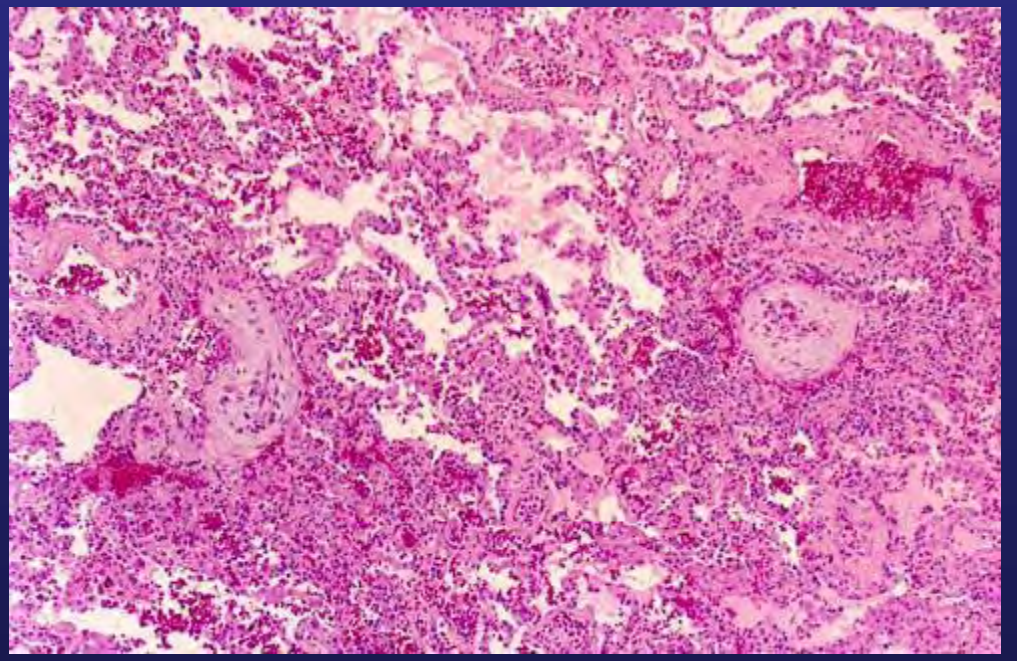
- Fibrosis



Interstitial Lung Disease (Fibrosis) in Scleroderma



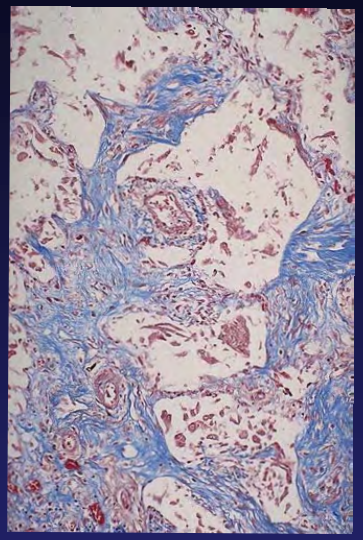
➢Normal Lung



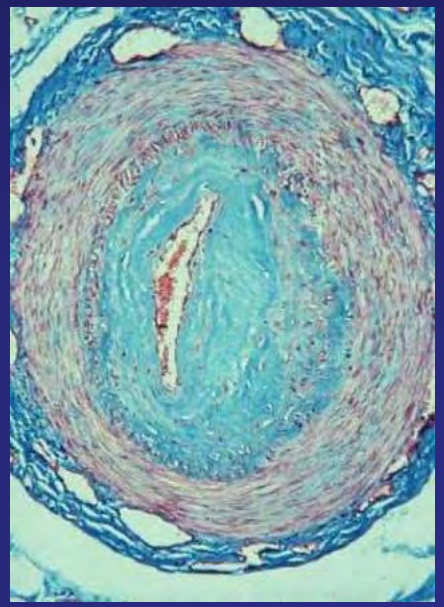
➢Scleroderma Lung: Fibrosis

Scleroderma: two types of complications:

- Fibrosis (scar formation)

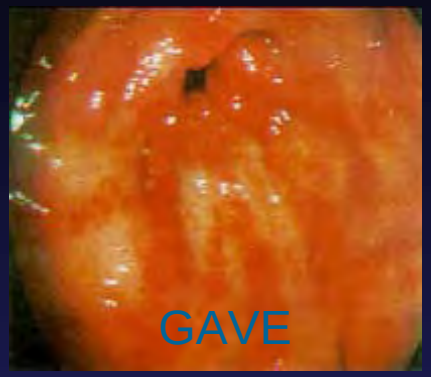


- **Vascular** (blood vessel damage)

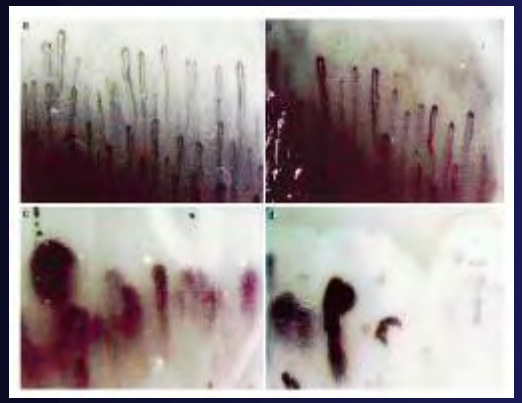


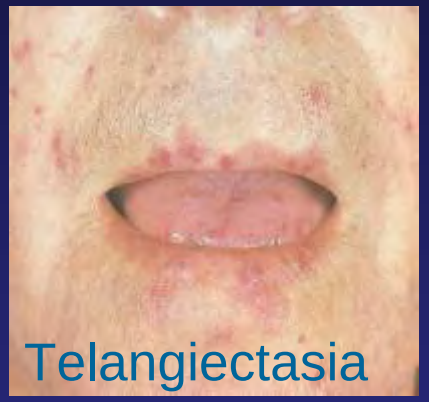
Scleroderma: Vascular Complications

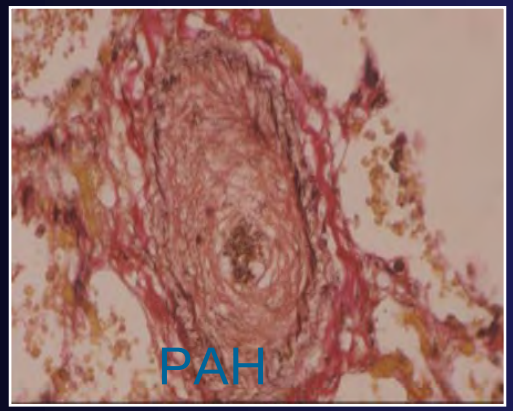

Raynaud

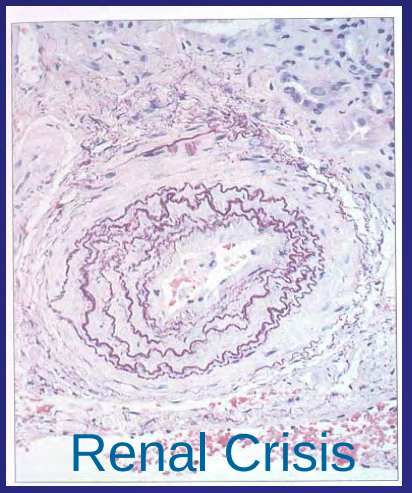

GAVE

Nailfold capillaries



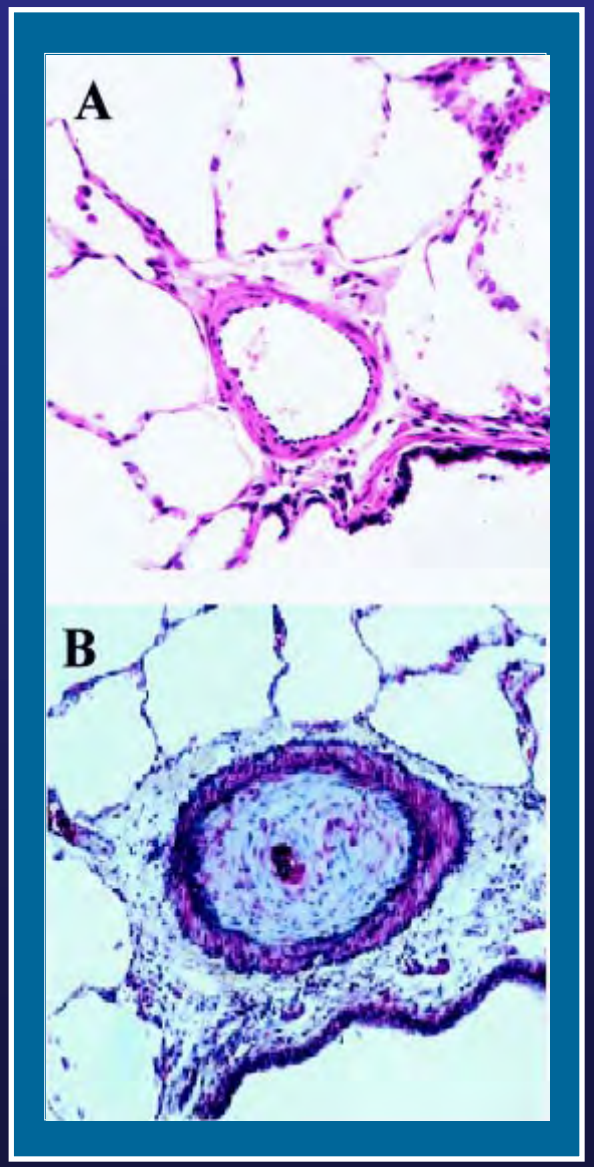

Telangiectasia


PAH


Renal Crisis

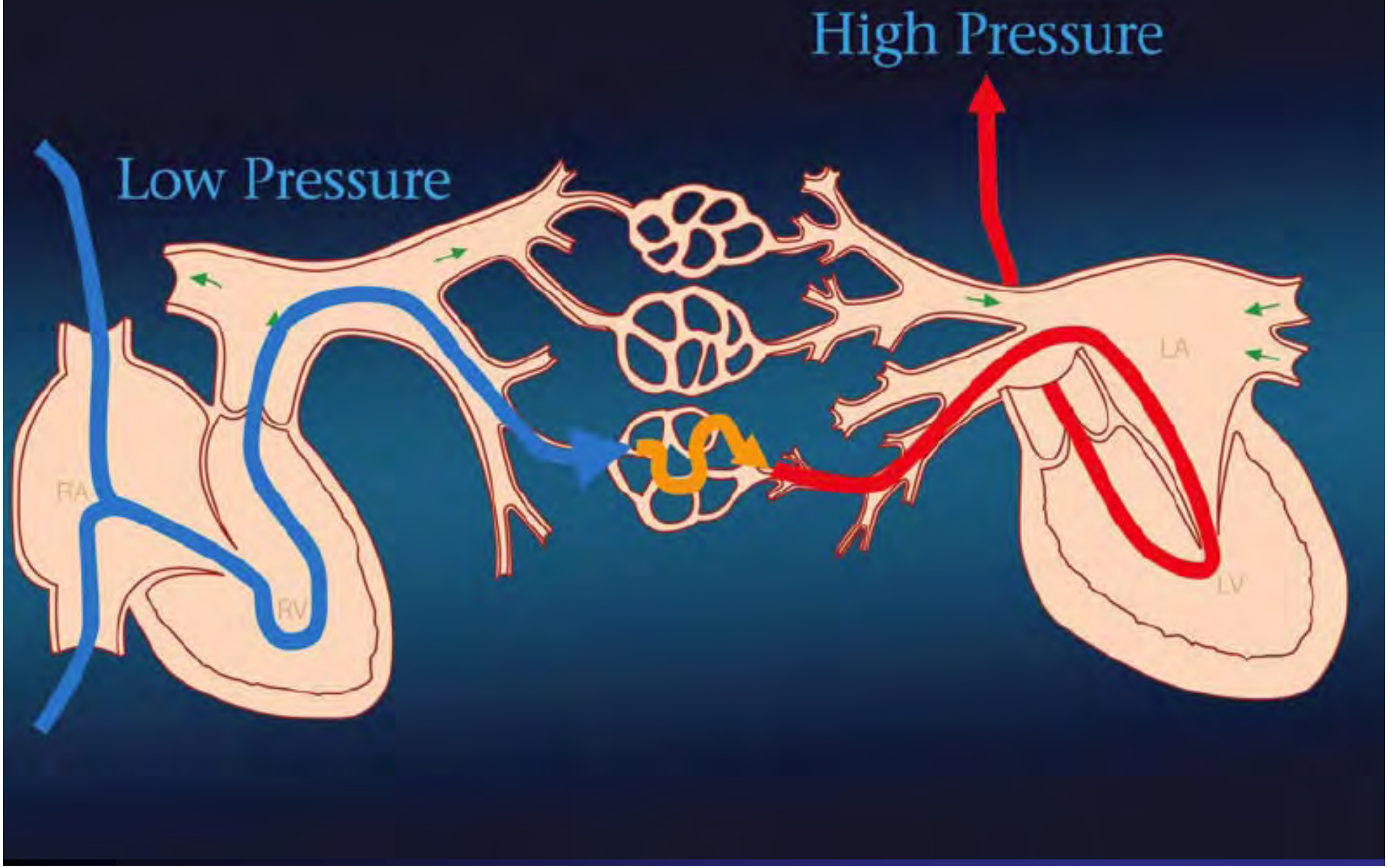
Pulmonary arterial hypertension (PAH) in scleroderma

PAH in scleroderma: definitions



- PASP >25 mmHg at rest
- 20-40% of scleroderma patients
- Late complication (often > 5 yrs)
- Risk factors
  - limited >> diffuse
  - Antibodies to U3RNP, fibrillarin
  - HLA DRw52

➢PAH : Pathophysiology



Symptoms of PAH in scleroderma

Fatigue, reduced exercise tolerance
Shortness of breath; may occur only w exercise
Chest pain; palpitations
Lightheadedness, loss of consciousness
Leg swelling

May have no symptoms until disease advanced

Functional Classification of PAH (WHO)

Class	Description
I	Patients with PH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients with PH who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients with PH who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients with PH who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity.

Shortness of Breath in scleroderma *may be due to*:

- Pulmonary Arterial Hypertension
- Interstitial Lung Disease
- Heart Disease (left)
- Anemia
- Physical deconditioning

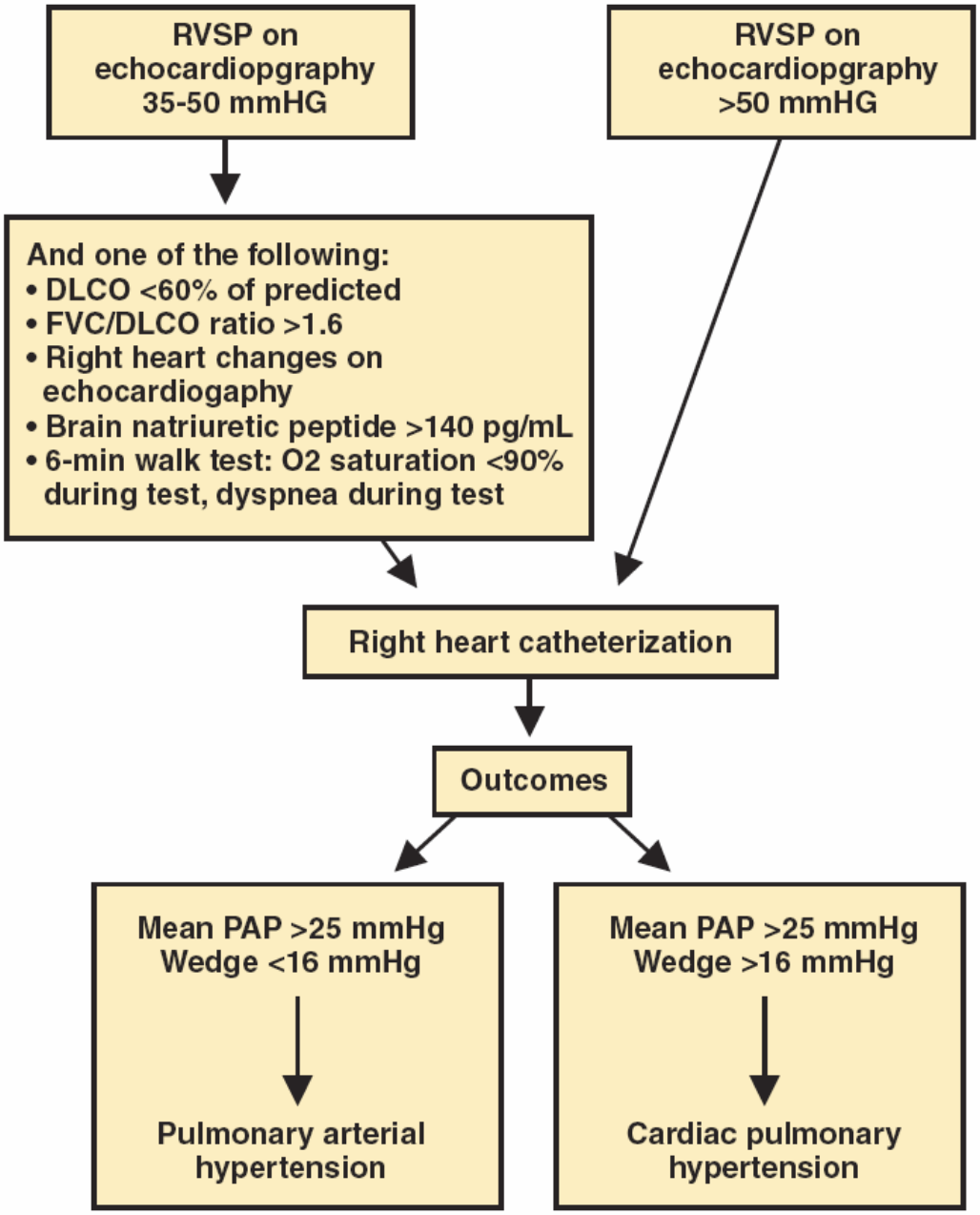
Evaluation

Evaluation of PAH in scleroderma:
- Basic principles

- Screening, early recognition
- Accurate diagnosis, full evaluation
- Serial monitoring

Evaluation of PAH in scleroderma

- History, exam
- PFT
- Radiology (XR, CT)
- 6 min walk test
- ECHO/Doppler
- Right heart cath



Pulmonary Function Testing: PFT

Evaluation of PAH in scleroderma: Pulmonary Function Testing (PFT)

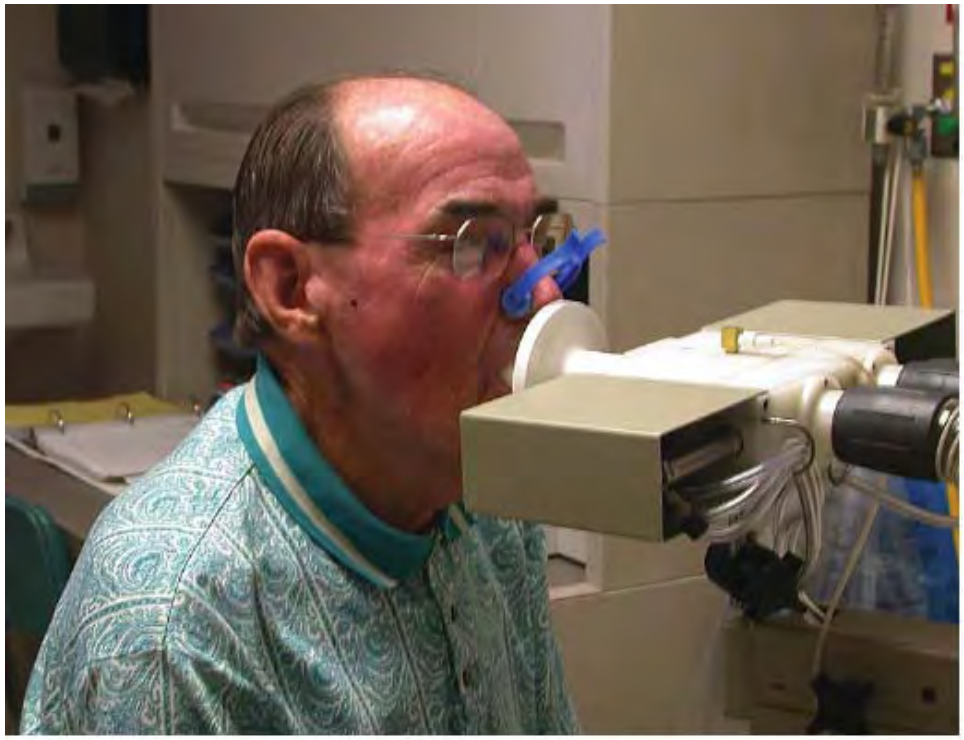


Fig. 1—Patient undergoing pulmonary function testing.

PFT Results

PHYSICIAN: DEMAITE

		Pre-Drug* E		
Spirometry		Actual	Predicted	%Pred
FVC	(L)	3.02	4.03	75
FEV1	(L)	2.48	2.79	89
FEV1/FVC	(%)	82	69	119
FEF25-75%	(L/S)	2.38	2.69	89
FEF25%	(L/S)	6.18	7.46	83
FEF50%	(L/S)	3.11	4.76	65
FEF75%	(L/S)	0.84	1.65	51
FEFmax	(L/S)	6.23	8.28	75
FIF50%	(L/S)	6.40		

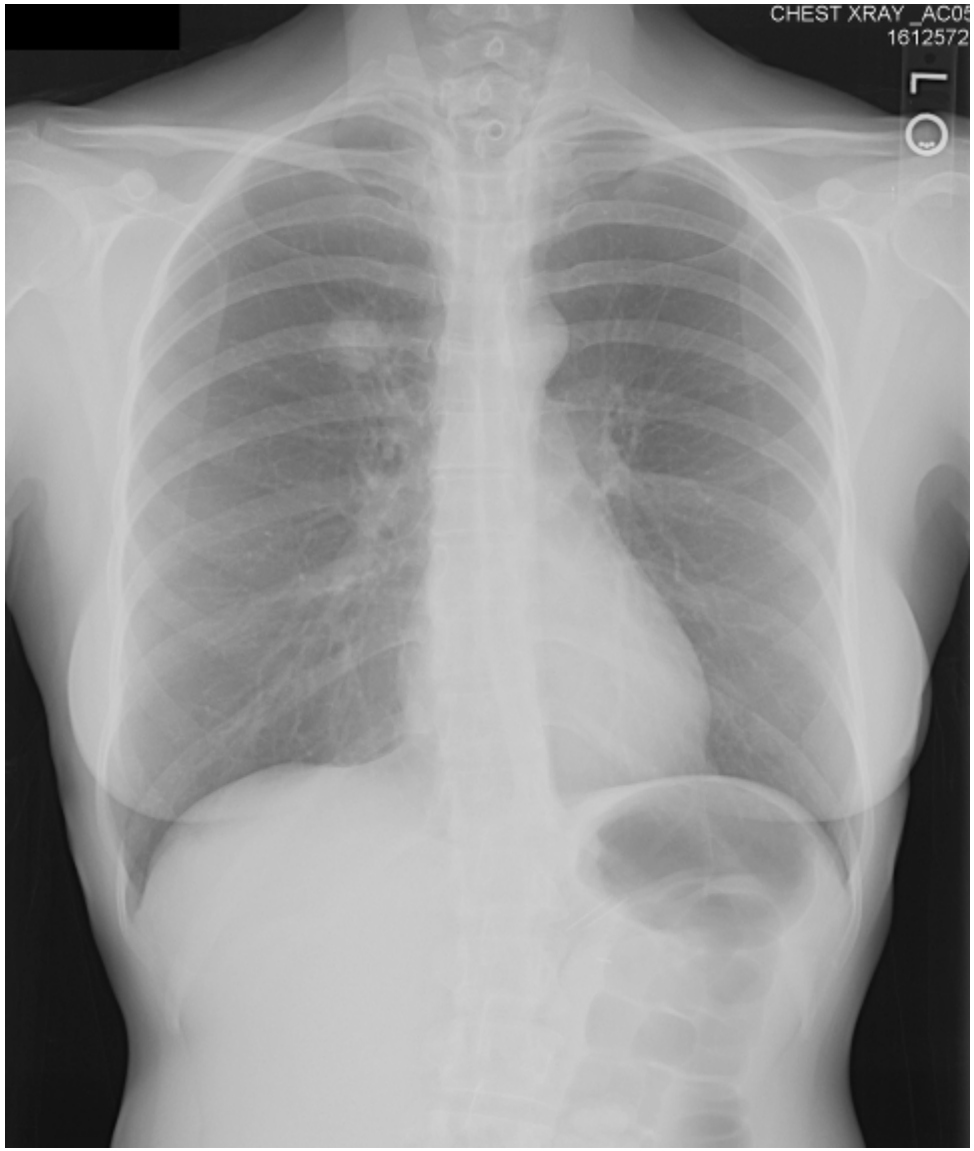
		Pre-Drug*		
Spirometry		Actual	Predicted	%Pred
MVV	(L/MIN)	110	111	99
Test Length	(SEC)	12.00		

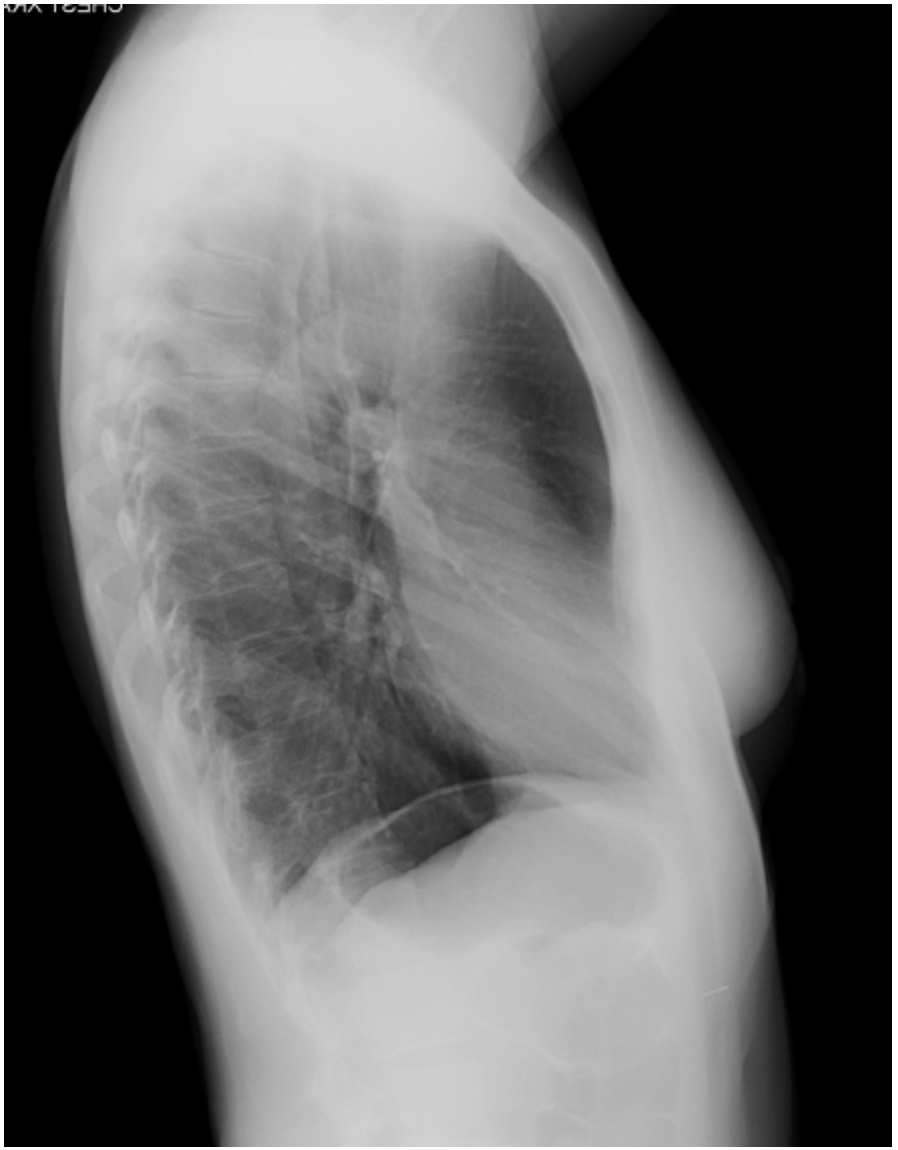
	Pre-Drug* Avgm		
Diffusion	Actual	Predicted	%Pred
Dsb ml/min/mmHg	13.28	24.99	53
Dsb(adj) ml/min/mmHg	14.05	24.99	56
VA(sb) (L)	3.76	6.30	60
D/VA	3.53	3.97	89
Volume Inspired (L)	2.88		

	Pre-Drug* (M)		
Blood Gases	Actual	Predicted	%Pred
pH	7.44	(7.35-7.45)	
PaCO2 (mm HG)	37.00	(35.00-45.00)	
PaO2 (mm HG)	88.00	(80.00-100.00)	
HCO3 (mEq/L)	24.28	(22.00-26.00)	
HbO2 (%)	95.00		

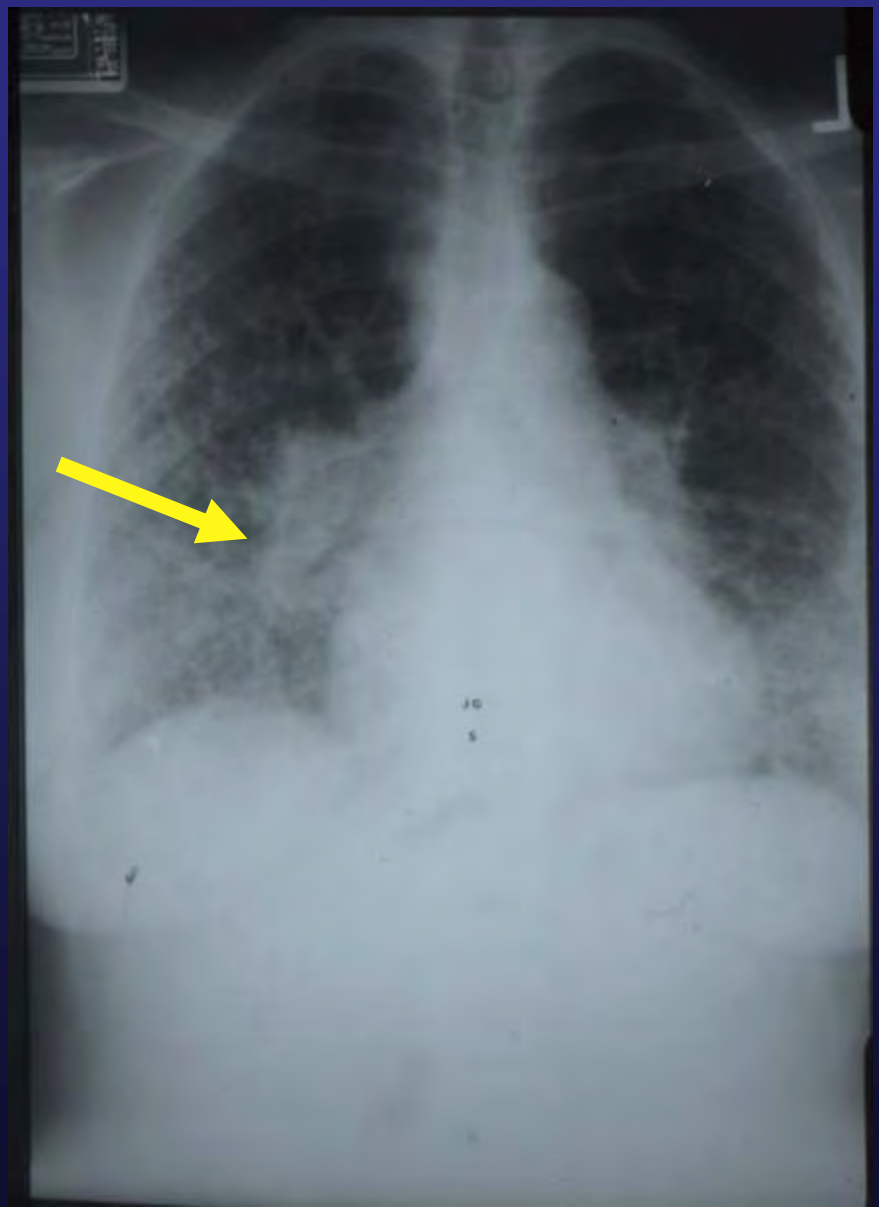
Radiology (X rays, CT scan)

Normal Chest X ray

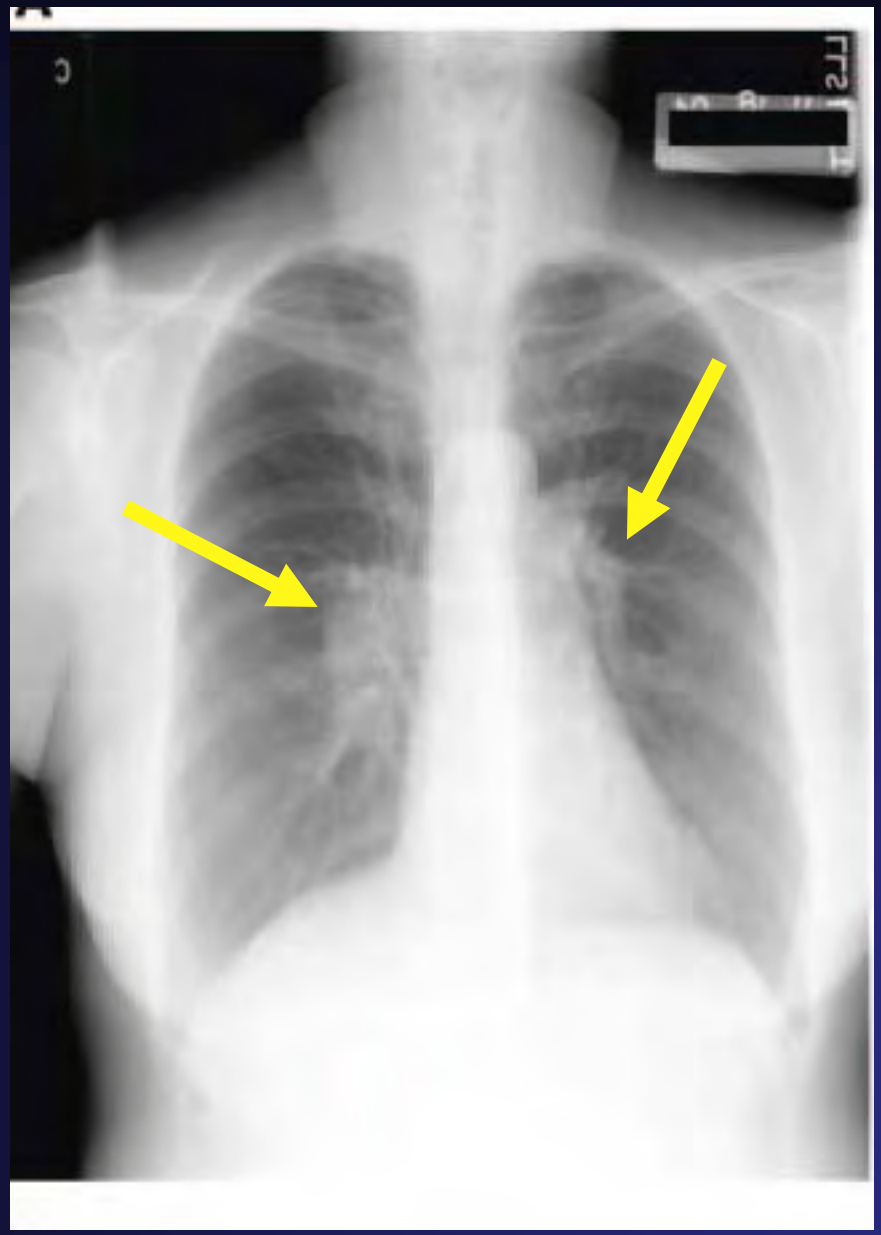




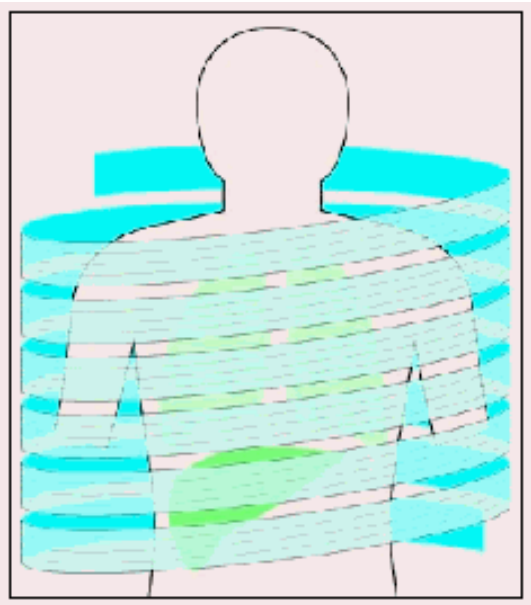
Scleroderma Chest X ray (fibrosis)

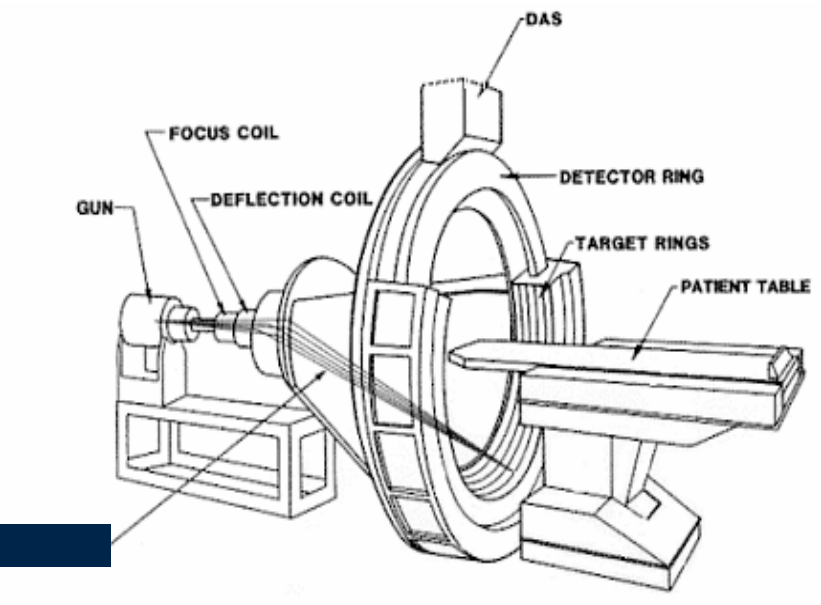


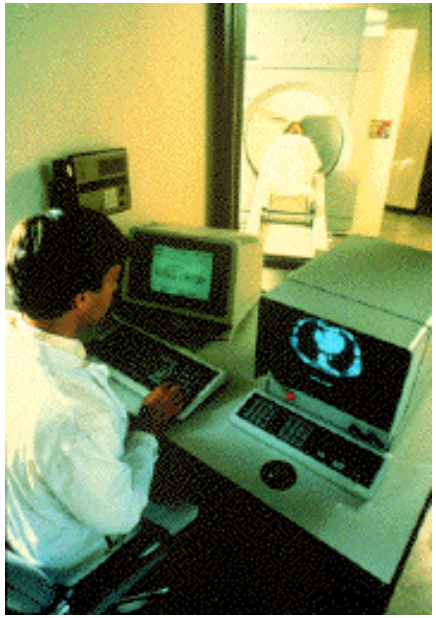
Scleroderma Chest X ray (PAH)



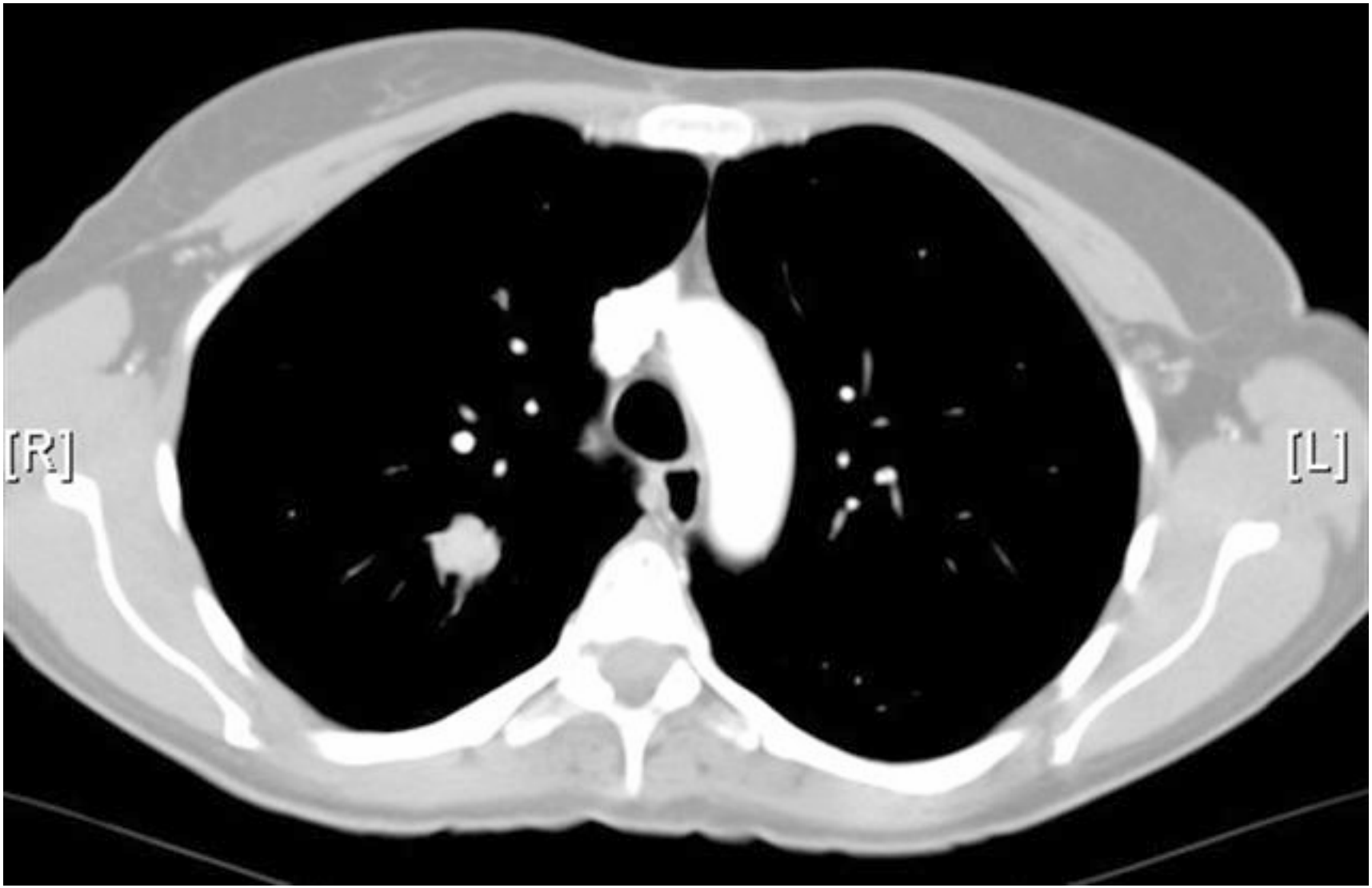
CT Scan




DAS
FOCUS COIL
DETECTOR RING
GUN
DEFLECTION COIL
TARGET RINGS
PATIENT TABLE

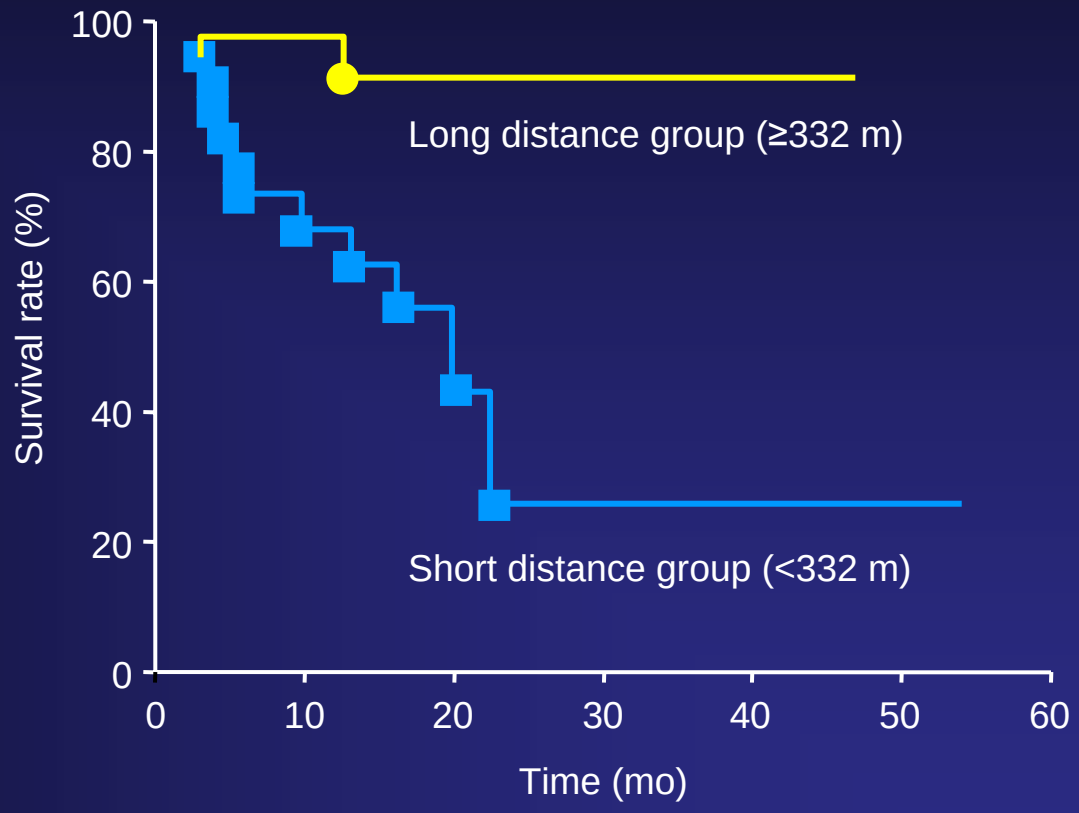


CT scan: Normal



6 min walk test

6-Min Walk Test



Miyamoto S et al. *Am J Resp Med.* 2000;161:487-492.

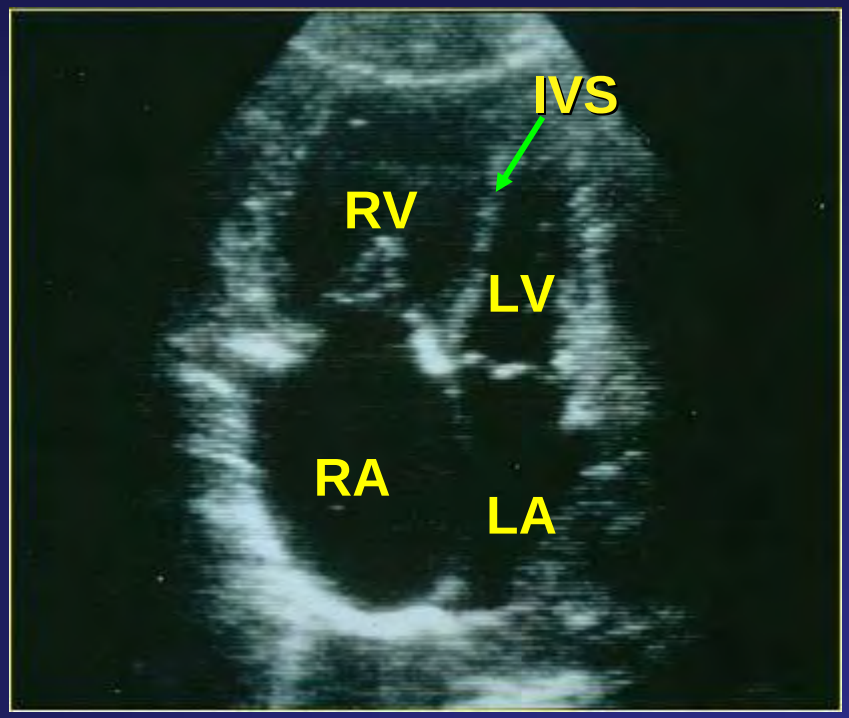
ECHO/Doppler

Echo/Doppler

- Non-invasive, reproducible
- Very useful for screening for PAH
- However, false positives and false negatives occur
- Only *estimates* (not *measures*) PA pressure

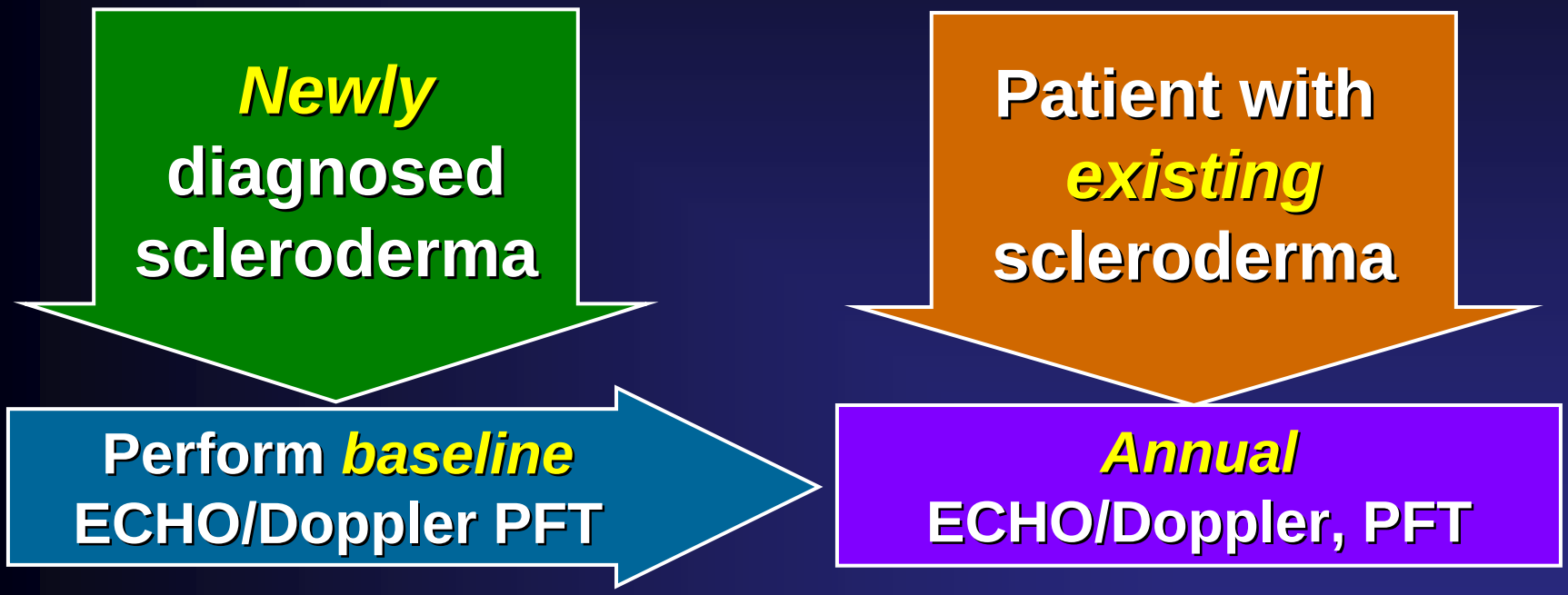
PH: ECHO findings

- **Increased PASP**
- R atrial and ventricular hypertrophy
- Flattening of intraventricular septum
- Small LV
- Dilated PA



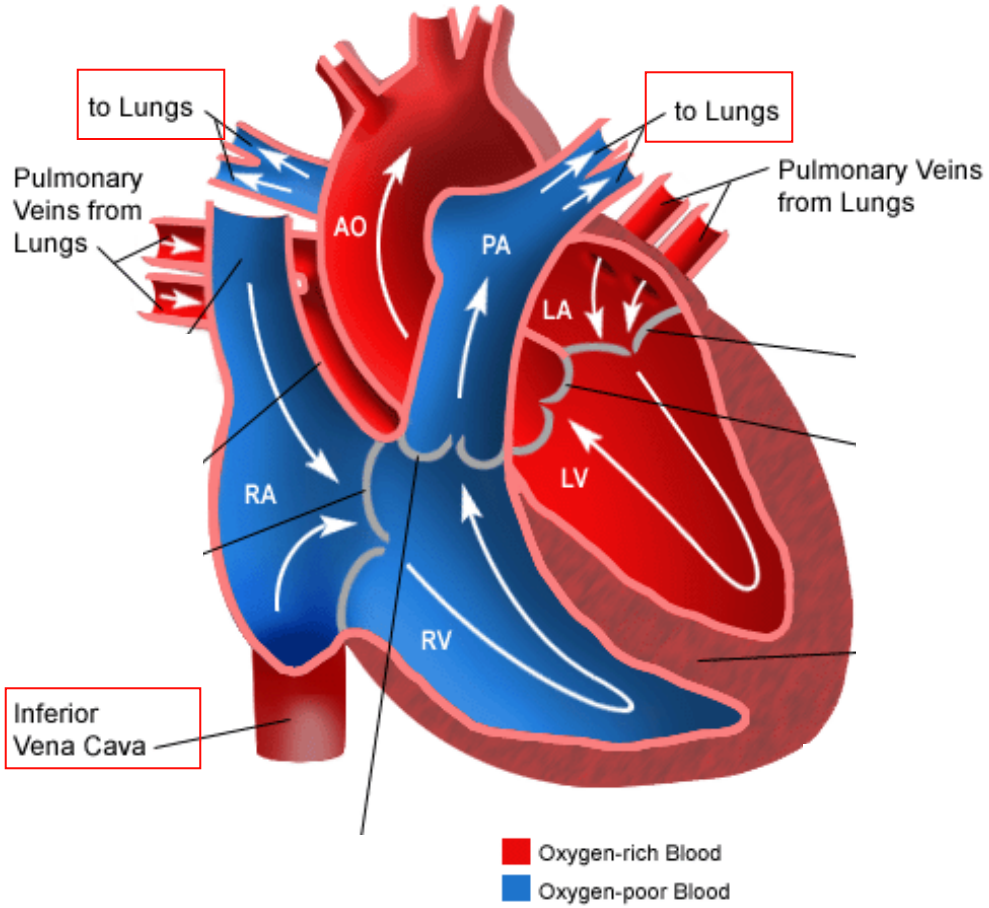
McGoon M et al for the American College of Chest Physicians. *Chest.* 2004;126:14S-34S.

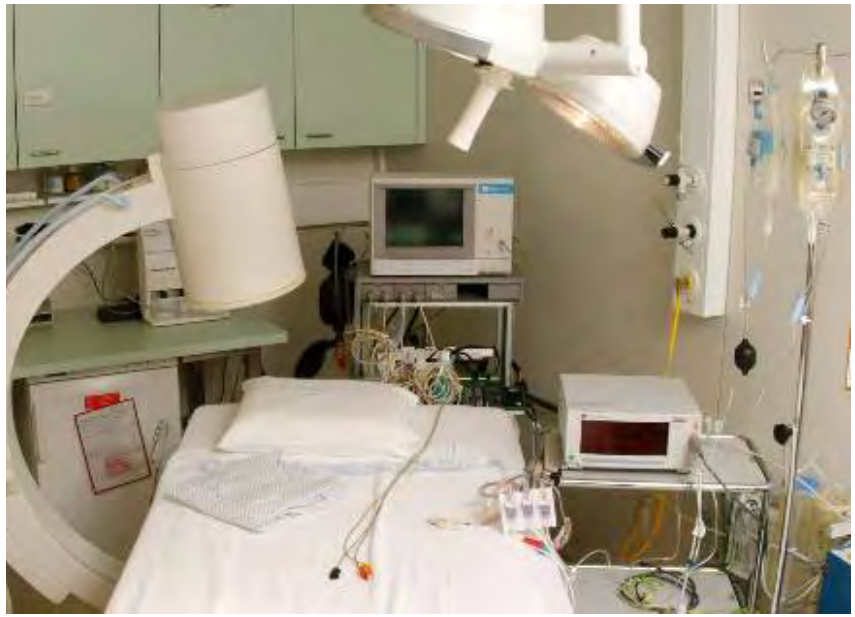
Screening for PAH in scleroderma



McGoon M et al for the American College of Chest Physicians. *Chest.* 2004;126:14S-34S.

Right Heart Catheterization

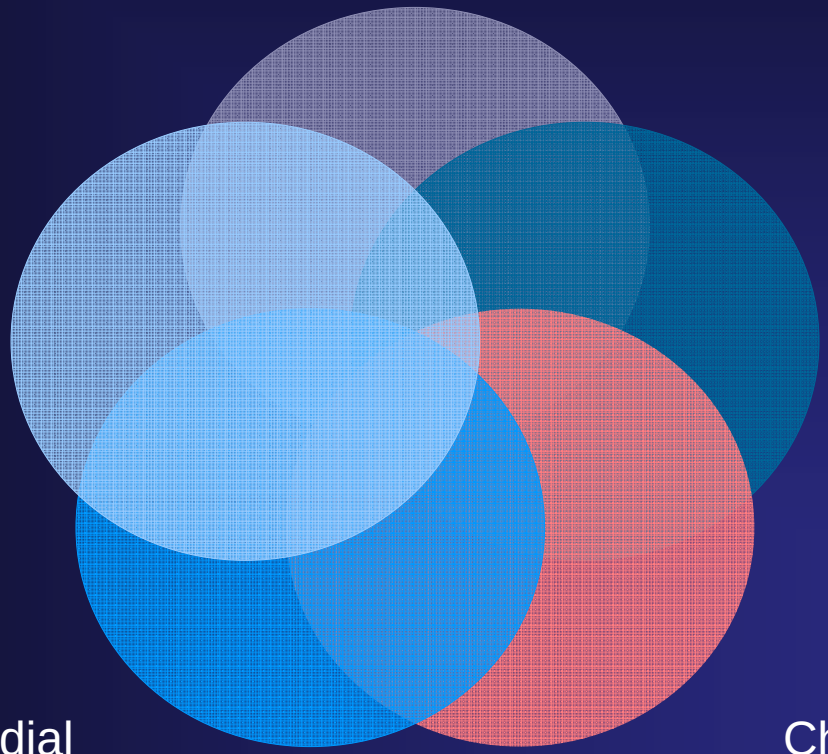




Right Heart Catheterization
-why needed?

--Measure PA pressure
--r/o other causes of elevated pressure

RHC: Rule out other Causes of PH



Treatment

PAH Therapy: 2 Approaches

- SUPPORTIVE

  Prevent vasoconstriction hypoxia), reduce edema, increase cardiac function, prevent blot clots; avoid pulmonary infection, pregnancy; vascular protection/repair?

- SPECIFIC

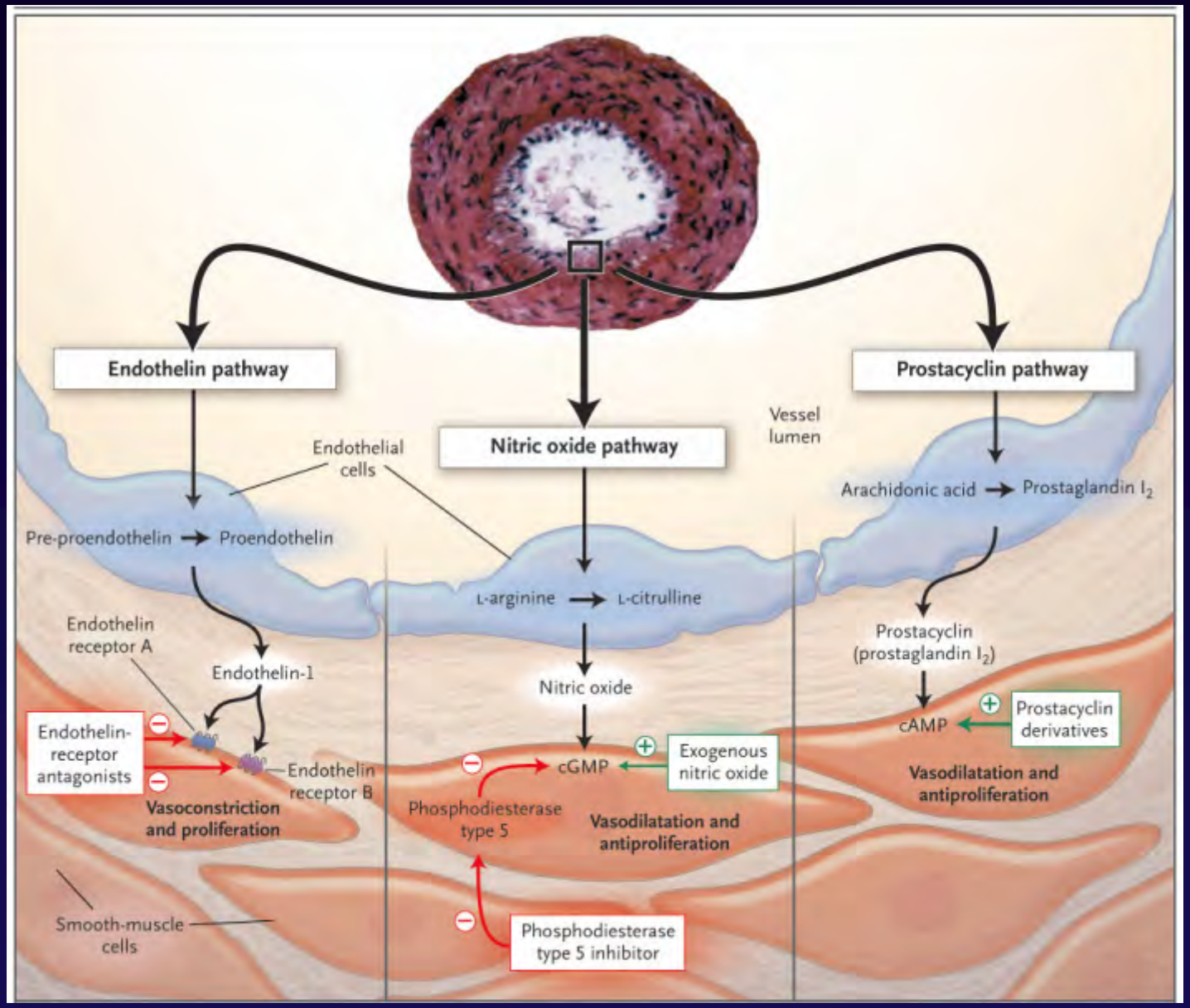
  Pulmonary vasodilatation, increased RV function, reduced platelet aggregation/clotting; vascular healing?

PAH Supportive Therapy

- Low-flow oxygen
- Digoxin (Lanoxin®)
- Furosemide (Lasix®)
- Spironolactone (Aldactone®)
- Losartan; ACE inhibitors
- Warfarin (Coumadin®)
- Calcium channel blockers [?]
- **Statins [?]**

PAH-specific Treatment

Pathogenesis of PAH: Therapeutic targets



FDA-Approved PAH Therapies

Prostacyclin Derivatives

- Epoprostenol: continuous infusion IV
- Iloprost: inhaled 6x – 9x per day
- Treprostinil: continuous infusion (sc or IV)

Endothelin Receptor Antagonists

- Bosentan: oral 2X per day
- Ambrisentan: oral once daily

Phosphodiesterase-5 Inhibitors

Sildenafil: oral 3x per day

FDA-Approved Therapies: issues

Prostacyclin Derivatives

Endothelin Receptor Antagonists

Phosphodiesterase-5 Inhibitors

- **Approved only for > Class II PAH**
  - ***? Would earlier treatment be better?***
- **Expensive!**
- **Specialty pharmacy/controlled distribution**
- **Used in combination?**

Goals of PAH Therapy

- IMPROVE QUALITY OF LIFE

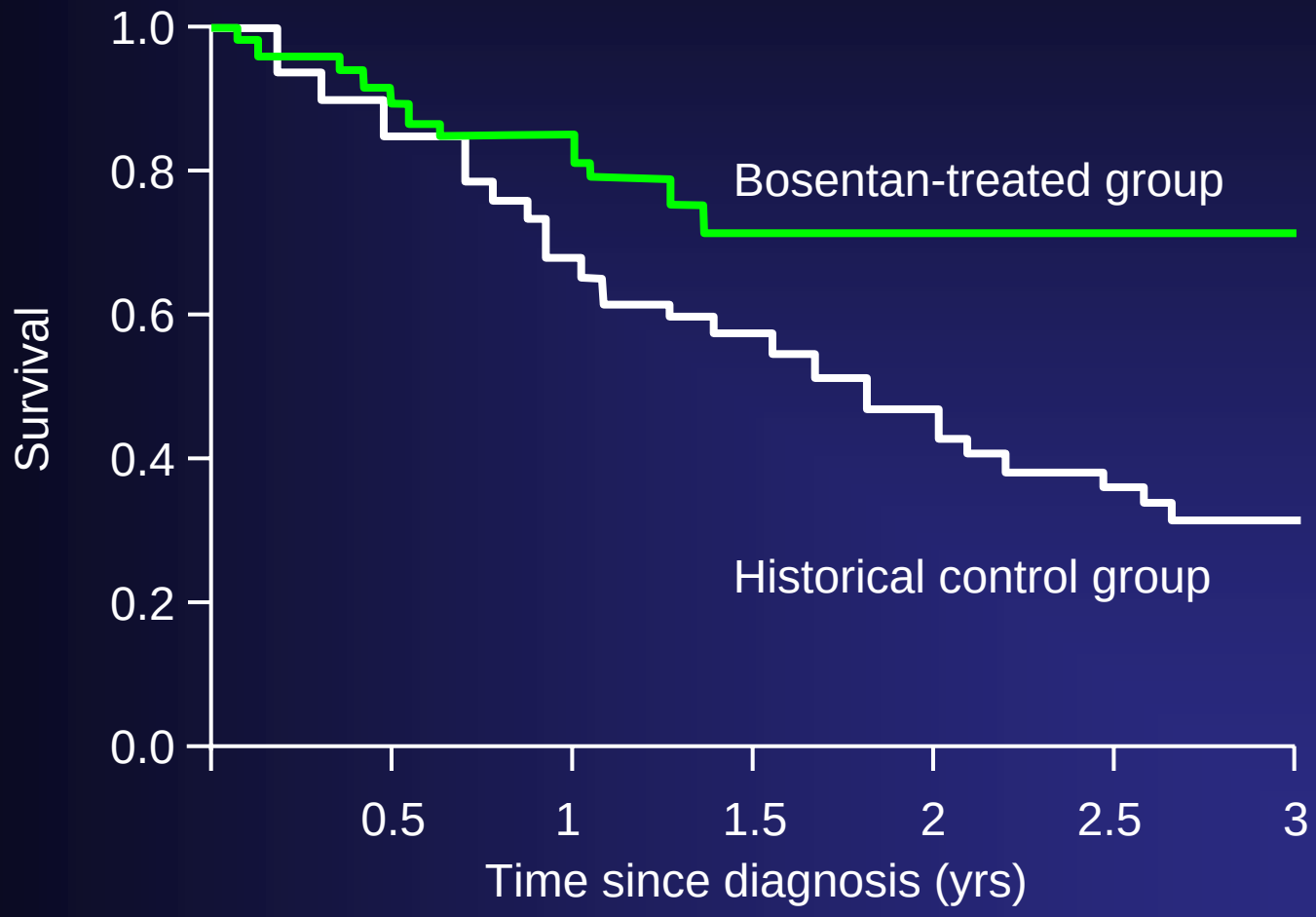
  Achieve WHO Functional Class II

  Normalize pulmonary hemodynamics

  Improve 6 min walk test (>380 m)

- IMPROVE SURVIVAL

PAH in Scleroderma: improving Survival



Williams DH et al. *Heart.* 2006;92:926 -932.

In the Pipeline: Investigational Therapies

- Tadalafil
- Inhaled treprostinil
- Oral treprostinil
- Oral beraprost
- Inhaled vasoactive intestinal peptide (VIP)
- Imatinib (Gleevec)

PAH in scleroderma: **take-home points**

- Early recognition - necessitates regular screening
- Full expert evaluation for accurate diagnosis; integrated multi-specialty team approach (lung, GI, cardiac issues; rheumatologist)
- RHC generally required for accurate diagnosis

PAH in scleroderma: **take-home points**

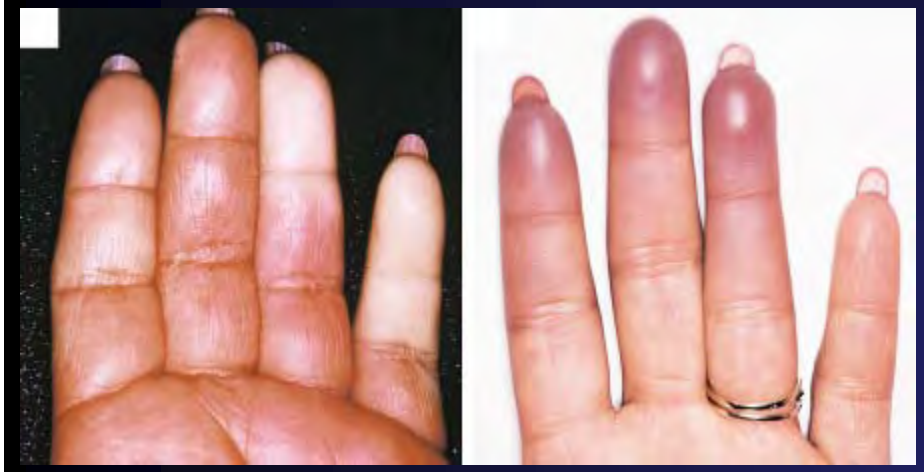
- Early treatment may be important
- Both supportive and specific therapies used
- Which is the best drug? Combination?
- Close monitoring, serial assessment of response
- Best care provided in specialized centers
- Promising pipeline of novel therapies

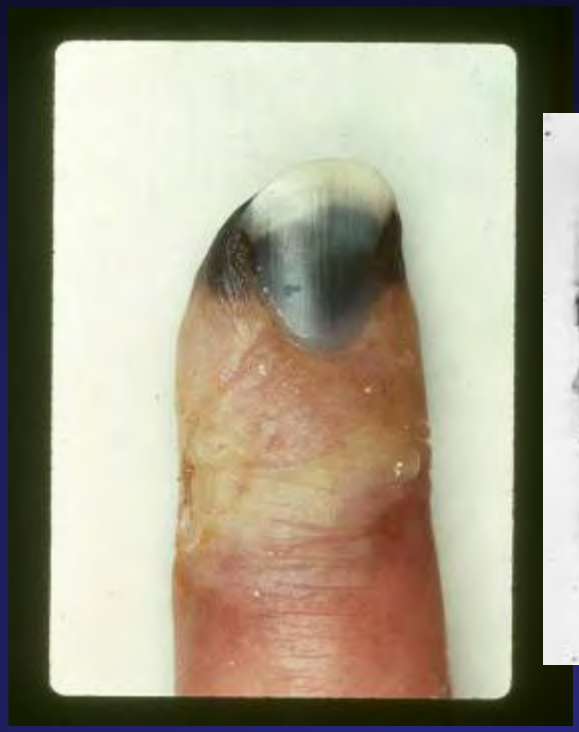
Better understanding of PH in scleroderma needed: PHAROS

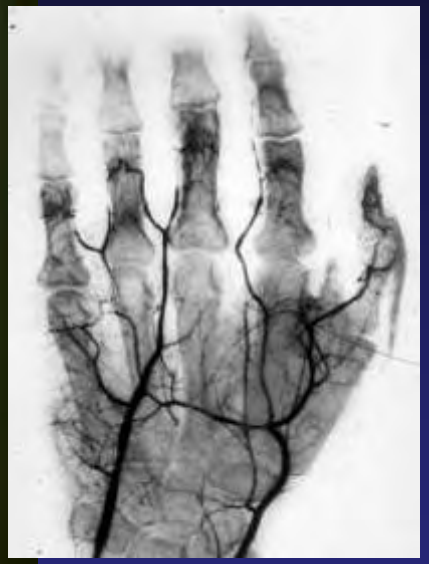
Objectives	• To determine time to definite pulmonary arterial hypertension (PAH) and risk factors for PAH in patients at high risk • To determine outcome of treatment in patients with PAH
Entry criteria	• DLCO <55% of predicted • FVC/DLCO >1.6 • PASP (echocardiography) >40 mmHg
Study protocol	*Yearly physician visits with:* • Pulmonary function tests • Echocardiography • 6-minute walk test • Laboratory tests Twice yearly patient questionnaires (e-mail or mail) about medication and function
Outcomes	*For at-risk patients:* • Time to definite PAH (mean PAP >25 mmHg with wedge < 16 mmHg on right heart catheterization) *For definite PAH patients* • Time to changes in medication, hospitalization, death, and changes in 6-minute walk distance, oxygen saturation, and patient dyspnea questionnaires

- Interstitial Lung Disease (Fibrosis)
- in Scleroderma

Raynaud Phenomenon





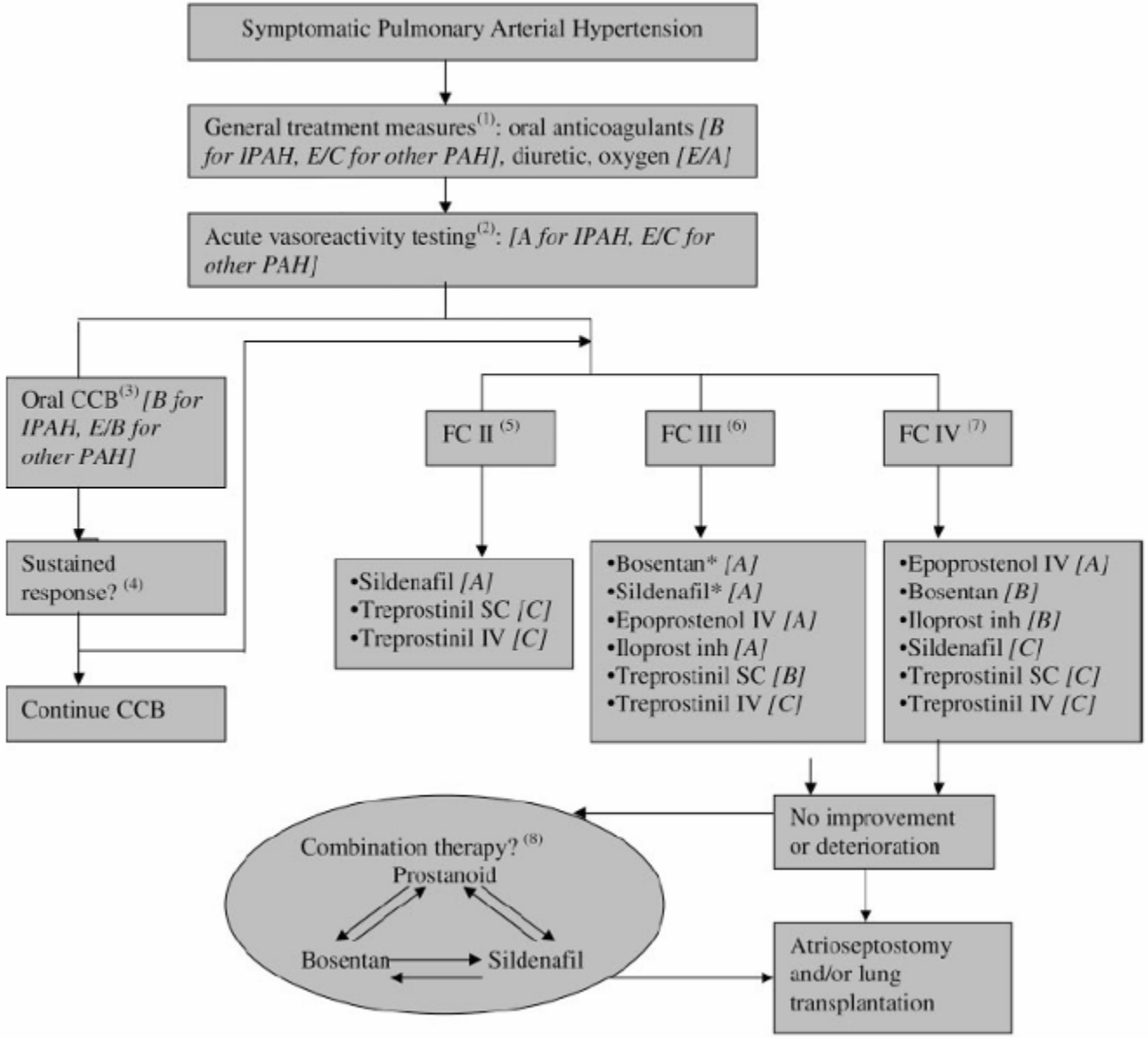


Reversible ***Irreversible***

NYHA/WHO Functional Classification

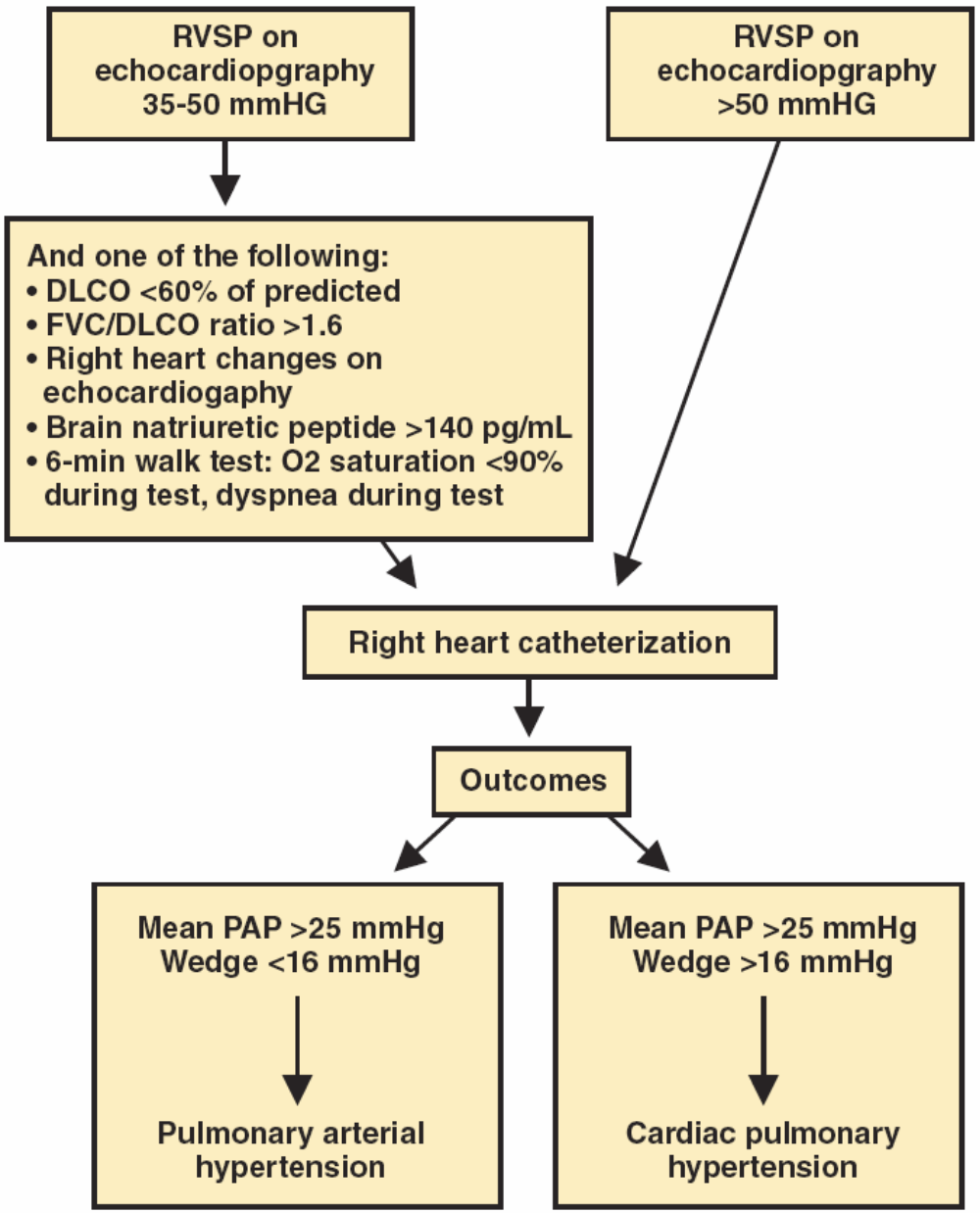
•Class I	**Symptoms do not limit physical activity. Ordinary physical activity does not cause undue discomfort.**
•Class II	**Slight limitation of physical activity. The patient is comfortable at rest, but symptoms with ordinary physical activity.**
•Class III	**Marked limitation of physical activity. The patient is comfortable at rest, but symptoms with minimal physical activity.**
•Class IV	**Inability to carry out any physical activity. The patient may experience symptoms even at rest. Discomfort increased by any physical activity. These patients manifest signs of right heart failure.**

Rich et al. *WHO Symposium on PPH*. Evian, France,1998.

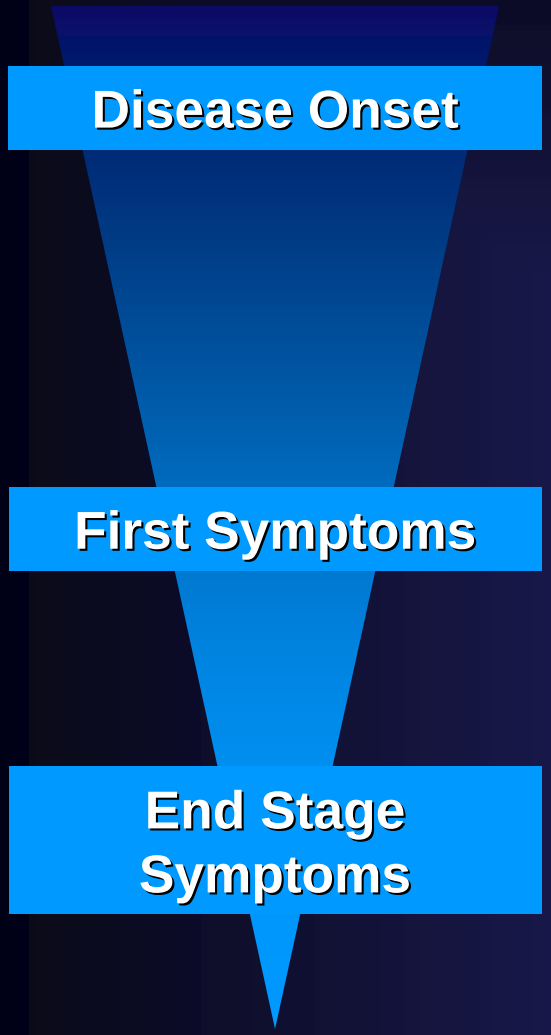


➢ **ACCP 2007 update**

Lower	Determinants of Risk	Higher
No	**Clinical Evidence of RV Failure**	Yes
Gradual	**Progression**	Rapid
II, III	**WHO Class**	IV
Longer (>400 m)	**6 Minute Walk 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


RVSP on echocardiopgraphy 35-50 mmHG
RVSP on echocardiopgraphy >50 mmHG
And one of the following:
• DLCO <60% of predicted
• FVC/DLCO ratio >1.6
• Right heart changes on echocardiogaphy
• Brain natriuretic peptide >140 pg/mL
• 6-min walk test: O2 saturation <90% during test, dyspnea during test
Right heart catheterization
Outcomes
Mean PAP >25 mmHg Wedge <16 mmHg
Pulmonary arterial hypertension
Mean PAP >25 mmHg Wedge >16 mmHg
Cardiac pulmonary hypertension

Signs and Symptoms of PAH



No early symptoms

Screening

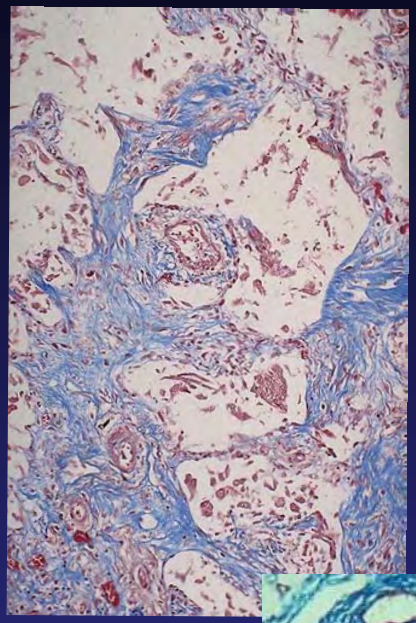
Progressive dyspnea on exertion, fatigue, palpitations, chest pain, dizziness, syncope, coughing

Symptoms and signs of right heart failure, edema, ascites

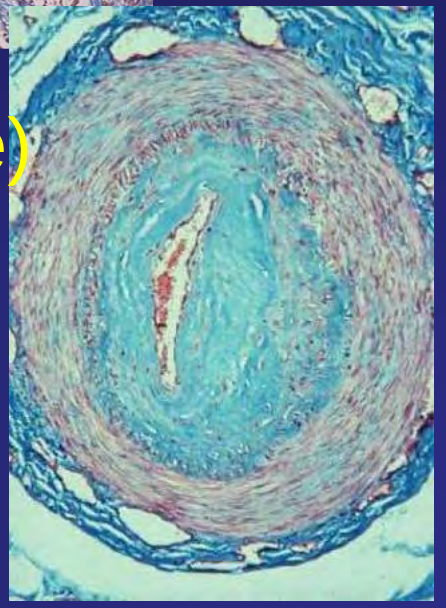
D'Alonzo GE et al. *Ann Internal Med.* 1991;115:343-349.
Gaine SP et al. *The Lancet,* 1998. 352; 719-725.

Scleroderma complications: two types

- Fibrosis (scar formation)



- Vascular (blood vessel damage)



Lung Involvement in Scleroderma

- Frequent (up to 60%)
- Major complication
- No cure - but improved management
- Rich pipeline of new drugs in development
- Early accurate diagnosis, evaluation crucial

What causes irreversible vascular damage?

Vascular Damage in Scleroderma

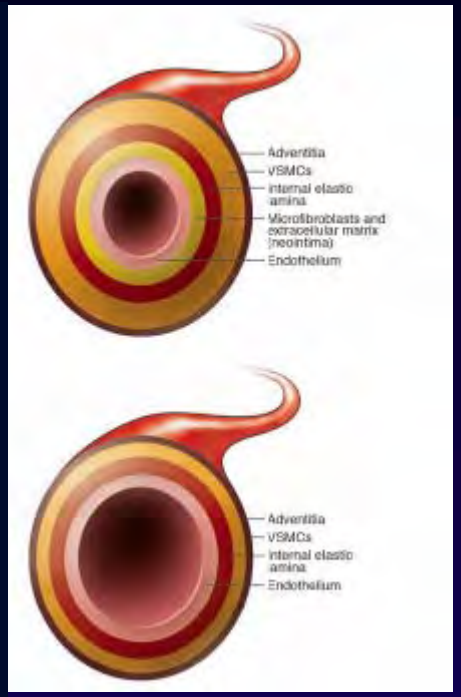
Mechanical injury
Hypoxia, ROI
Drugs/viruses (?)
Anti-EC Ab
Granzyme
Immune complex
Inflammation

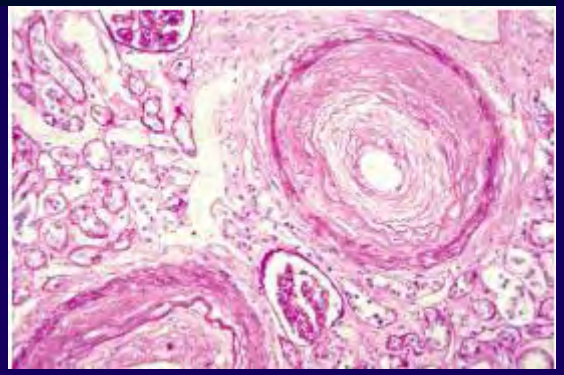
Injury of endothelium

Activation

Remodeling, narrowing

Slow blood flow

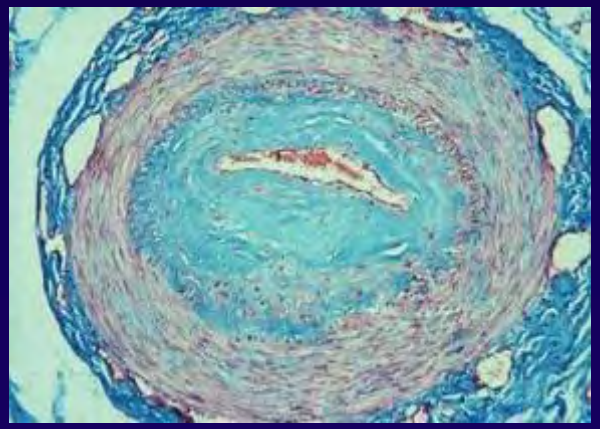




Blood clot

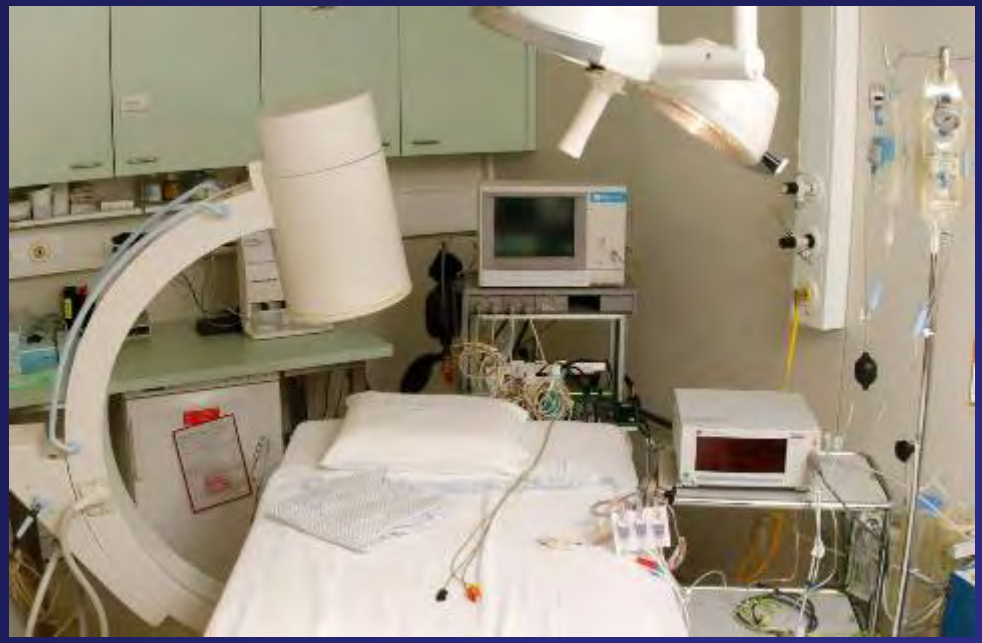
Blockage

Infarction



PAH Definition: Hemodynamic (Right Heart Catheterization)

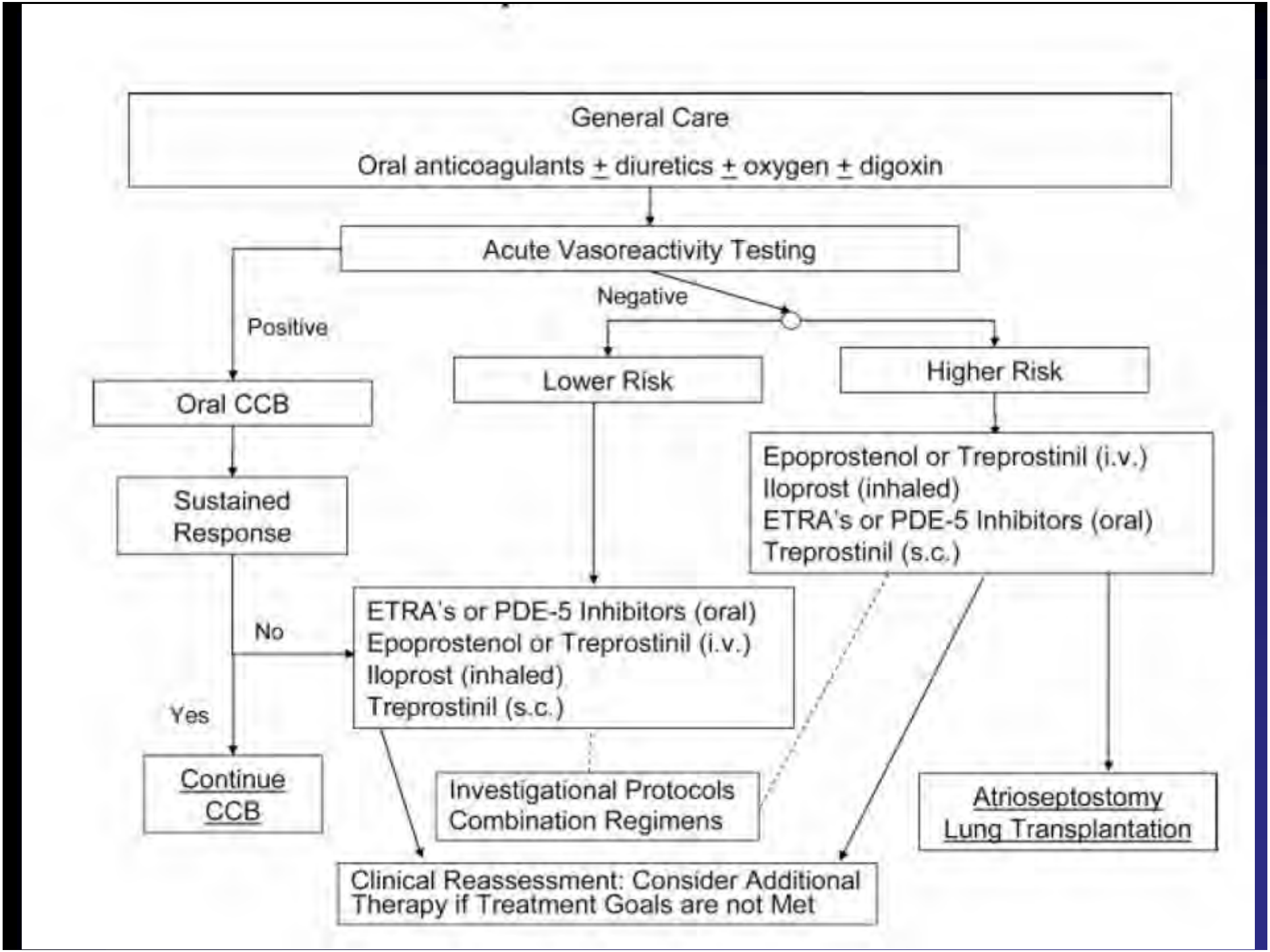
- Increased mean pulmonary arterial pressure (mPAP) (>25 mm Hg at rest)
- Normal PCWP (<15 mm Hg)
- Pulmonary vascular resistance (PVR) >3 WU



Gaine SP, Rubin LJ. *Lancet.* 1998;352:719-725.

Treatment of Scleroderma PAH

- Until recently, PAH was not widely recognized
- Pathogenesis of PAH poorly understood
- No specific treatments available
- Significant mortality


General Care
Oral anticoagulants ± diuretics ± oxygen ± digoxin
Acute Vasoreactivity Testing
Positive
Negative
Oral CCB
Lower Risk
Higher Risk
Sustained Response
Epoprostenol or Treprostinil (i.v.)
Iloprost (inhaled)
ETRA's or PDE-5 Inhibitors (oral)
Treprostinil (s.c.)
No
ETRA's or PDE-5 Inhibitors (oral)
Epoprostenol or Treprostinil (i.v.)
Iloprost (inhaled)
Treprostinil (s.c.)
Yes
Continue CCB
Investigational Protocols
Combination Regimens
Atrioseptostomy
Lung Transplantation
Clinical Reassessment: Consider Additional Therapy if Treatment Goals are not Met