Brigham and Women's Hospital
Founding Member, Mass General Brigham

Pulmonary Hypertension (for the General Pulmonologist)

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- Clinical focus: Pulmonary vascular disease, right heart failure, unexplained exertional intolerance
- Research focus: Mechanisms of pulmonary vascular remodeling

DISCLOSURES

- United Therapeutics – Investigator, Study PI, Steering Cmt Chair
- Acceleron/Merck – Investigator, and Steering Committee member
- Aria-CV – PI
- Insmed – Chair, DSMB
- Janssen R&D – Investigator Initiated Grant
- R01HL158077 – Co-I
- R01HL160025 – Co-I

Objective

Review	Review the classification of pulmonary hypertension
Review	Review the evaluation of a patient with suspected pulmonary hypertension
Review	Review the current approach to treatment

Case 1-PAH

33 yo woman $G_2P_{1(5\text{-yo male})}Sab_1$ with a history of Raynaud's

3-year history of DOE, more rapidly progressing 6-months prior to presentation

Treated for asthma with LABA / ICS without change

- Multiple steroid tapers without effect

1 month prior to presentation, pre-operative CXR (for gyn surgery) revealed enlarged pulmonary arteries

Very symptomatic when climbing stairs or an incline

Case 1-PAH

Past Medical History
- Raynaud's
- "Asthma"

Family History
- No pulmonary or cardiac disease

Social History
- No history of smoking, alcohol, recreational drug, or anorexigens / stimulants use

Medications - none

HR: 113 SBP: 109 / 78 mmHg

O_2 saturation: 93% (RA)

No JVD

Bibasilar soft rales at the bases

Normal 1st heart sound but louder 2nd heart sound and no audible murmurs

2+ peripheral edema

When to Suspect PAH

Early

Late

Symptoms

- Dyspnoea on exertion (WHO-FC)
- Fatigue and rapid exhaustion
- Dyspnoea when bending forward (bendopnoea)
- Palpitations
- Haemoptysis
- Exercise-induced abdominal distension and nausea
- Weight gain due to fluid retention
- Syncope (during or shortly after physical exertion)

Rare symptoms due to pulmonary artery dilation[a]

- Exertional chest pain:
  dynamic compression of the left main coronary artery
- Hoarseness (dysphonia):
  compression of the left laryngeal recurrent nerve (cardiovocal or Ortner´s syndrome)
- Shortness of breath, wheezing, cough, lower respiratory tract infection, atelectasis:
  compression of the bronchi

Signs of PH

- Central, peripheral, or mixed cyanosis
- Accentuated pulmonary component of the second heart sound
- RV third heart sound
- Systolic murmur of tricuspid regurgitation
- Diastolic murmur of pulmonary regurgitation

Signs of RV backward failure

- Distended and pulsating jugular veins
- Abdominal distension
- Hepatomegaly
- Ascites
- Peripheral oedema

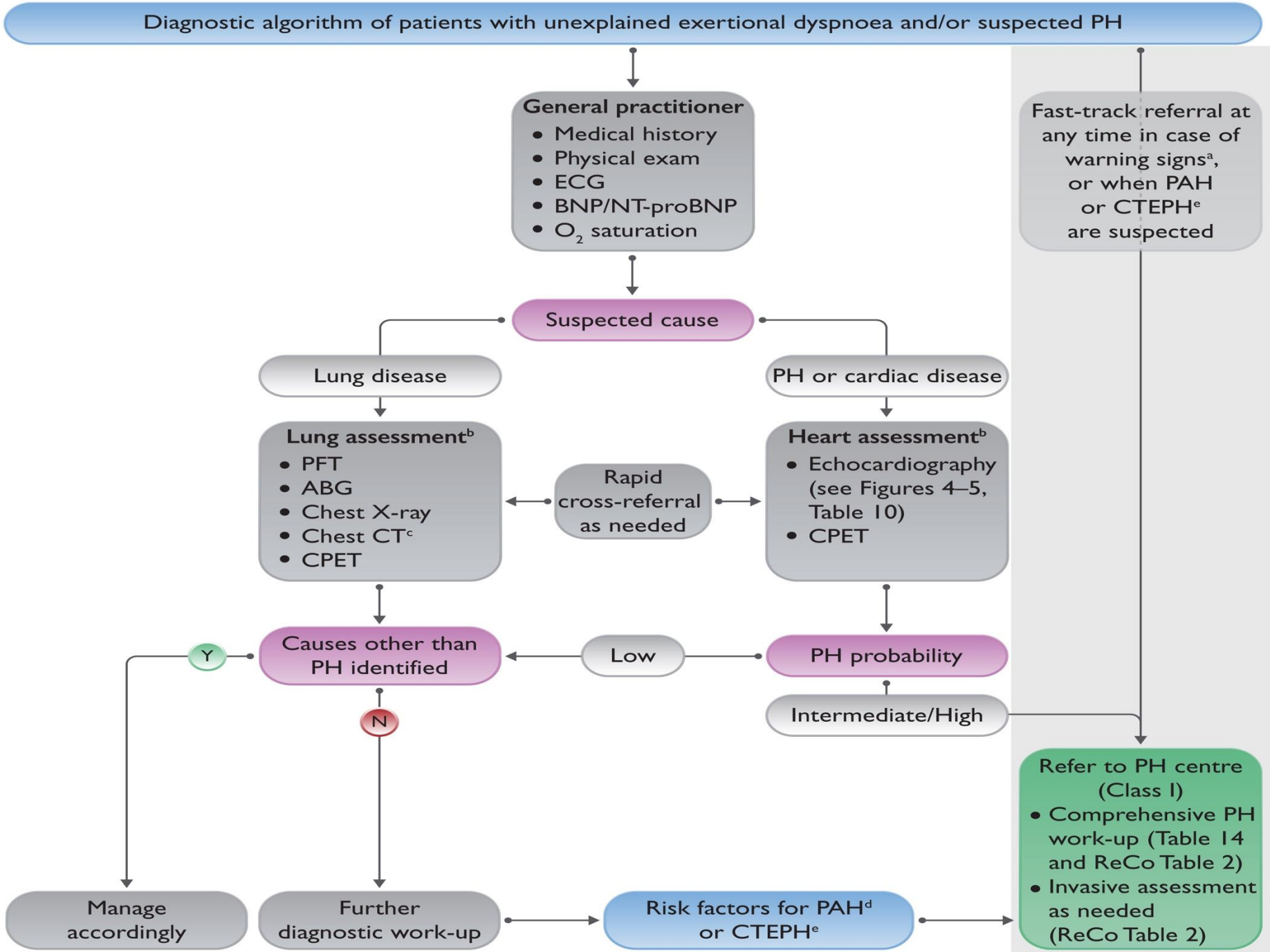
Signs pointing towards underlying cause of PH

- Digital clubbing: Cyanotic CHD, fibrotic lung disease, bronchiectasis, PVOD, or liver disease
- Differential clubbing/cyanosis: PDA/Eisenmenger's syndrome
- Auscultatory findings (crackles or wheezing, murmurs): lung or heart disease
- Sequelae of DVT, venous insufficiency: CTEPH
- Telangiectasia: HHT or SSc
- Sclerodactyly, Raynaud's phenomenon, digital ulceration, GORD: SSc

Signs of RV forward failure

- Peripheral cyanosis (blue lips and tips)
- Dizziness
- Pallor
- Cool extremities
- Prolonged capillary refill

Eur Heart J, ehac237, https://doi.org/10.1093/eurheartj/ehac237



Eur Heart J, ehac237, https://doi.org/10.1093/eurheartj/ehac237

33 yo Woman with Dyspnea

[redacted]
Female Caucasian
67in 224lb
Room:909
Loc:206

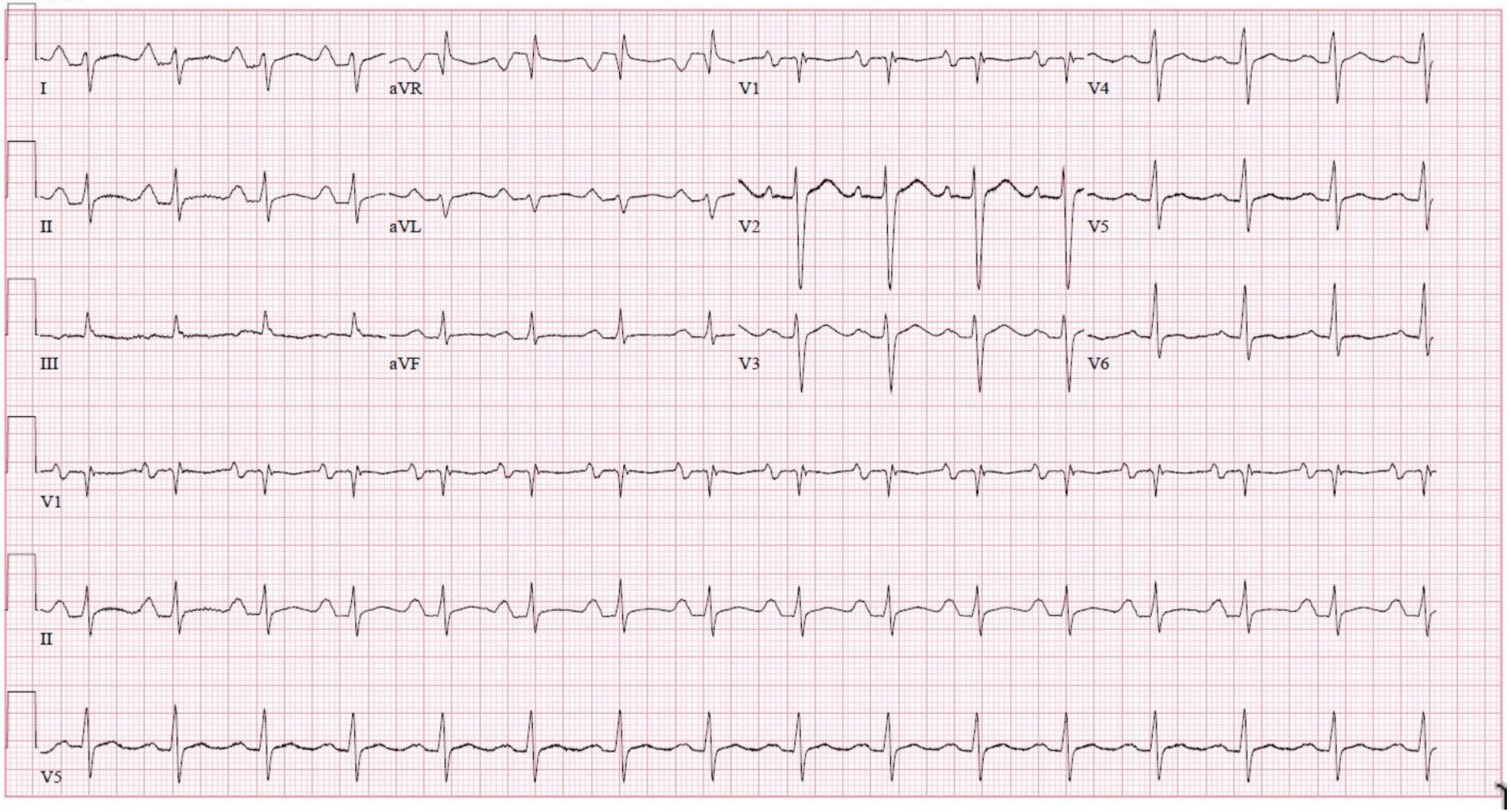
Vent. rate	94	BPM
PR interval	220	ms
QRS duration	120	ms
QT/QTc	576/720	ms
P-R-T axes	26 122	24
BP	88/48	mmHg

Sinus rhythm with 1st degree A-V block
Right axis deviation
Right atrial enlargement
Abnormal ECG
When compared with ECG of 23-APR-2023 05:04, (unconfirmed)
Non-specific change in ST segment in Lateral leads
Nonspecific T wave abnormality, improved in Lateral leads
QT has lengthened
Electronically signed by ROSENBAUM M.D., LISA (519) on 4/24/2023 6:09:54 PM

Technician:System System
Test ind:I49.9

Referred by: ELAZER EDELMAN
Confirmed By: LISA ROSENBAUM M.D.

F Number:



Case 1-PAH

Pulmonary Function Tests

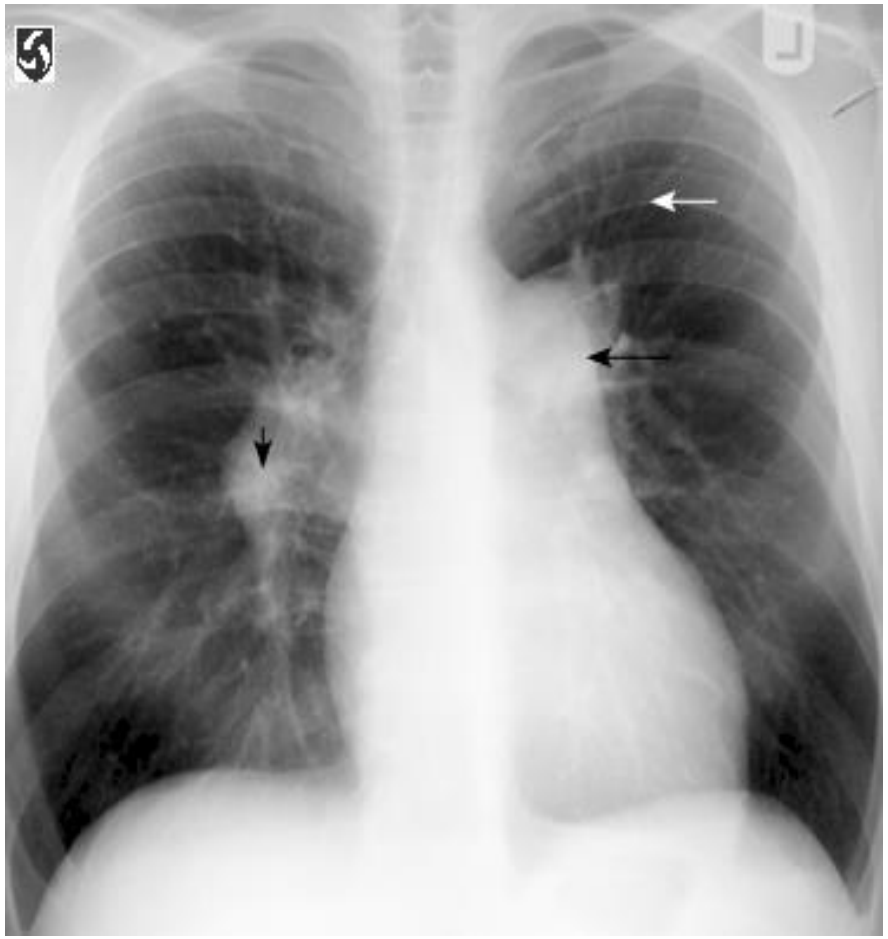
- Normal Spirometry
- Normal Lung Volumes
- Lower limit of normal DLCO

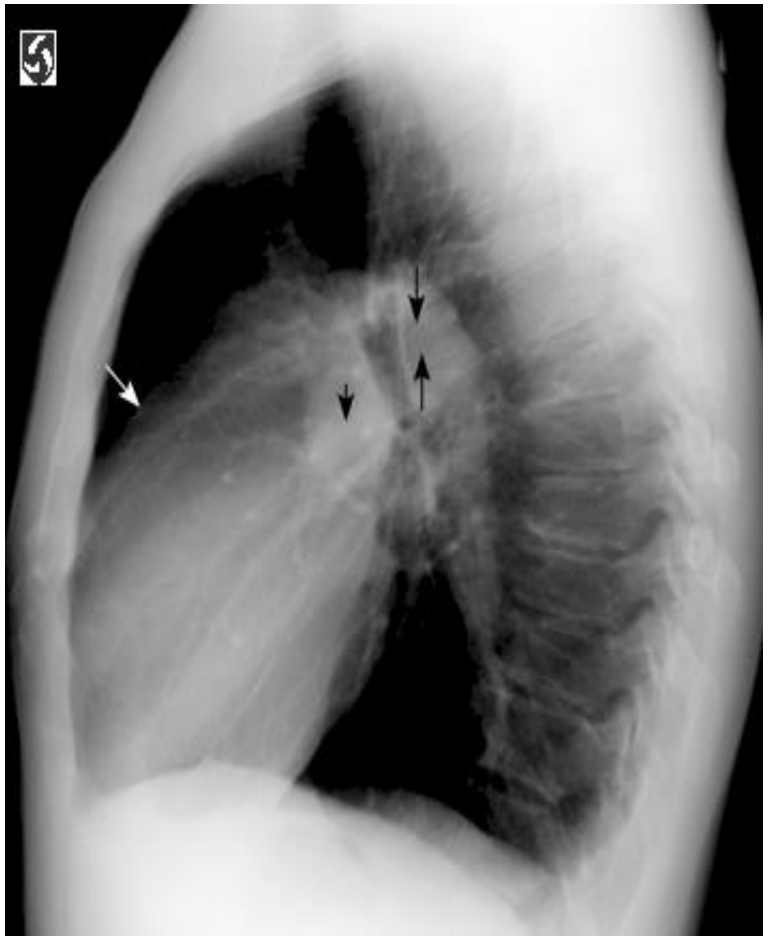
Normal metabolic profile, liver function tests, blood counts and thyroid function tests

NT-proBNP - 1836

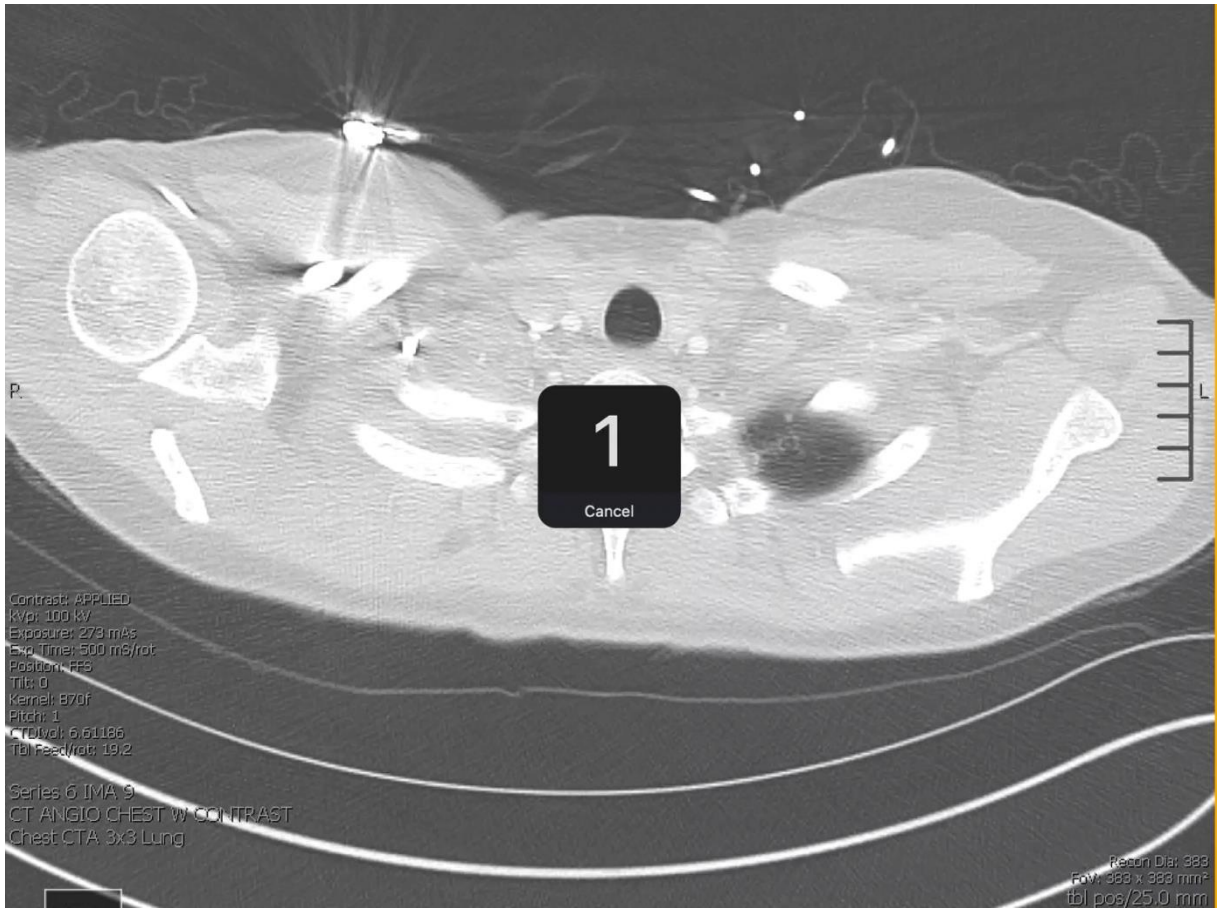
ANA + 1:320 and other auto-immune serology's negative

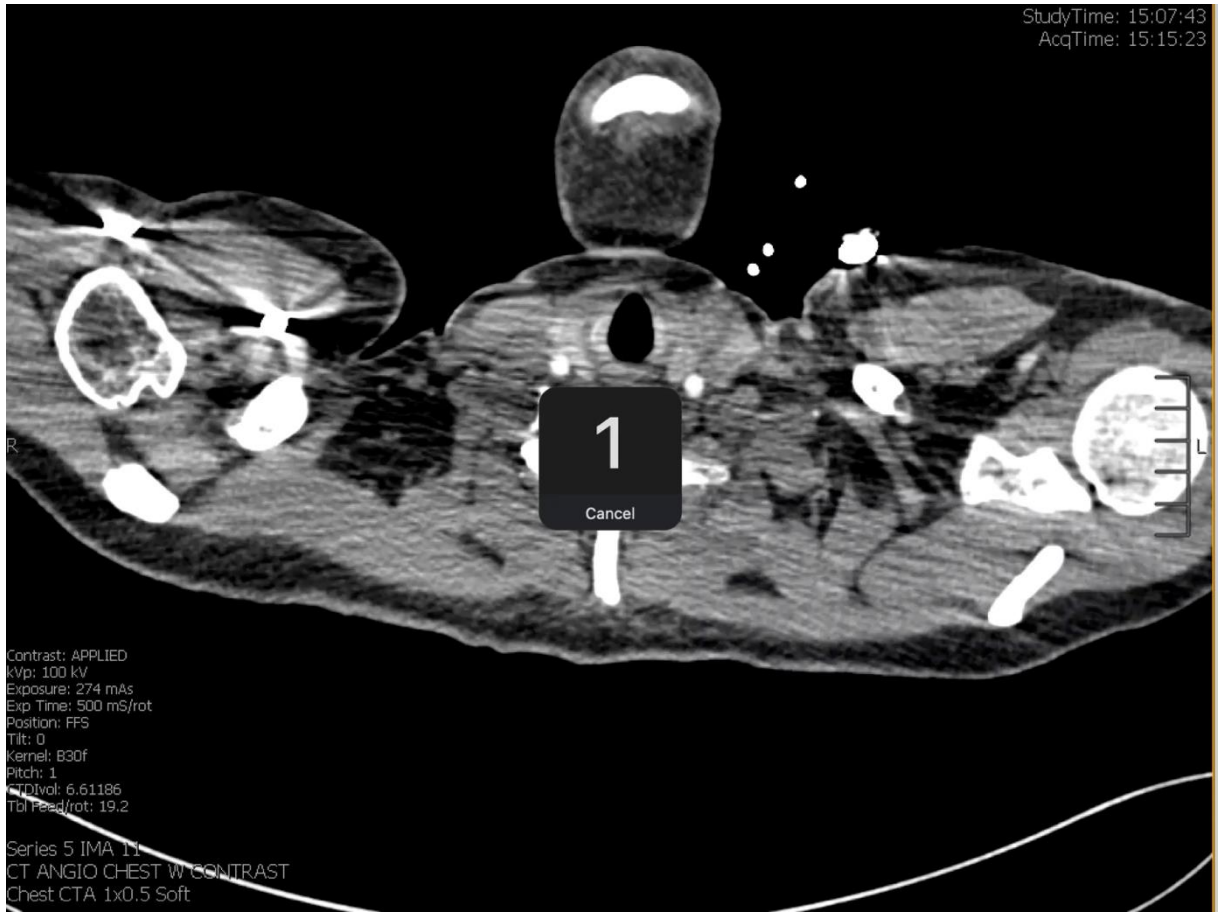
Chest Radiograph





CTA


P
L
1
Cancel
Contrast: APPLIED
kVp: 100 kV
Exposure: 273 mAs
Exp Time: 500 mS/rot
Position: FFS
Tilt: 0
Kernel: B70f
Pitch: 1
CTDIvol: 6.61186
Tbl Feed/rot: 19.2
Series 6 IMA 9
CT ANGIO CHEST W CONTRAST
Chest CTA 3x3 Lung
Recon Dia: 383
FoV: 383 x 383 mm²
tbl pos/25.0 mm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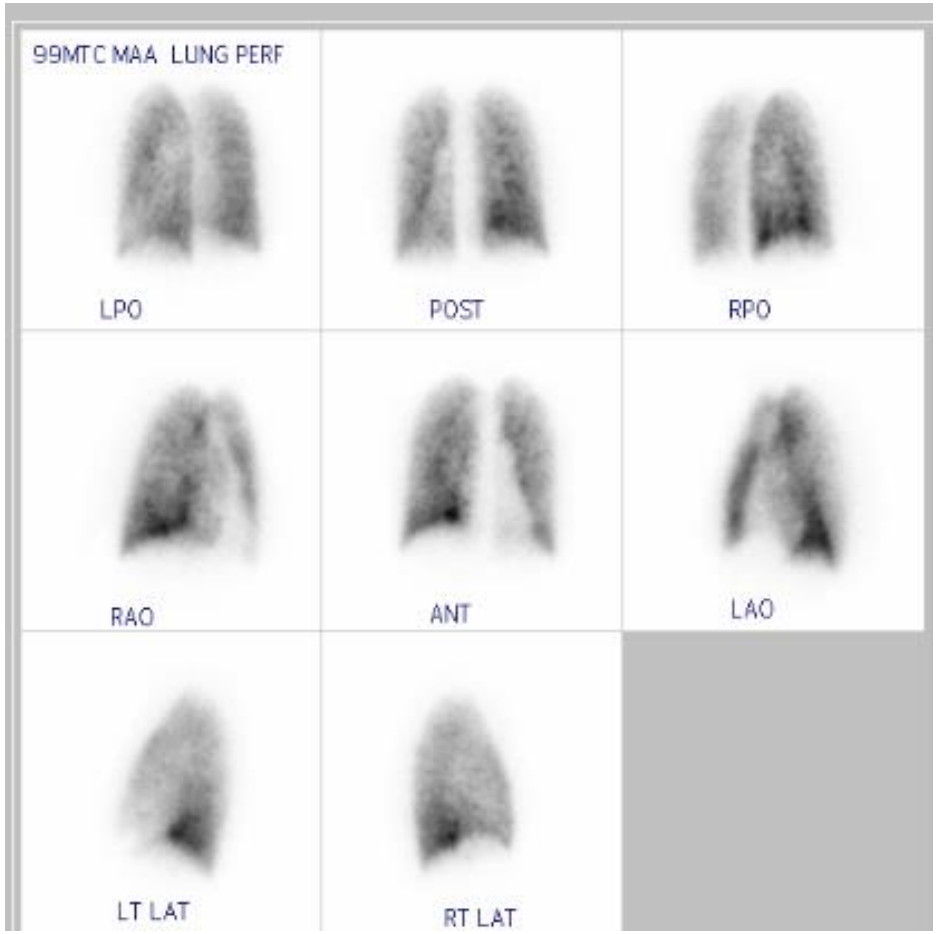
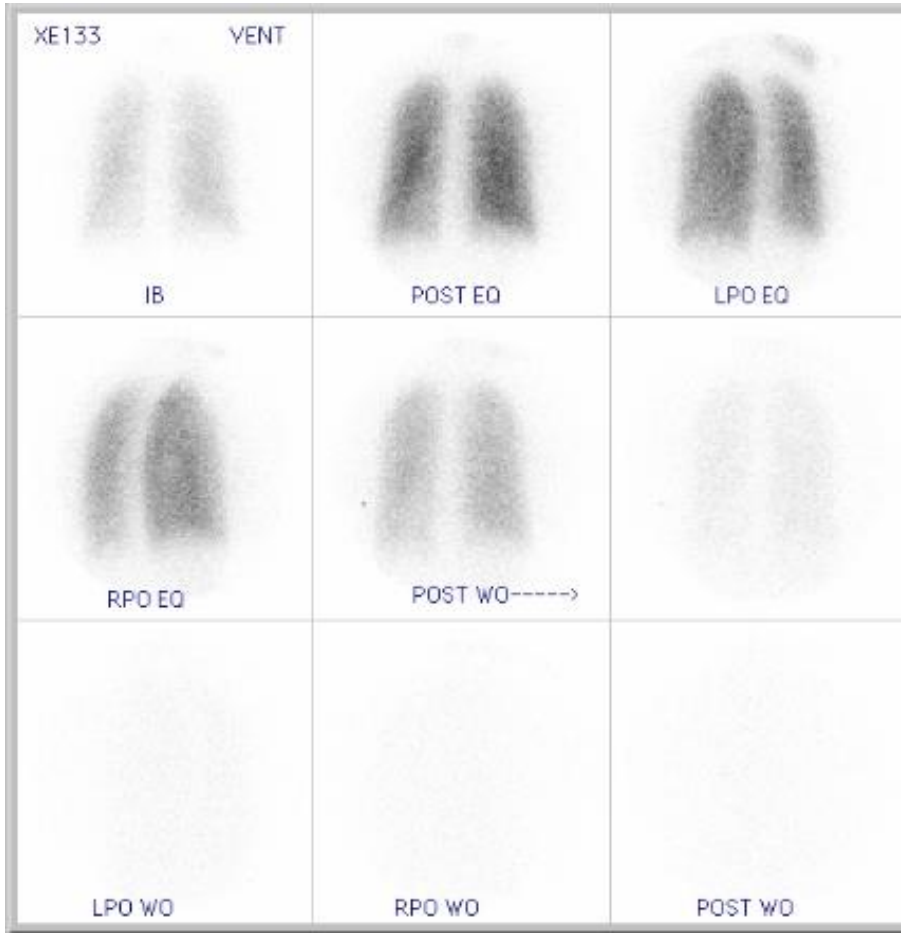
CTDIvol: 6.61186
Tbl Feed/rot: 19.2
Series 5 IMA 11
CT ANGIO CHEST W CONTRAST
Chest CTA 1x0.5 Soft

VQ Scan


99MTC MAA LUNG PERF
LPO
POST
RPO
RAO
ANT
LAO
LT LAT
RT LAT


XE133
VENT
IB
POST EQ
LPO EQ
RPO EQ
POST WO----->
LPO WO
RPO WO
POST WO

Patient #1: Physical Examination

Six Minute Walk

- 318 meters Borg 5
- Desaturations to 89% during 6MW

Chest CT

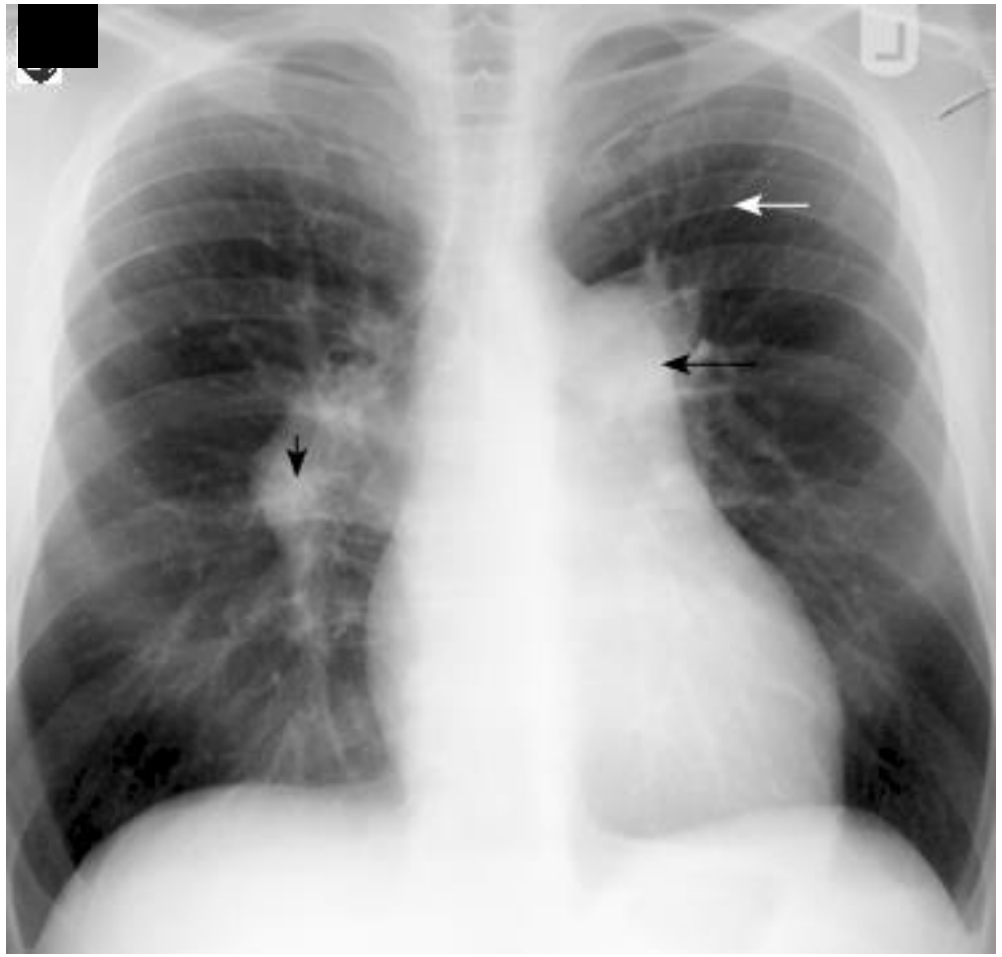
- No signs of interstitial lung disease or pulmonary emboli

V/Q scan

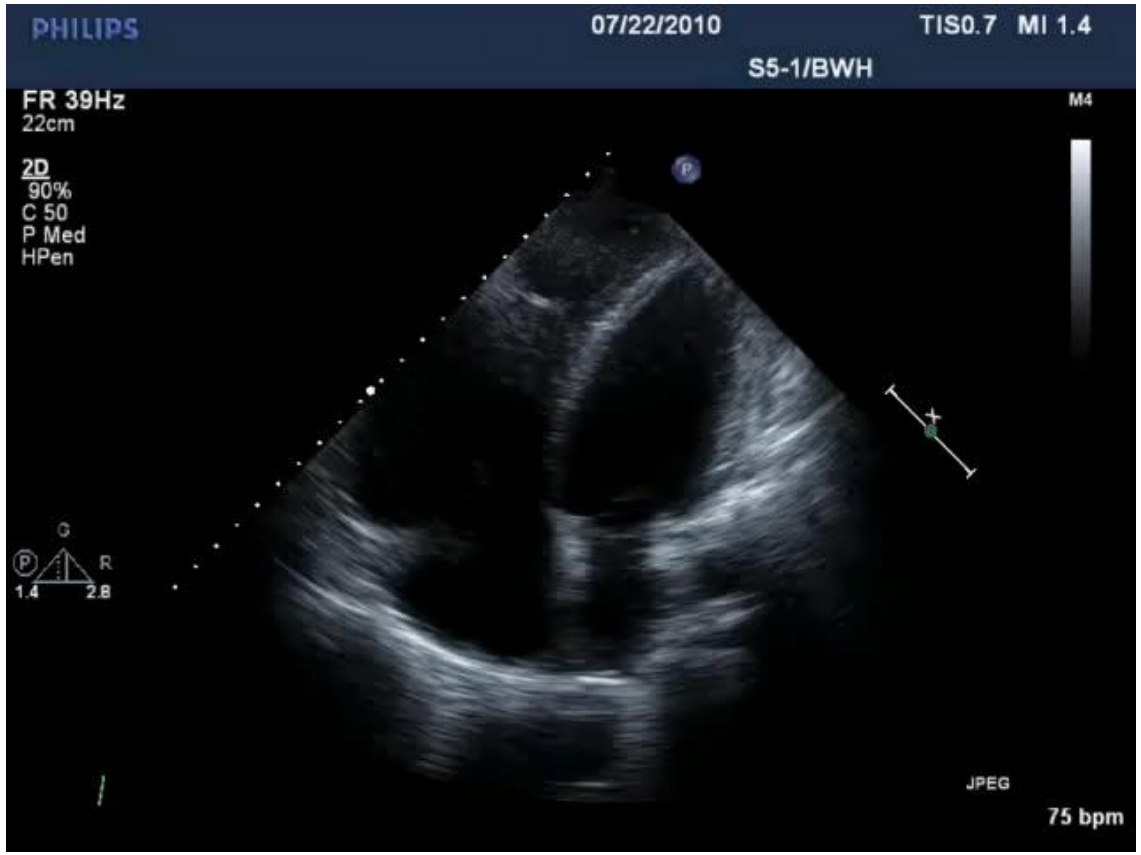
- No evidence of large obstructive clot

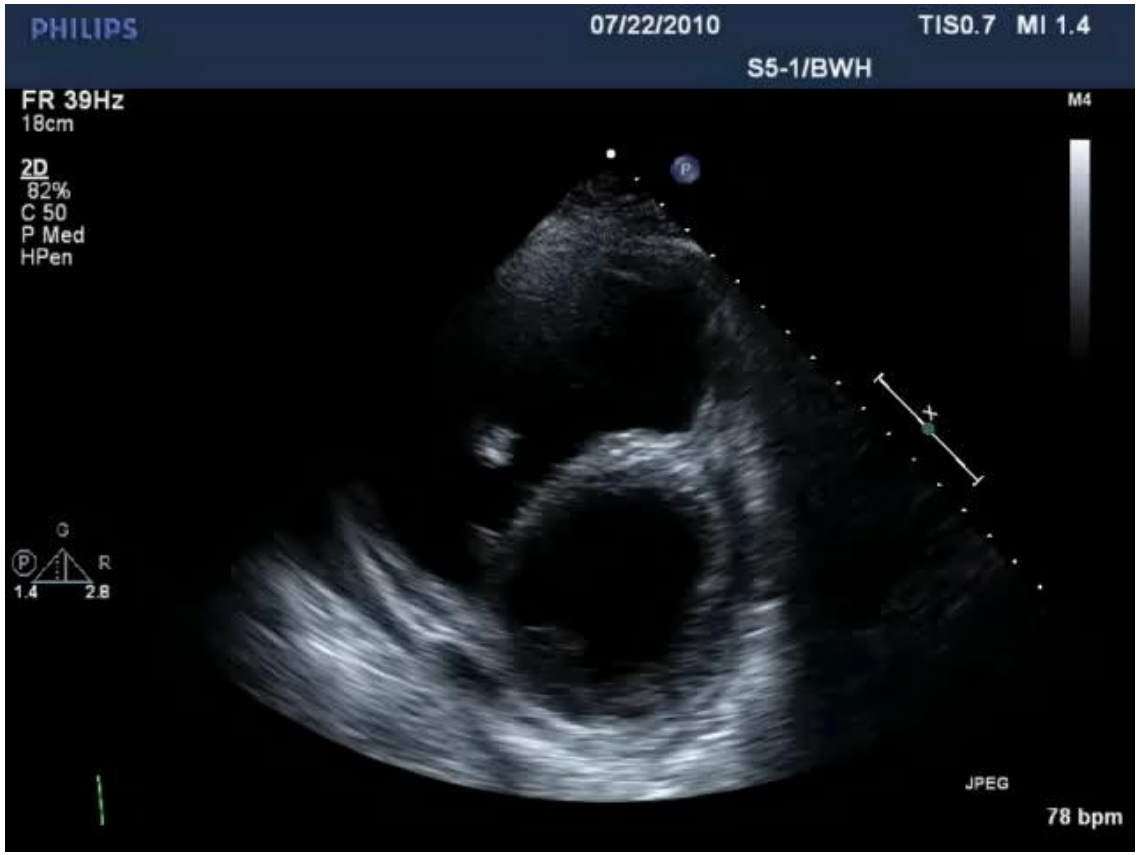
EKG

- RAD, RVH, P-pulmonale

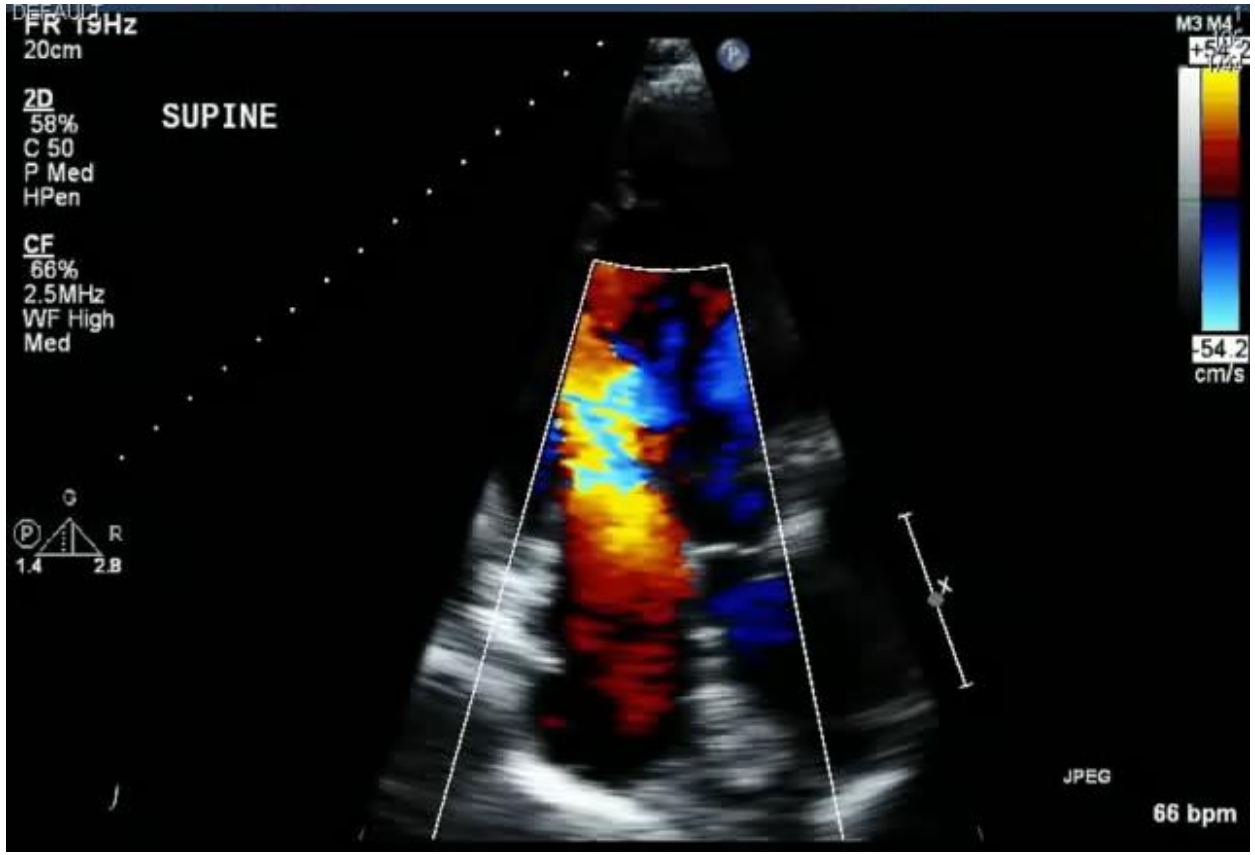


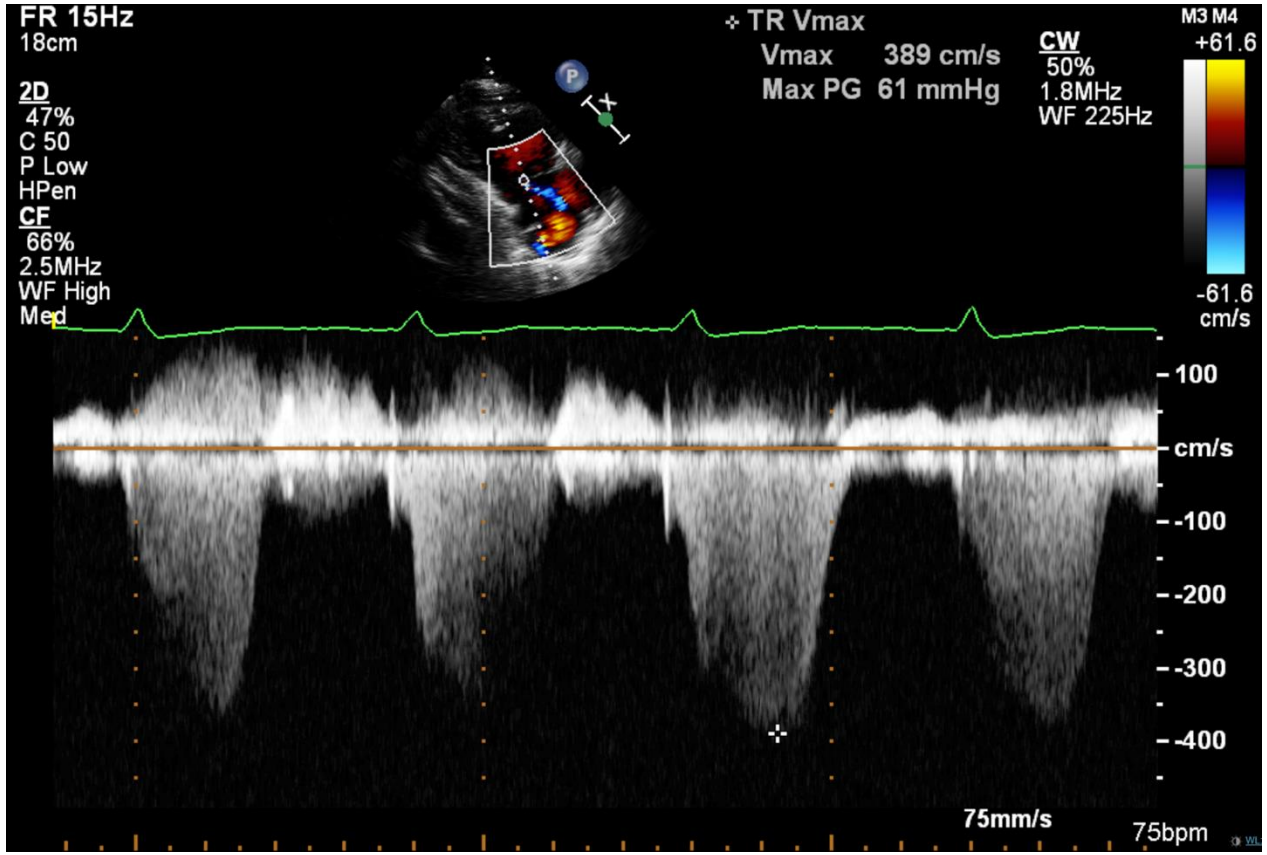
33 yo Woman with Dyspnea





33 yo Woman with dyspnea
Tricuspid Regurgitation

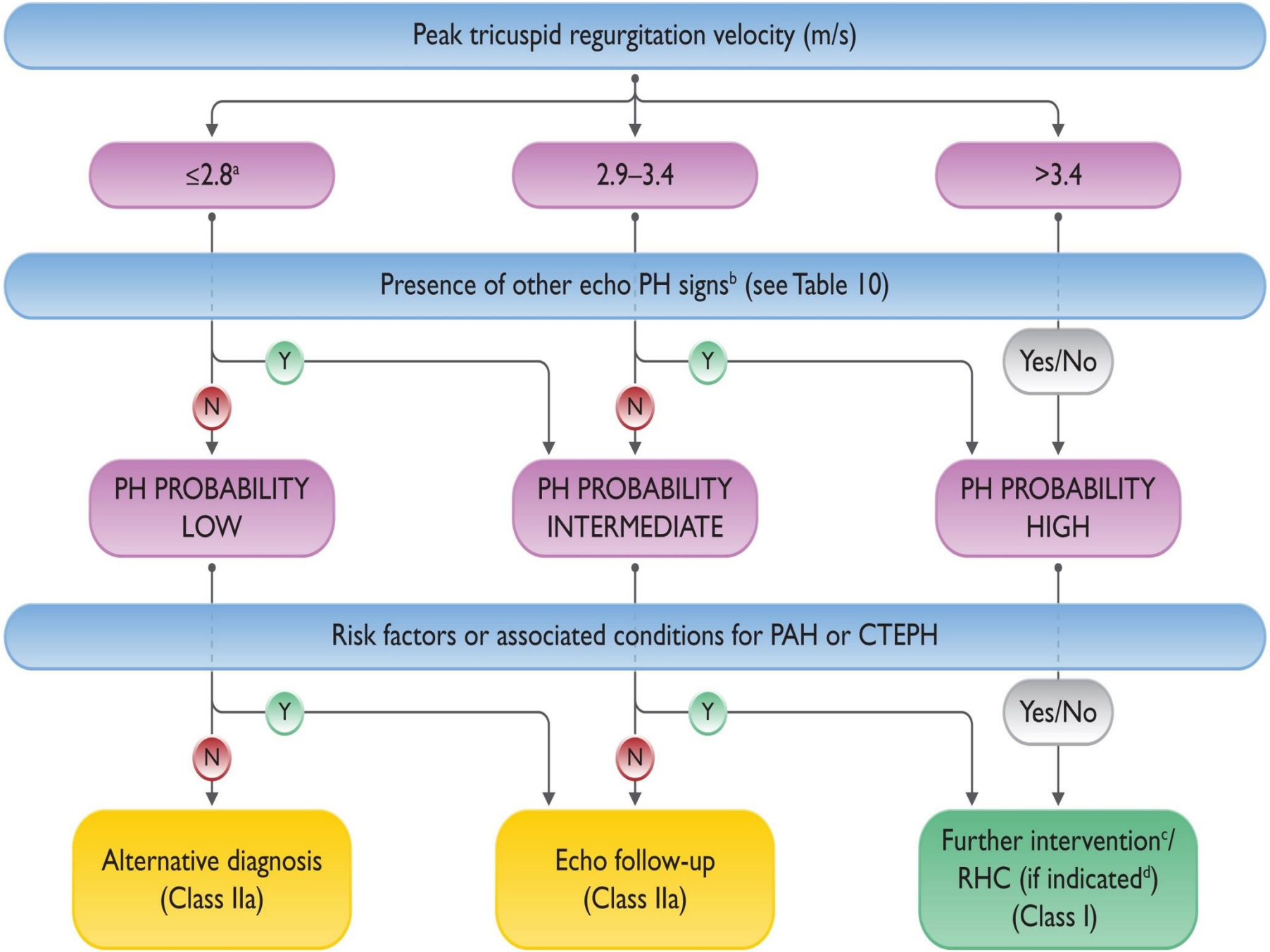




Modified Bernoulli's Equation:

$4 \times (V)^2 + RAP = RVSP\ (PASP)$

RVSP ~ 78



Eur Heart J, ehac237, https://doi.org/10.1093/eurheartj/ehac237

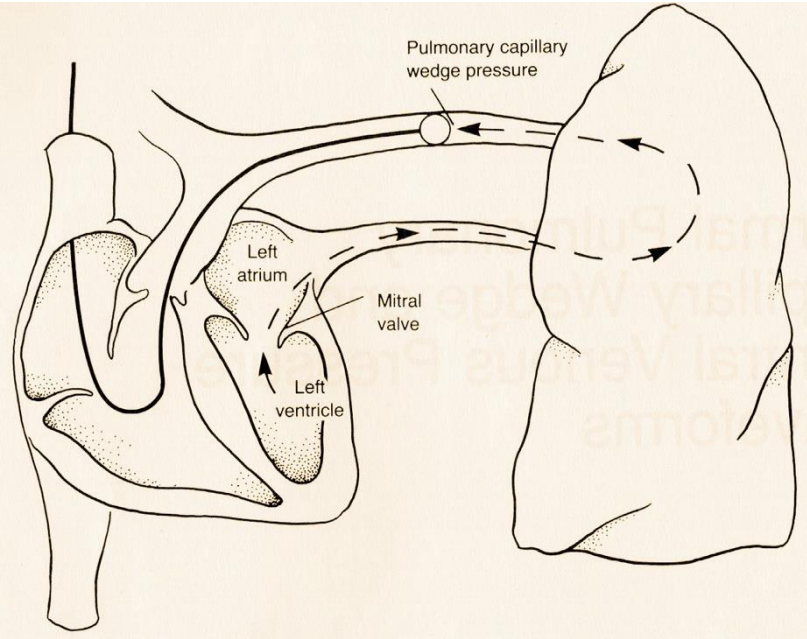
Information obtained from the PAC

Directly measured

- CVP
- PA pressure
- PCWP
- Cardiac output
- SvO_2

Calculated from directly measured data

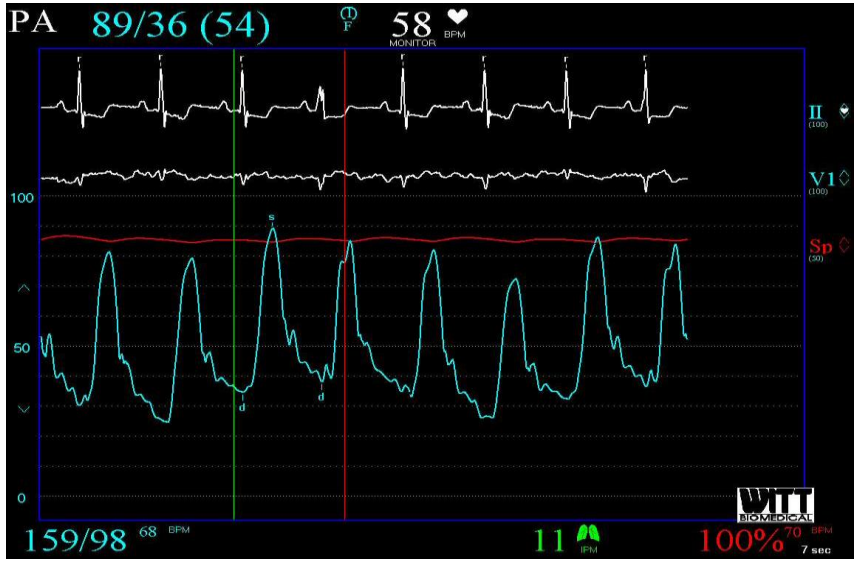
- Stroke volume / index
- Cardiac index
- Systemic vascular resistance
- Pulmonary vascular resistance
- Oxygen delivery

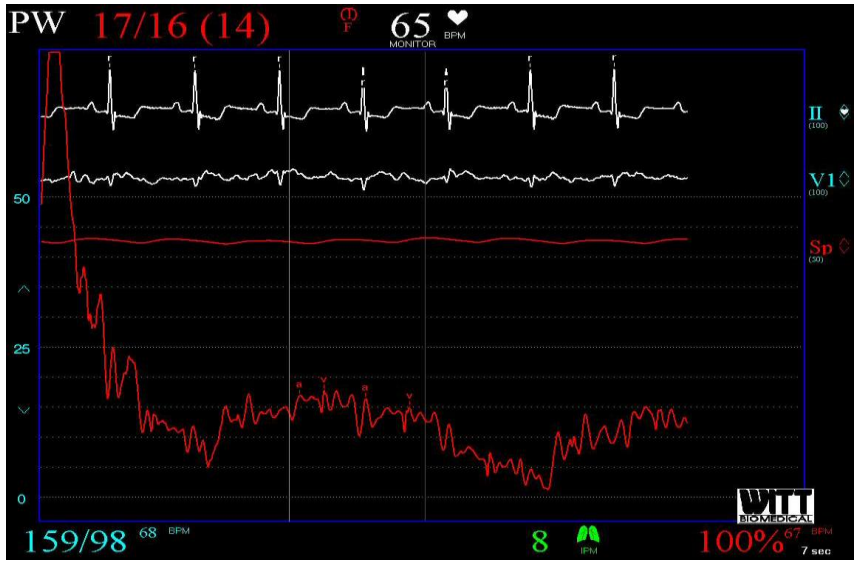


Case 1-PAH

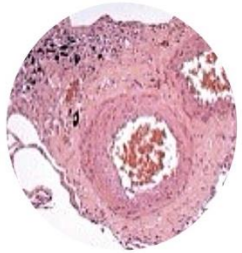
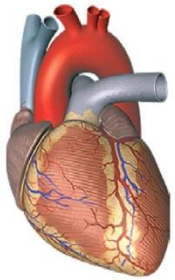
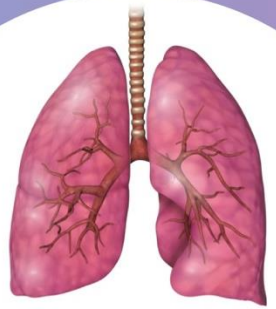
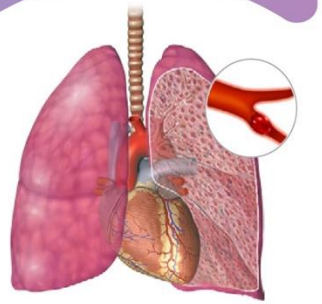
RHC:

- RA (CVP) 17
- RV 87/12 (RVEDP: 21)
- PAP 89/36 (54)
- PCWP 14
- CO/CI 4.6/1.8
- PVR 710 (9wu); SVR 871
- 40ppm NO – No response



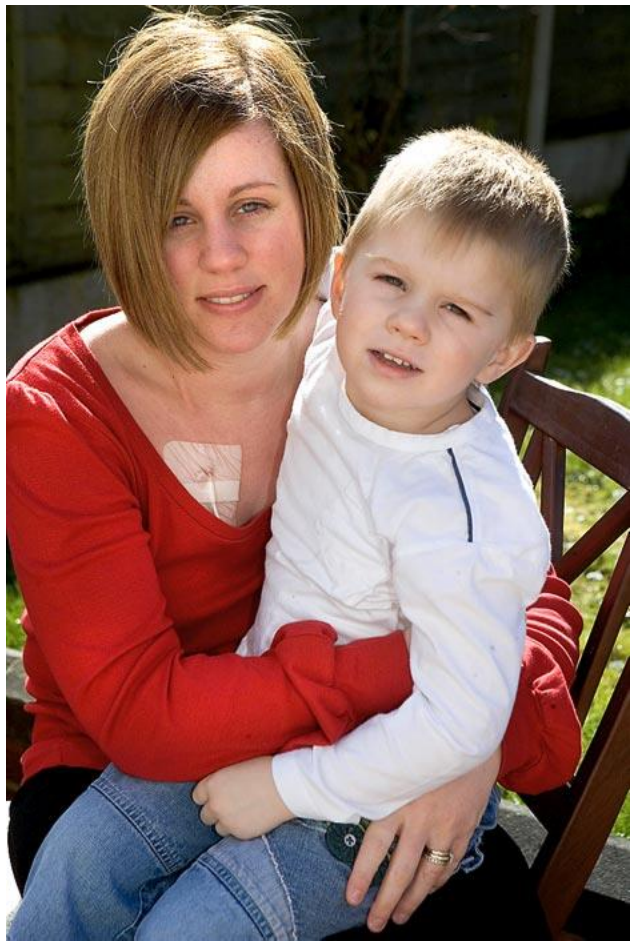


Updated Classification System

Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematological disorders • Systemic disorders
PREVALENCE				
Rare	Very common	Common	Rare	Rare

Eur Heart J, ehac237, https://doi.org/10.1093/eurheartj/ehac237

Case 1-PAH



Severe PAH, NYHA Functional Class 3b

- HR 113
- SBP 109
- 6-MWD 318m, BDS 5
- NT-proBNP – 1836
- REVEAL Score >8

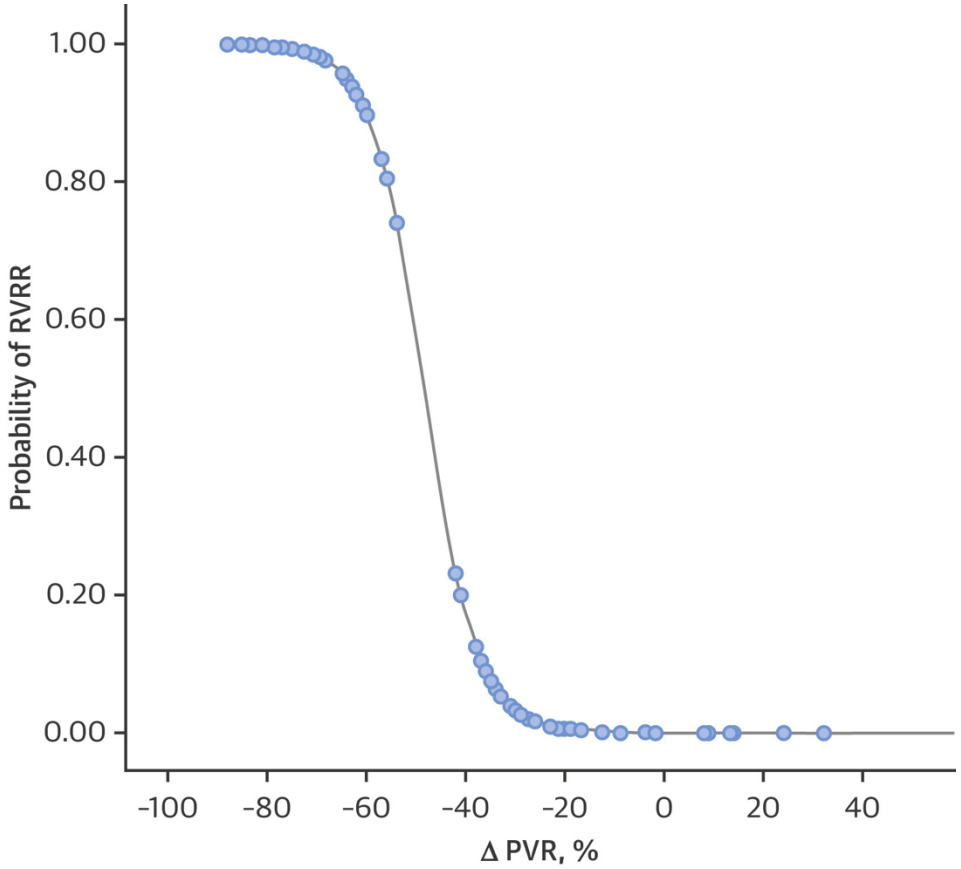
How do we treat this patient?

How do we monitor and follow-up this patient ?

Pulmonary Arterial Hypertension:
Goals of Therapy

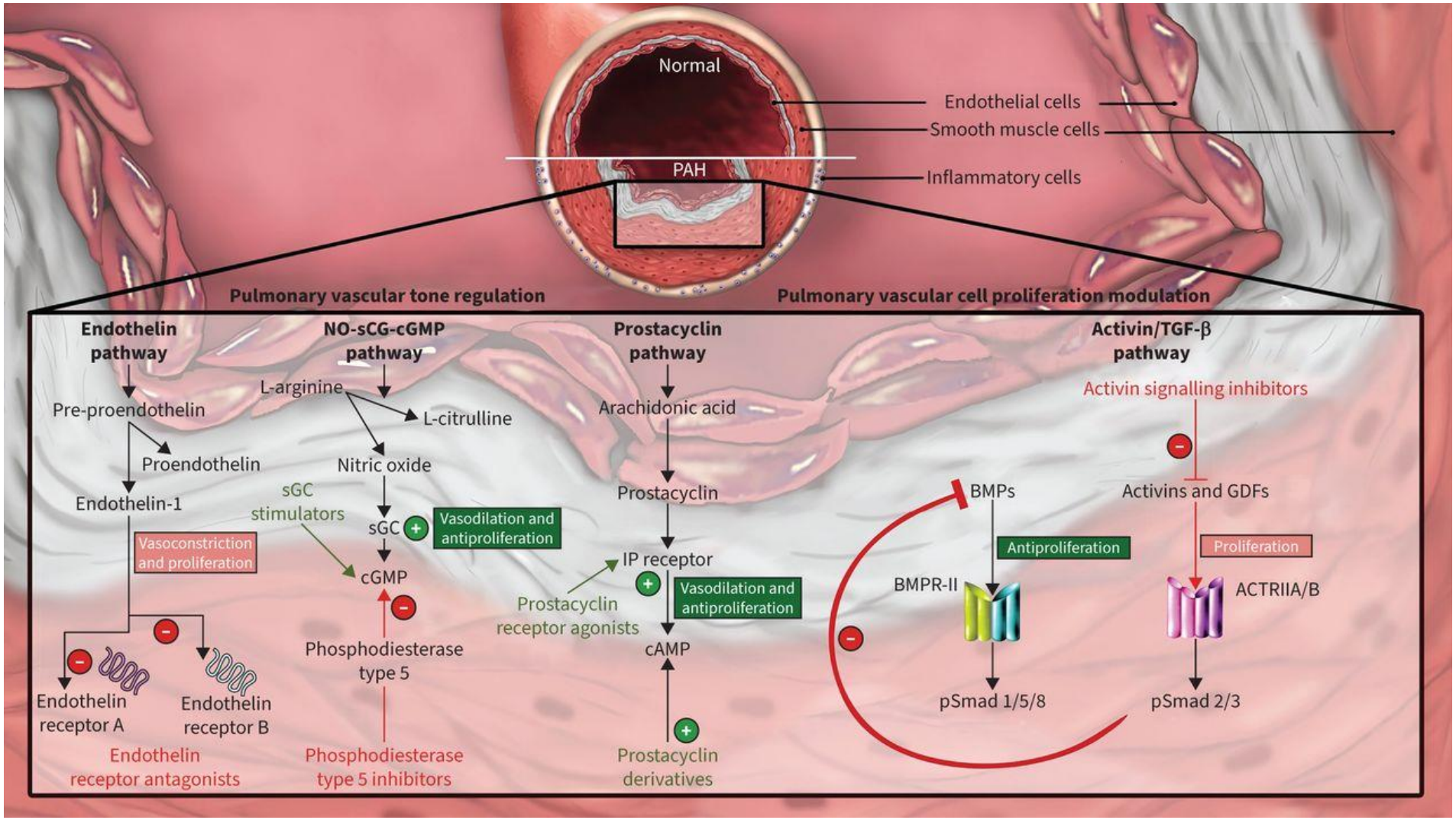
- Improve exercise capacity
- Improve functional class
- Prevent clinical worsening
- Improve survival
- Improve hemodynamics

  - At least a 50% reduction in PVR
  - mPA < 25 mmHg



J Am Coll Cardiol. 2019 Apr 2;73(12):1463-1482

Targets for established and emerging therapies in pulmonary arterial hypertension



Pulmonary Vascular Tone Regulation

Vascular Cell Proliferation Modulation

Eur Respir J 2023;62:2301726

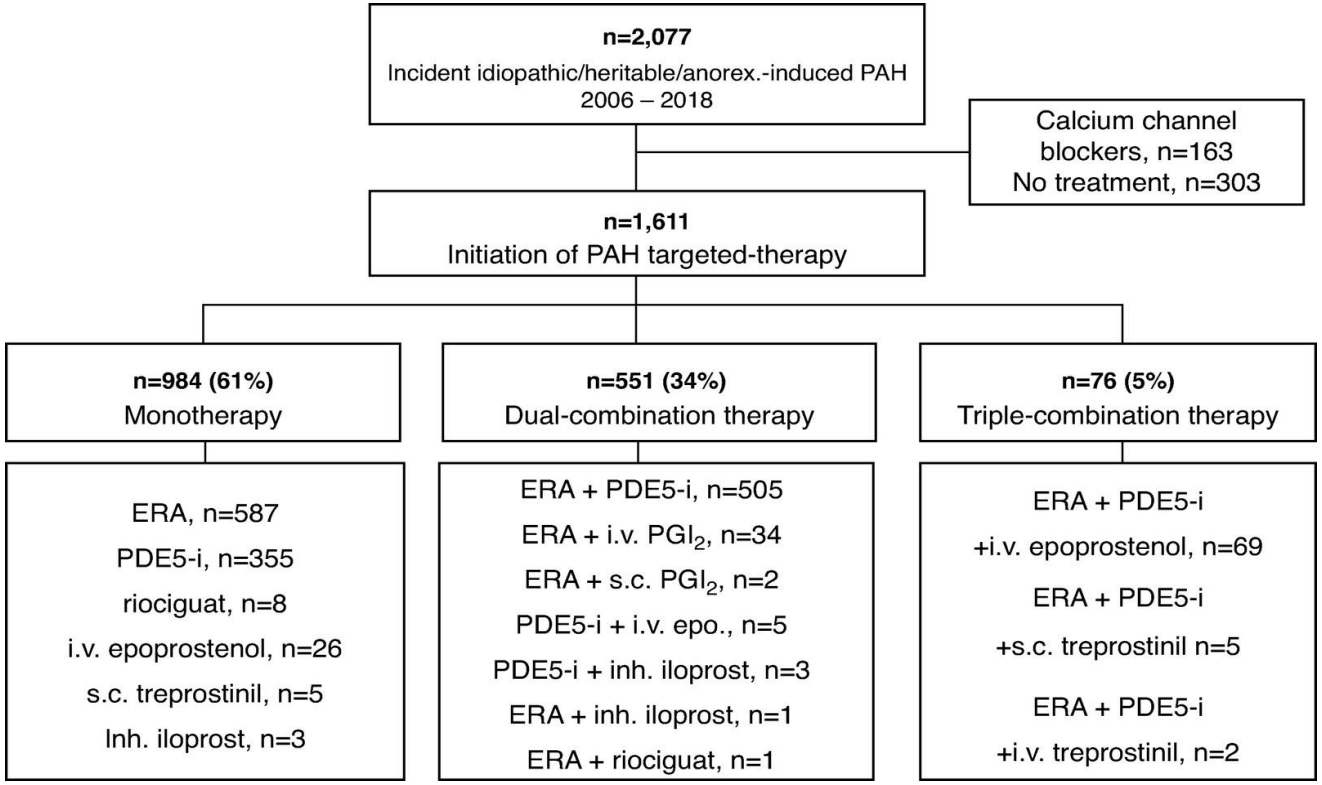
Expected Adverse Effects of PAH-Specific Therapies

Most PAH medications have class-related adverse effects, often due to vasodilatory properties of the medications

- ERAs
  - Edema
- PDE-5 inhibitors
  - Flushing, headache
- Prostacyclins
  - Headache, flushing, jaw pain, nausea
- Riociguat (sGC inhibitor)
  - Flushing, headache
- Selexipag (IP receptor agonist)
  - Headache, flushing, nausea
- Activin Inhibitors
  - Sotatercept – Increased Hgb, telangiectasias, epistaxis

In addition, PAH medications are often up-titrated on the basis of tolerability

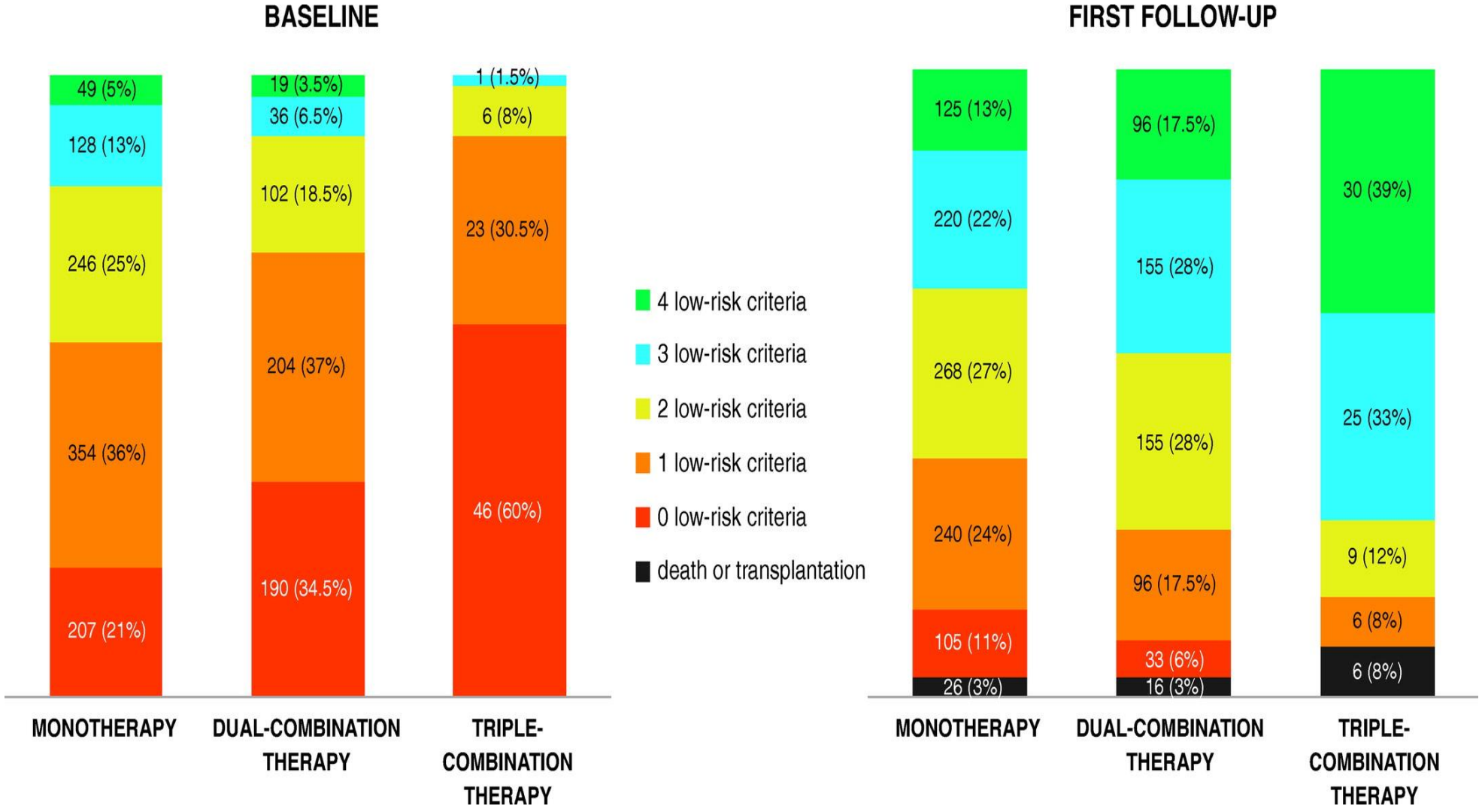
Association between Initial Treatment Strategy and Long-Term Survival in Pulmonary Arterial Hypertension



Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or	<50	50–199	200–800	>800
NT-proBNP,[a] ng/L	<300	300–649	650–1100	>1100

Am J Respir Crit Care Med. 2021 Oct 1;204(7):842-854.

Association between Initial Treatment Strategy and Long-Term Survival in Pulmonary Arterial Hypertension



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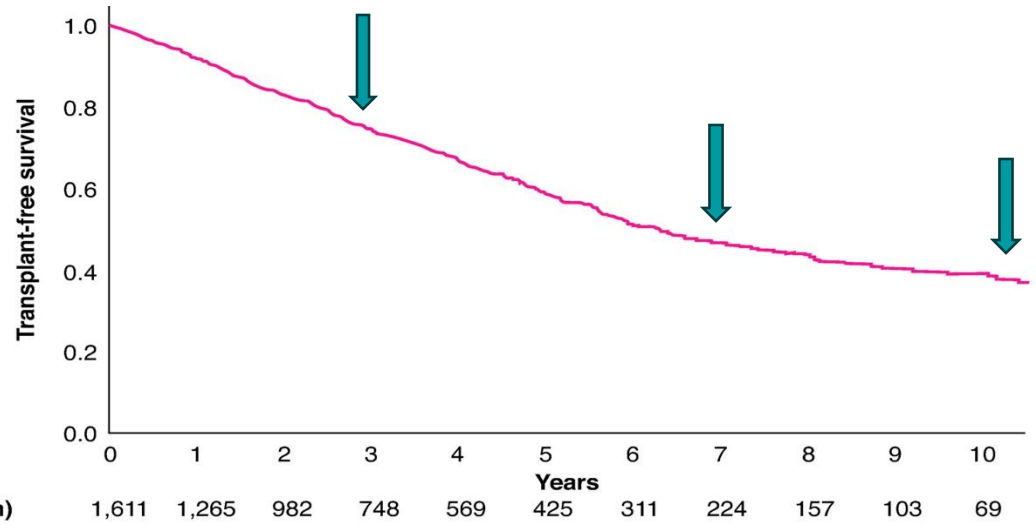
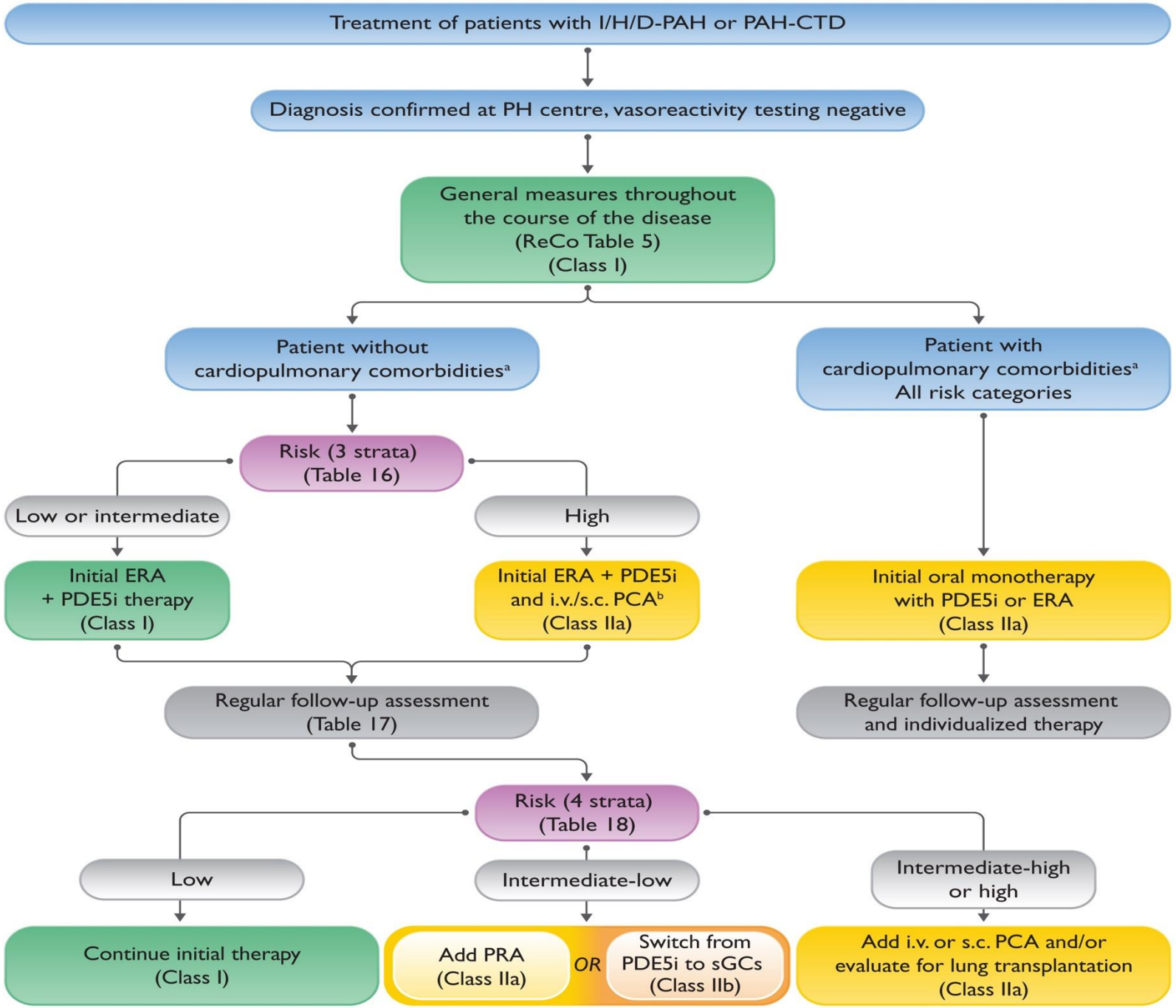


Am J Respir Crit Care Med. 2021 Oct 1;204(7):842-854.



Eur Heart J, ehac237, https://doi.org/10.1093/eurheartj/ehac237

Treatment Algorithm

General Measures	Supportive Therapy
• Avoid pregnancy • Influenza and pneumococcal immunization • Psychological counseling • Supervised exercise training • Supplemented oxygen • Regional anesthesia preferred over general anesthesia	• Diuretics • Long-term oxygen therapy • Anticoagulant therapy • Iron deficiency correction • Use of ACEi, AT1-antagonists, β-blockers, ivabradine only if specifically indicated • Treatment of arrhythmias

Note: **Oral anticoagulant therapy is not recommended in associated forms of PAH, while in IPAH, HPAH and DT-PAH the data on efficacy is more conflicting**. The decision about anticoagulation has to be made on a case-by-case basis after an individual risk–benefit analysis.

Galié N, et al. *Eur Respir J*. 2016;37:67–119.

Follow-up Monitoring Schedule

Parameter	Baseline (pretreatment)	Every 3-6 months	3-4 Months after start or change in therapy	If clinical worsening
Clinical assessment WHO functional class ECG	X	X	X	X
6-MWD / CPET	X	X	X	X
BNP / NT-proBNP	X	X	X	X
ECHO	X		(X)	X
Right heart catheterization	X		(X)	X

Case 1-PAH

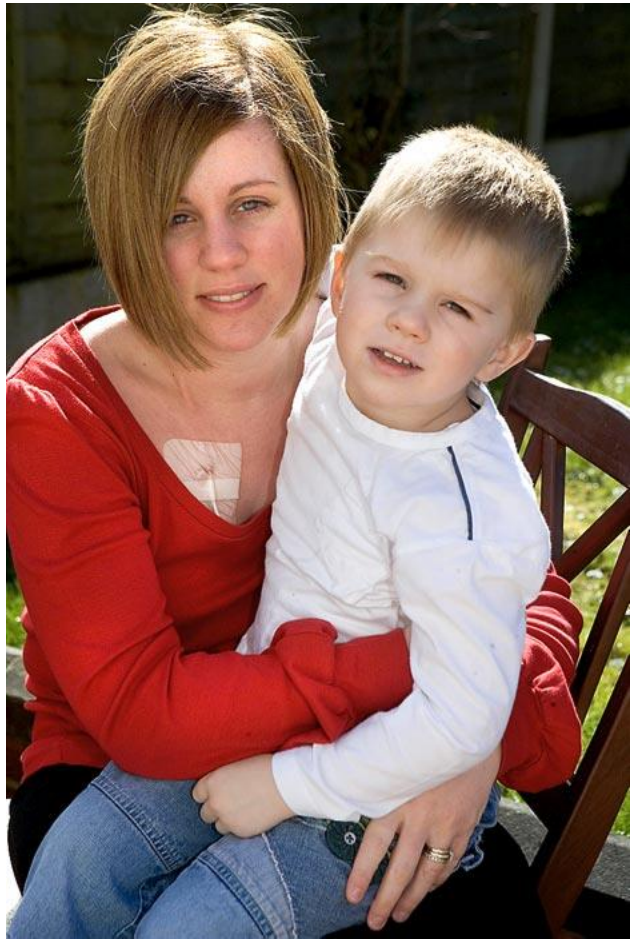
Severe PAH, NYHA Functional Class 3b

- 6-MWD 318m, BDS 5

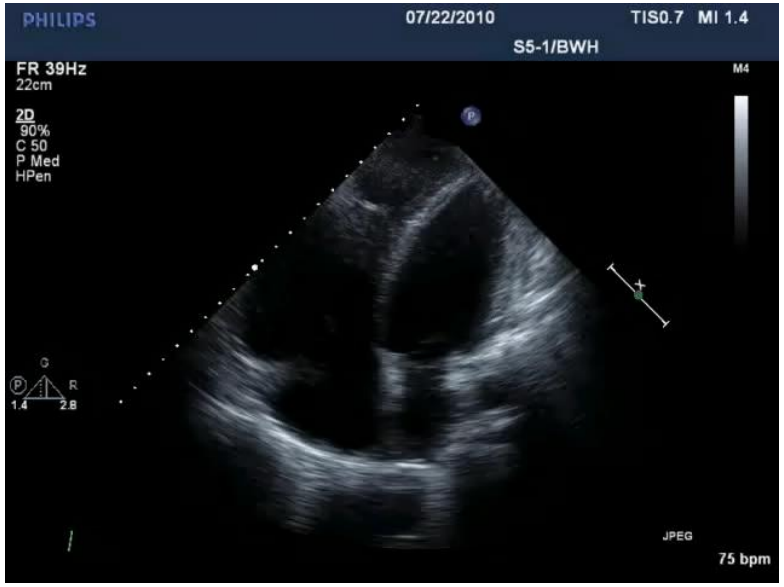
Treated with the prostacyclin analog *treprostinil* and PDE5i *tadalafil* with a good clinical response, *ambrisentan* was added two weeks later

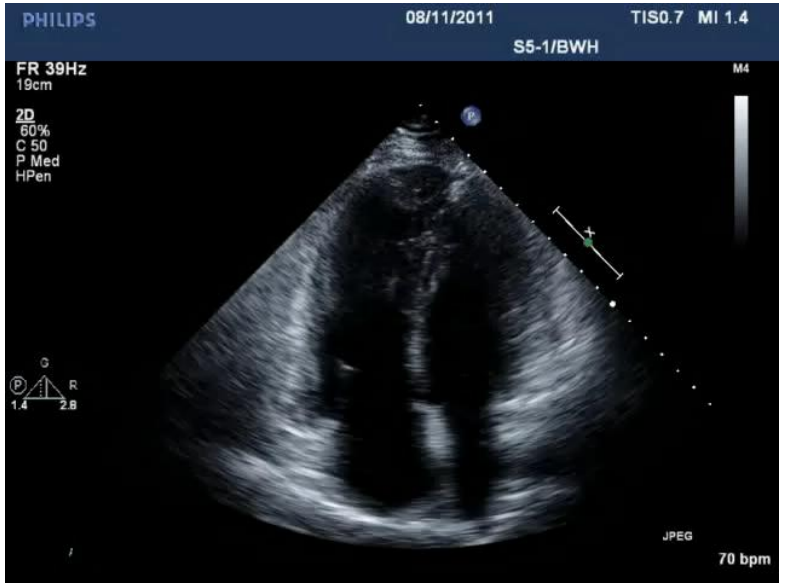
Repeat ECHO, after 6-months demonstrated improvement in RV size and function

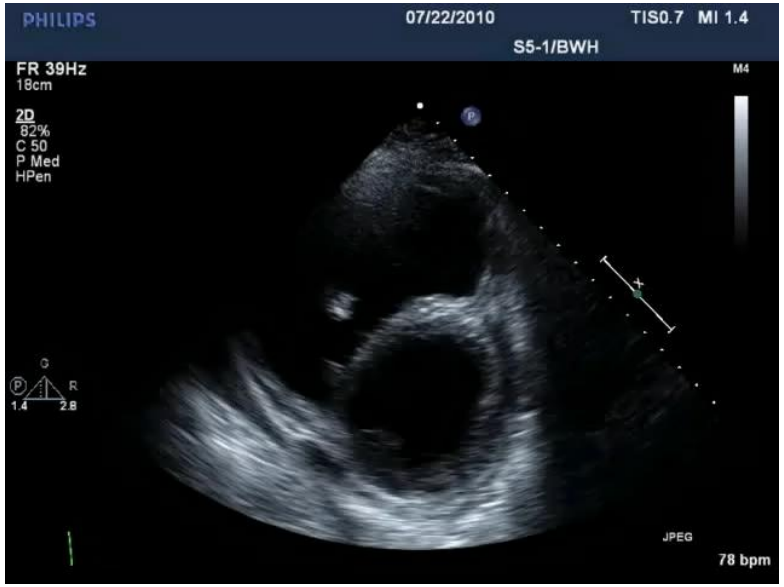
- PAsp now estimated at 72 mmHg
- 6-MWD – 448m Borg – 3
- WHO Functional Class 2

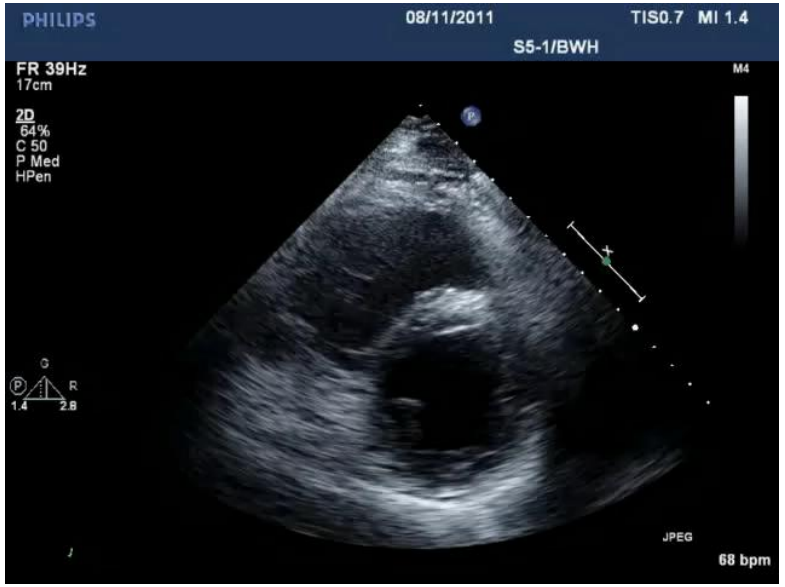


6-months later

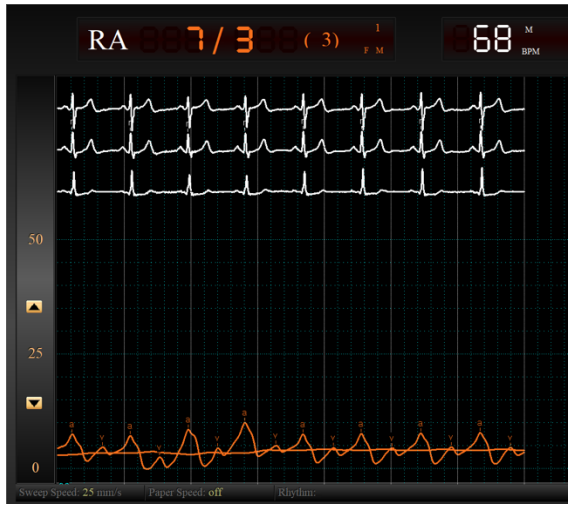


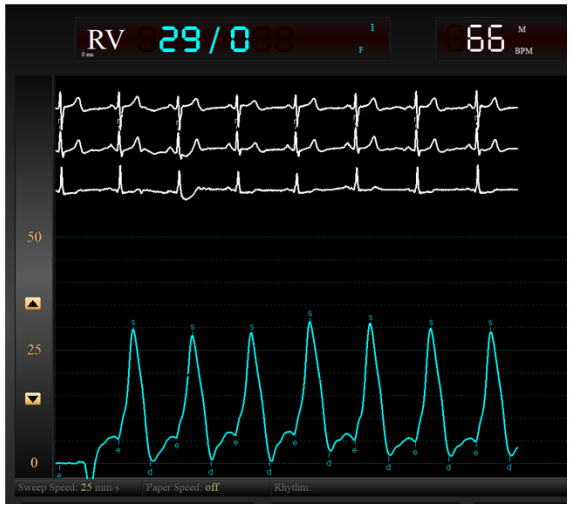


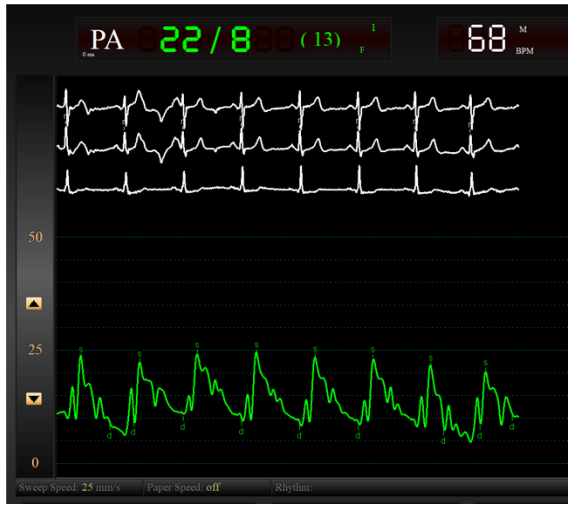


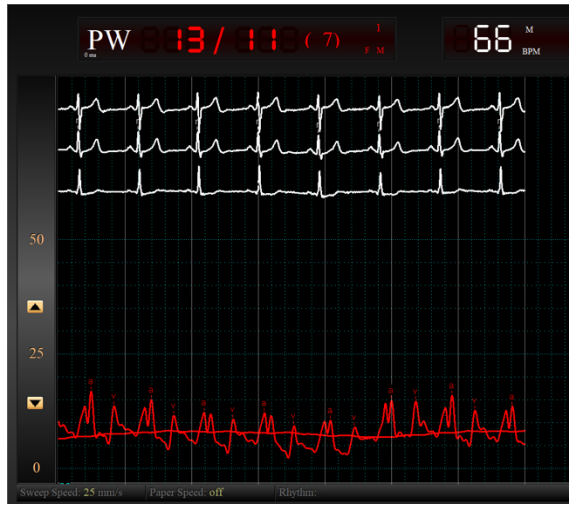


2.5 years later









Treprostinil titrated to 66 ng/kg/min
Ambrisentan 10mg daily
Tadalafil 20mg tablets 2-tablets daily
Participant in SPECTRA study of Sotatercept
WHO FC 1

- RHC:
  - PAP 22/8
  - mPA 13
  - PCWP 7
  - CO/CI 5.6/2.8
  - PVR 1.5 Wu

Summary - MOC REFLECTIVE STATEMENT

- Cardiac Echo is an excellent screening tool, but does not provide a diagnosis
- RHC is *essential and required* for diagnosis of all forms of pulmonary hypertension
- With development of new therapies, we are seeing improved outcomes
- Outcomes provide a clear rational for combination therapy
- Treatment must be individualized to not only severity but to patient preference and lifestyle
- There is still plenty of room for additional therapeutic targets

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