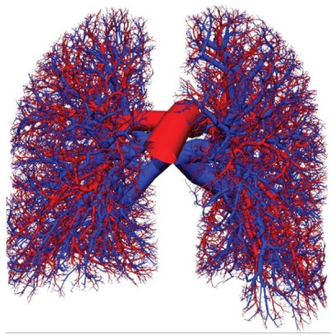

## Pulmonary Vascular Disease Program

### Brigham and Women's Hospital
### Harvard Medical School

# Assessment and Treatment of Pulmonary Hypertension


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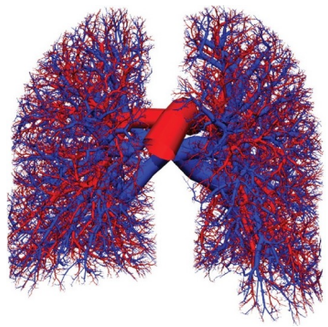
Harvard Medical School


BRIGHAM AND WOMEN'S HOSPITAL

PVDOMICS

PHA CCC Center of Comprehensive Care

HARVARD MEDICAL SCHOOL



# Pulmonary Vascular Disease Program

## Brigham and Women's Hospital
## Harvard Medical School

- Disclosures
- Clinical Trial Steering Committees
  - Delivery Trial – United Therapeutics and Medtronic - PI
  - INCREASE Trial – United Therapeutics - PI
  - PERFECT Trial – United Therapeutics - PI
  - Sotatercept Trial – Acceleron
  - ASPIRE Trial – Aria CV – PI
- Janssen R&D – Research Grant
- AI Therapeutics – Research Grant
- R01HL158077 – Co-I
- R01HL160025 – Co-I

BWH BRIGHAM AND WOMEN'S HOSPITAL

PVDOMICS

PHA CCC Center of Comprehensive Care

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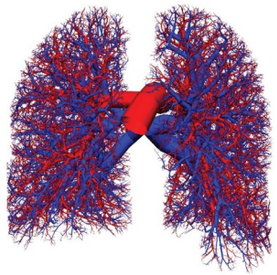


# Pulmonary Vascular Disease Program

## Brigham and Women's Hospital
## Harvard Medical School

- Learning Objectives
  - Updates on Pulmonary Hypertension definition and approach to diagnosis
  - Therapeutic options
  - Selection of appropriate combinations of PAH therapy based on empirical data
  - Expanding the treatment horizon

# Case 1-PAH

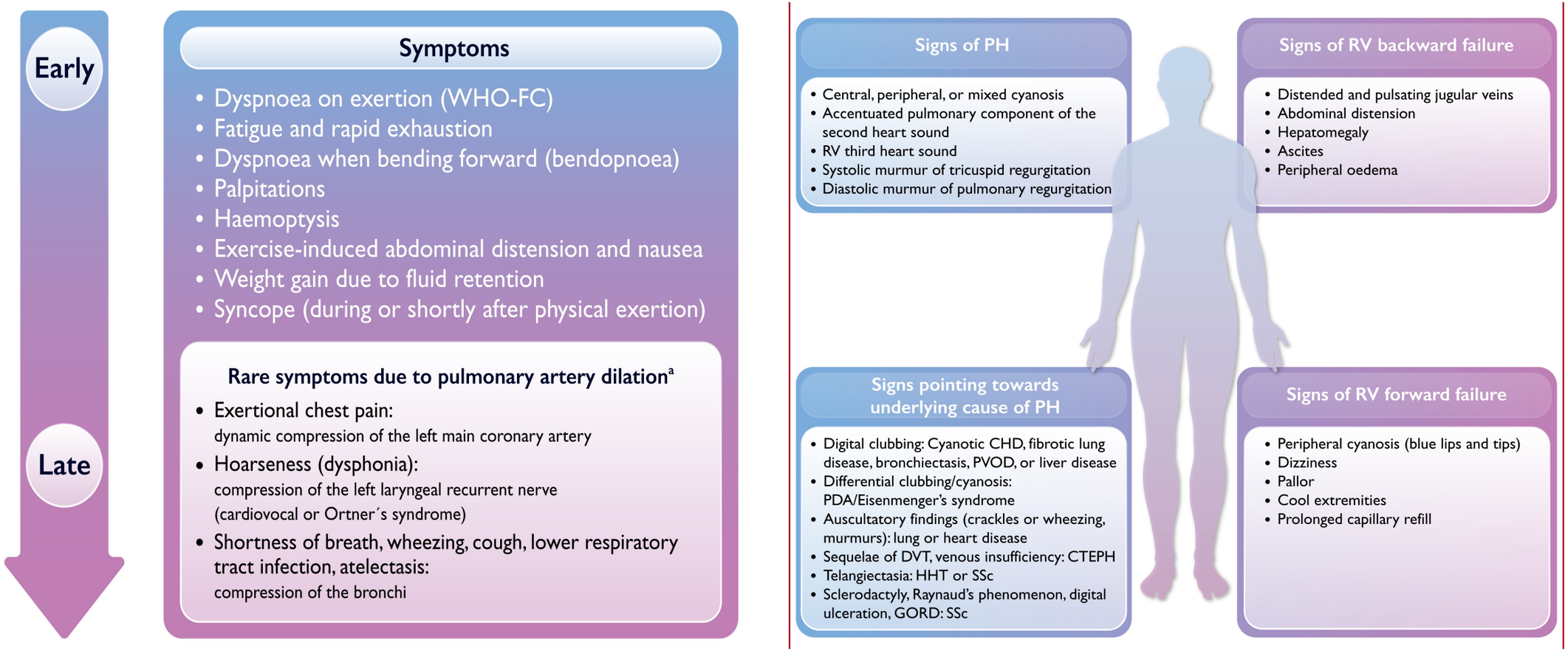
- 33 yo woman $G_2P_{1(5\text{-yo male})}Sab_1$ with a history of Raynaud's
- 3-year history of DOE, more rapidly progressing 6-months prior to presentation
- Treated for asthma with LABA / ICS without change
  - Multiple steroid tapers without effect
- 1 month prior to presentation, pre-operative CXR (for gyn surgery) revealed enlarged pulmonary arteries
- Very symptomatic when climbing stairs or an incline

# Case 1-PAH

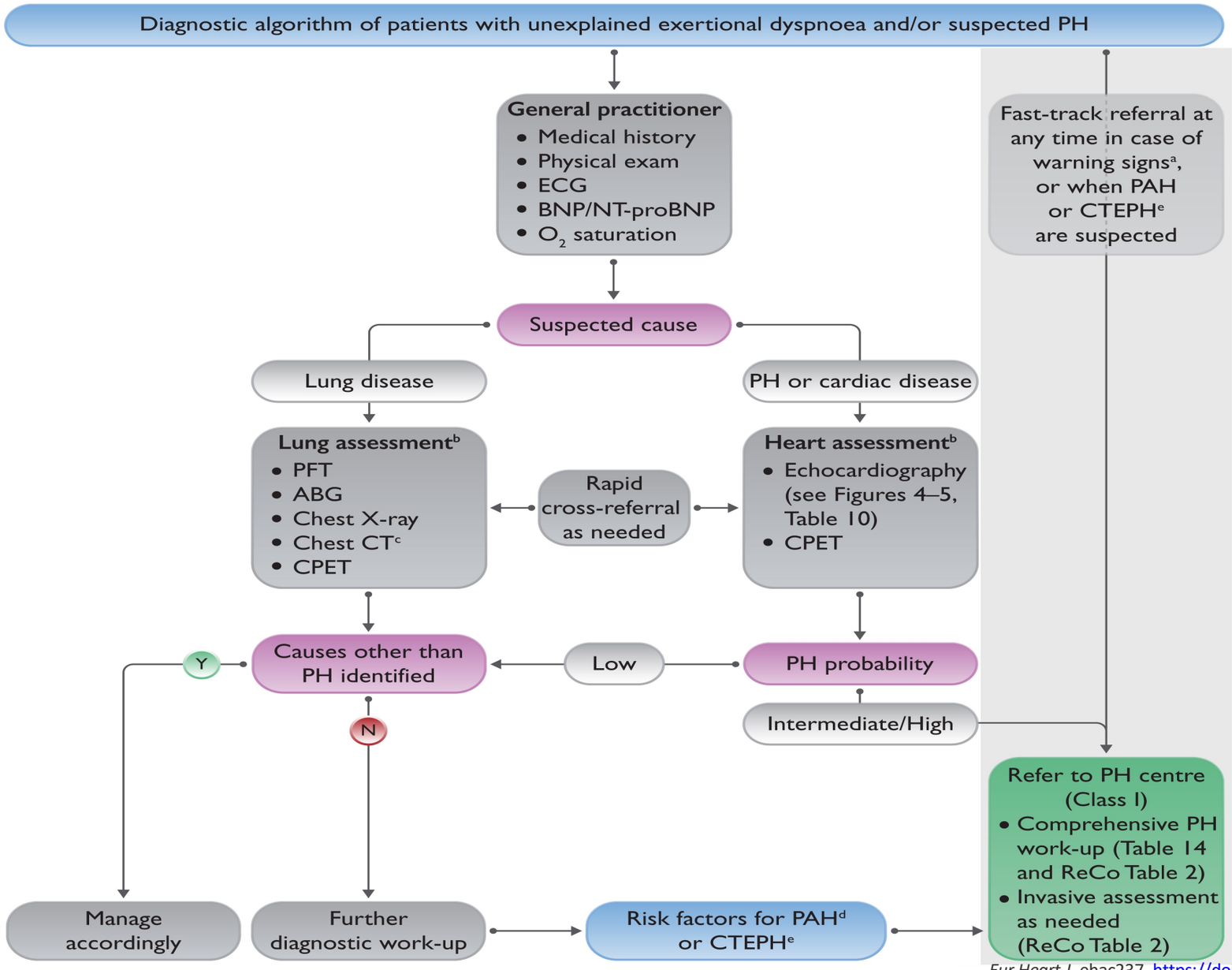
- Past Medical History
  - Raynaud's
  - "Asthma"
- Family History
  - No pulmonary or cardiac disease
- Social History
  - No history of smoking, alcohol, recreational drug, or anorexigens / stimulants use
- Medications - none

- 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

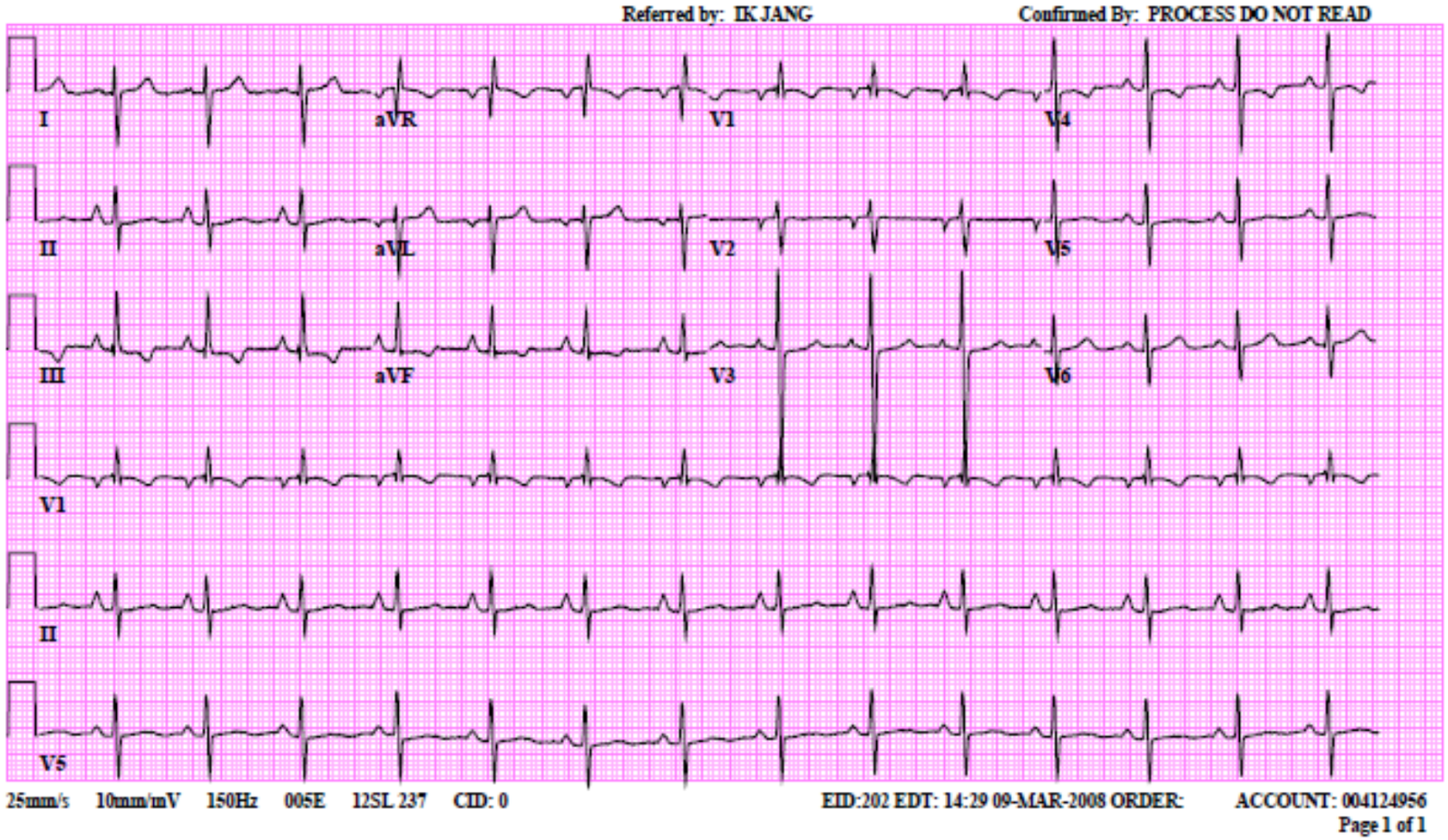



*Eur Heart J*, ehac237, https://doi.org/10.1093/eurheartj/ehac237




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

# 33 yo Woman with Dyspnea




BRIGHAM AND WOMEN'S HOSPITAL

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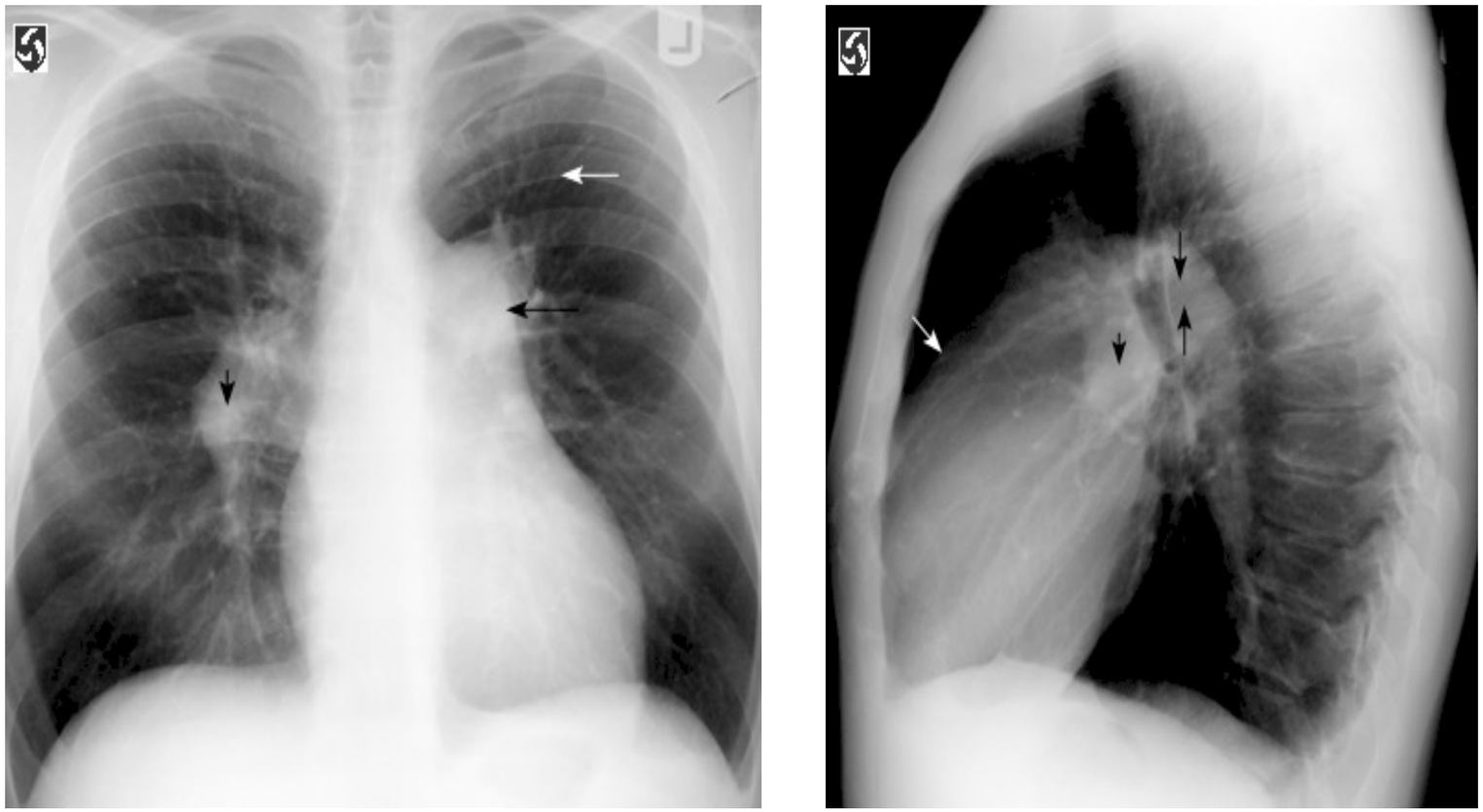
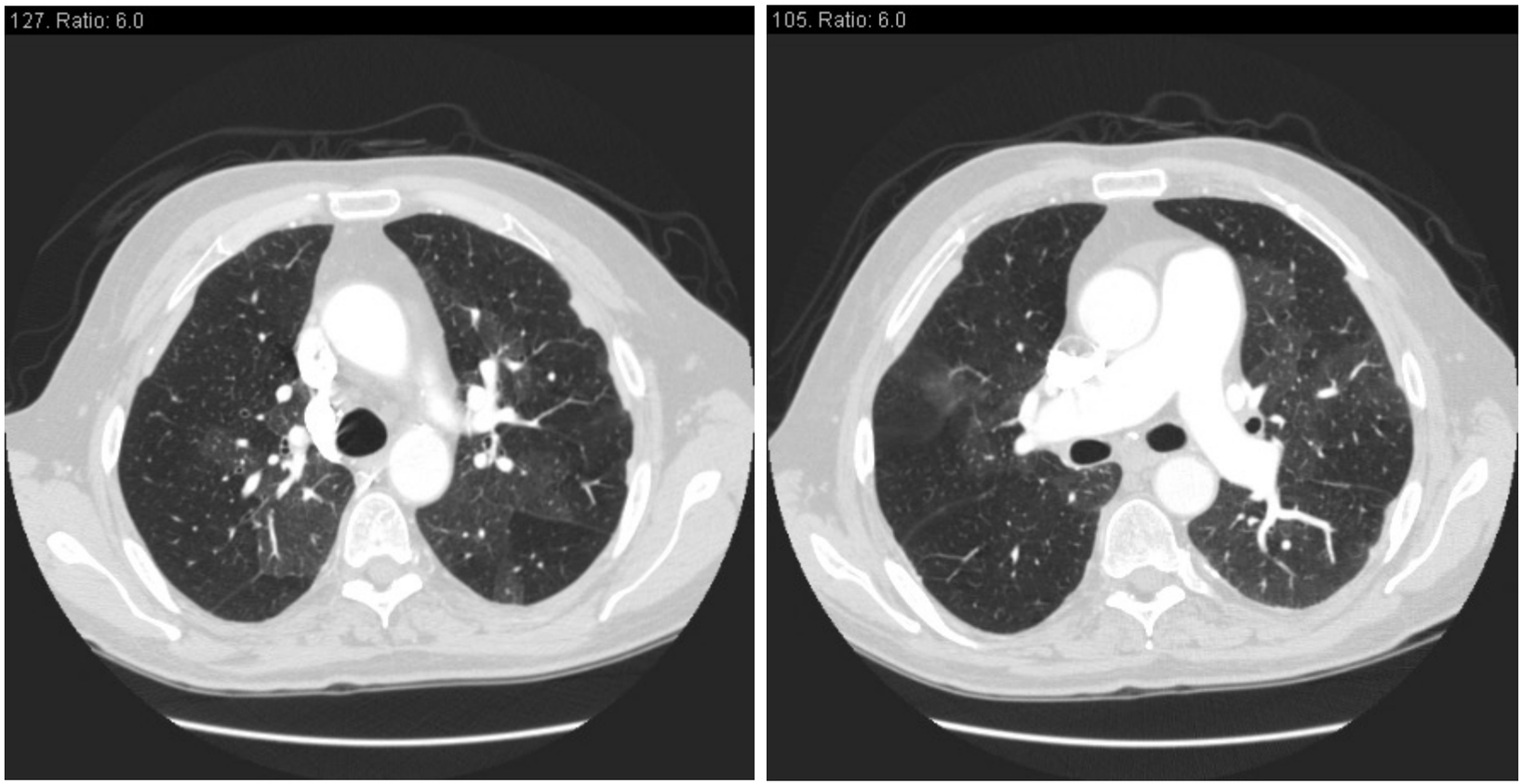
# Case 1-PAH

- 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

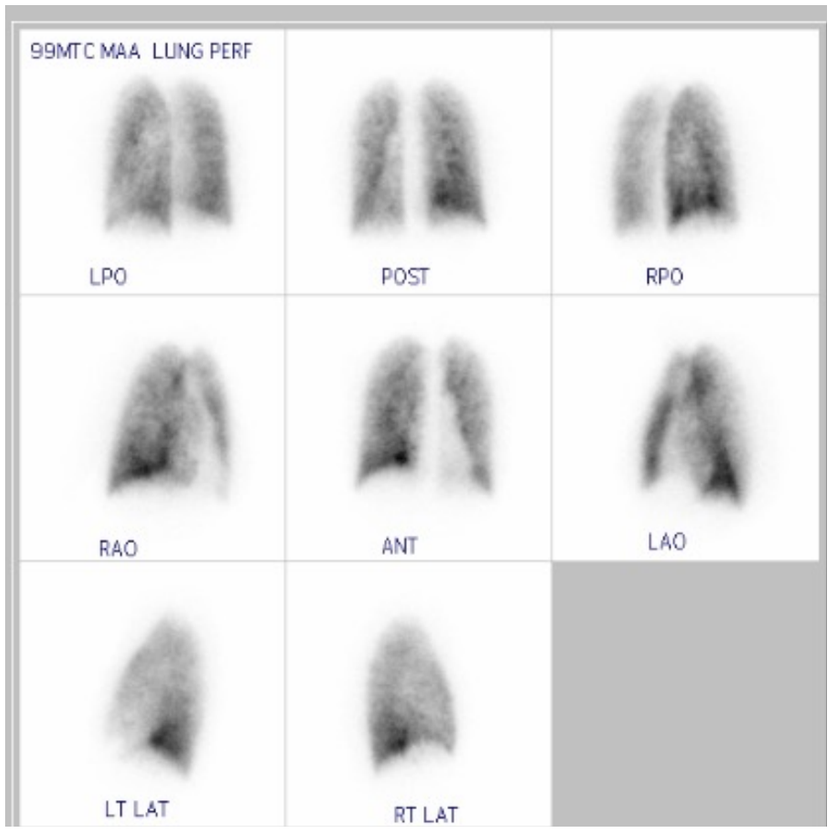
# Chest Radiograph

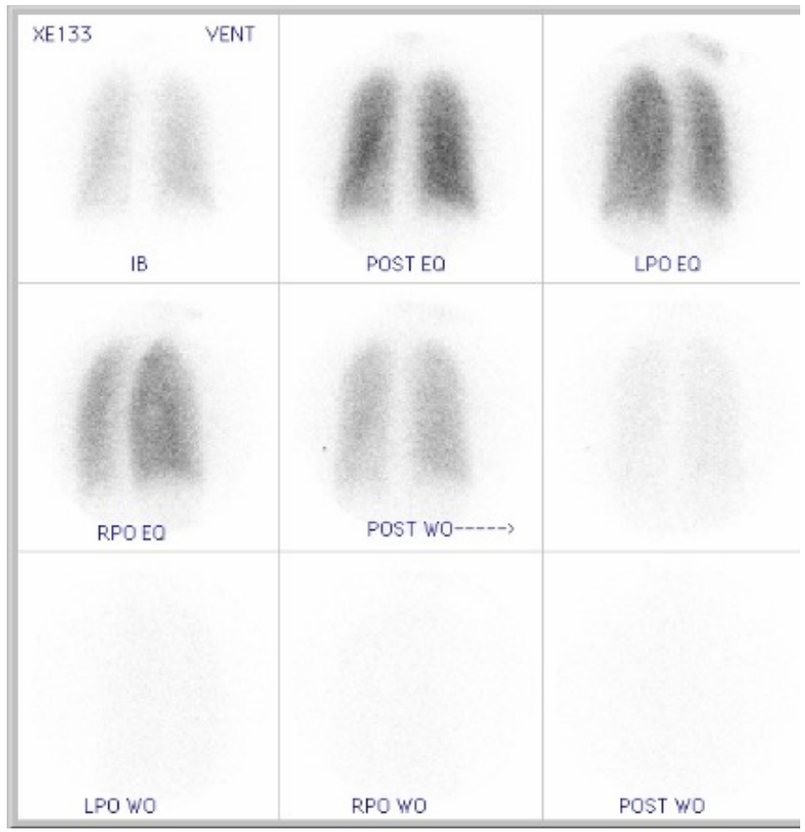


# CTA



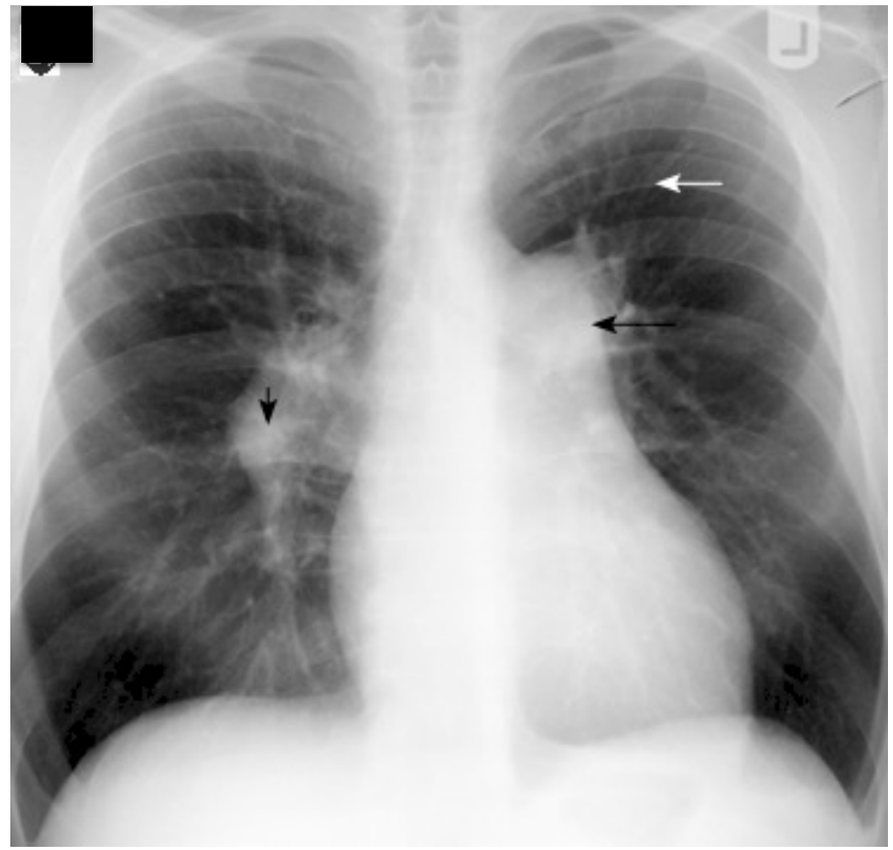
# VQ Scan


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

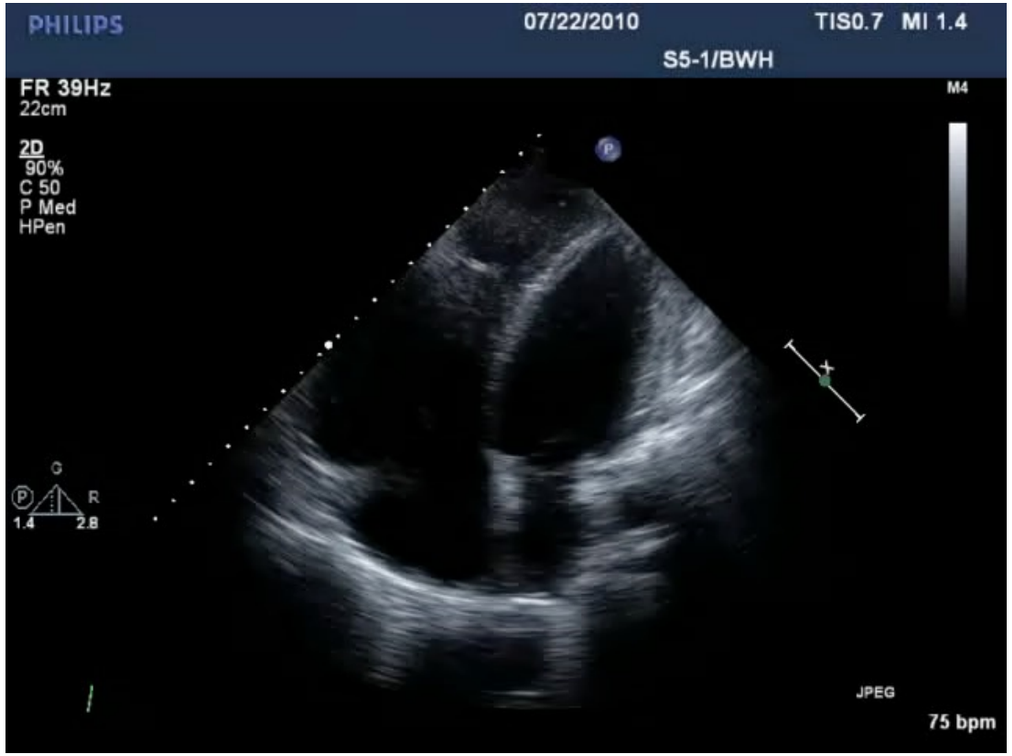

XE133
VENT
IB
POST EQ
LPO EQ
RPO EQ
POST WO----->
LPO WO
RPO WO
POST WO

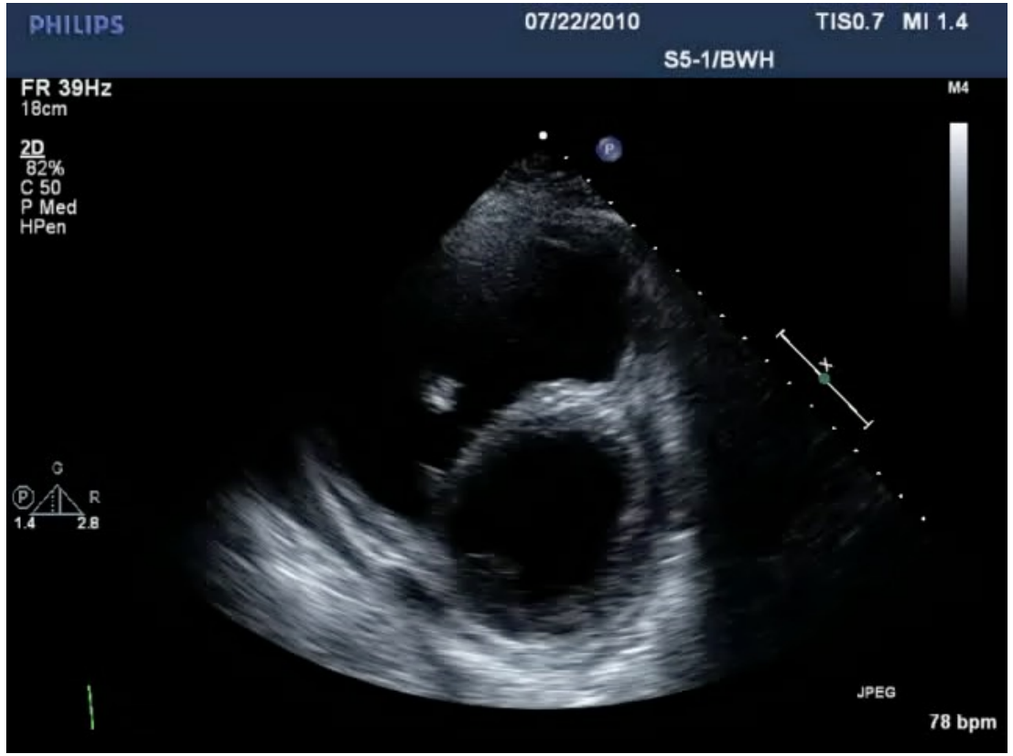
# Patient #1: Physical Examination

- 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

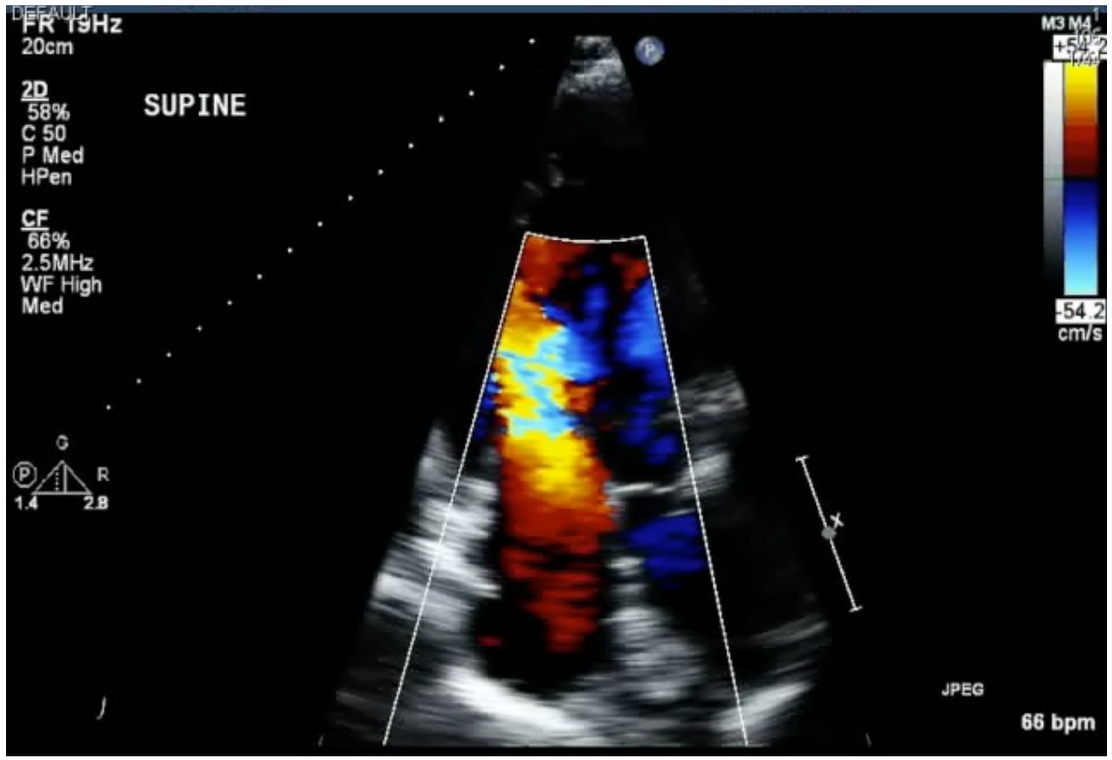


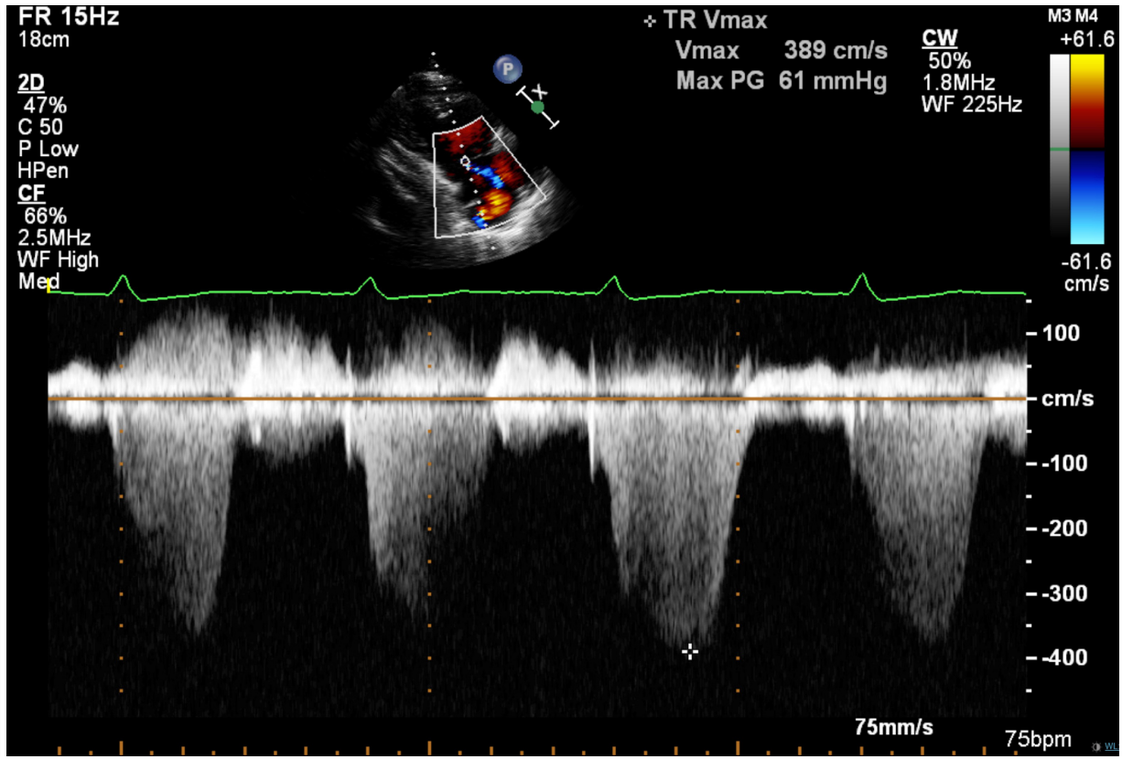
# 33 yo Woman with Dyspnea



# 33 yo Woman with dyspnea
# Tricuspid Regurgitation

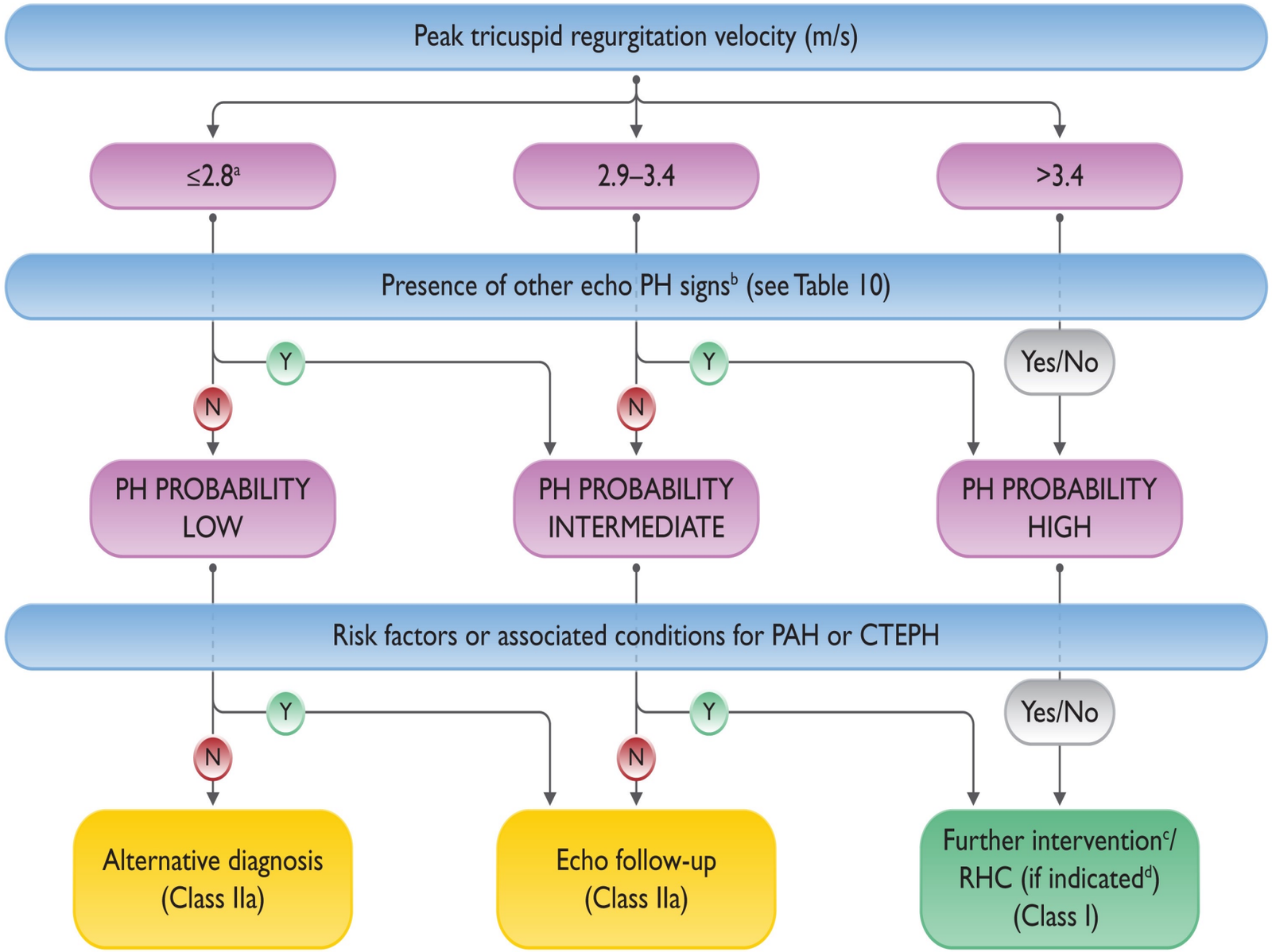



Modified Bernoulli's Equation:

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

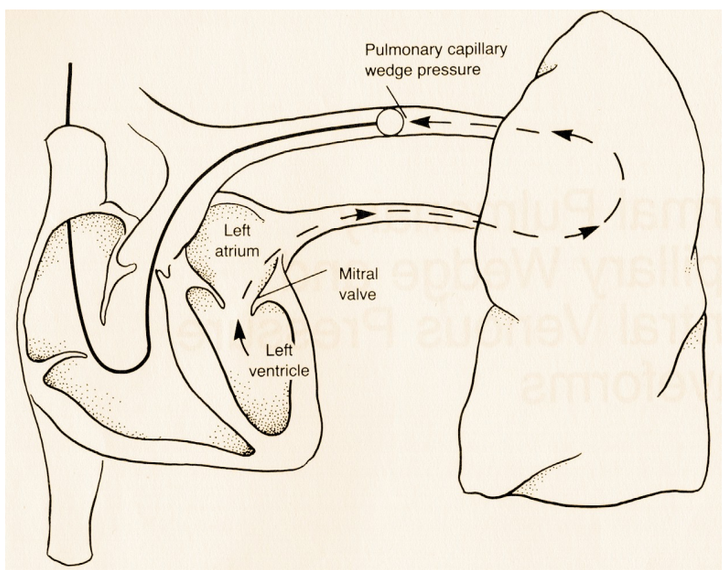
RVSP ~ 78




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

# Information obtained from the PAC

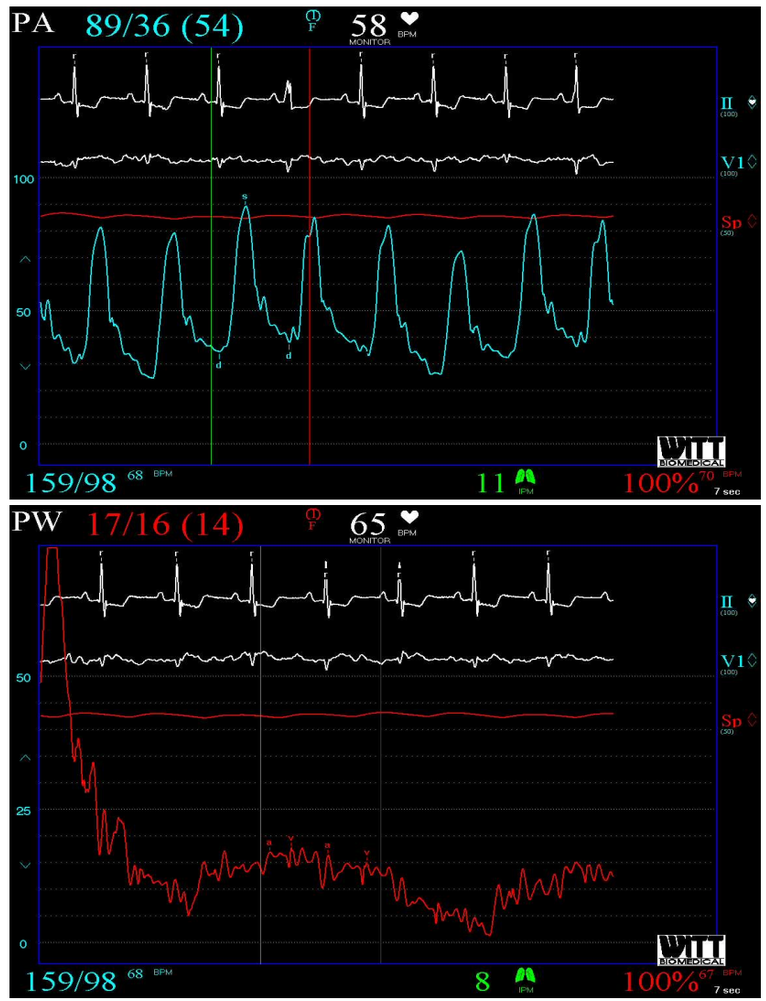
- Directly measured
  - CVP
  - PA pressure
  - PCWP
  - Cardiac output
  - $SvO_2$



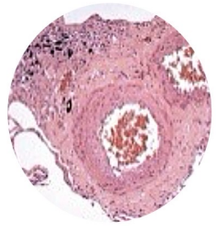
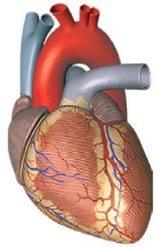
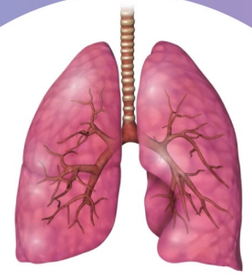
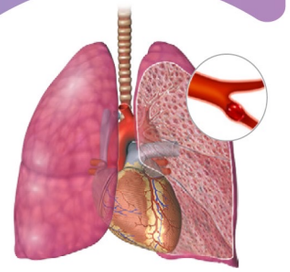
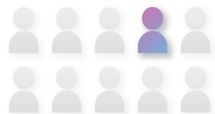
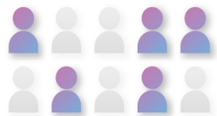
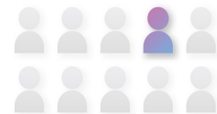
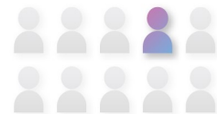

- Calculated from directly measured data
  - Stroke volume / index
  - Cardiac index
  - Systemic vascular resistance
  - Pulmonary vascular resistance
  - Oxygen delivery

# 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

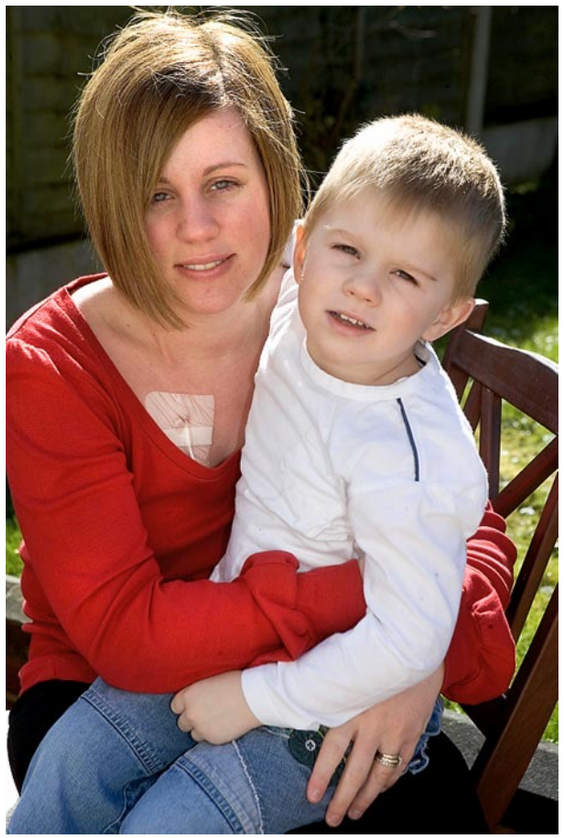


# Updated Classification System

| 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<br>• Associated conditions | • IpcPH<br>• CpcPH | • Non-severe PH<br>• Severe PH | • CTEPH<br>• Other pulmonary obstructions | • Haematological disorders<br>• Systemic disorders |
| PREVALENCE | | | | |
| Rare | Very common | Common | Rare | Rare |
|  |  |  |  |  |

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

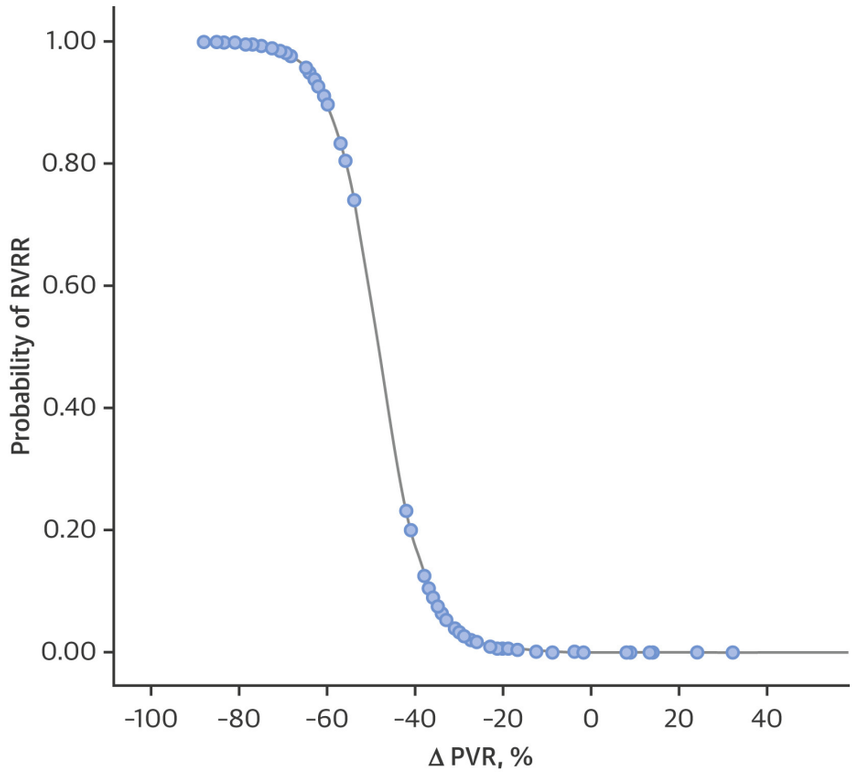
# Case 1-PAH



- 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 ?

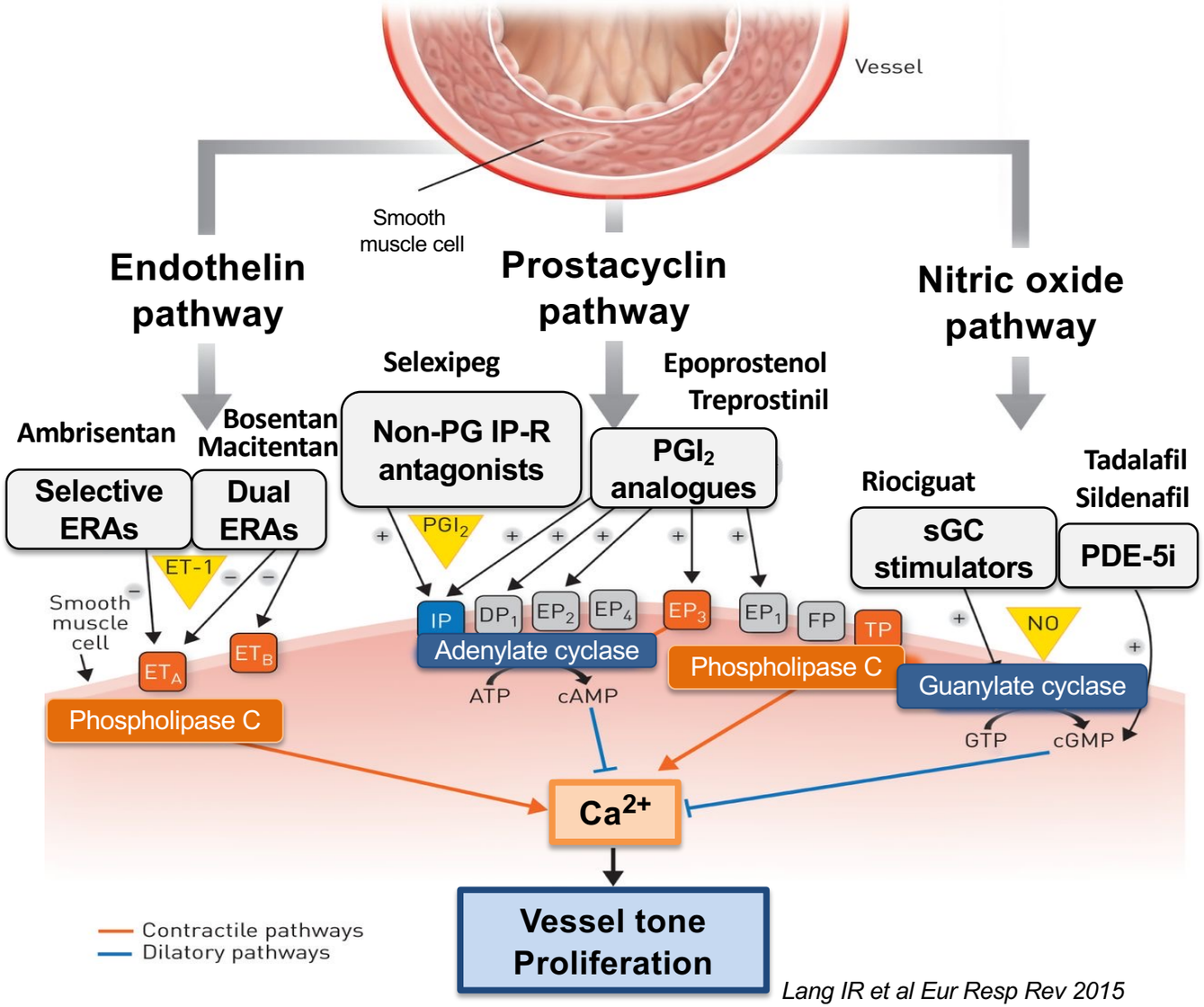
# Pulmonary Arterial Hypertension:
## *Goals of Therapy*

- 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

# Current Therapeutic Targets in PAH




*Lang IR et al Eur Resp Rev 2015*

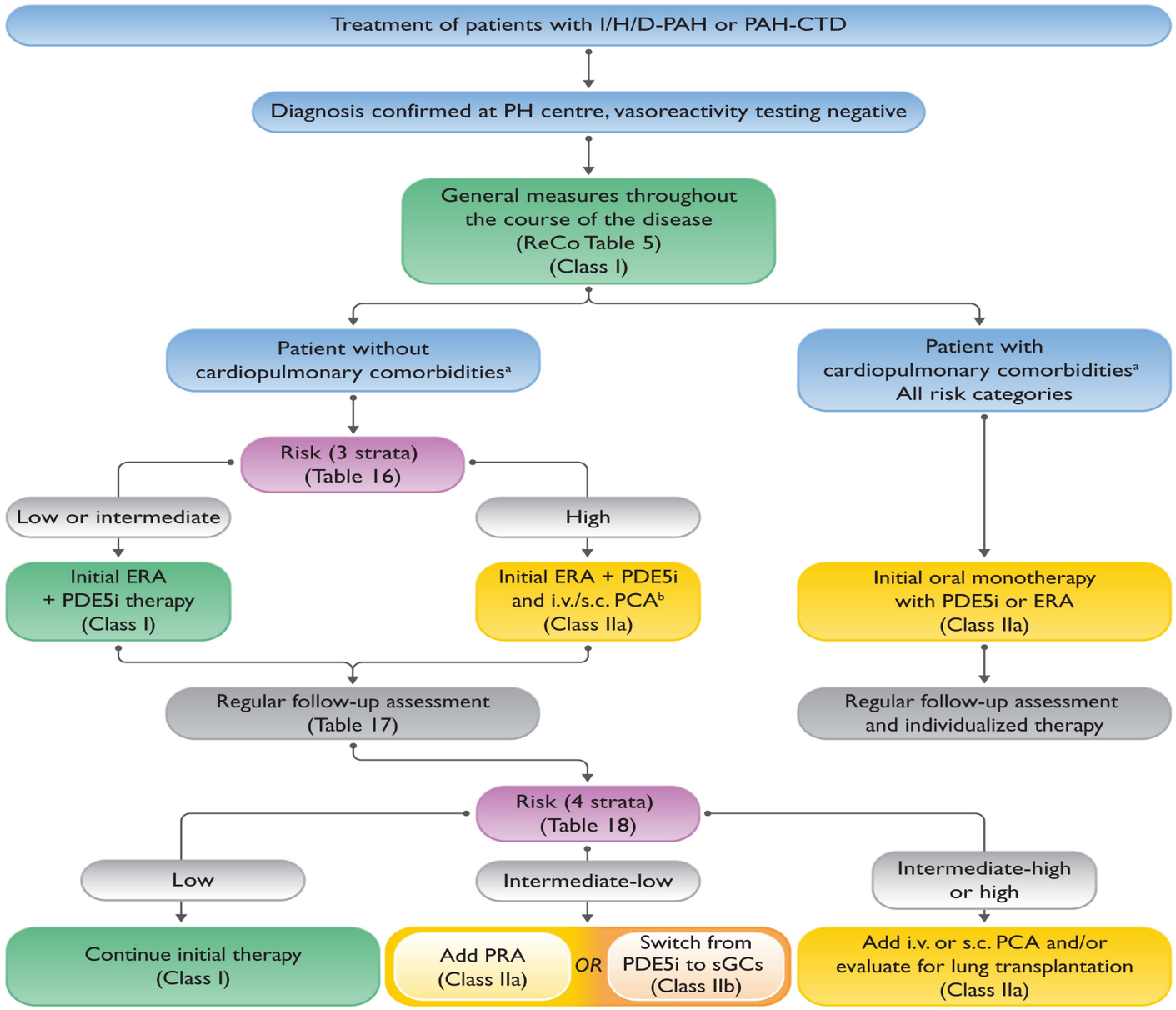
# Expected Adverse Effects of PAH-Specific Therapies

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

| Determinants of prognosis (estimated 1-year mortality) | Low risk (<5%) | Intermediate risk (5–20%) | High risk (>20%) |
|---|---|---|---|
| **Clinical observations and modifiable variables** | | | |
| Signs of right HF | Absent | Absent | Present |
| Progression of symptoms and clinical manifestations | No | Slow | Rapid |
| Syncope | No | Occasional syncope[a] | Repeated syncope[b] |
| WHO-FC | I, II | III | IV |
| 6MWD[c] | >440 m | 165–440 m | <165 m |
| CPET | Peak $VO_2$ >15 mL/min/kg (>65% pred.)<br>$VE/VCO_2$ slope <36 | Peak $VO_2$ 11–15 mL/min/kg (35–65% pred.)<br>$VE/VCO_2$ slope 36–44 | Peak $VO_2$ <11 mL/min/kg (<35% pred.)<br>$VE/VCO_2$ slope >44 |
| Biomarkers: BNP or NT-proBNP[d] | BNP <50 ng/L<br>NT-proBNP <300 ng/L | BNP 50–800 ng/L<br>NT-proBNP 300–1100 ng/L | BNP >800 ng/L<br>NT-proBNP >1100 ng/L |
| Echocardiography | RA area <18 $cm^2$<br>TAPSE/sPAP >0.32 mm/mmHg<br>No pericardial effusion | RA area 18–26 $cm^2$<br>TAPSE/sPAP 0.19–0.32 mm/mmHg<br>Minimal pericardial effusion | RA area >26 $cm^2$<br>TAPSE/sPAP <0.19 mm/mmHg<br>Moderate or large pericardial effusion |
| cMRI[e] | RVEF >54%<br>SVI >40 $mL/m^2$<br>RVESVI <42 $mL/m^2$ | RVEF 37–54%<br>SVI 26–40 $mL/m^2$<br>RVESVI<br>42–54 $mL/m^2$ | RVEF <37%<br>SVI <26 $mL/m^2$<br>RVESVI >54 $mL/m^2$ |
| Haemodynamics | RAP <8 mmHg<br>CI ≥2.5 $L/min/m^2$<br>SVI >38 $mL/m^2$<br>$SvO_2$ >65% | RAP 8–14 mmHg<br>CI 2.0–2.4 $L/min/m^2$<br>SVI 31–38 $mL/m^2$<br>$SvO_2$ 60–65% | RAP >14 mmHg<br>CI <2.0 $L/min/m^2$<br>SVI <31 $mL/m^2$<br>$SvO_2$ <60% |



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




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

# Treatment Algorithm

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



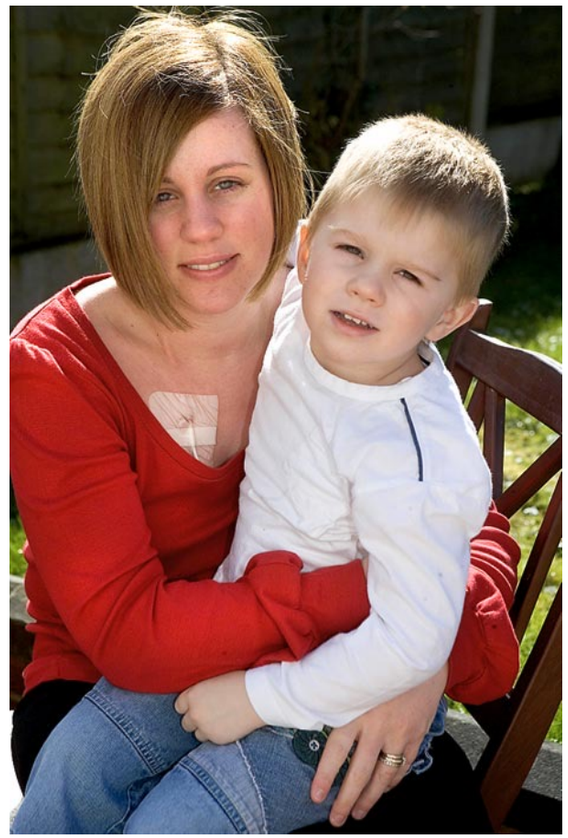
Galié N, et al. *Eur Respir J*. 2016;37:67–119.

# Follow-up Monitoring Schedule

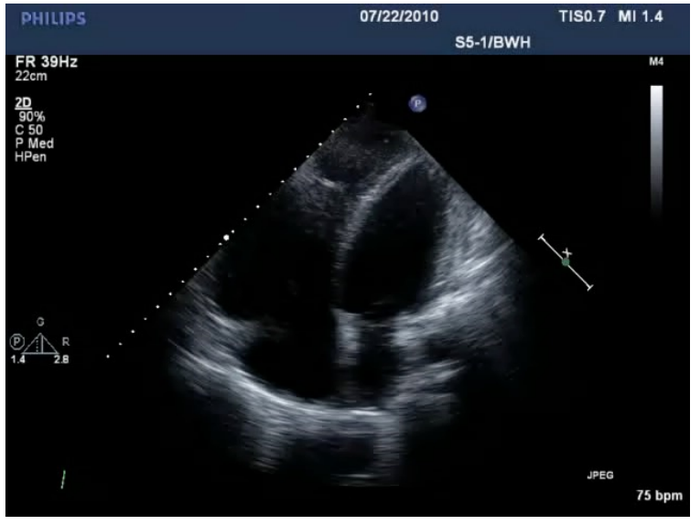
| Parameter | Baseline (pretreatment) | Every 3-6 months | 3-4 Months after start or change in therapy | If clinical worsening |
|---|---|---|---|---|
| Clinical assessment<br>WHO functional class<br>ECG | X | X | X | X |
| 6-MWD / CPET | X | X | X | X |
| BNP / NT-proBNP | X | X | X | X |
| ECHO | X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

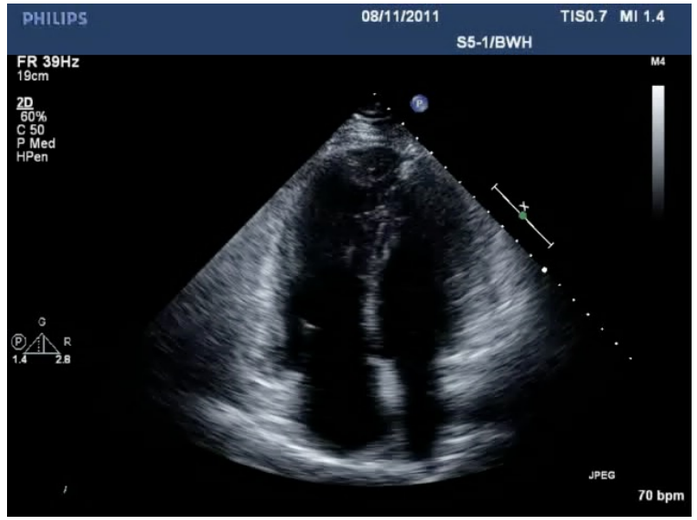
# Case 1-PAH

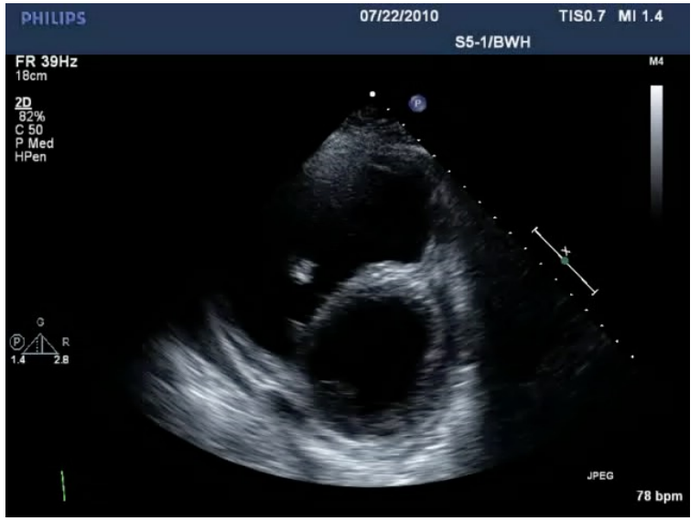
- Severe PAH, NYHA Functional Class 3b
  - 6-MWD 318m, BDS 5
- Treated with the prostacyclin analog *treprostinil* and PDE5i *tadalafil* with a good clinical response, *ambrisentan* was added two weeks later
- Repeat ECHO, after 6-months demonstrated improvement in RV size and function
  - PAsp now estimated at 72 mmHg
  - 6-MWD – 448m Borg – 2
  - NYHA Functional Class 1

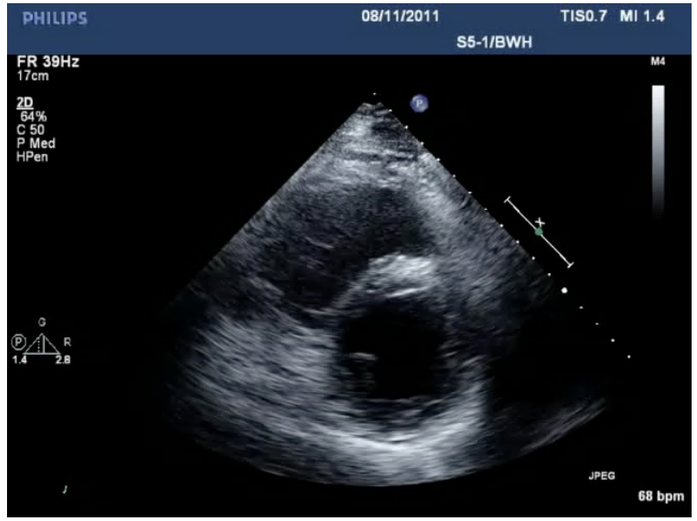


# 6-months later

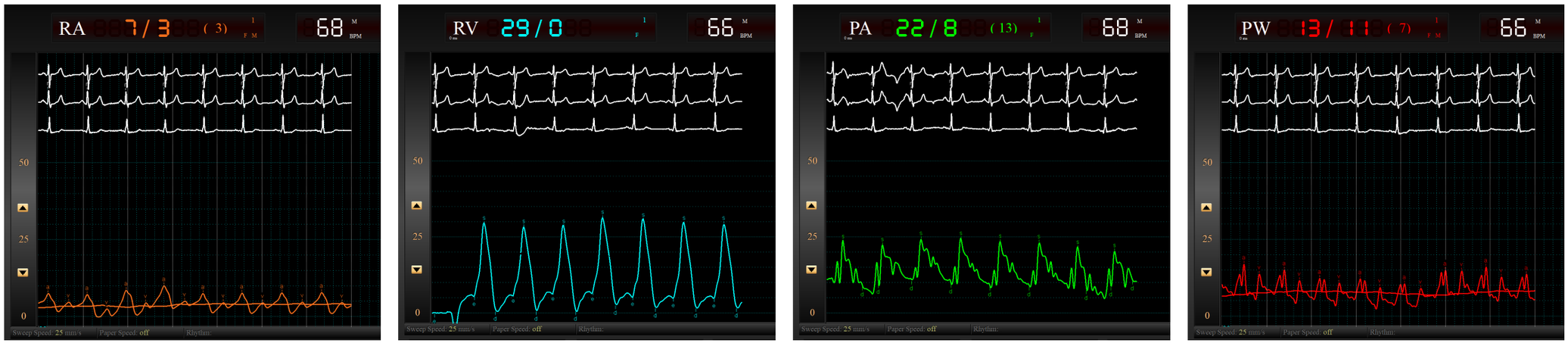


# 2.5 years later




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

# Conclusions

- PH exhibits a complex pathogenesis
- Improved outcomes, but long way to go
- Clear rational for combination therapy
- Clear benefit to treating patients with interstitial lung disease and pulmonary hypertension
- Room for additional therapeutic targets

# Pulmonary Vascular Disease Program

## Brigham and Women's Hospital
## Harvard Medical School

- David Systrom, MD
- Barbara Cockrill, MD
- Elizabeth Gay, MD
- Paul Yu, MD
- Brad Maron, MD
- Jane Leopold, MD

- Hari Mallidi, MD
- Will Oldham, MD, PhD
- Farbod Rahaghi, MD, PhD
- Brad Wertheim, MD
- Eileen Harder, MD
- Shelsey Johnson, MD
- Wei Qi, MD

- Charlie Lee, PA-C
- Stephanie Perella, PA-C
- Olivia Vayer
- Diana Acuna
- Emily Harris
- Ava Blackman
- Katie Lewine, MS
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