



ACC Middle East  
Conference 2018

# **Pulmonary Hypertension Due to Left Heart Disease**

Ammar Chaudhary, MBChB, FRCPC  
Advanced Heart Failure & Transplantation  
King Faisal Specialist Hospital and Research Center - Jeddah



Le Meridian Jeddah  
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# Outline

- **Definition & Classification**
- **Pathobiology**
- **Diagnosis**
- **Management**

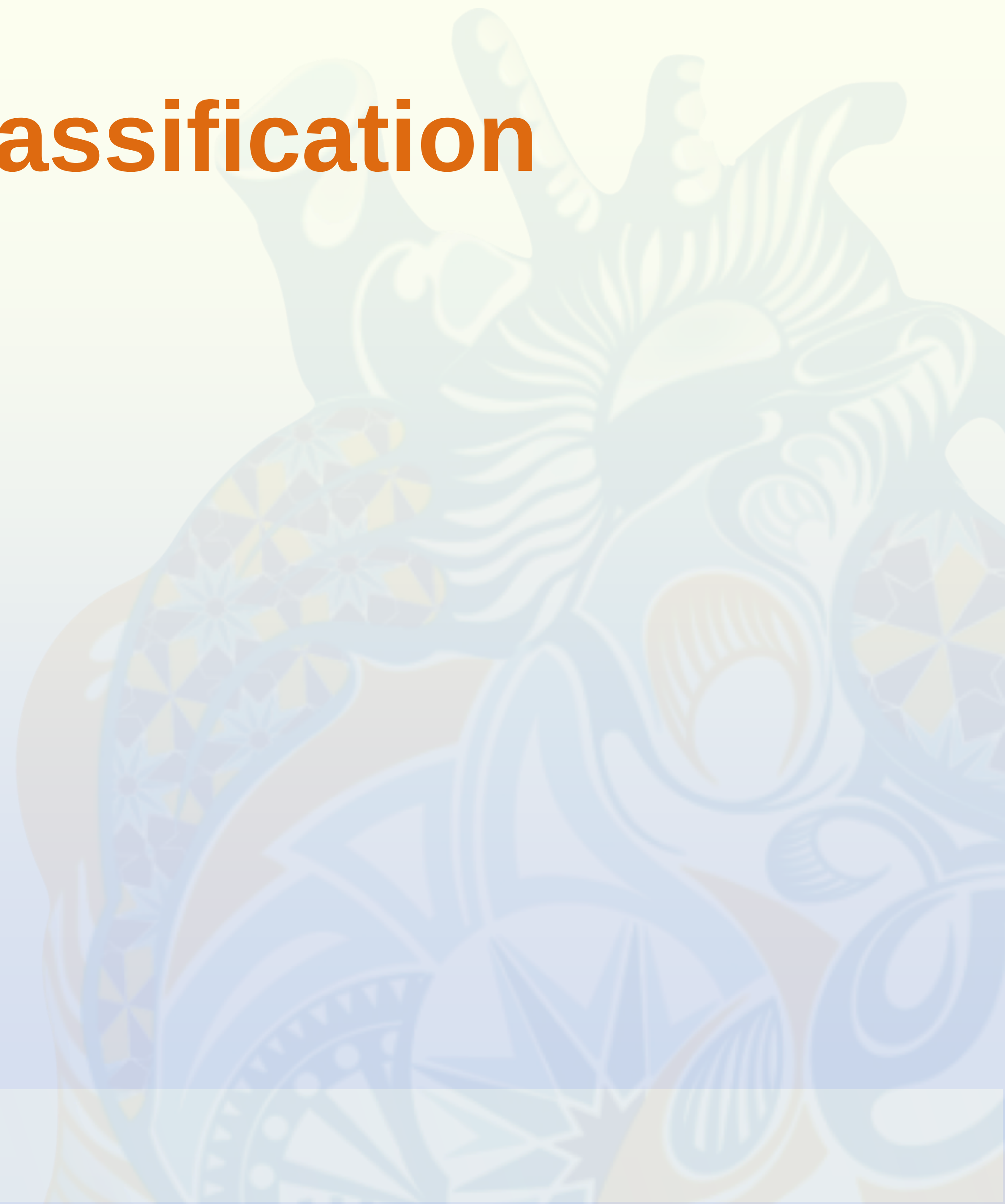


# Definition & Classification

- **Group I PH**
- **Group II PH**
- **Group III PH**
- **Group IV PH**
- **Group V PH**

# Definition & Classification

- **Group I PH**
- **Group II PH: Left heart disease**
- **Group III PH**
- **Group IV PH**
- **Group V PH**



# Definition & Classification

- **Group I PH: PAH - idiopathic, genetic, drugs, CTD, HIV**
- **Group II PH: Left heart disease**
- **Group III PH: lung disease and hypoxia (COPD, ILD, OSA)**
- **Group IV PH: CTEPH**
- **Group V PH: hematologic (SCA), sarcoidosis, metabolic**

# Definition & Classification

- **Group II PH: Left heart disease**

**Heart failure with reduced EF (HFrEF)**

**Heart failure with preserved EF (HFpEF)**

**Valvular heart disease**

**Congenital heart disease**

# Epidemiology

| Study<br>(n) <sup>a</sup>                      | Definitions/Selection<br>Criteria Used                                            | Overall Prevalence<br>of PH                | Phenotype of PH          |                           | Impact on Outcomes                                                                                                     |
|------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------|--------------------------|---------------------------|------------------------------------------------------------------------------------------------------------------------|
|                                                |                                                                                   |                                            | Ipc-PH                   | Cpc-PH                    |                                                                                                                        |
| Catheter based studies                         |                                                                                   |                                            |                          |                           |                                                                                                                        |
| Ghio et al. <sup>1</sup><br>(n = 379)          | EF: <35%<br>mPAP >20 mm Hg<br>iPc-PH vs Cpc-PH: not analyzed                      | 62%                                        | –                        |                           | mPAP increases of 5 mm Hg had an<br>adjusted HR of 1.1 for overall survival.                                           |
| Miller et al. <sup>20</sup><br>(n = 463)       | EF: ≤40%<br>mPAP ≥25 mm Hg<br>PAWP ≥15 mm Hg<br>iPc-PH vs Cpc-PH: PVR ≥3 WU       | 77%                                        | 43%<br>(TPG:<br>9 mm Hg) | 57%<br>(TPG:<br>17 mm Hg) | Patients with Cpc-PH had a 2-fold increase<br>in mortality.                                                            |
| Gerges et al. <sup>5</sup><br>(n = 836)        | EF: <45%<br>mPAP ≥25 mm Hg<br>PAWP ≥15 mm Hg<br>iPc-PH vs Cpc-PH: DPG ≥7 mm<br>Hg | 69%                                        | 84%                      | 16%                       | Cpc-PH patients had decreased survival<br>versus iPc-PH (median survival<br>72 mo vs 110 mo)                           |
| Benza et al. <sup>21</sup><br>(n = 412)        | EF: <40%<br>mPAP >25 mm Hg<br>iPc-PH vs Cpc-PH: not analyzed                      | 63%                                        | –                        |                           | Patients with PH had higher HF<br>hospitalization rates vs non PH (0.77/year<br>vs 0.37/year) <sup>b</sup>             |
| Echocardiography based studies                 |                                                                                   |                                            |                          |                           |                                                                                                                        |
| Miller et al. <sup>39</sup><br>(n = 1541)      | EF ≤40%<br>PASP ≥45 mm Hg                                                         | 35%                                        | –                        |                           | No outcome analysis                                                                                                    |
| Szwejkowski et al. <sup>40</sup><br>(n = 1612) | Qualitative LVSD<br>PH not defined                                                | RVSP ≥45 mm Hg: 48%<br>RVSP >52 mm Hg: 24% | –                        |                           | Every 5 mm Hg increase in RVSP is<br>associated with a 6% increase in mortality                                        |
| Shalaby et al. <sup>37</sup><br>(n = 270)      | Mean EF 23%<br>No predefined criteria for PH                                      | 35% PASP >45 mm Hg                         | –                        |                           | PASP >45 mm Hg was associated with a 2.6<br>fold risk of death or transplant and a 6 fold<br>increase in HF-admissions |
| Damy et al. <sup>41</sup><br>(n = 270)         | EF <45%<br>RVTG >35 mm Hg                                                         | 29%                                        | –                        |                           | RVTG >35 mm Hg was associated with a 2<br>fold increase in mortality <sup>b</sup> .                                    |

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| Catheter based studies                         |                                                                                |                                            |                       |                        |                                                                                                                  |
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Prevalence of PH in HFrEF

RHC: 62% - 77% (~70%)

Echo: 29% - 35% (~30%)

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| Leung et al. <sup>25</sup><br>(n = 455)     | EF ≥50%<br>PASP >25 mm Hg<br>PAWP: 15 mm Hg                                                     | 52.5%      | –               |        | No outcomes studied                                                |
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| Lam et al. <sup>16</sup><br>(n = 203)       | EF ≥50%<br>PASP >35 mm Hg<br>PAWP: 11.96 + 0.596 <sup>a</sup> E/e'                              | 83%        |                 |        | There was a 30% increase in mortality per 10 mm Hg of PASP.        |
| Shah et al. <sup>24</sup><br>(n = 450)      | EF ≥45%<br>TR velocity: >2.9 m/s<br>ADHF                                                        | 36%        |                 |        | Higher PAP was predictive of HF admission and cardiovascular death |
| Vanhercke et al. <sup>43</sup><br>(n = 192) | Age: ≥75 years<br>EF ≥50%<br>PH: TR gradient >30 mm Hg                                          | 51%        | –               |        | PH was an independent predictor of all-cause mortality.            |

Prevalence of PH in HFpEF  
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- **Pulmonary hypertension: mean PAP  $\geq 25$  mmHg (Rest Sup RHC)**

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# Definition & Classification

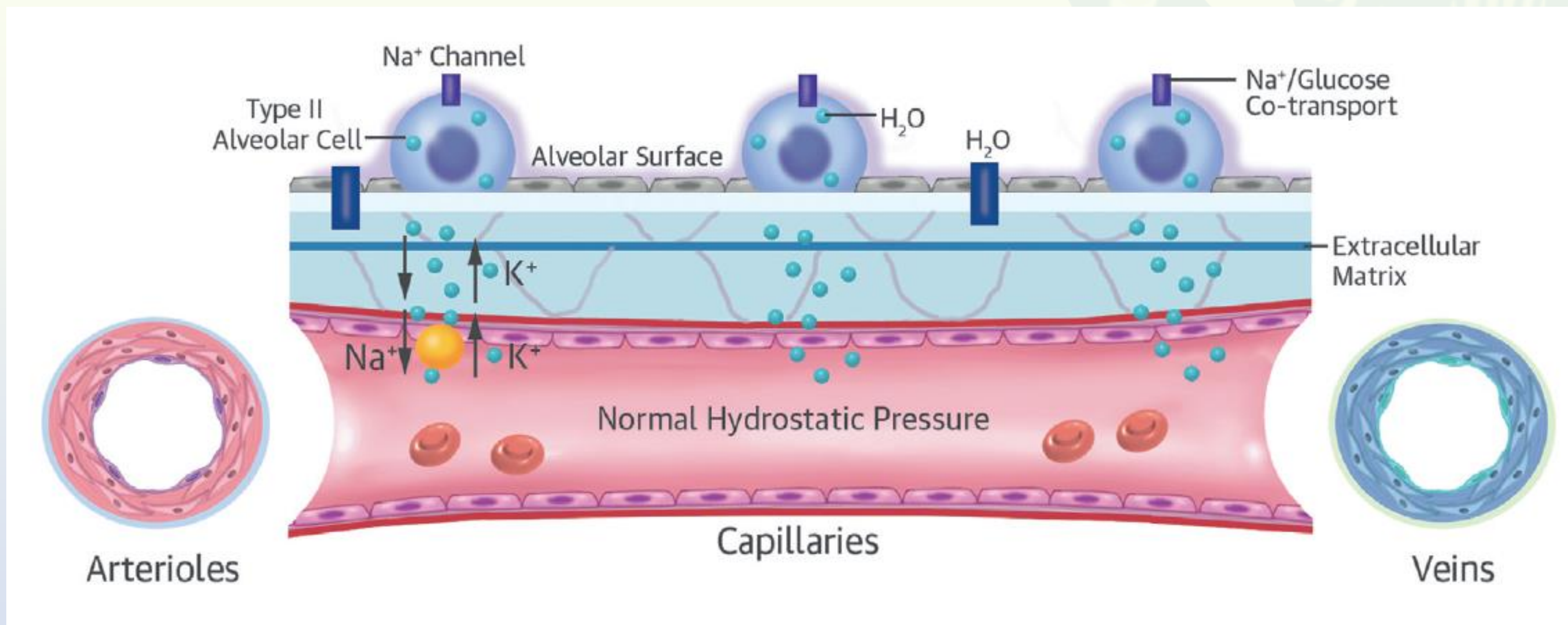
- Normal mean PAP  $14 \pm 3$  mm Hg\*
- Pulmonary hypertension: mean PAP  $\geq 25$  mmHg (Rest Sup RHC)
- PH & PAWP  $\leq 15$  mmHg  $\rightarrow$  PAH

Normal PAWP  $8 \pm 3$  mm Hg\*

# Definition & Classification

- Normal mean PAP  $14 \pm 3$  mm Hg\*
- Pulmonary hypertension: mean PAP  $\geq 25$  mmHg (Rest Sup RHC)
- PH & PAWP  $\leq 15$  mmHg  $\rightarrow$  PAH
- PH & PAWP  $> 15$  mmHg  $\rightarrow$  Group II PH

Normal PAWP  $8 \pm 3$  mm Hg\*



# Pathobiology

Increased lung capillary pressure



# Pathobiology

Increased lung capillary pressure



Alveolar edema



# Pathobiology

Increased lung capillary pressure



Alveolar edema



Impaired Na<sup>+</sup> K<sup>+</sup> ATPase  
Metalloproteinase activation  
Reduced membrane tensile strength

# Pathobiology

Increased lung capillary pressure



Alveolar edema



Impaired  $\text{Na}^+$   $\text{K}^+$  ATPase  
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Capillary Stress Failure



# Pathobiology

Increased lung capillary pressure



Alveolar edema



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Capillary Stress Failure

Chronic LAP elevation



Injury-inflammation

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Capillary Stress Failure

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Injury-inflammation

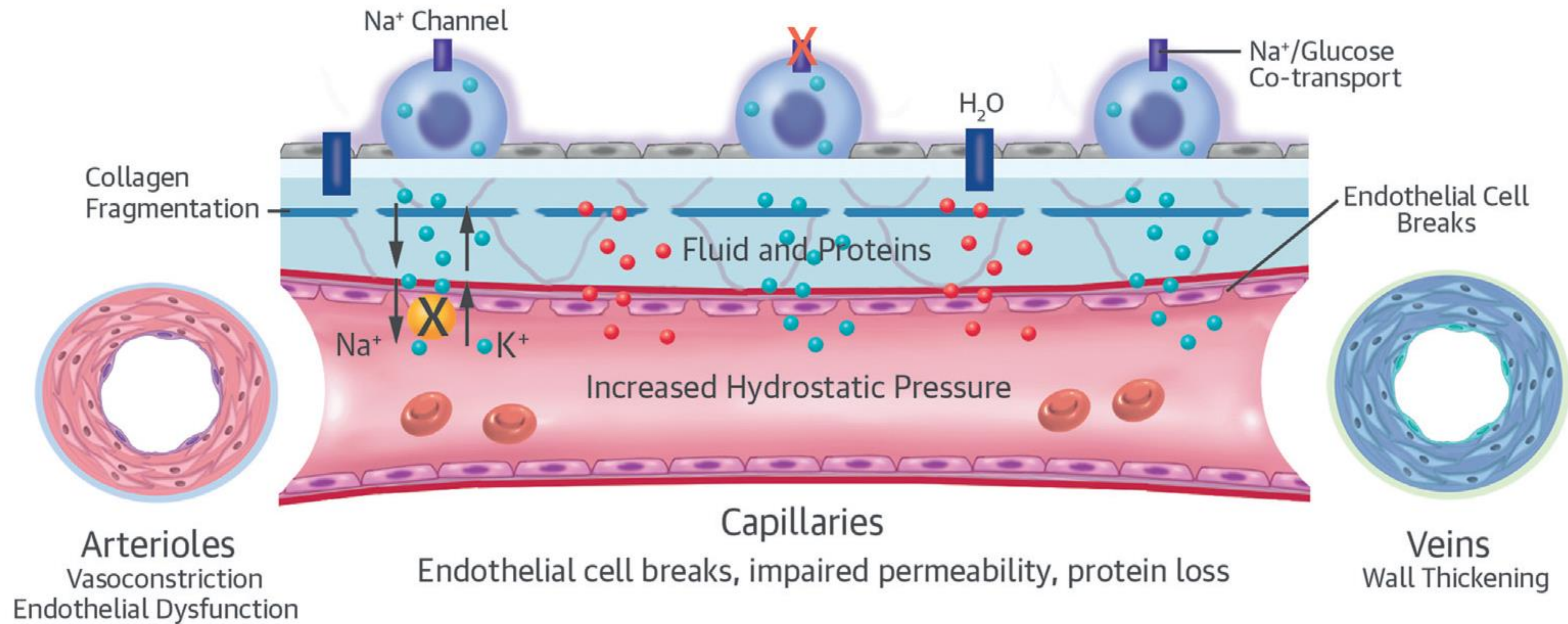


Reduced NO, prostacyclin  $\text{PGI}_2$   
Excess endothelin-1, angiotensin II,  
TGF, caveolin proteins

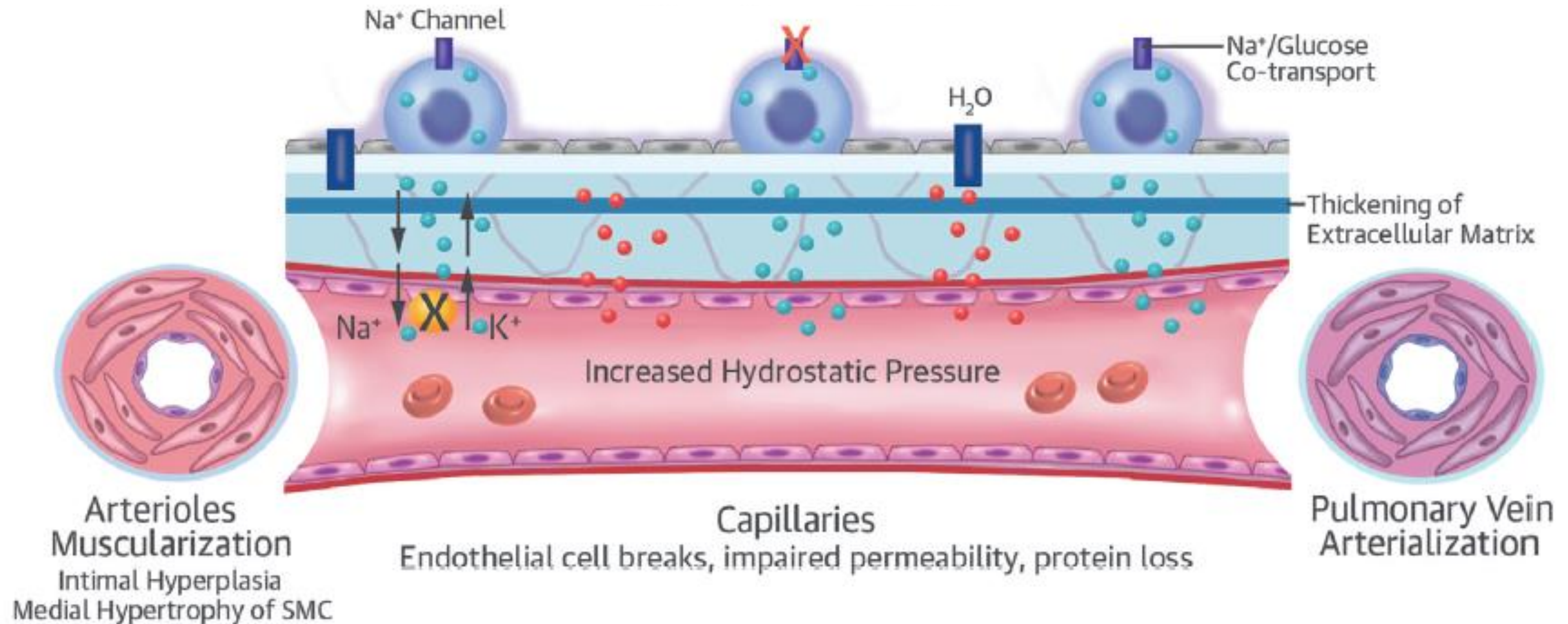


Pulmonary vascular remodelling

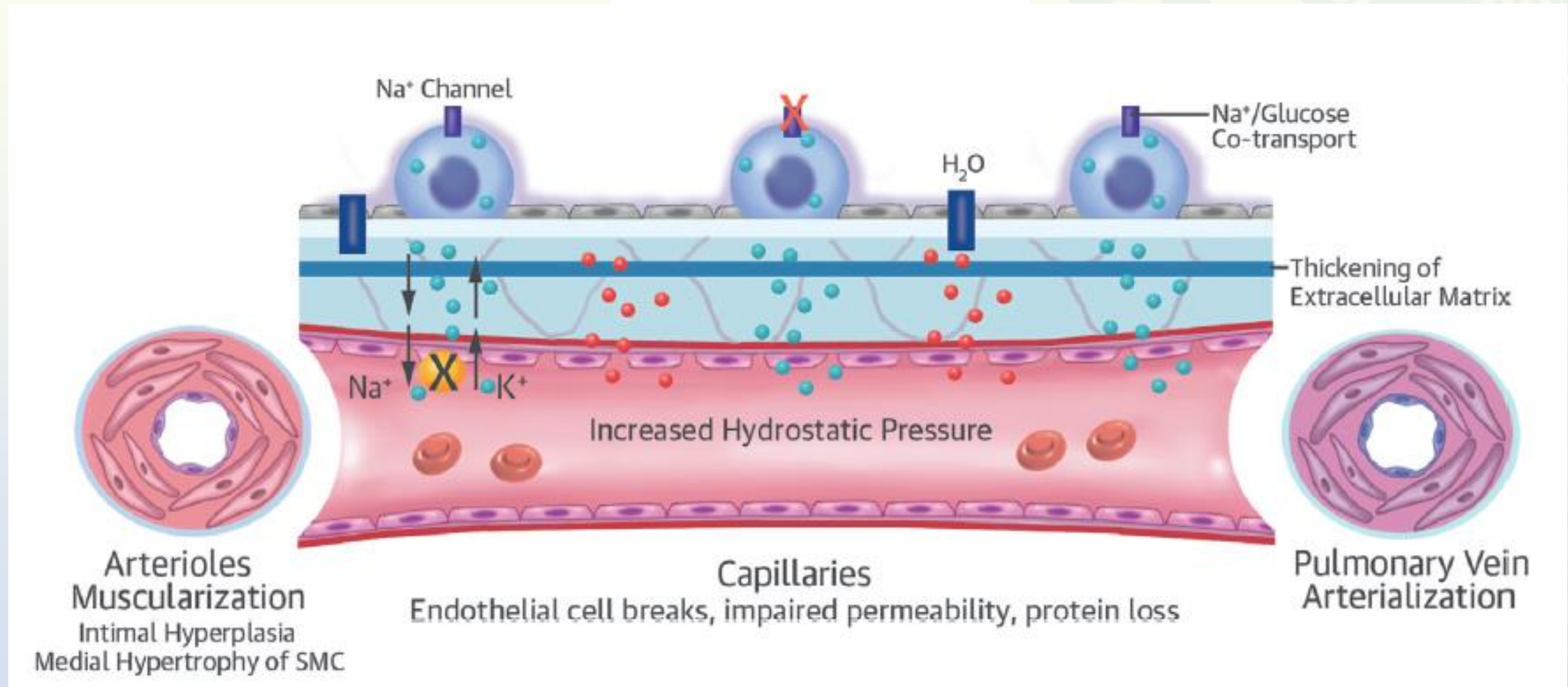
# Capillary Stress Failure



# Pulmonary Vascular Remodelling



# Pulmonary Vascular Remodelling



**Low-impedence, high capacitance → high-impedence, low capacitance**

# Classification

- **“Passive” PH**

**$mPAP \geq 25$  mmHg,  $PAWP > 15$  mmHg**

**$TPG (mPAP - PAWP) \leq 12$  mmHg**

**$PVR (TPG / CO) < 3.0$  W.U.**

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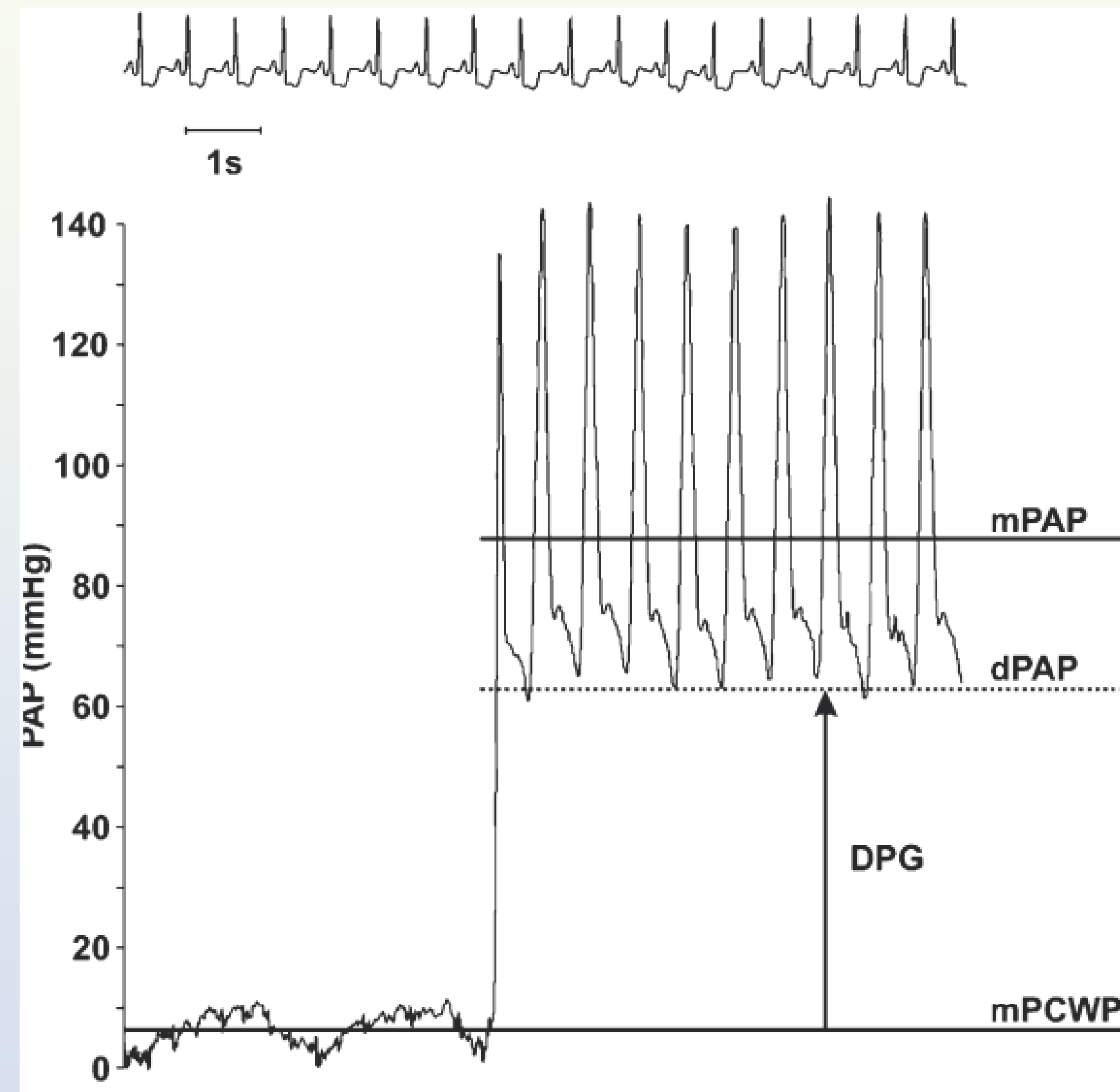
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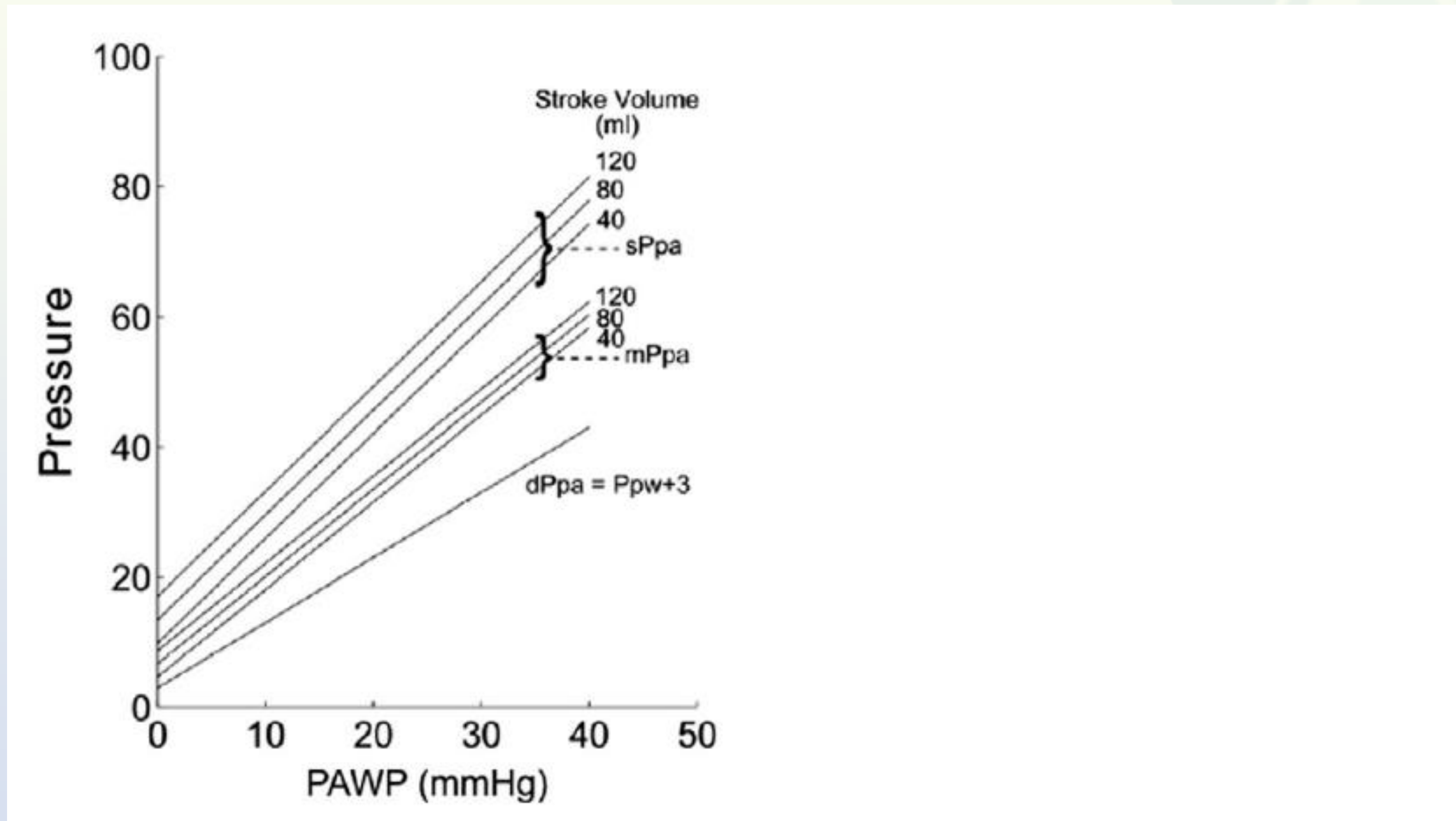
**$TPG > 12$  mmHg**

**$PVR > 3.0$  W.U.**

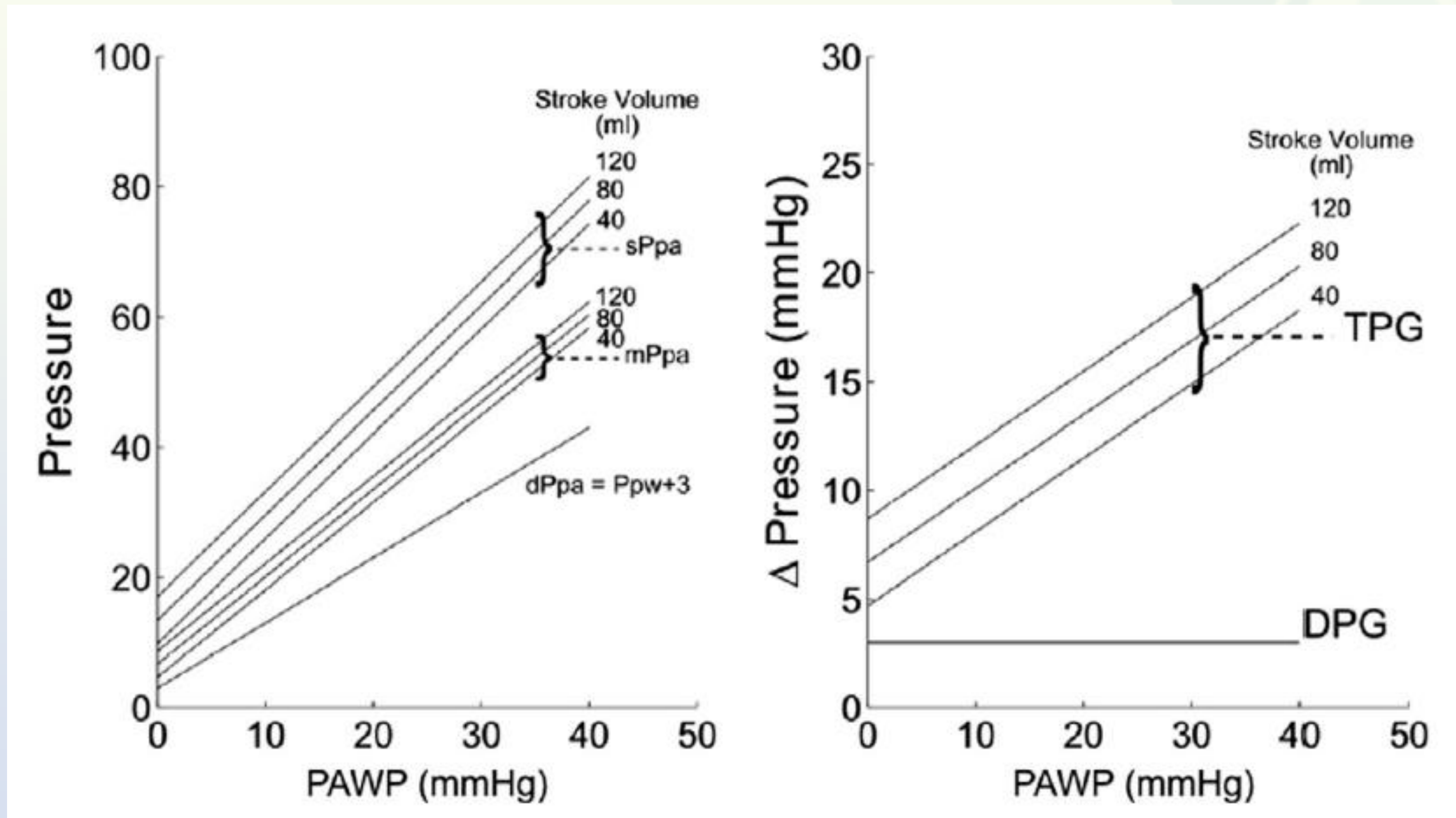
# Diastolic Pressure Gradient

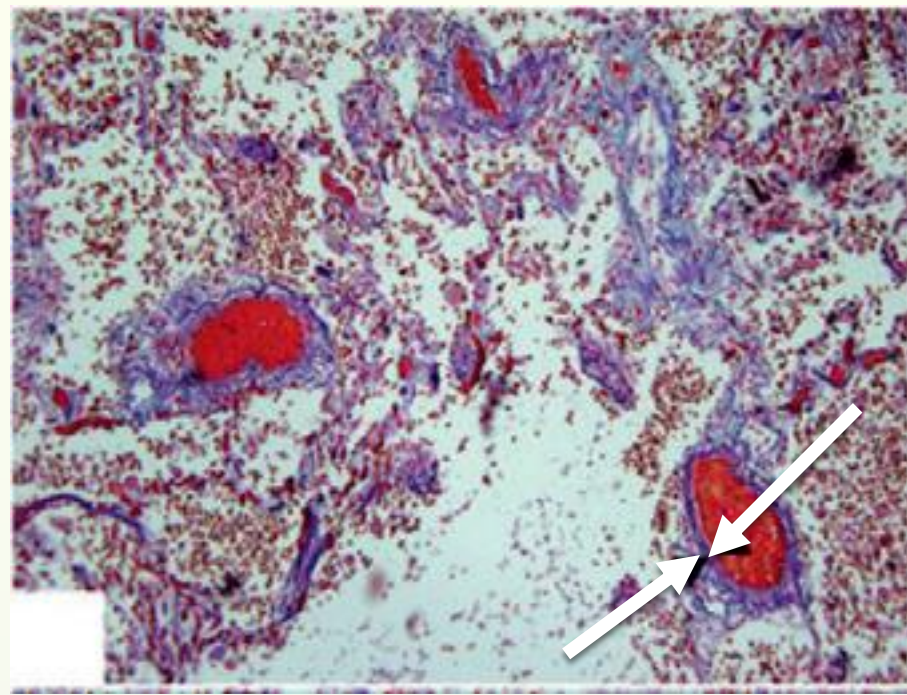


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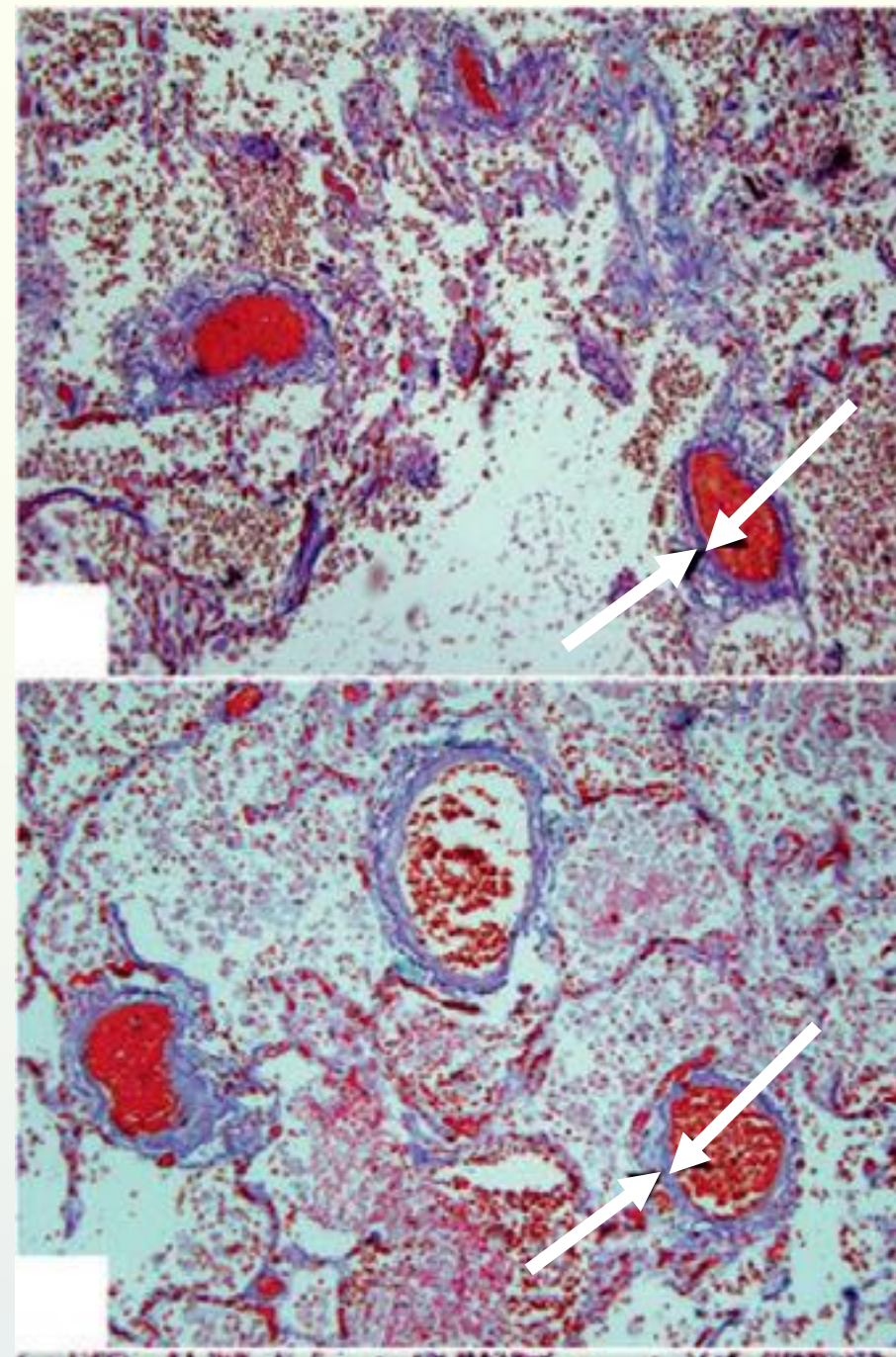


# Diastolic Pressure Gradient



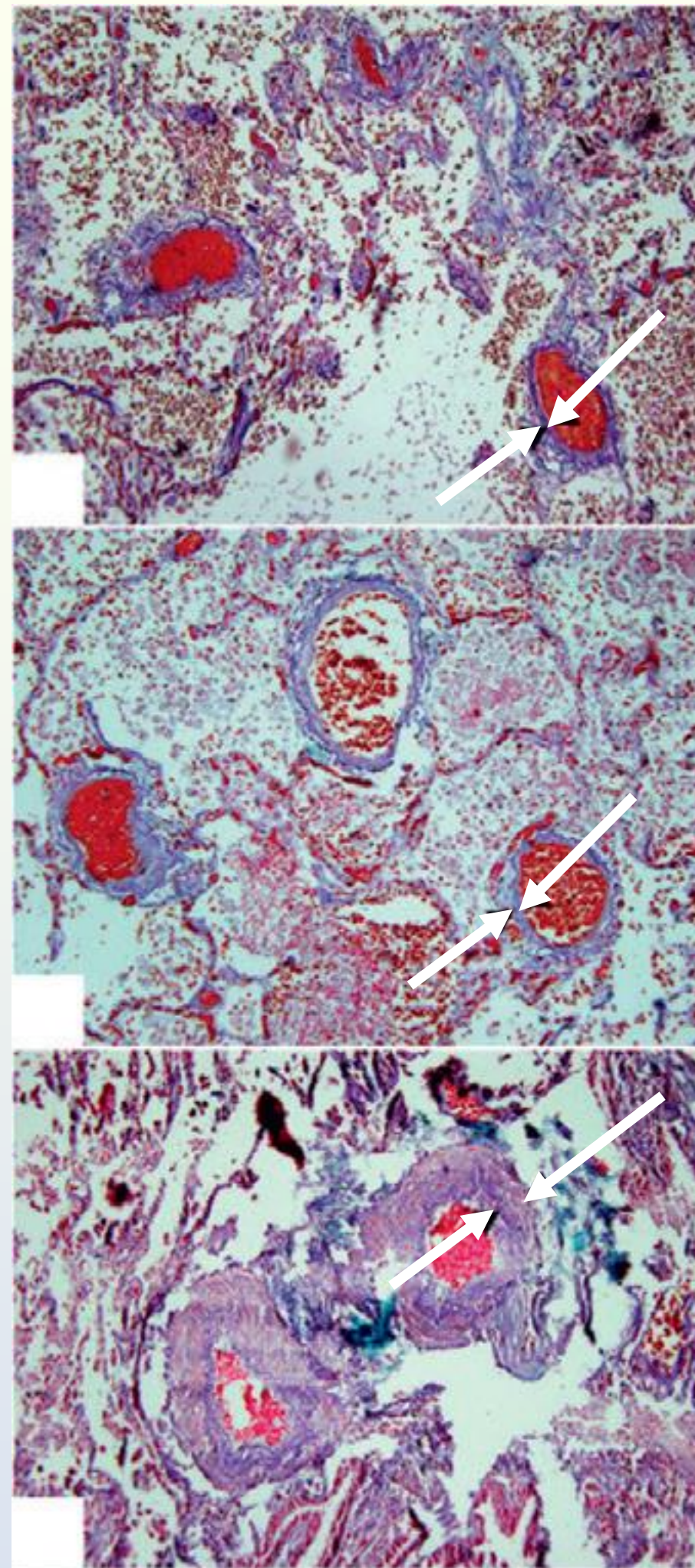


mPAP > 25 mmHg, PAWP > 15 mmHg  
**TPG < 12 mmHg, DPG 3 mmHg**



mPAP > 25 mmHg, PAWP > 15 mmHg  
TPG < 12 mmHg, DPG 3 mmHg

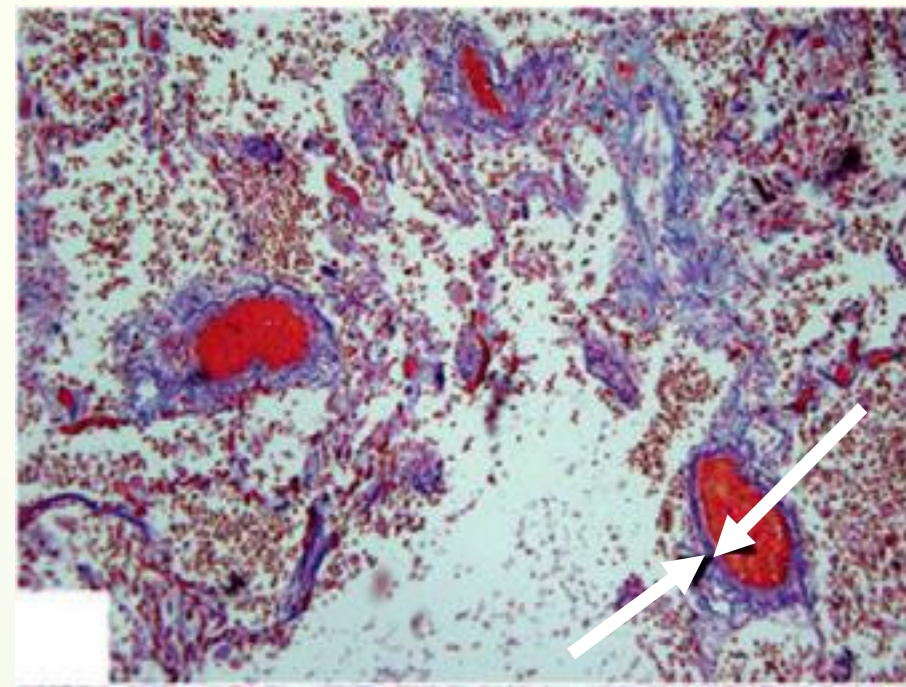
mPAP > 25 mmHg, PAWP > 15 mmHg  
**TPG > 12 mmHg, DPG 5 mmHg**



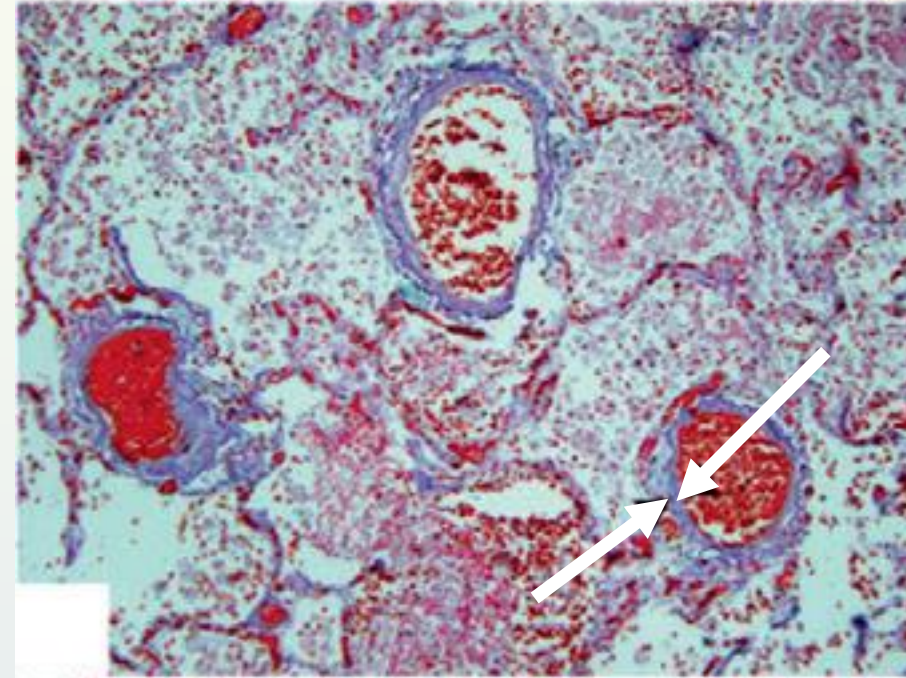
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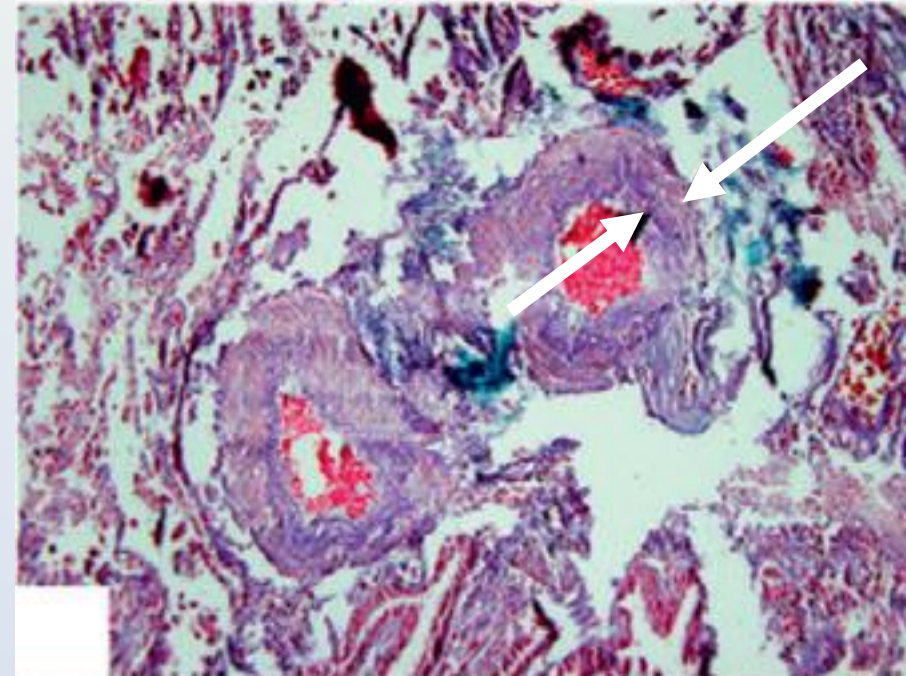
mPAP > 25 mmHg, PAWP > 15 mmHg  
**TPG > 12 mmHg, DPG 13 mmHg**



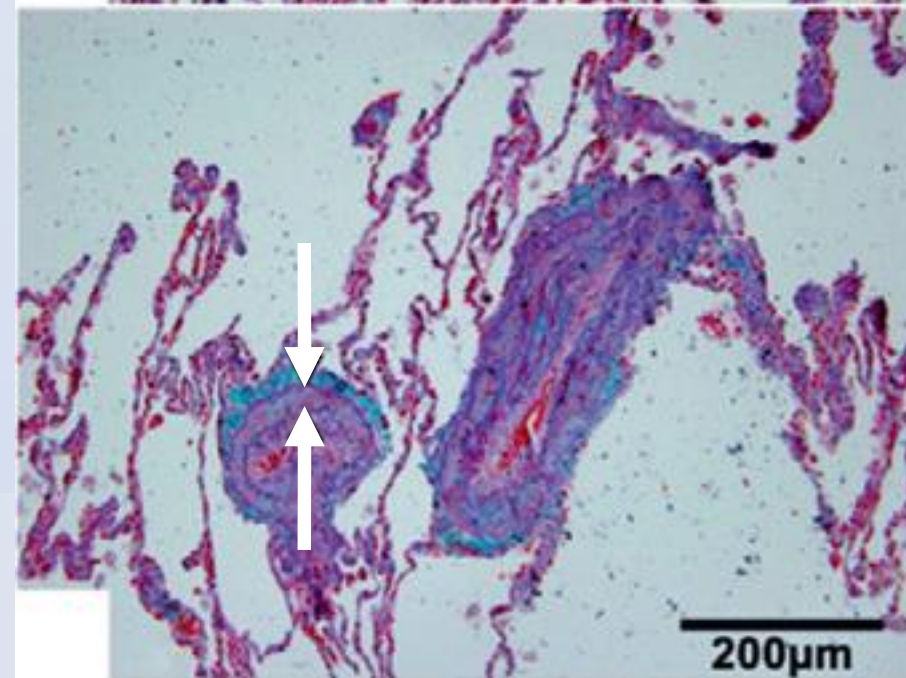
mPAP > 25 mmHg, PAWP > 15 mmHg  
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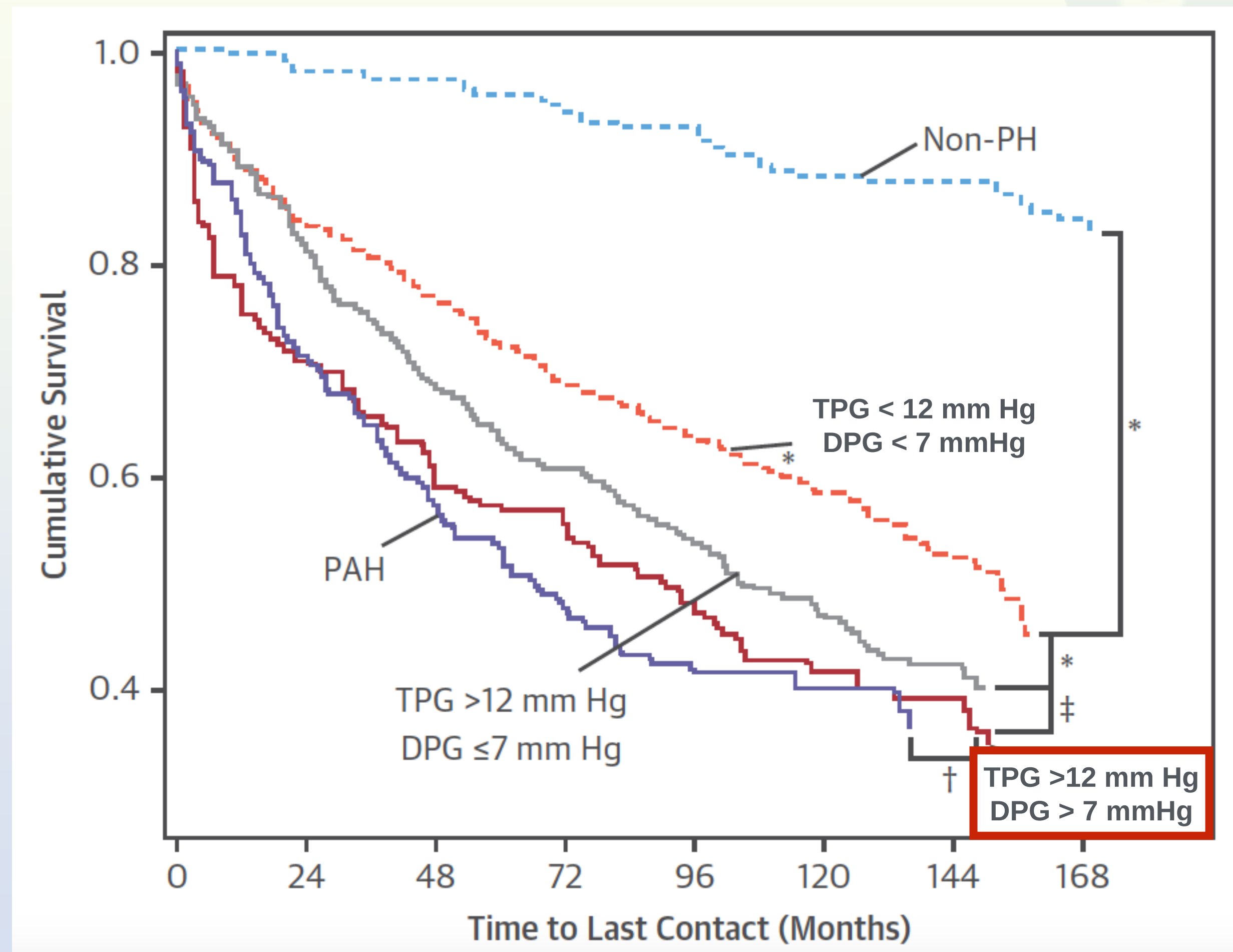
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TPG > 12 mmHg, DPG 5 mmHg



mPAP > 25 mmHg, PAWP > 15 mmHg  
TPG > 12 mmHg, DPG 13 mmHg



mPAP > 25 mmHg, PAWP < 15 mmHg  
TPG > 12 mmHg, DPG > 7 mmHg



# Classification

- “Passive” PH

**mPAP  $\geq$  25 mmHg, PAWP  $>$  15 mmHg**

**TPG (mPAP - PAWP)  $\leq$  12 mmHg**

**PVR (TPG / CO)  $<$  3.0 W.U. and/or**

**DPG  $<$  7 mmHg**

- “Reactive”, “Out-of-proportion” PH

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**DPG  $\geq$  7 mmHg**

# Classification

- “Passive” PH → **lpc-PH**  
mPAP  $\geq 25$  mmHg, PAWP  $> 15$  mmHg  
TPG (mPAP - PAWP)  $\leq 12$  mmHg  
PVR (TPG / CO)  $< 3.0$  W.U. and/or  
**DPG  $< 7$  mmHg**
- “Reactive”, “Out-of-proportion” PH → **Cpc-PH**  
mPAP  $\geq 25$  mmHg, PAWP  $> 12$  mmHg  
TPG  $> 12$  mmHg  
PVR  $> 3.0$  W.U. and/or  
**DPG  $\geq 7$  mmHg**

# Epidemiology

| Study (n) <sup>a</sup>                         | Definitions/Selection Criteria Used                                            | Overall Prevalence of PH | Phenotype of PH       |                        | Impact on Outcomes                                                                                               |
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|                                                |                                                                                |                          | Ipc-PH                | Cpc-PH                 |                                                                                                                  |
| Catheter based studies                         |                                                                                |                          |                       |                        |                                                                                                                  |
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| Benza et al. <sup>21</sup><br>(n = 412)        | EF: <40%<br>mPAP >25 mm Hg<br>iPc-PH vs Cpc-PH: not ana                        |                          |                       |                        | Patients with PH had higher HF                                                                                   |
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Ipc-PH vs. Cpc-PH in HFrEF

RHC: 84% vs 16%

Median survival: 110 mo vs. 72 mo

Ipc-PH vs. Cpc-PH in HFrEF  
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|                                             |                                                                                     |            | Ipc-PH          | Cpc-PH |                                                                                                    |
| Catheter based studies                      |                                                                                     |            |                 |        |                                                                                                    |
| Leung et al. <sup>25</sup><br>(n = 455)     | EF ≥50%<br>PASP >25 mm Hg<br>PAWP: 15 mm Hg                                         | 52.5%      | –               |        | No outcomes studied                                                                                |
| Hurdman et al. <sup>42</sup><br>(n = 157)   | Cut-off for diastolic dysfunction not specified<br>PASP >25 mm Hg<br>PAWP: 15 mm Hg | 62%        | –               |        | No significant difference in outcome between PH-HFpEF vs PH-HFrEF                                  |
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| Benza et al. <sup>21</sup><br>(n = 116)     | EF: ≥40%<br>mPAP >25 mm Hg<br>iPc-PH vs Cpc-PH: not analyzed                        | 47%        | –               |        | Patients with PH had higher HF hospitalization rates vs non PH (0.77/year vs 0.37/year, p < 0.01)† |
| Echocardiography based studies              |                                                                                     |            |                 |        |                                                                                                    |
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IpcPH vs. CpcPH in HFpEF

RHC: 77% vs. 23%

Median survival: 102 mo. vs. 54 mo

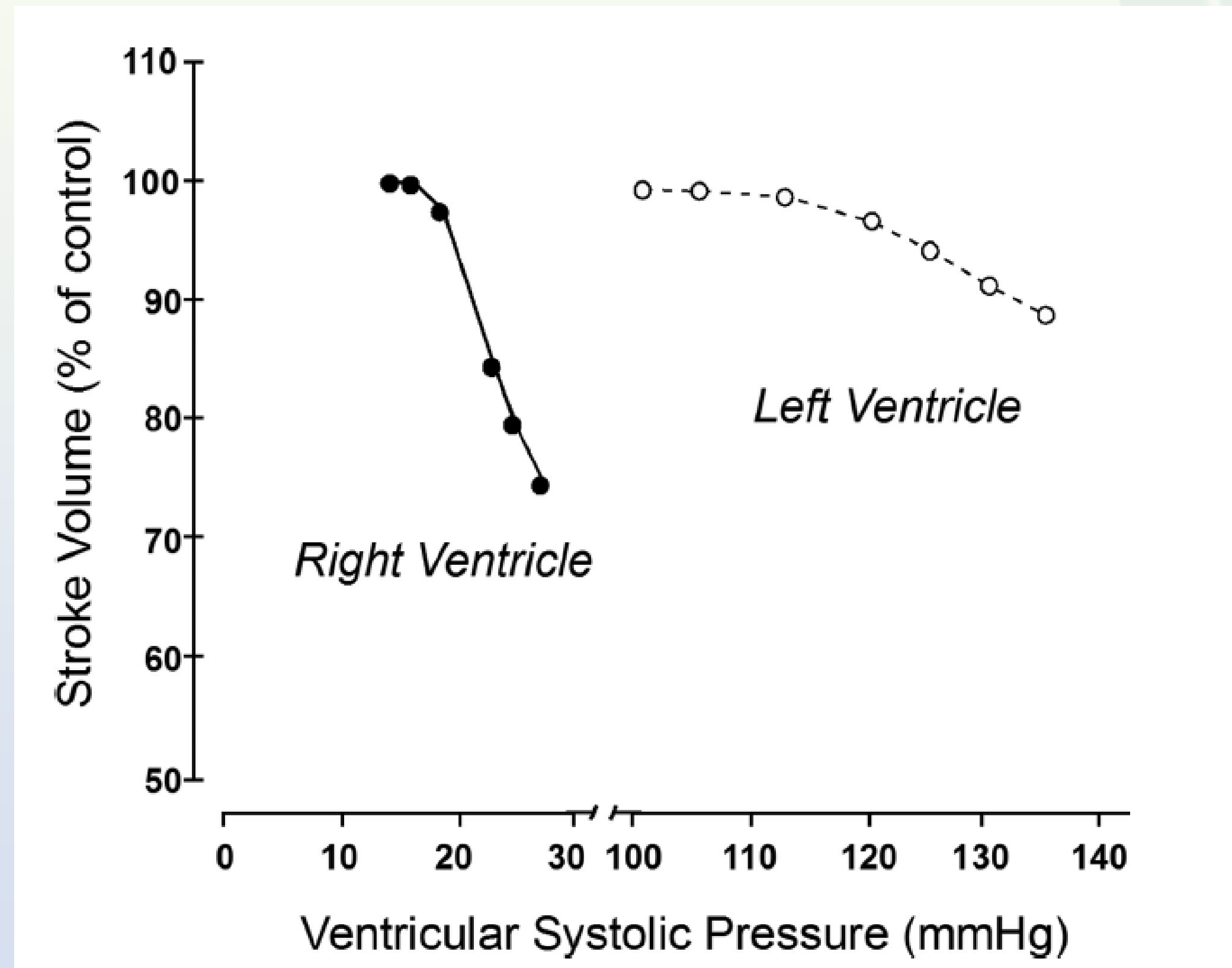
IpcPH vs. CpcPH in HFpEF

RHC: 77% vs. 23%

Median survival: 102 mo. vs. 54 mo

# The RV in PH

## Afterload sensitivity of the right ventricle



# The RV in PH

- **RV-PA un-coupling**

Failure of RV contractility (intrinsic function) to counteract increase in PA pressure (afterload)

- **RV-LV Septal Interaction**

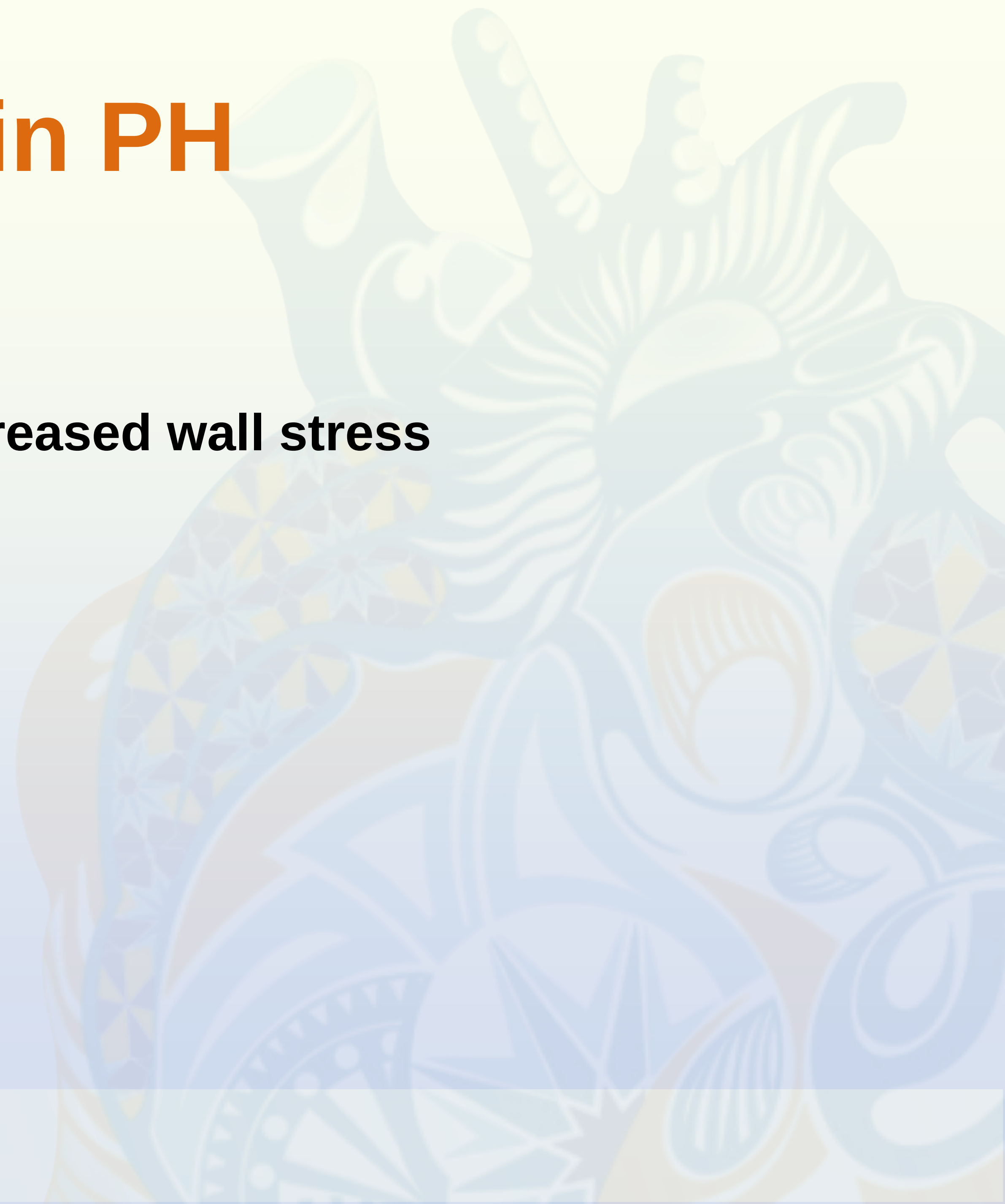
Diastolic interaction - ventricular competition for filling in a non-distensible pericardium

Systolic interaction - 20-40% of RV SP is due to LV contraction, 4-10% of LVSP due to RV

# The RV in PH

- **RVH, RV enlargement, and RV Failure:**

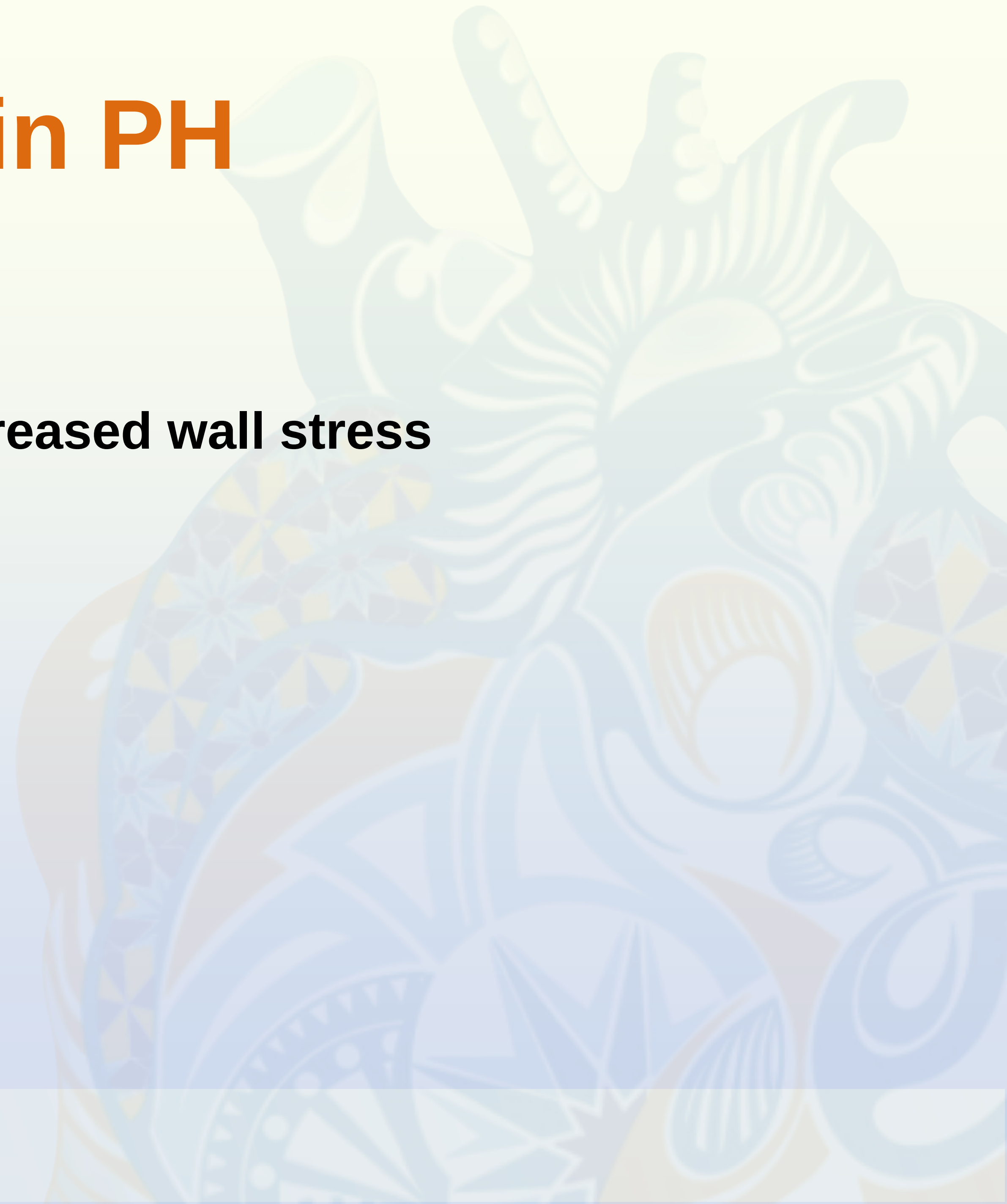
**Subendocardial ischemia and increased wall stress**



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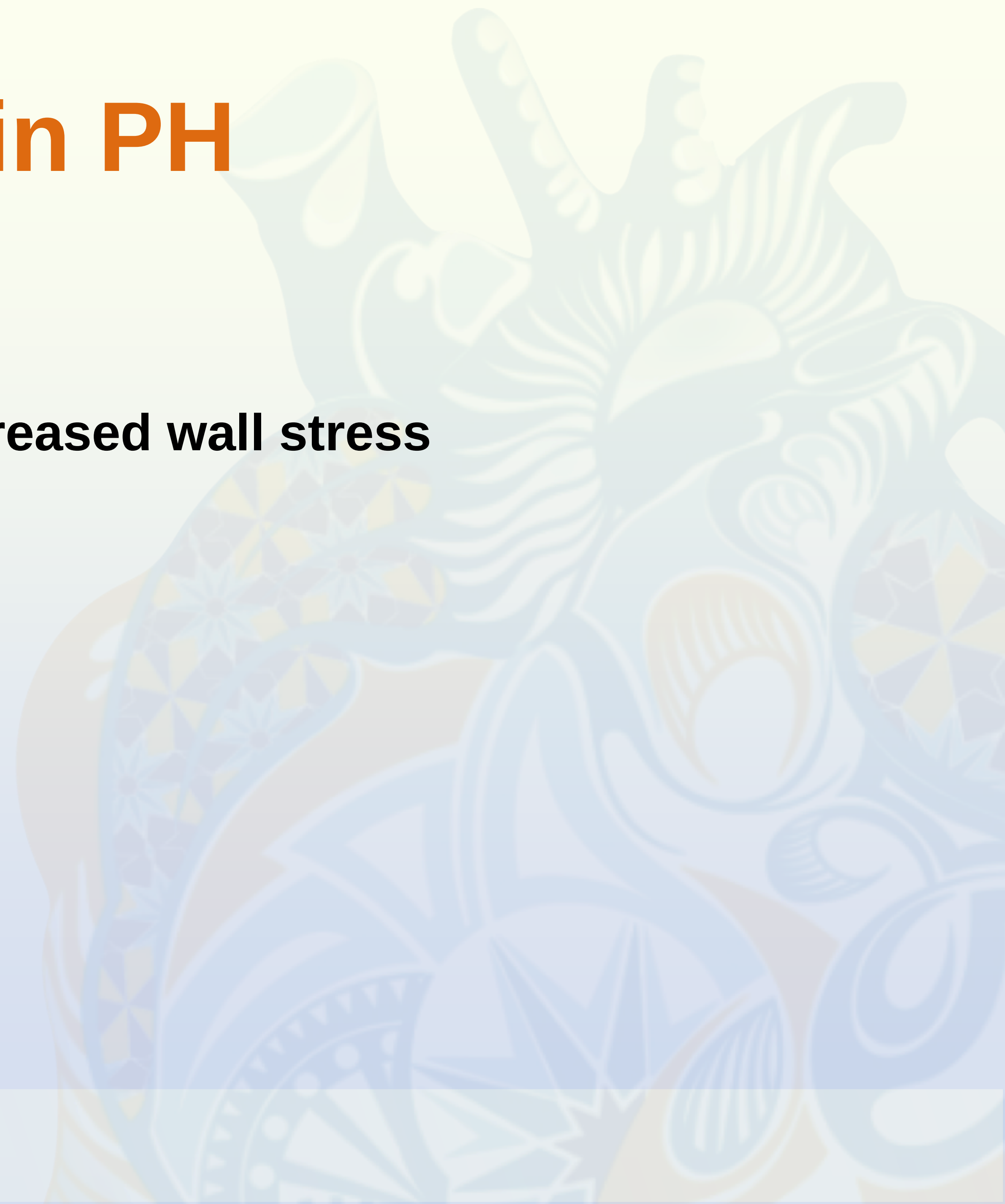
**Subendocardial ischemia and increased wall stress  
LV underfilling**



# The RV in PH

- **RVH, RV enlargement, and RV Failure:**

**Subendocardial ischemia and increased wall stress**  
**LV underfilling**  
**Functional TR**



# The RV in PH

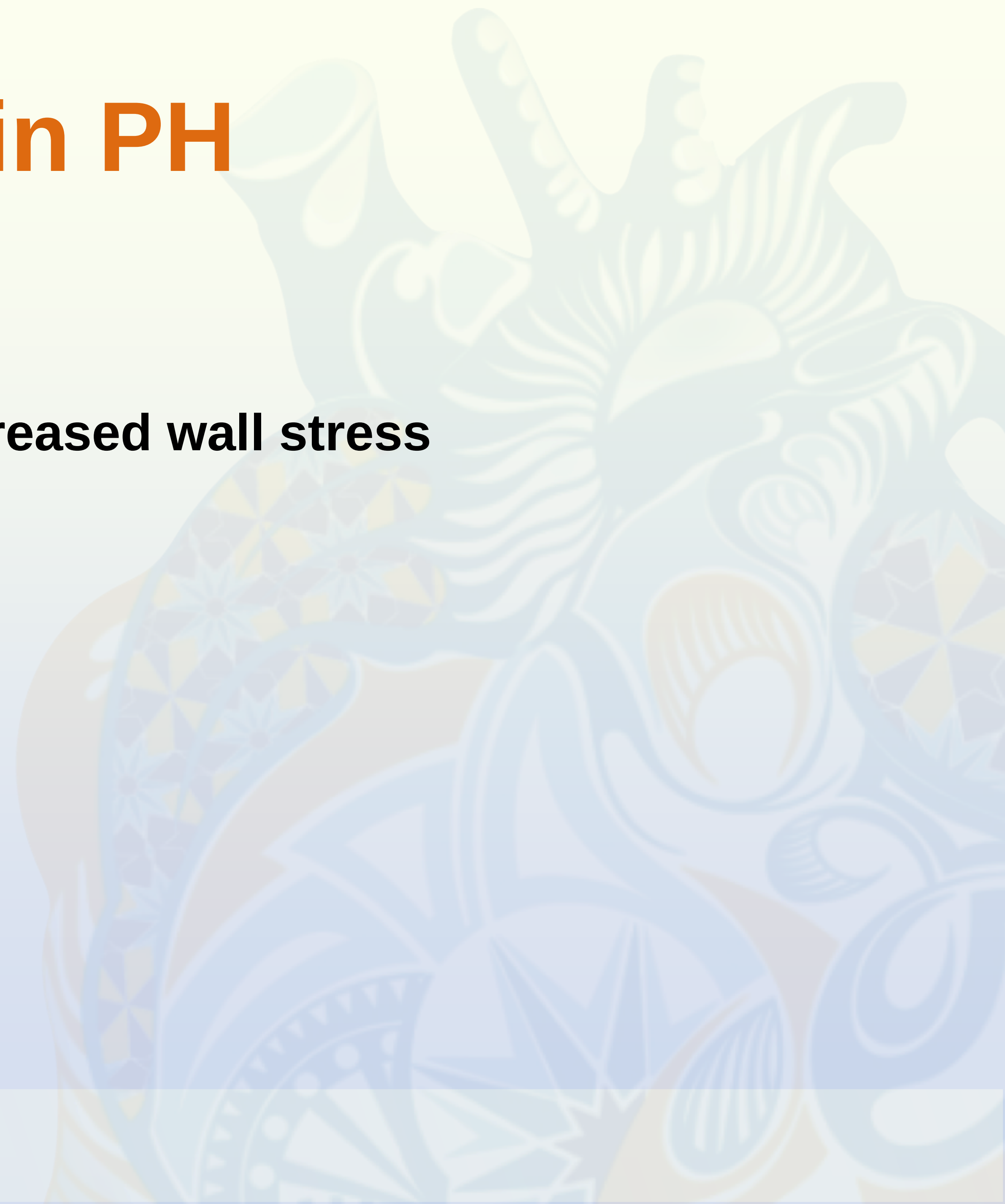
- **RVH, RV enlargement, and RV Failure:**

**Subendocardial ischemia and increased wall stress**

**LV underfilling**

**Functional TR**

**Thoracic duct compression**



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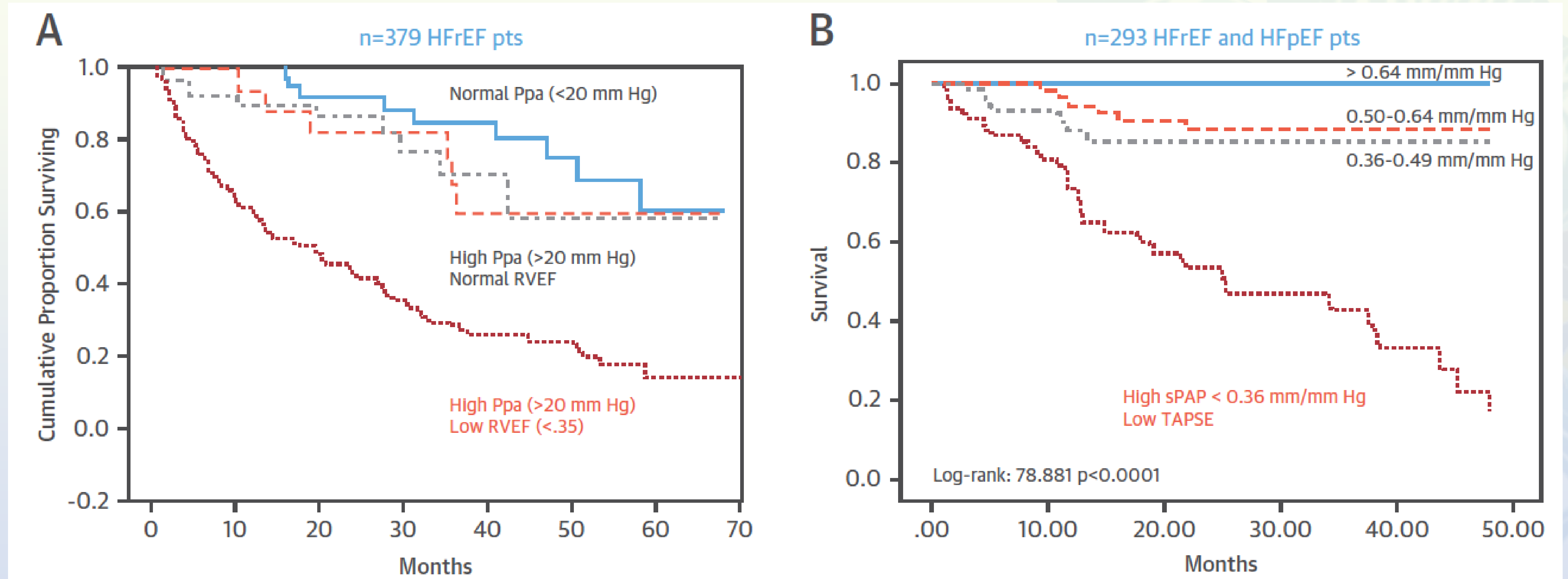
**Renal congestion**

**Bowel edema**

**Ascites**

**Microbial translocation**

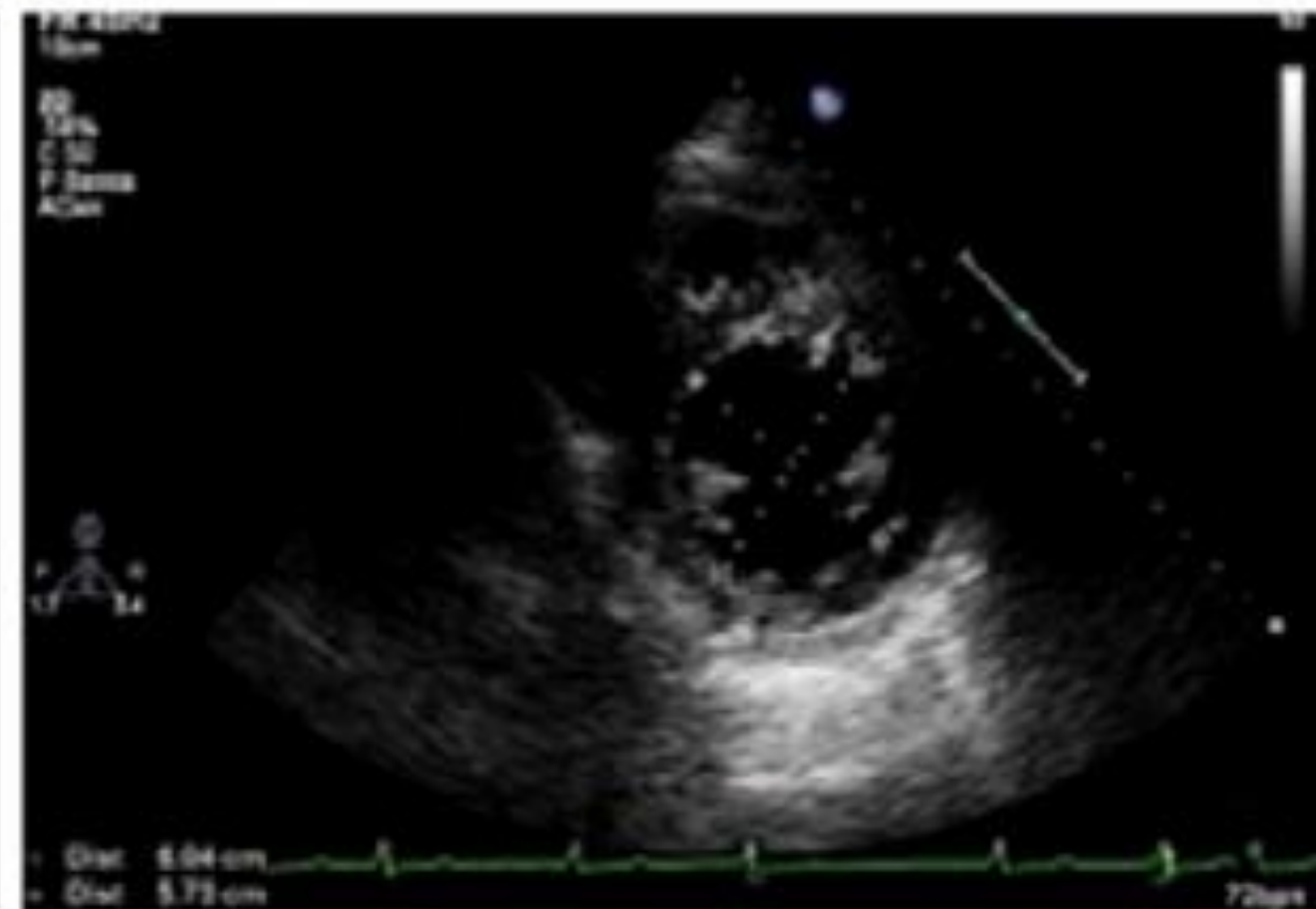
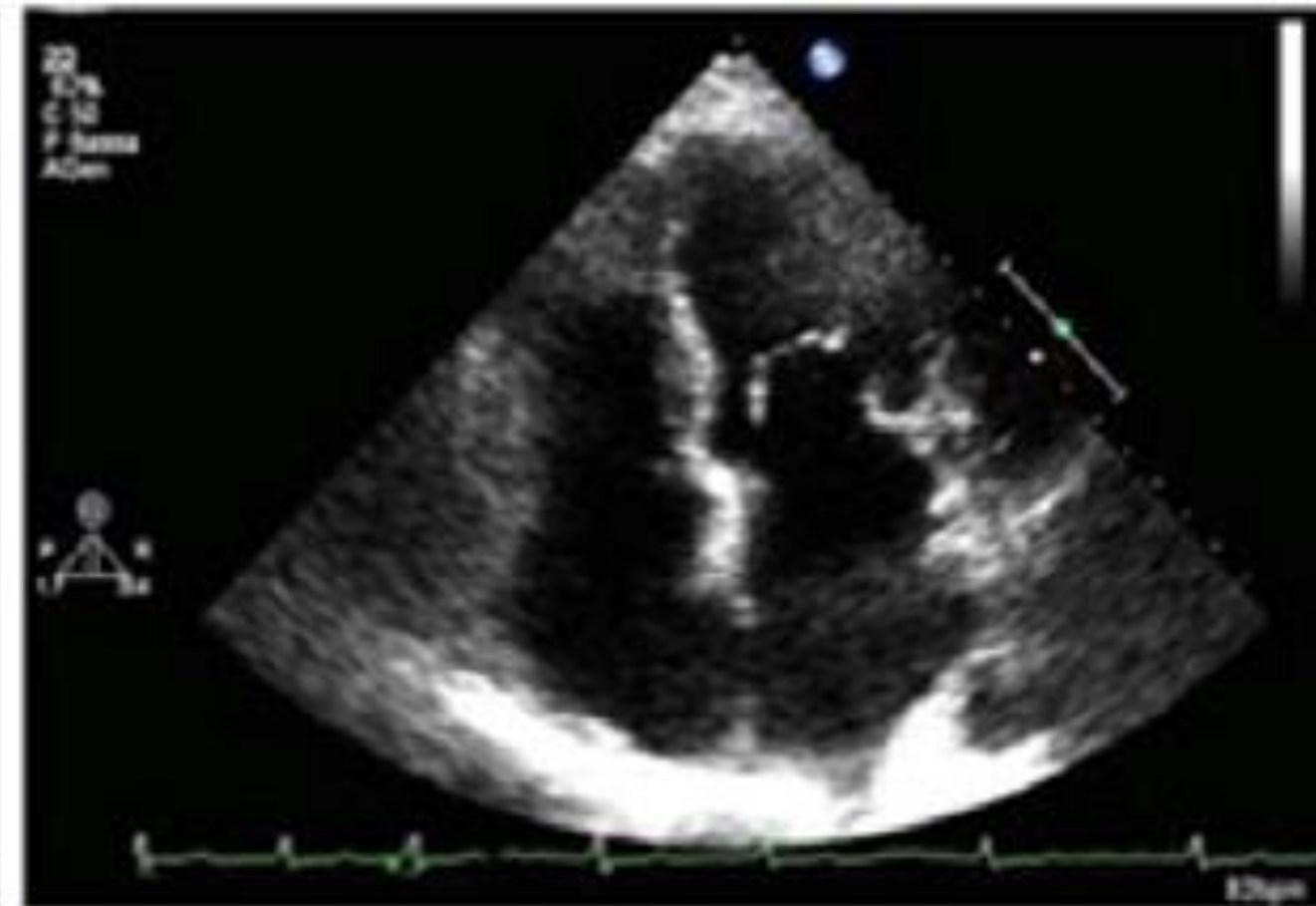
# Impact of RV Failure on Prognosis



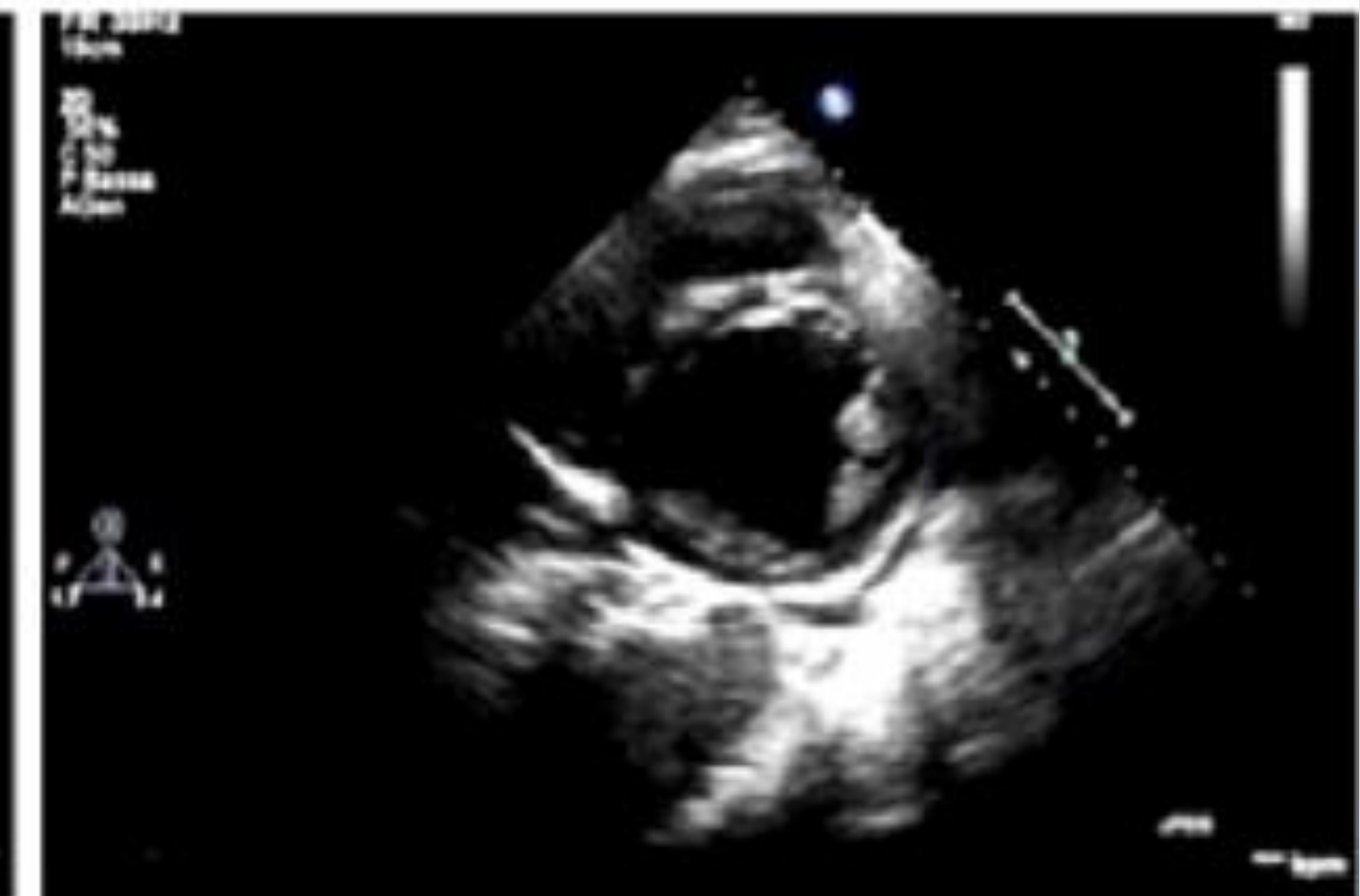
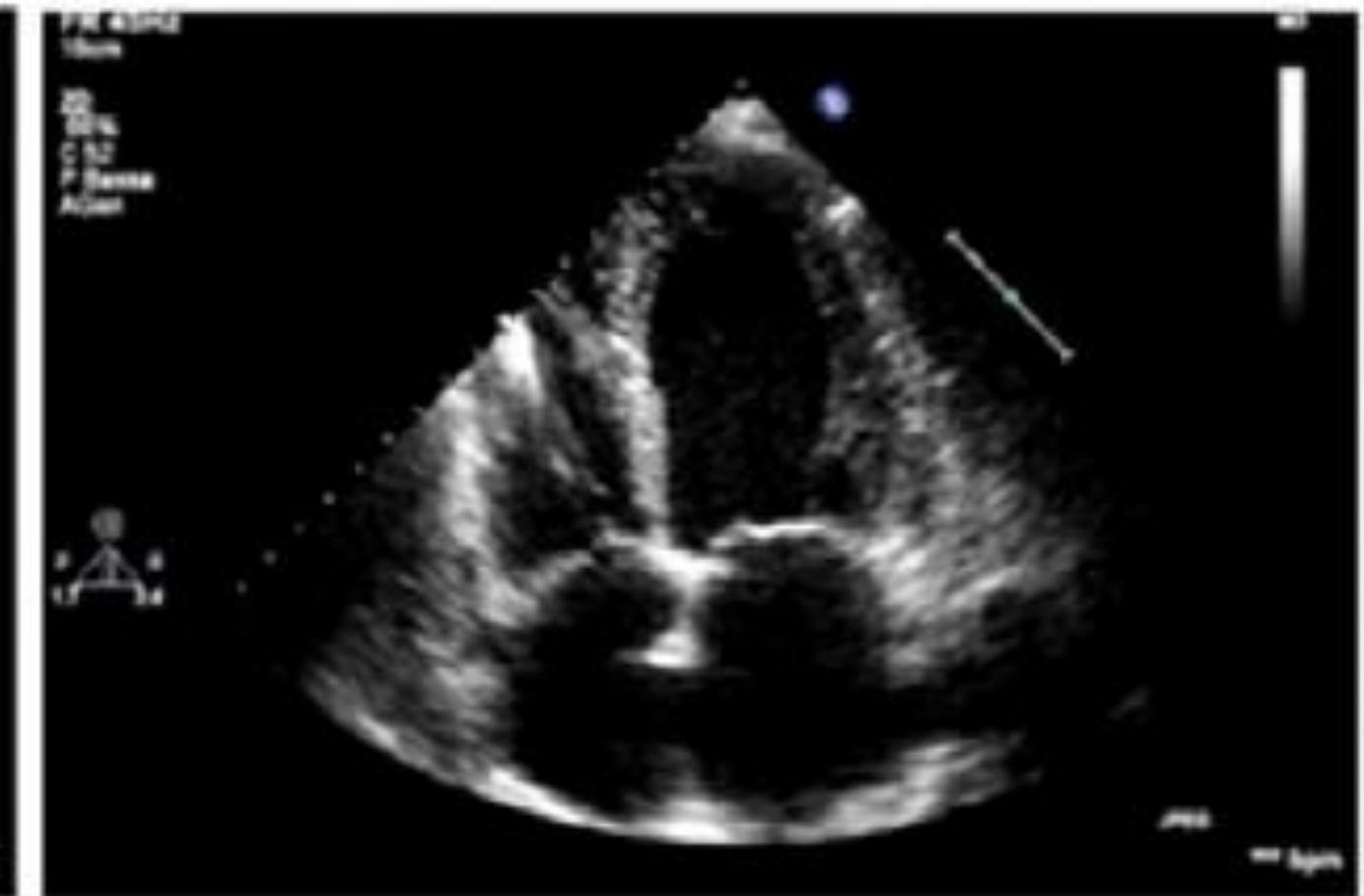
PAH



Cpc-PH



lpc-PH



TAPSE < 17

FAC < 35%

S' < 9.5

# Diagnosis

- Doppler-echo: The non-invasive RHC**

PASP =  $(4V^2 \text{ peak jet velocity of TR}) + \text{RA pressure}$

PADP  $(4v^2 \text{ of end diastolic PR velocity}) + \text{RA pressure}$

Mean PAP = PADP + 1/3 pulse pressure

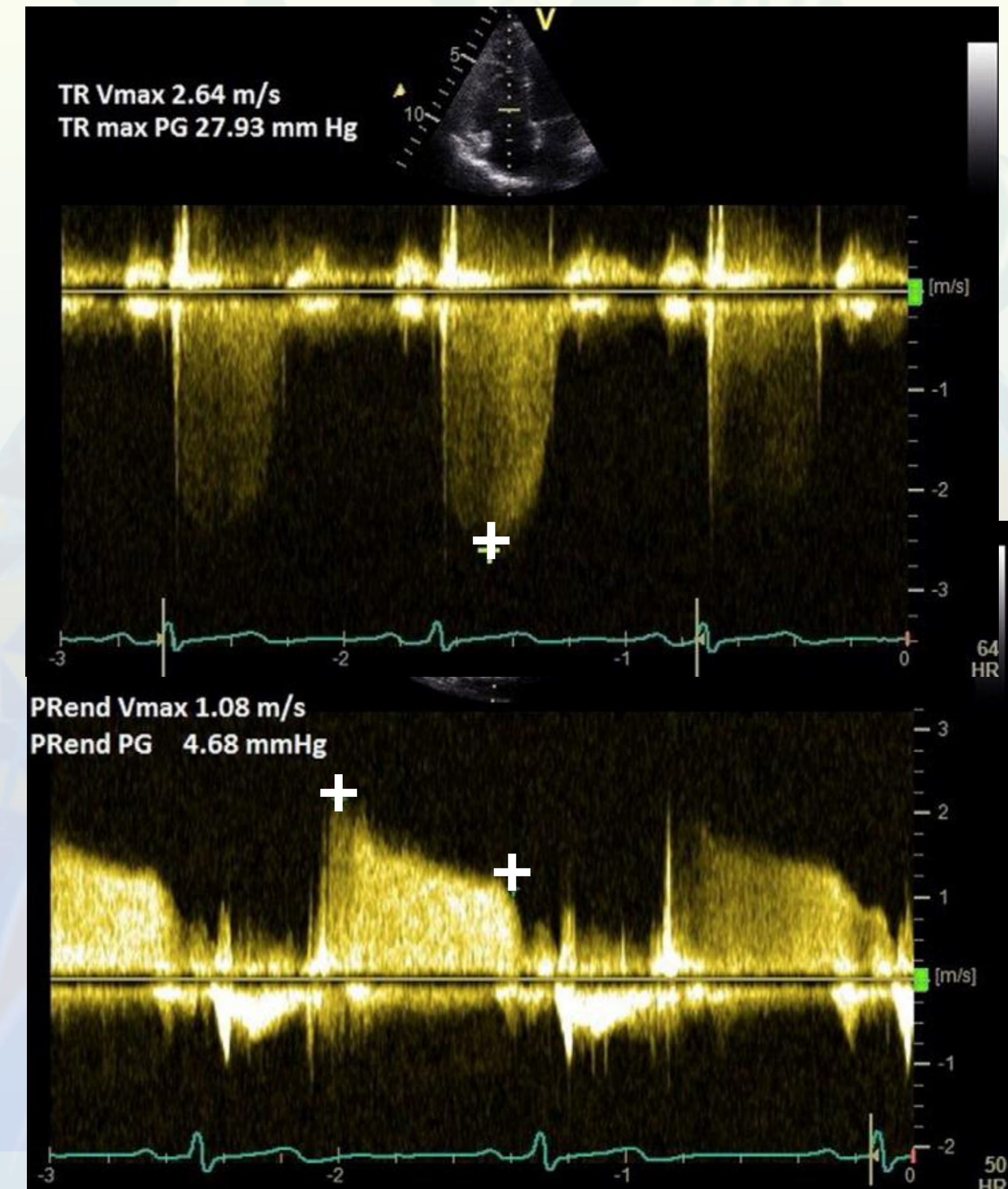
Mean PAP =  $(4V^2 \text{ early PR jet velocity}) + \text{RA pressure}$

Mean PAP = TVI of TR jet + RA pressure

Mean PAP =  $0.61 \times \text{PASP} + 2 \text{ mmHg}$

Mean PAP =  $79 - (0.45 \times \text{AT})$

PCWP =  $1.24 * (E/e') + 1.9$



# Therapeutic Strategies

- **Lower LA pressure**

Ensure sufficient diuretic dosing to achieve decongestion  
Fluid and salt restriction

- **Aerobic exercise training**

- **Treat co-morbidities**

# Nitric Oxide and cGMP Modulation

| Study                                        | N   | Intervention                             | LVEF  | Criteria                                                       | End-points               | Results                                    |
|----------------------------------------------|-----|------------------------------------------|-------|----------------------------------------------------------------|--------------------------|--------------------------------------------|
| Guazzi M, et al.<br>2011 (1)                 | 44  | Sildenafil 50 mg<br>tid                  | > 50% | HFpEF<br>HTN<br>PASP>40 (55)                                   | Hemodynamic<br>6, 12 mos | ↓ RA, mPAP<br>↓ PCWP<br>↑ TAPSE            |
| RELAX Trial<br>2013 (2)                      | 215 | Sildenafil 20 mg<br>tid                  | > 50% | NYHA II-IV<br>NT-ProBNP > 400<br>or diastolic stress test      | Peak VO2<br>24 wks       | No difference in<br>VO2<br>Hypotension, RF |
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PDE5 Inhibitor

Organic nitrate

Inorganic nitrite

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# Prostacyclin Pathway

| Study                                   | N   | Intervention             | LVEF  | Criteria                            | End-points          | Results                                     |
|-----------------------------------------|-----|--------------------------|-------|-------------------------------------|---------------------|---------------------------------------------|
| FIRST Trial<br>Califf R, et al.<br>1997 | 471 | Epoprostenol<br>infusion | < 25% | NYHA IIIB/IV<br>CI < 2.2, PCWP > 15 | Mortality           | mPAP 38 mm Hg<br>↑ CI ↓ PCWP<br>↑ mortality |
| Grossman et al.<br>2015                 | 8   | Iloprost<br>inhaled      | > 50% | NYHA III/IV<br>PASP > 50 mm Hg      | Hemodynamic         | ↓ mPAP 7 mm Hg<br>↓ PVR 2 W.U.              |
| ClinicalTrials.gov<br>NCT03037580       | 310 | Treprostinol<br>oral     | > 45% | Group II PH by RHC<br>HFpEF         | Δ 6MWD<br>at 24 mos | Pending<br>(2020)                           |

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# Endothelin Pathway

| Study                                     | N    | Intervention | LVEF  | Criteria                                                      | End-points    | Results                                                      |
|-------------------------------------------|------|--------------|-------|---------------------------------------------------------------|---------------|--------------------------------------------------------------|
| ENABLE Trials<br>Packer M, et al.<br>2017 | 1613 | Bosentan     | < 35% | NYHA IIIB/IV                                                  | Mortality     | No difference<br>in mortality<br>↑ HF hosp<br>↑ periph edema |
| MELODY-1<br>Vachiéry J, et al<br>2018     | 63   | Macitentan   | ≥ 30% | NYHA II/III<br>CpcPH by RHC<br>(PVR ≥ 3 and<br>DPG ≥ 7 mm Hg) | Edema<br>NYHA | ↑ Edema<br>↑ NYHA                                            |

# Endothelin Pathway

| Study                                     | N    | Intervention | LVEF  | Criteria                                                      | End-points    | Results                                                      |
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# Management of PH Post Valve Intervention

- SIOVAC

N = 200

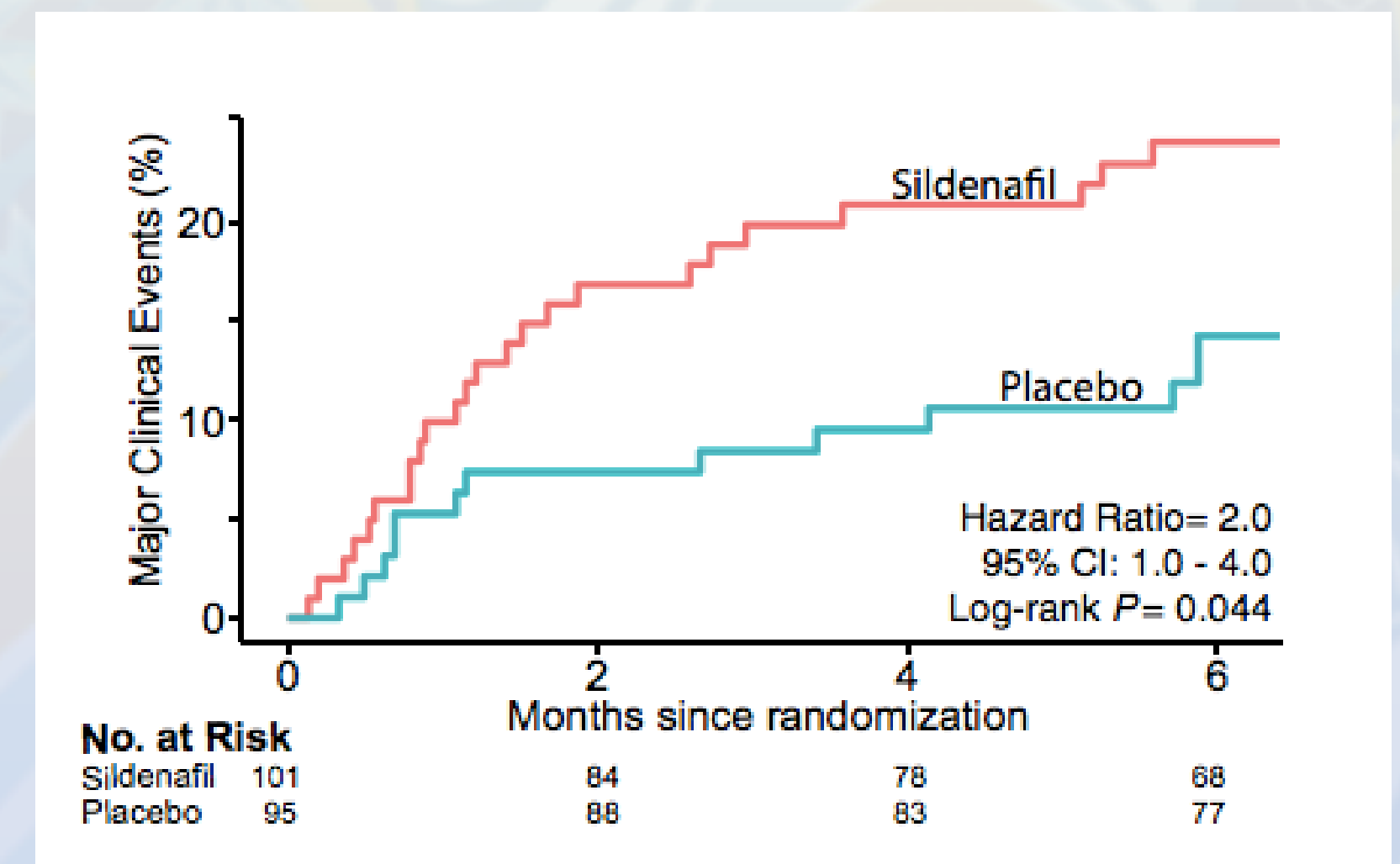
mPAP > 30 mm Hg on RHC

Percutaneous valve replacement / repair < 1 yr earlier

Rx: Sildenafil 40 mg tid vs placebo

Primary outcome: composite score of MACE, WHO, PGA

Worsening score with sildenafil (doubled risk of MACE)



# PH in advanced HFrEF

- **Advanced HF patients**

GDMT

Sildenafil in select patients with RV dysfunction and Cpc-PH TPG  $> 20$ ,  
PCWP  $< 20$ , DPG  $> 10$ , PVR  $> 5$

- **LVAD**

Effective unloading of the LV

PDE5 inhibitors post LVAD implantation with persistent PVR elevation\*

\*Tedford R, et al. Circ Heart Fail. 2008;1(4):213

# Conclusions

- **Group II PH is the leading cause of pulmonary hypertension, mostly driven by HFrEF and HFpEF**
- **Introduction of multiple indices of pulmonary hemodynamics allows better phenotyping of group II PH**
- **Future trials will likely target the subgroup of Cpc-PH, who present with pulmonary vascular disease, elevated PVR, and RV dysfunction**