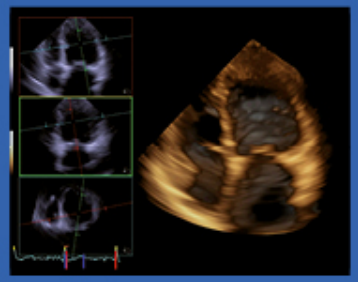


EuroValve
March 27 - 28, 2015

l'institut du thorax

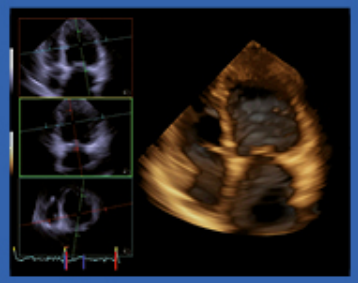
Pulmonary Hypertension in Aortic Stenosis

Thierry Le Tourneau

Institut du Thorax
Inserm UMR 1087
Nantes, France

Nice, 27 March 2015

www.eurovalvecongress.com



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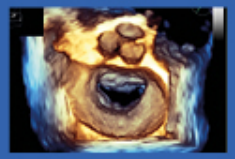
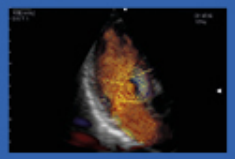
Faculty disclosure

Thierry Le Tourneau

I disclose the following financial relationships:

Paid speaker for GE, Philips, Biopharma, Servier, BMS, Daiichi

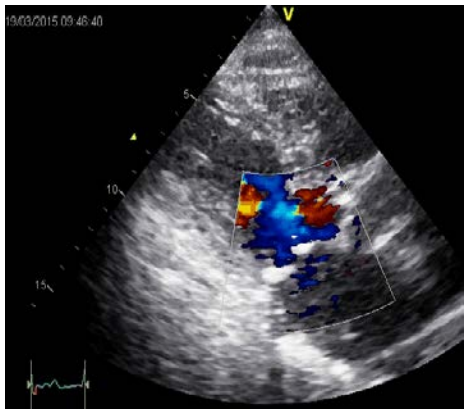


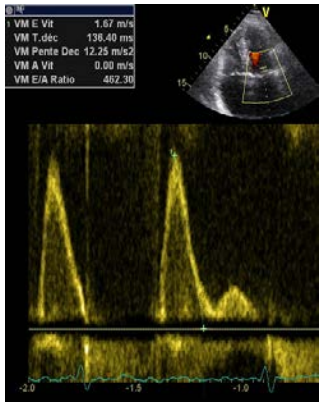



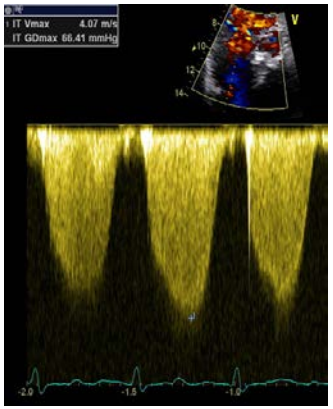
www.eurovalvecongress.com

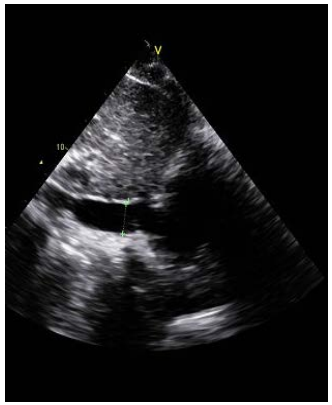
Clinical Case

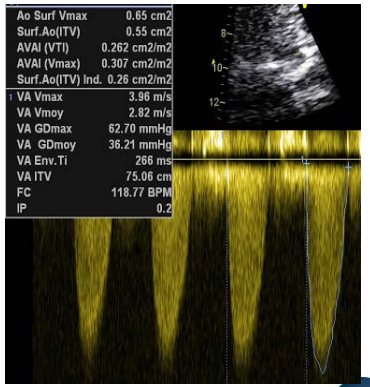
75 yrs old woman, diabetic, overweight (104 kg/169 cm), Hodgkin when she was 60 yrs old with chest radiation, fenfluramine for 9 months at 50 yrs, AF, Class 3 NYHA

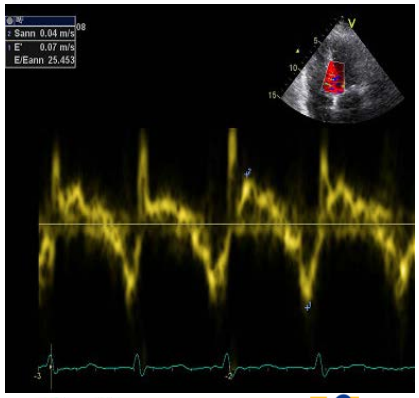












Clinical Case

Right heart catheterization:

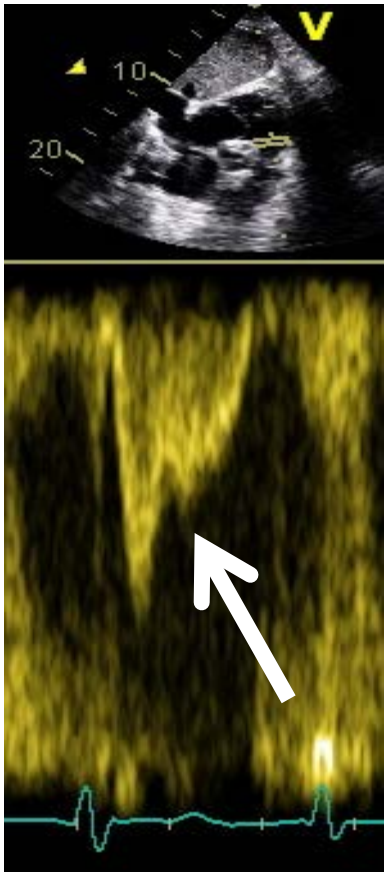
-CO: 2.8 L/min/m²

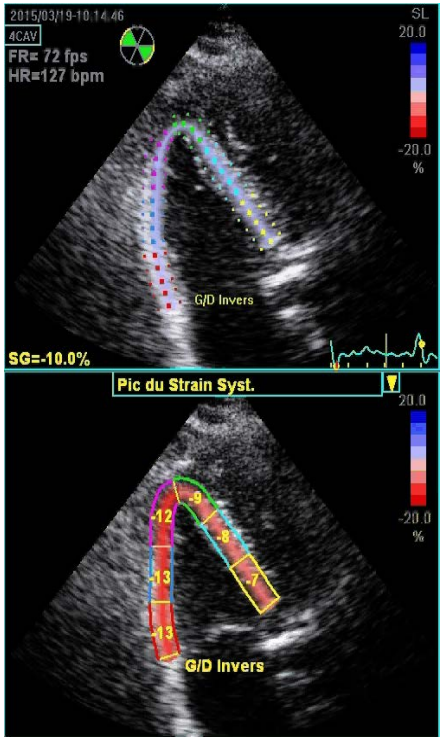
-PAWP: 30 mmHg

-PAP S/D/Mean: 90/37/47

-RAP: 20 mmHg

-PVResist: 6.7 Wood Units





⇒ Post-capillary PH

⇒ Reactive or Mixed ?

Pathophysiology of PH

	Pulmonary Vasculature	Systemic Vasculature
Resistance (R)	0.25-1.6, ≤ 3 Wood Units	9-20 Wood Units
Compliance (C), mL/mmHg	3.8	2.5
Compliance (C)	Inversely related to R	No direct relation to R
Compliance (C)	15-20% in the Pulm artery and main branches, the rest over the entire arterial system	80% in the aorta (central)
Changes in R in Pathol	x 18	x 1.2
Changes in C in Pathol	/ 20	/ 3
Steady afterload	RV work: 67-77%	LV work: 87-90%
Pulsatile afterload	RV work: 23-33%	LV work: 10-13%

Saouti N, Eur Respir Rev 2010; 19: 197-203
Saouti N, Am J Respir Crit Care Med 2010; 182: 1315-20

Pathophysiology of PH

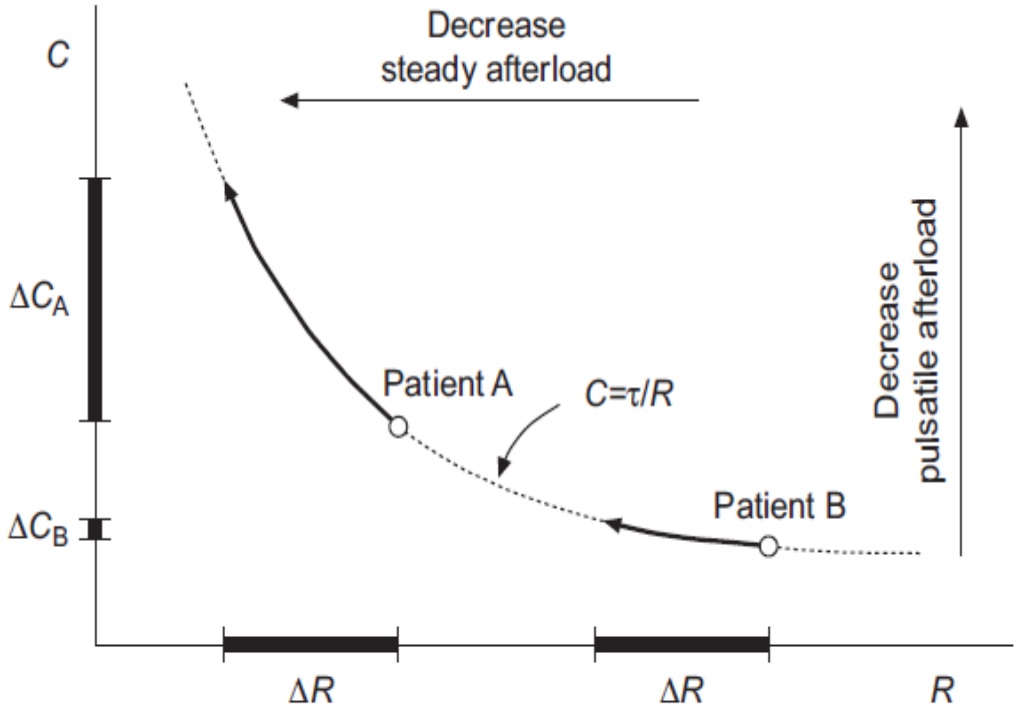


FIGURE 4. Inverse hyperbolic relationship between pulmonary arterial compliance (C) and pulmonary resistance (R). Δ: change.

Lankhaar JW, Eur J Heart 2008; 29: 1688-95

Pathophysiology of PH

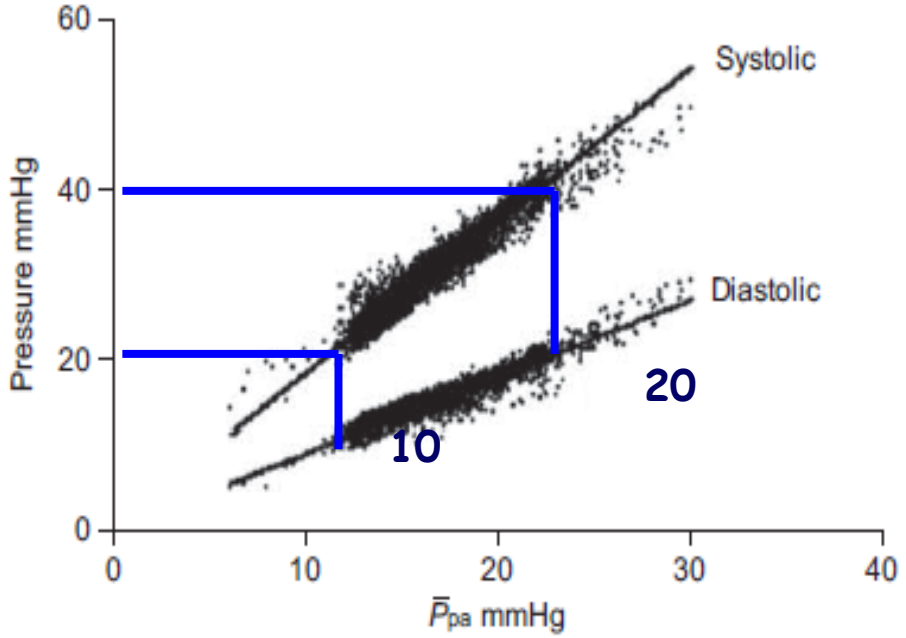


FIGURE 5. Proportional relationship between systolic and diastolic pulmonary artery pressures with mean pulmonary artery pressure ($\bar{P}_{pa}$). Systolic: $y=1.49x$, $R^2=0.93$; diastolic: $y=0.74x$, $R^2=0.91$.

PASP= 1.49 mean PAP

PADP= 0.74 mean PAP

In passive post-capillary PH with or without MR :

PASP = 2 PADP or 2 PAWP

Syyed R, Chest 2008; 133: 633-39

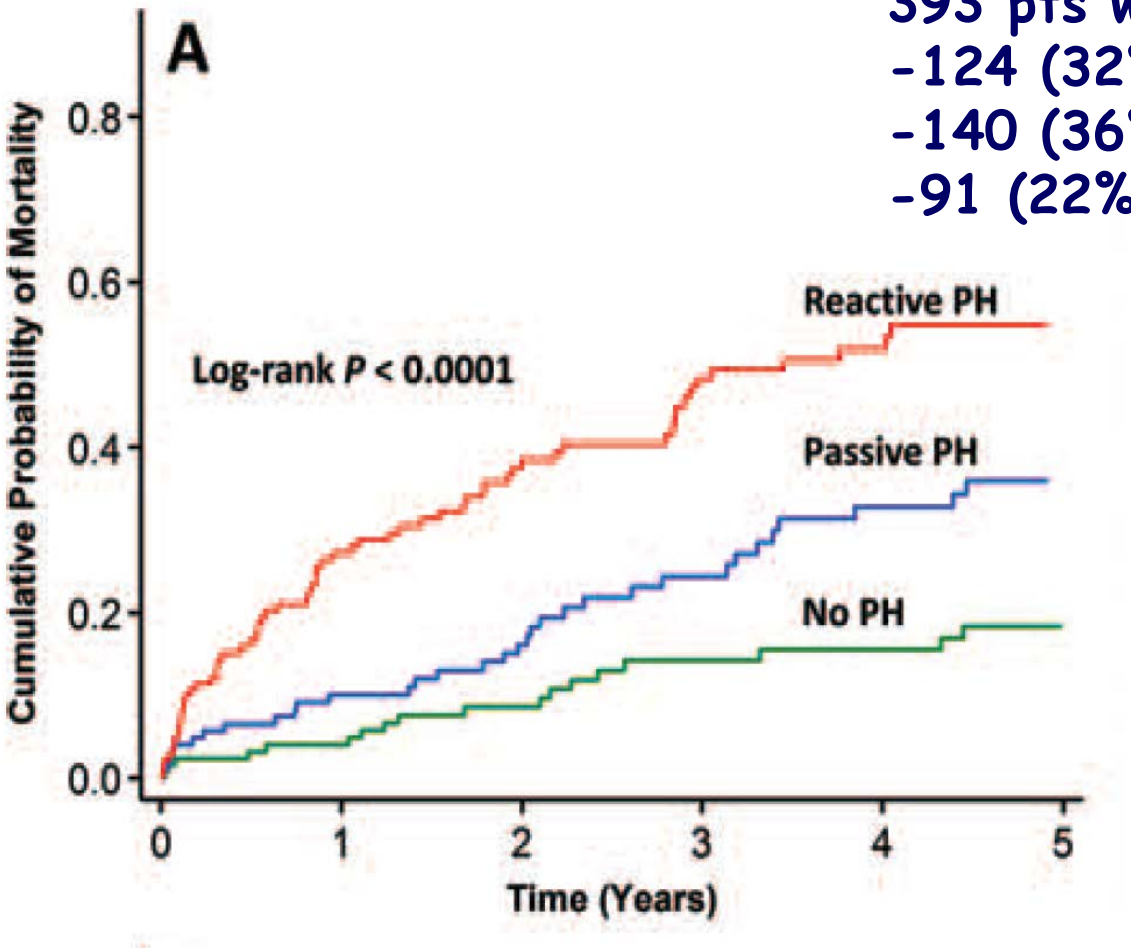
Pathophysiology of PH

- PHT in Left-sided Pathology
  - **Pure post-capillary pulmonary hypertension**: passive backward transmission of pressure elevation. Normal trans-pulmonary pressure gradient (≤ 12 mmHg) and PVR are low
  - **Reactive PHT**: dissociation between PAWP and PASP. Elevation in PVR and TPG (>12 mmHg) related to an increase in vasomotor tone and/or to pulmonary vascular remodeling
  - **Fixed PHT**: reactive PHT non reversible under acute pharmacological testing
  - **Mixed PHT**: association of Post-cap and Pre-cap etiology

Galie, Eur Respir J 2009; 34: 1219-63

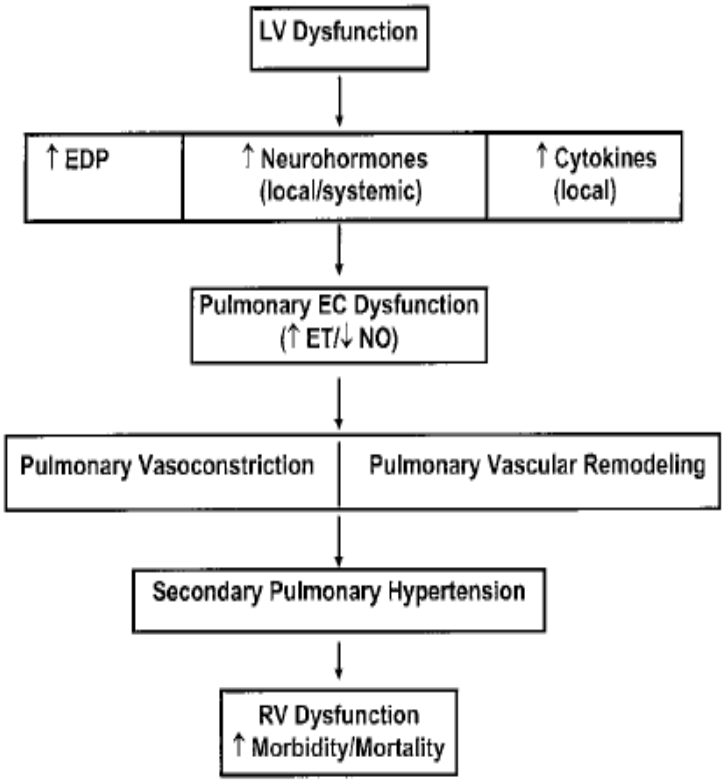
Pathophysiology of PH

393 pts with Heart Failure
-124 (32%): Passive PH
-140 (36%): Reactive PH
-91 (22%): No PH

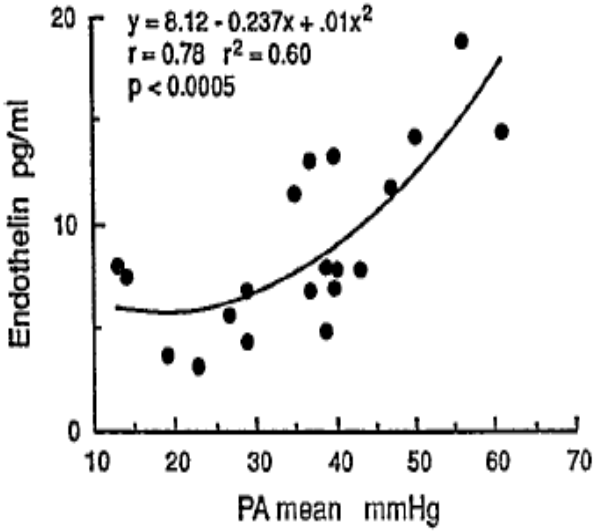


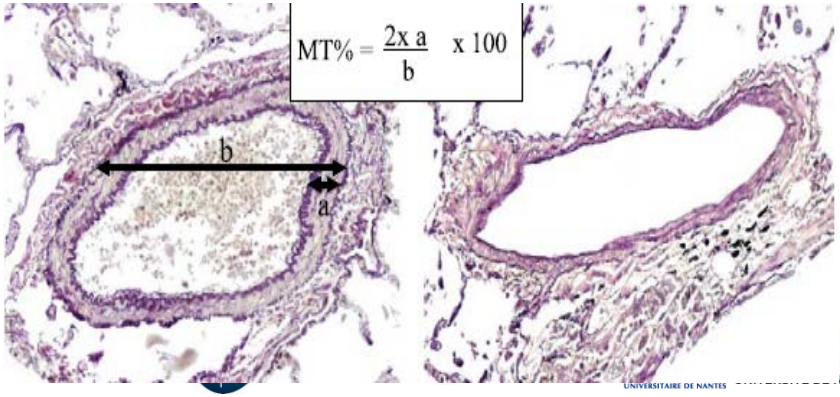
Dragu R, Eur Heart J Heart Fail 2015; 17: 74-80

Pathophysiology of PH



Reactive post-capillary PH: Vascular Remodeling





Denzil L, Circulation 2000
Delgado JF, Eur J Heart Fail 2005

Pathophysiology of PH

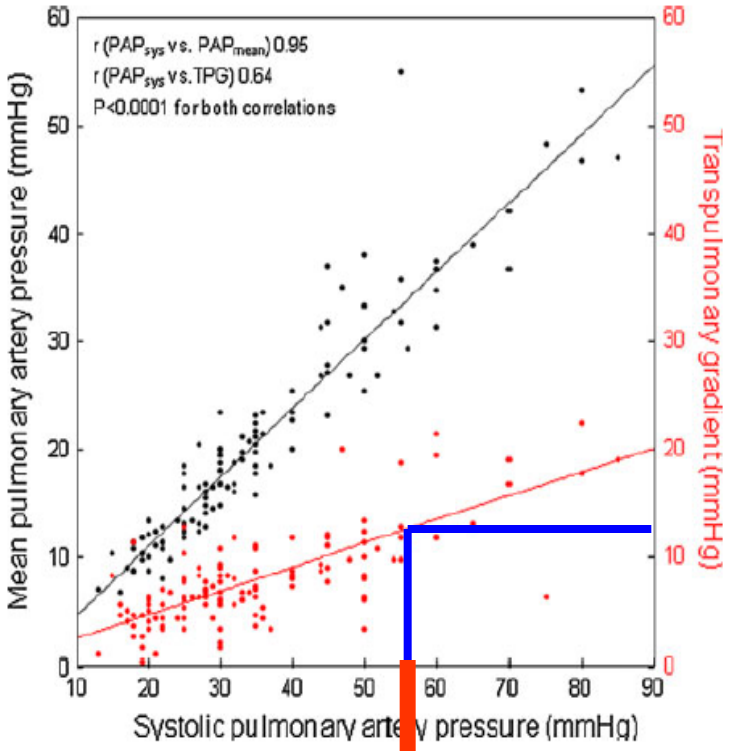


Fig. 4 Correlation of systolic pulmonary artery pressure with mean pulmonary artery pressure and transpulmonary gradient in the 148 patients who underwent right heart catheterization

200 pts with severe AS referred to surgery

TPG = 12 mmHg

PASP = 55-60 mmHg

Zuern CS, Clin Res Cardiol 2012; 101: 81-88

Determinants of PH in AS

- LV EDP, LAP, PAWP
- Age (Older)
- Woman
- LV diastolic dysfunction, myocardial stiffness
- Aortic valve surface area
- Mitral Regurgitation or stenosis
- Pulmonary disease (COPD…)

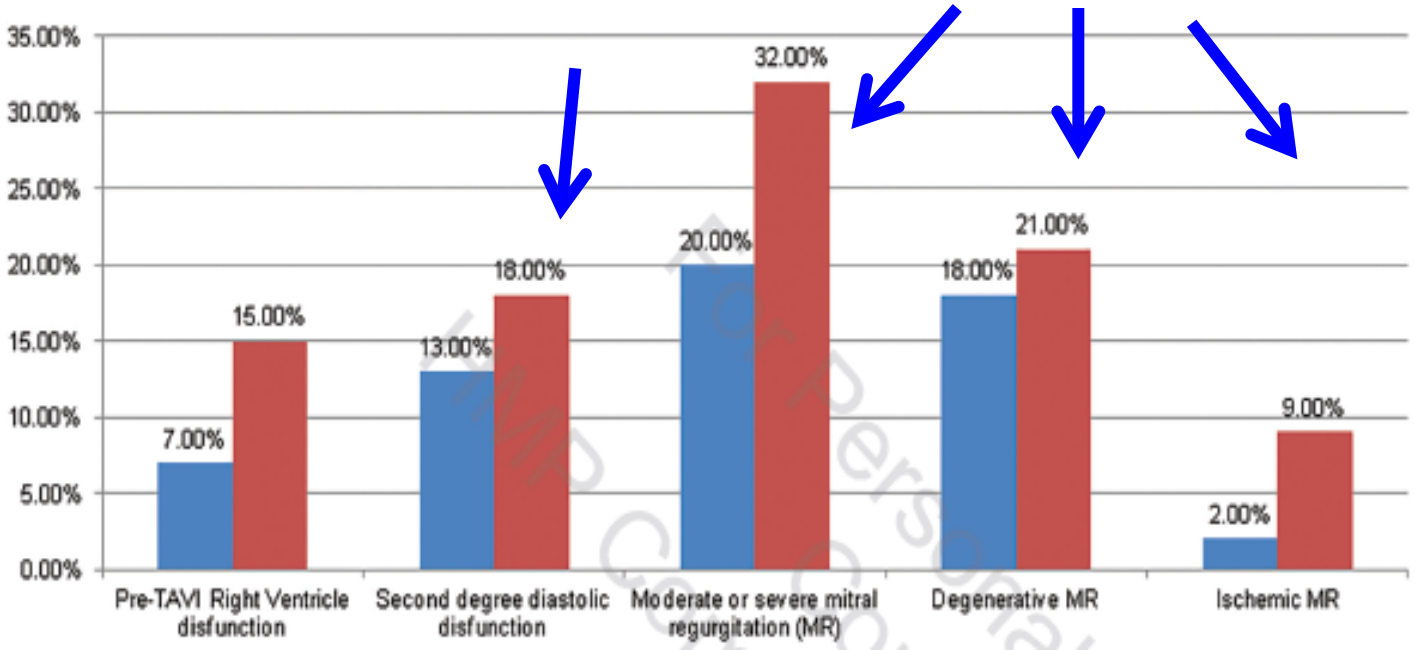
Roselli EE, J Th CV Surg 2012; 144: 1067-74

Prevalence and Determinants of PH in AS

Multicenter European Registry
674 patients TAVI
Pulm pressure by echography

PHT: PASP > 40 mmHg

PHT: 319 (47%)



D'Ascenzo F, J Invasiv Cardiol 2015; 27: 114-119

Prevalence of PH in AS

Northern New England Cardiovascular Study

1116 patients AV Replacement ± CABG

Pulmonary pressure by right-sided catheterization

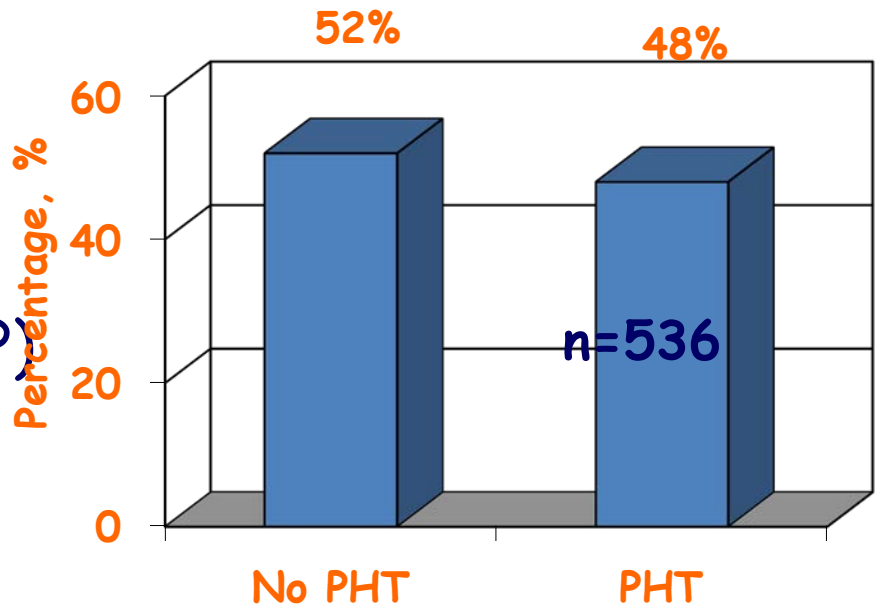
PHT : mean PAP ≥ 25 mmHg

None

Mild PHT: 35-44 mmHg (PASP)

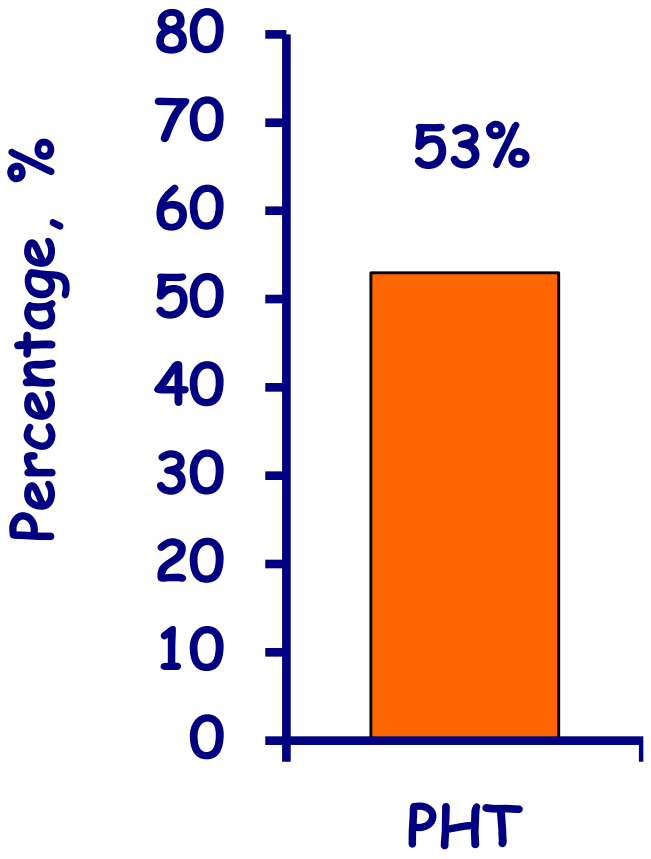
Moderate: 45-59

Severe: ≥ 60 **(10%)**



Zlotnick DM, Am J Cardiol 2013; 112: 1635-40

Prevalence of PH in AS



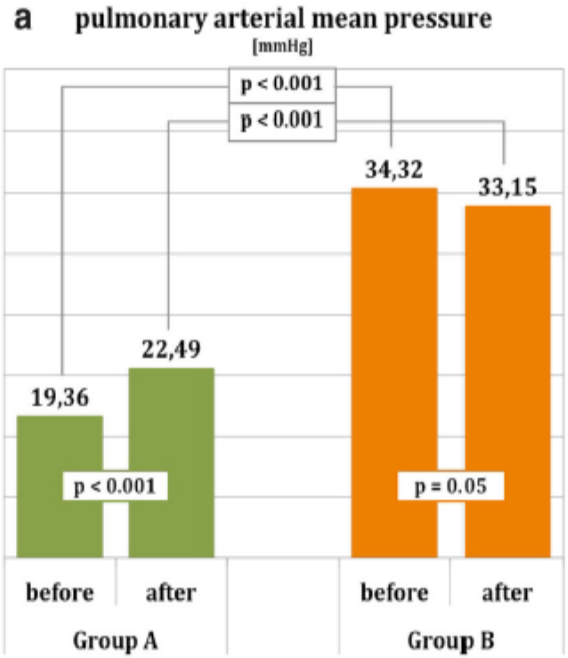
439 pts with severe AS, RH catheterization before TAVI

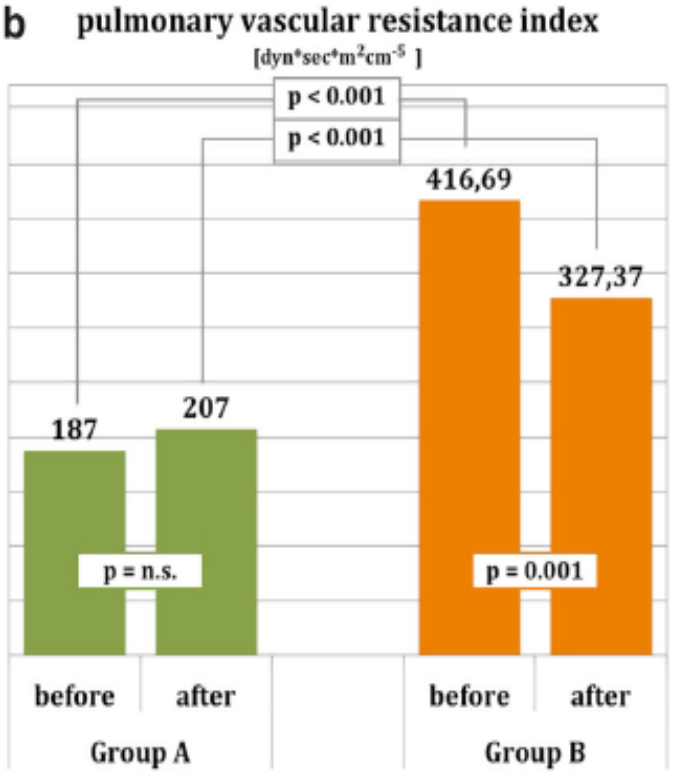
Schewel D, Clin Res Cardiol 2015; 104: 164-74

Changes after AV Replacement

439 pts, TAVI, 2009-2012

mean PAP < or ≥ 25 mmHg





Schewel D, Clin Res Cardiol 2015; 104: 164-74

Changes after AV Replacement

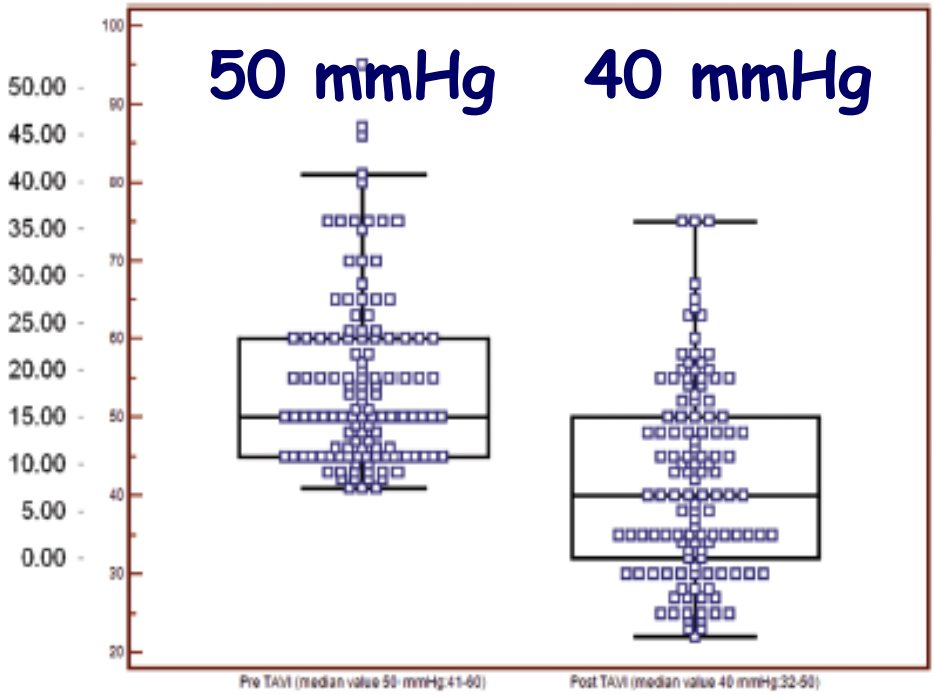


FIGURE 3. Reduction in sPAP for patients with baseline value >40 mm Hg.

Recovery of PASP

In most patients

477 days

D'Ascenzo F, J Invasiv Cardiol 2015; 27: 114-119

Influence on Outcome: In-Hospital Mortality

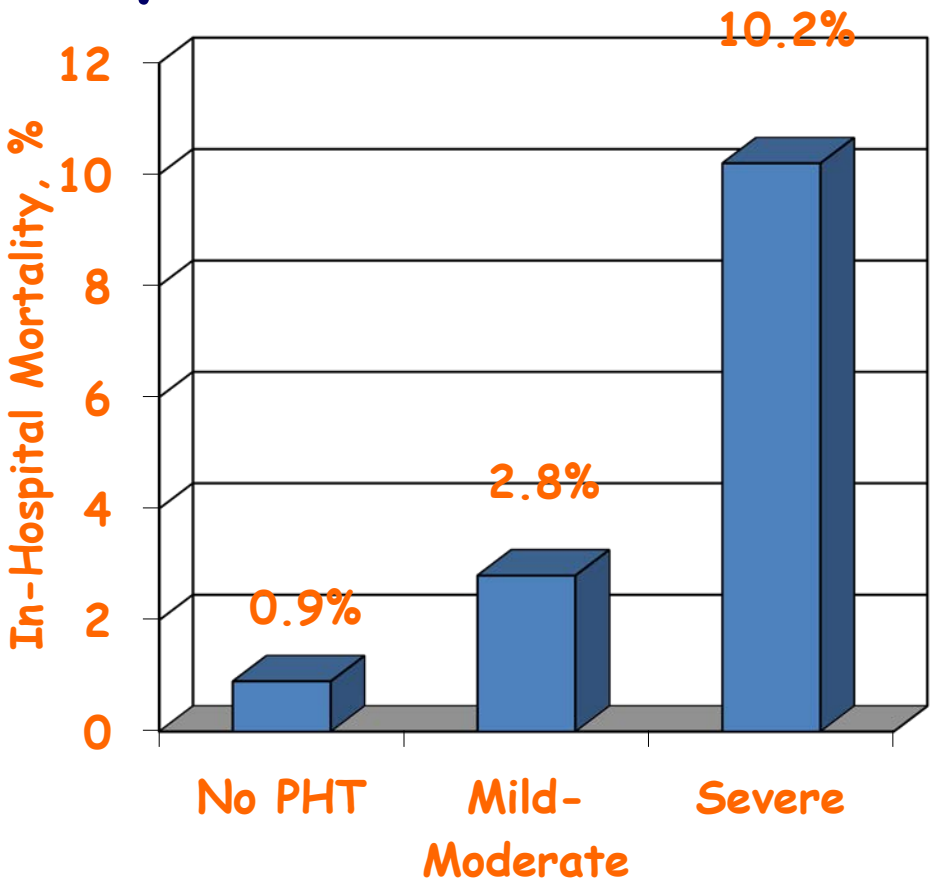
422 pts, isolated AVR, 2005-2010

PHT: PASP ≥ 35 mmHg

None

Mild-moderate PHT: 35-49 mmHg

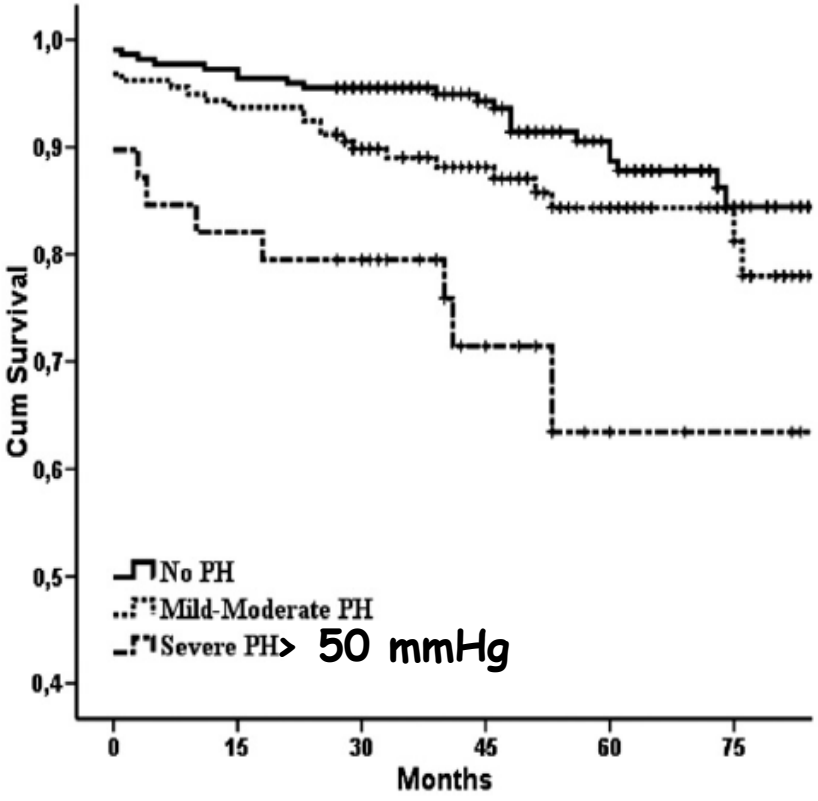
Severe: ≥ 50 **(9.2%)**

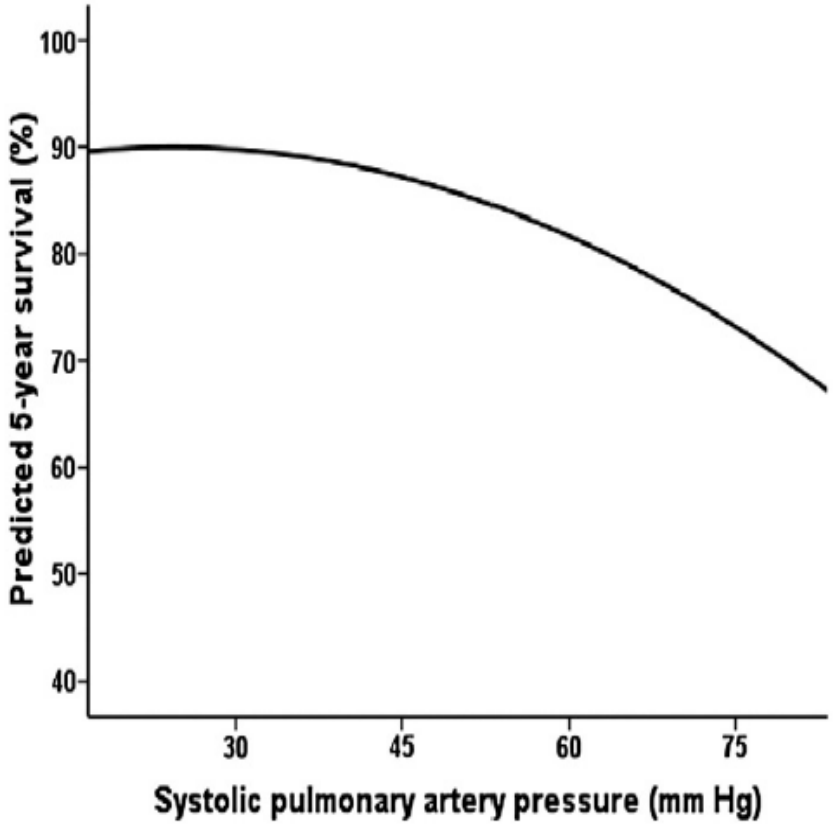


Miceli A, Int J Cardiol 2013; 168: 3556-9

Influence on Outcome

422 pts, isolated AVR, 2005-2010



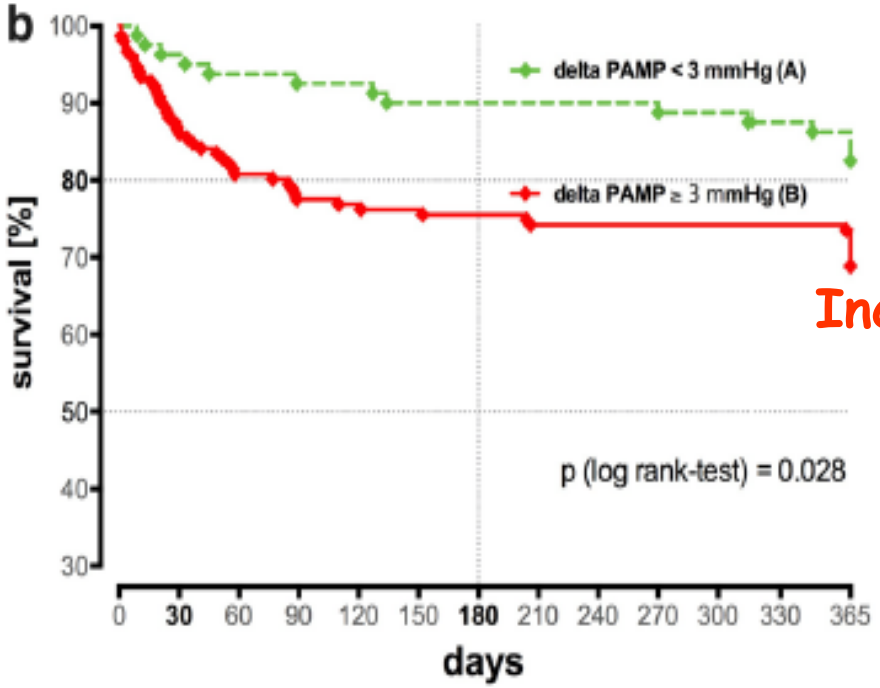


Miceli A, Int J Cardiol 2013; 168: 3556-9

Influence on Outcome

439 pts, TAVI, 2009-2012

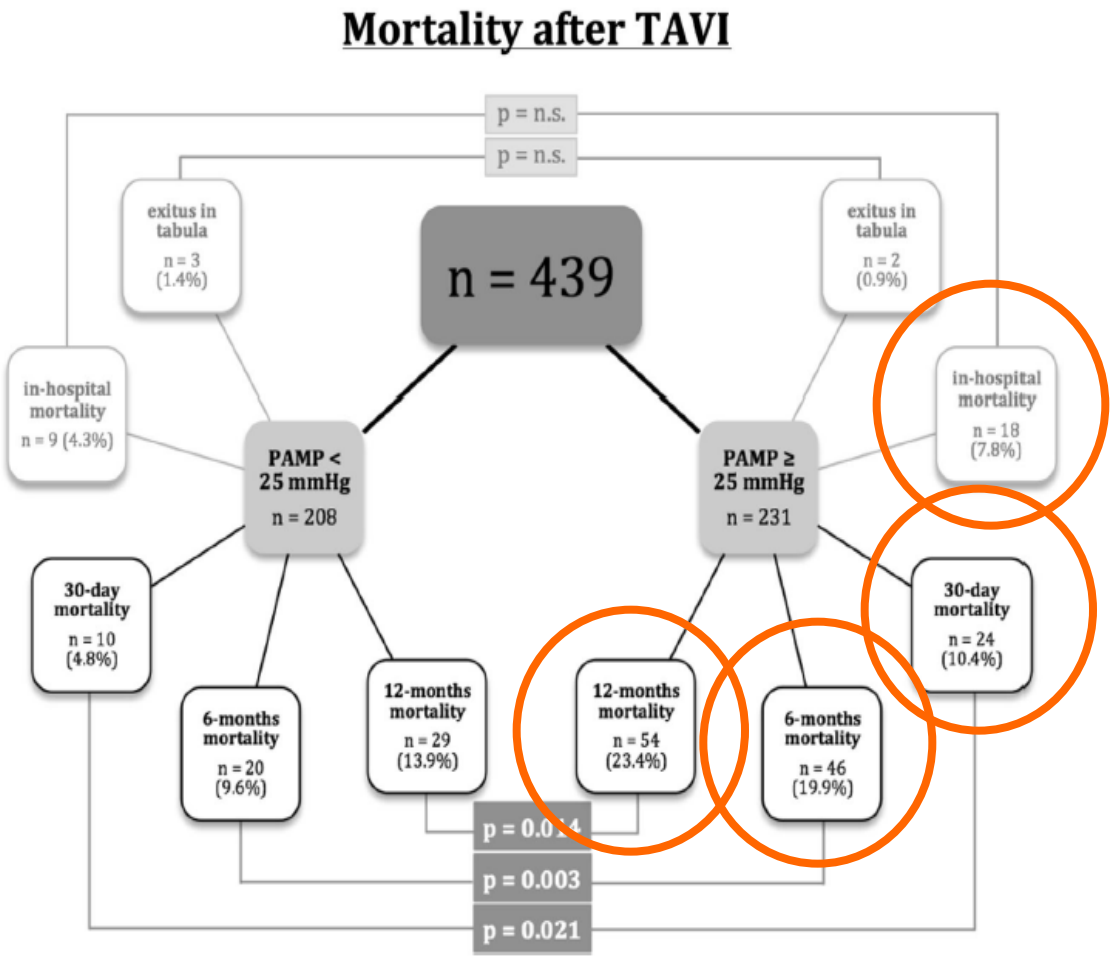
mean PAP < or ≥ 25 mmHg



Increase in PAMP

Schewel D, Clin Res Cardiol 2015; 104: 164-74

Influence on Outcome



Schewel D, Clin Res Cardiol 2015; 104: 164-74

Influence on Outcome

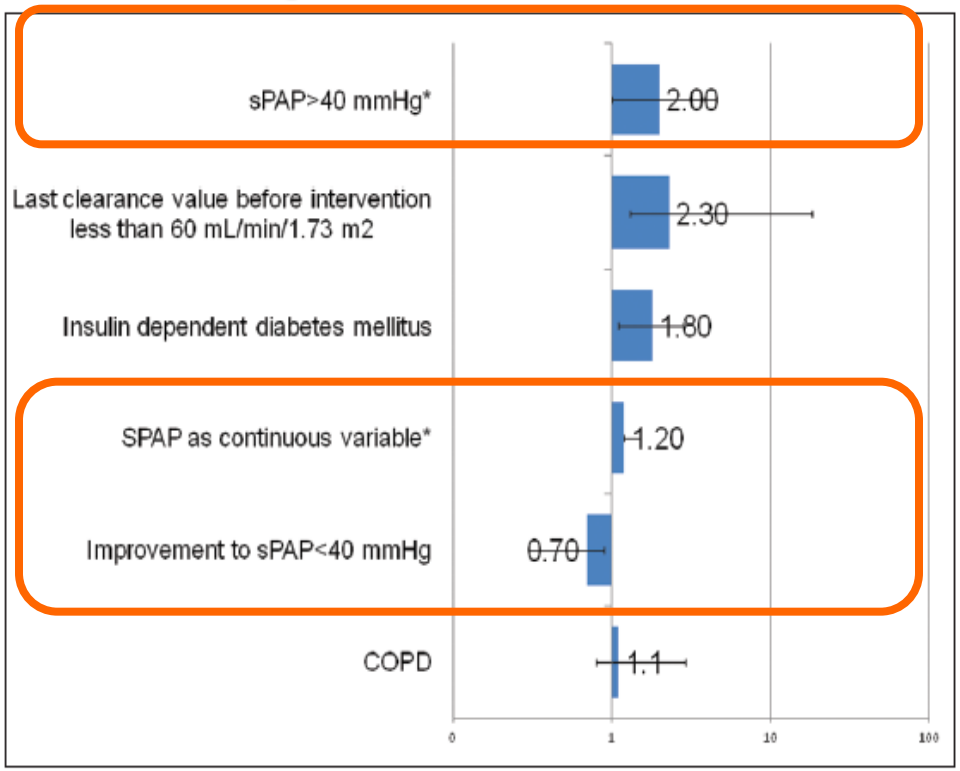


FIGURE 4. Independent predictors of all-cause death at mid-term follow-up.

D'Ascenzo F, J Invasiv Cardiol 2015; 27: 114-119

Clinical Case

- Euroscore I: 17.9%, II: 2.3% (including chronic pulmonary disease)
- Indication of Transcatheter Aortic Valve Implantation
- Moderate decrease in PASP to 65 mmHg, improvement in RV function
- Functional improvement

Conclusion

- PHT is a frequent finding in patients with severe AS (≈ 50%)
- PHT in AS is mainly post-capillary
- Post-cap PHT can be purely passive or can have a reactive component owing to vascular remodeling-vasoconstriction
- In addition to AS some pts share characteristics of HF-pEF such as obesity, diabetes, and can have severe LV diastolic dysfunction
- Although PASP decreases in most patients after AVR, PH can persist or worsen in some pts
- PH in AS: short and long-term worse in AS

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis
   - 1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in **bold**.
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

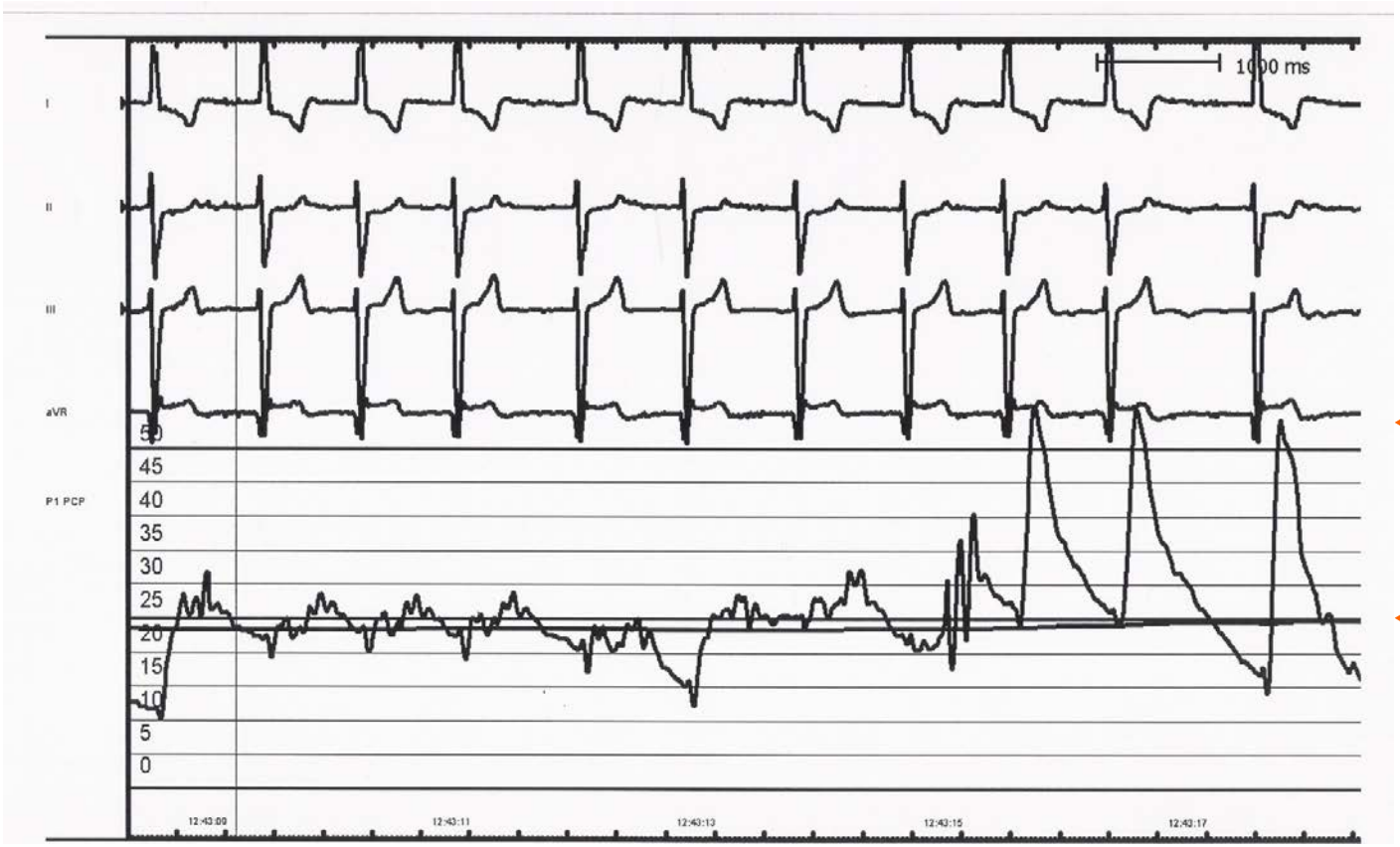
Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease
Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

Simonneau G. JACC 2013; 62 (Suppl D) : 34-41
Galie N, Eur Respir J 2009; 34: 1219-63

TPG = PAPm - PAWP

Pathophysiology of PH

Passive post-capillary pulmonary hypertension



← PASP = 55

← PAWP = 24
PADP

Pathophysiology of PH

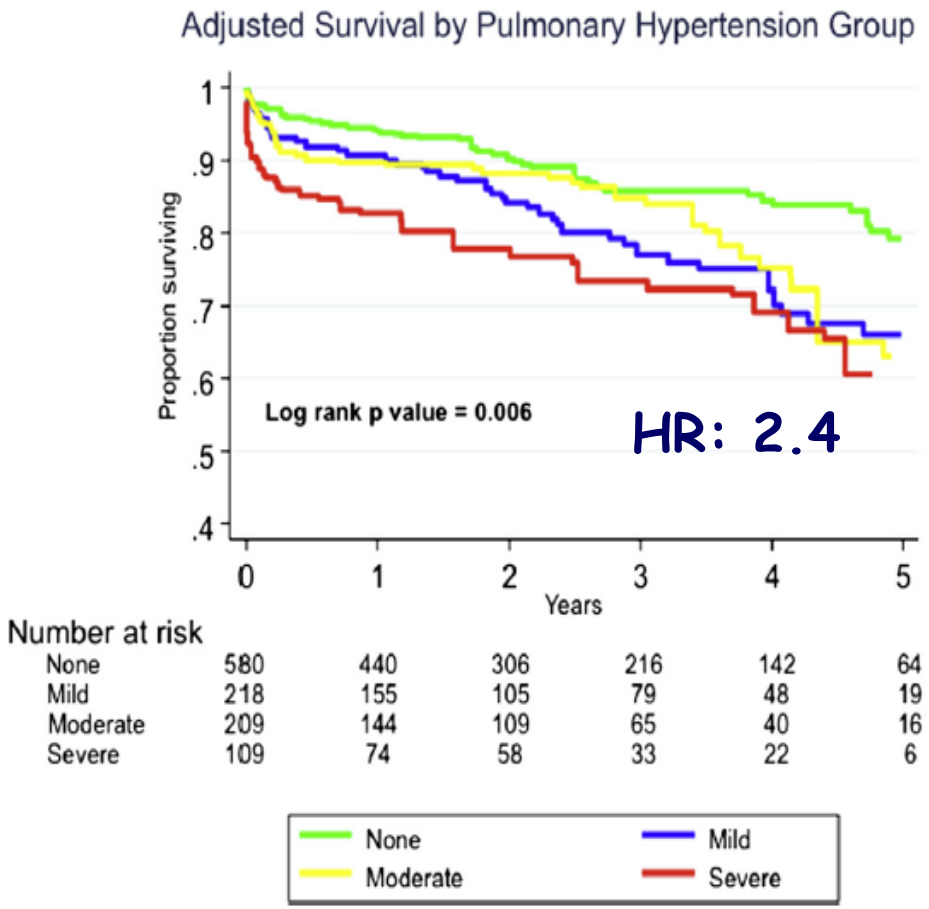
Reactive post-capillary pulmonary hypertension

PASP

PADP

PAWP

Influence on Outcome



Northern New England Cardiovascular Study
1116 patients AV Replacement ± CABG
Pulmonary pressure by right-sided catheterization

Systolic PHT :

None

Mild 35-44 mmHg

Moderate 45-59

Severe ≥ 60

Zlotnick DM, Am J Cardiol 2013; 112: 1635-40

Influence on Outcome

Table 3

Multivariate Cox regression analysis of risk factors for 5-year survival.

Variable	HR	95% CI	P
Extracardiac arteriopathy	2.8	1.6–4.9	<0.0001
Severe PH	2.4	1.2–4.6	0.01
NYHA III–IV functional class	2.3	1.3–4	0.003
Serum creatinine (mg/dl)	2.2	1.6–3.1	<0.0001
Age	1.08	1.03–1.13	0.03

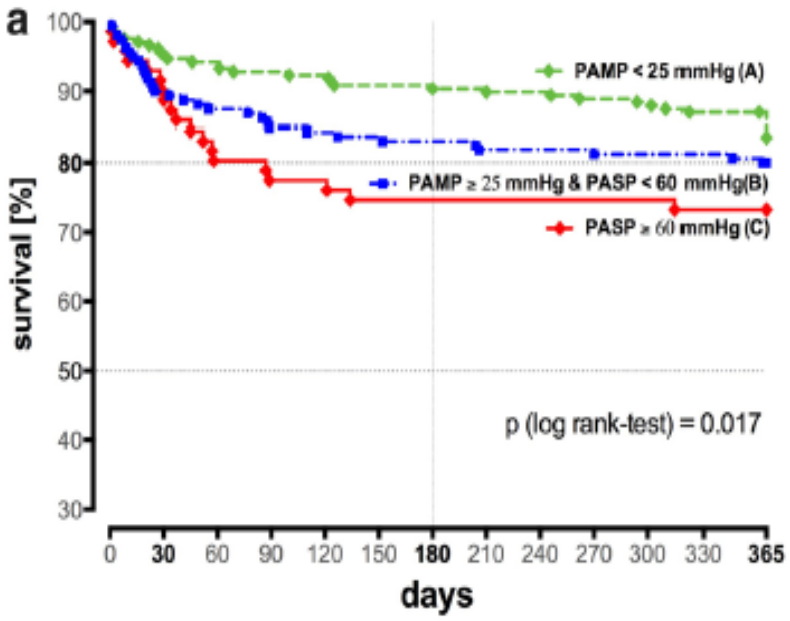
PH pulmonary hypertension; NYHA New York Heart Association.

Miceli A, Int J Cardiol 2013; 168: 3556-9

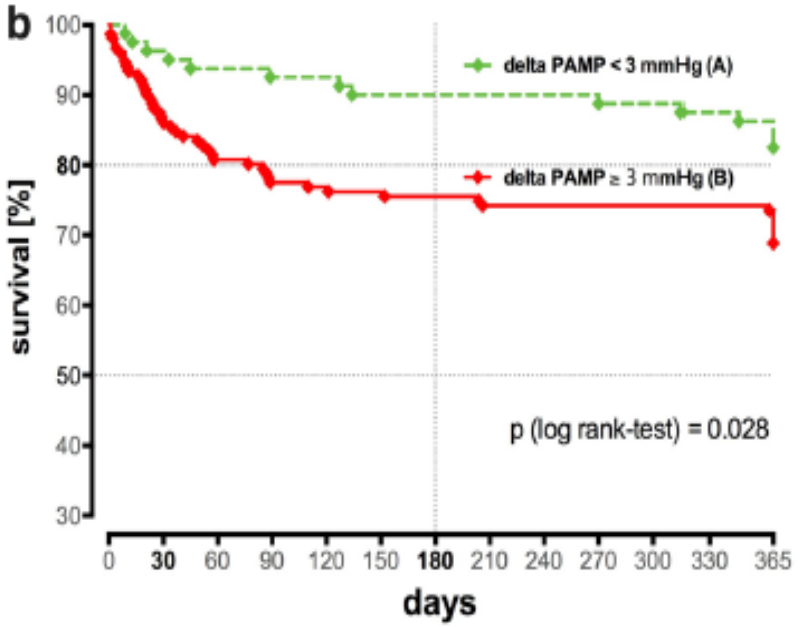
Influence on Outcome

439 pts, TAVI, 2009-2012

mean PAP < or ≥ 25 mmHg



Increase in PAMP



Schewel D, Clin Res Cardiol 2015; 104: 164-74

Pathophysiology of PH

- Markers of pulmonary vascular changes or of reactive post-capillary PH :
  - Pulmonary Diastolic - PAWP ≥ 7 mmHg
  - Mean PAP – PAWP > 12 mmHg
- Reactive PH: decrease in pulmonary compliance (or capacitance) and increase in RV pulsatile load

Rapp AH, Am J Cardiol 2001; 88: 823-4
Galie, Eur Respir J 2009; 34: 1219-63
Vachiery JL, JACC 2013 (suppl D); 25: 100-8
Dragu R, Eur Heart J Heart Fail 2015; 17: 74-80