



## Scompenso cardiaco sinistro e ipertensione polmonare

**Michele D'Alto**

**Department of Cardiology – PH Unit  
Monaldi Hospital – Naples, Italy**

# Financial disclosure

Honoraria from: Actelion/Janssen, Merck Sharp and Dohme, Dompè, Ferrer, AOP.

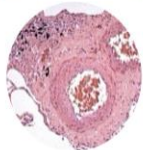
Member of a scientific advisory board for: Actelion/Janssen, Merck Sharp and Dohme, Dompè, Ferrer, AOP.

# Agenda

- Definition of PH in Heart failure
- Why left HF patients develop PH? Any consequence?
- HFpEF-PH or PAH? The differential diagnosis
- Therapy for PH due to left heart disease.

## CLINICAL CLASSIFICATION

### Pulmonary arterial hypertension (PAH)

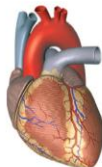


- Idiopathic/heritable
- Associated conditions

Rare



### PH associated with left heart disease



- lpcPH
- CpcPH

Very common



### PH associated with lung disease



- Non-severe PH
- Severe PH

Common



### PH associated with pulmonary artery obstructions



- CTEPH
- Other pulmonary obstructions

Rare



### PH with unclear and/or multifactorial mechanisms



- Haematological disorders
- Systemic disorders

Rare



## Updated haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	<b>mPAP &gt;20 mmHg</b>
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg <b>PVR &gt;2 WU</b>
Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg <b>PVR ≤2 WU</b>
Combined post- and pre-capillary PH	mPAP >20 mmHg PAWP >15 mmHg <b>PVR &gt;2 WU</b>
<b>Exercise PH</b>	<b>mPAP/CO slope between rest and exercise &gt;3 mmHg/L/min</b>

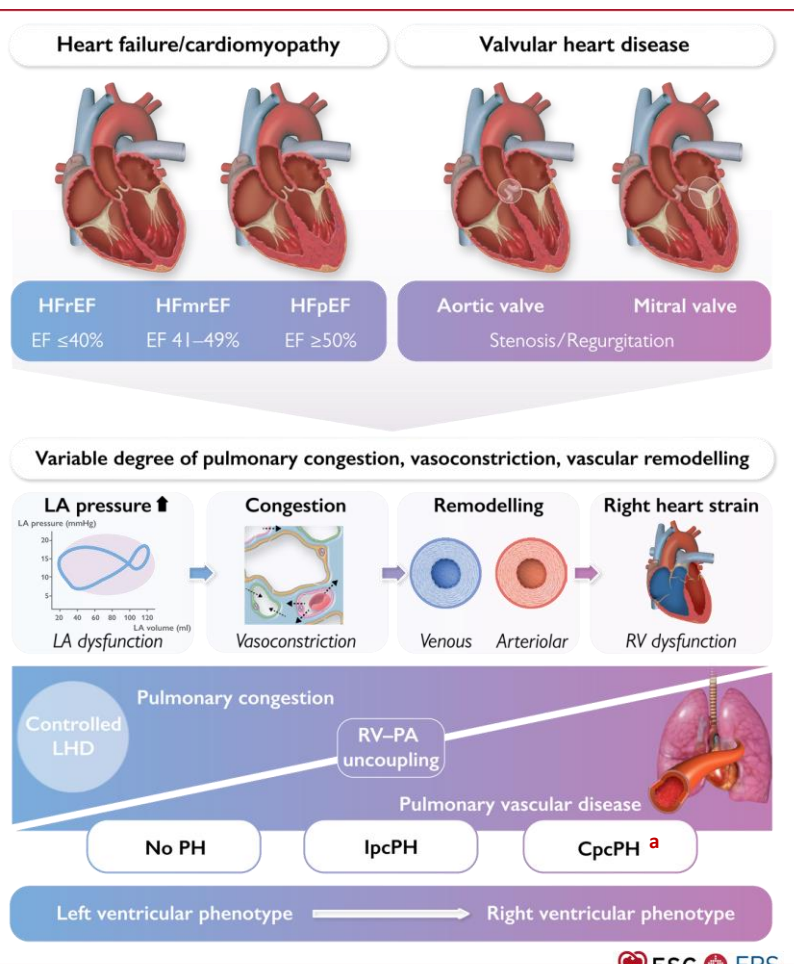
# Pulmonary hypertension associated with left heart disease (group 2)

Isolated post-capillary PH

mPAP >20 mmHg  
PAWP >15 mmHg  
**PVR ≤2 WU**

Combined post- and pre-capillary PH

mPAP >20 mmHg  
PAWP >15 mmHg  
**PVR >2 WU**



**<sup>a</sup>severe pre-capillary component in CpcPH: PVR >5 WU**

# Left Heart – Pulmonary Circulation – Right Heart

## PULMONARY CIRCULATION

### Superimposed components:

- Vasoconstriction
- NO availability
- Desensitisation to NP-induced vasodilation
- Arteriolar remodeling
- Venous congestion
- Metabolic factors
- Inflammatory cells

**Pulmonary vascular disease**  
(i.e. remodeling)

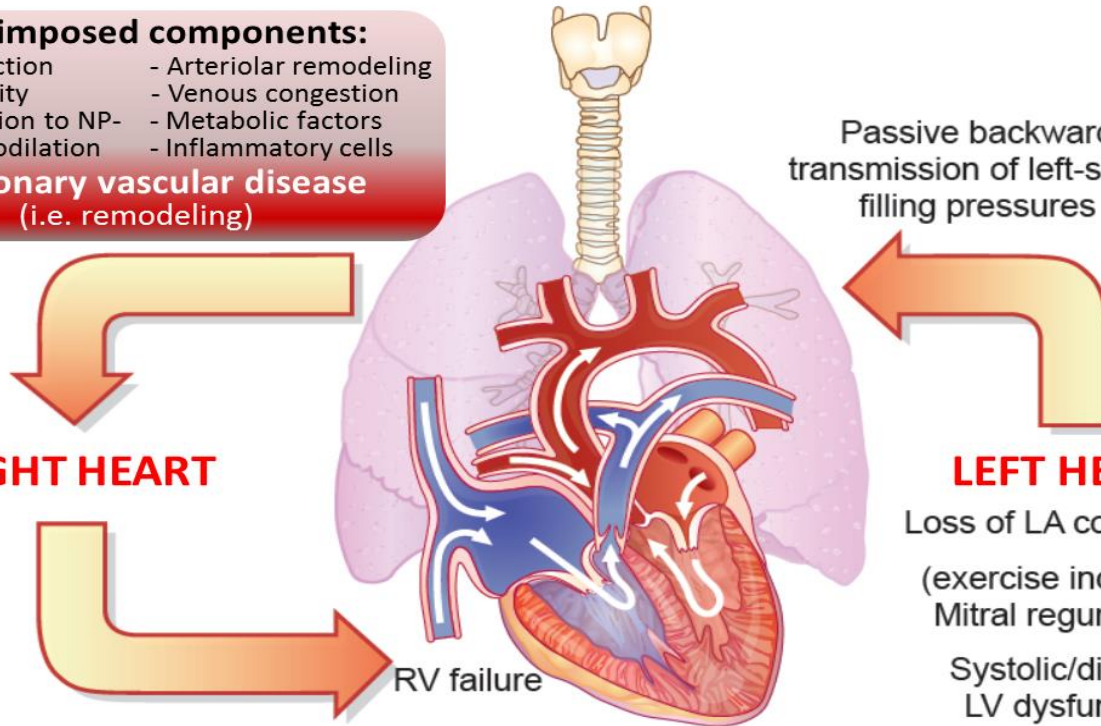
**RIGHT HEART**

RV failure

**LEFT HEART**

Loss of LA compliance  
(exercise increased)  
Mitral regurgitation  
Systolic/diastolic  
LV dysfunction

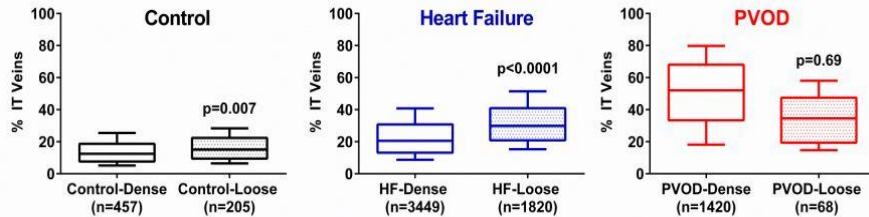
Passive backward  
transmission of left-sided  
filling pressures



# Arterial and Venous Remodeling in HFrEF and HFpEF

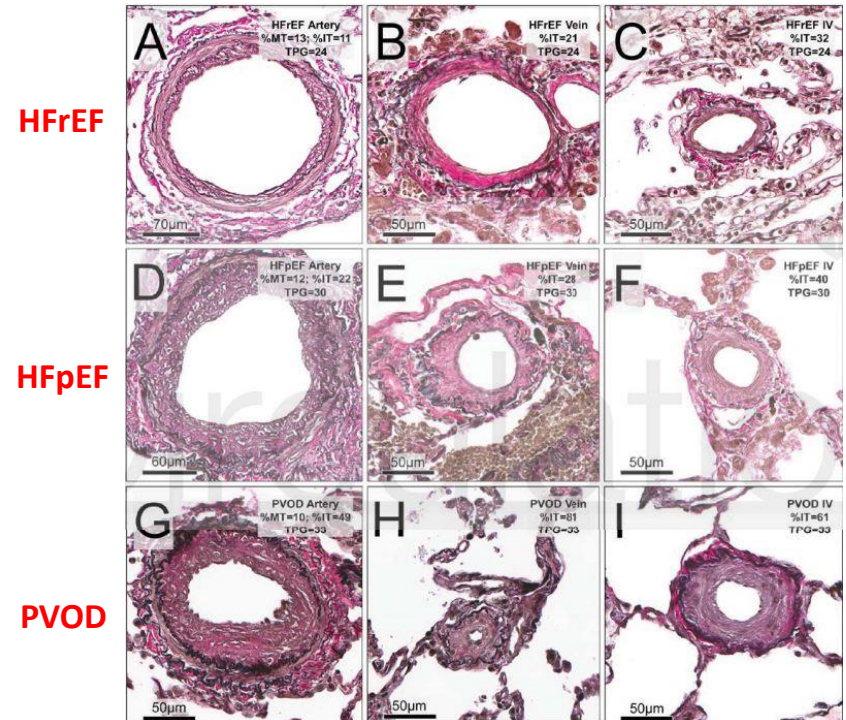
- 108 HF pts (53 preserved and 55 reduced) with PASP >40 mmHg
- 12 Controls
- 17 Pulmonary venous disease (PVOD)

**Figure S6.** Severity of intimal thickening in pulmonary veins with loose fibrosis/hyalinosis versus dense fibrosis intimal character



**HF pattern of remodeling correlates strongly with venous and capillary thickening similar to PVOD**

**Figure 5.** Pulmonary vascular structure in HF-PH and PVOD patients with elevated transpulmonary gradient



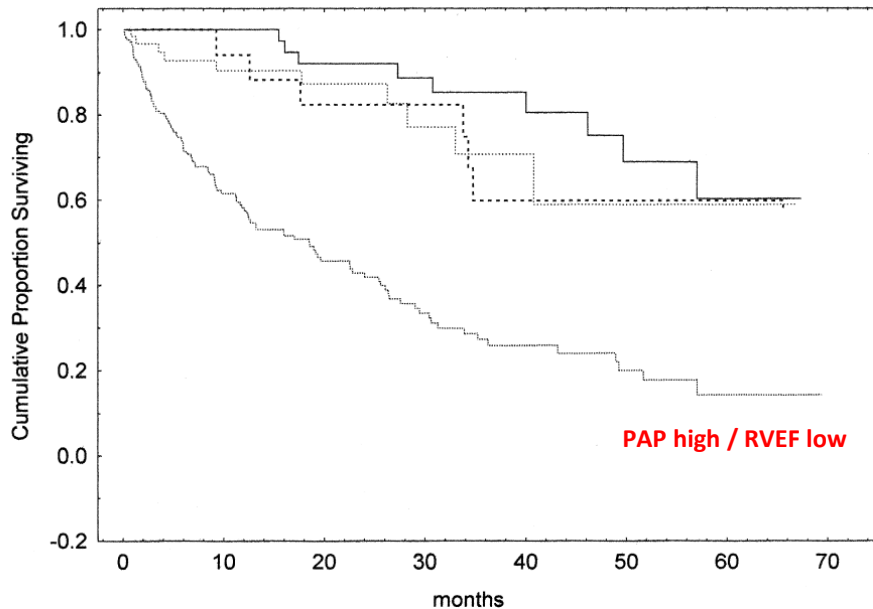


# Independent and Additive Prognostic Value of Right Ventricular Systolic Function and Pulmonary Artery Pressure in Patients With Chronic Heart Failure

Stefano Ghio, MD, FESC,\* Antonello Gavazzi, MD, FESC,\* Carlo Campana, MD,\*  
Corinna Inserra, MD,\* Catherine Klersy, MD,† Roberta Sebastiani, MD,\* Eloisa Arbustini, MD,‡  
Franco Recusani, MD,\* Luigi Tavazzi, MD, FESC, FACC\*

J Am Coll Cardiol 2001;37:183–8

RHC performed in 377 consecutive patients with HF



**Coupling between RV function and PAP.** The finding of an inverse relation between RV systolic function and PAP is in accordance with most previous pathophysiologic studies

does not seem to improve the prognostic stratification. In contrast, when PAP is high at rest despite optimized medical therapy, the prognosis of the patients is strongly related to RV performance. For example, reduced RVEF is a harbinger of high risk of death or urgent transplantation, whereas preserved RVEF implies a prognosis that is very similar to that of patients with normal PAP.

- Group 1 PAP low / RVEF high
- ..... Group 2 PAP low / RVEF low
- - - Group 3 PAP high / RVEF high
- . - . Group 4 **PAP high / RVEF low**

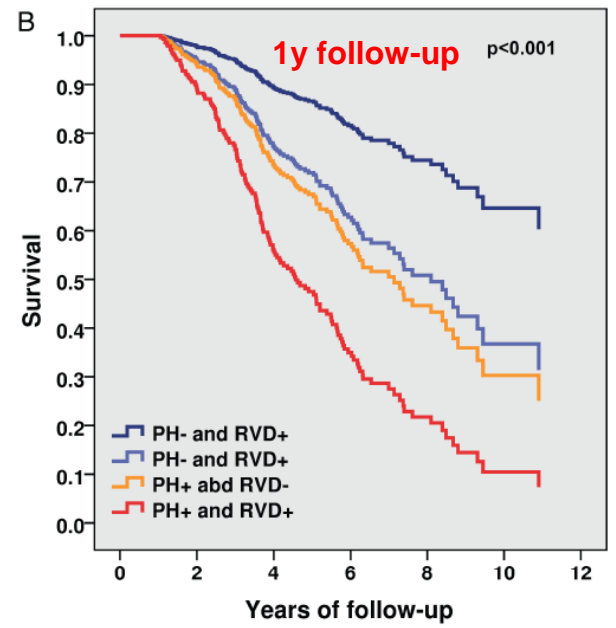
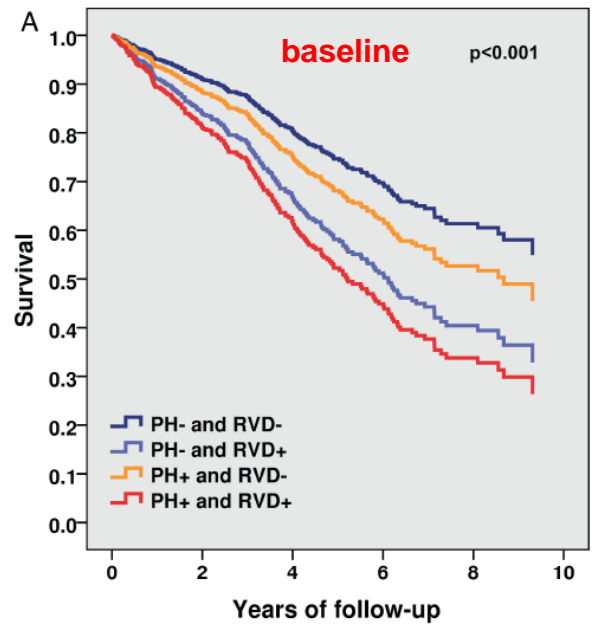
# Pulmonary hypertension and right ventricular dysfunction in heart failure: prognosis and 15-year prospective longitudinal trajectories in survivors

Evelyn Santiago-Vacas<sup>1,2,3</sup>, Josep Lupón<sup>1,2,4,5</sup>, Giovana Gavidia-Bovadilla<sup>6</sup>, Francisco Gual-Capllonch<sup>2</sup>, Marta de Antonio<sup>1,2</sup>, Mar Domingo<sup>1</sup>, Julio Núñez<sup>5,7,8</sup>, Elisabet Zamora<sup>1,2,4,5</sup>, Albert Teis<sup>2</sup>, Pedro Moliner<sup>1,2</sup>, Pau Codina<sup>1,2</sup>, Javier Santemas<sup>1</sup>, and Antoni Bayes-Genis<sup>1,2,4,5\*</sup>

Prospective, observational registry HF (1557 patients)

- PH if SPAP  $\geq 40$  mmHg;
- RV dysfunction if TAPSE  $\leq 16$  mm
- RV-arterial uncoupling if TAPSE/SPAP  $< 0.36$  mm/mmHg

Survival according to the presence of PH and RV dysfunction



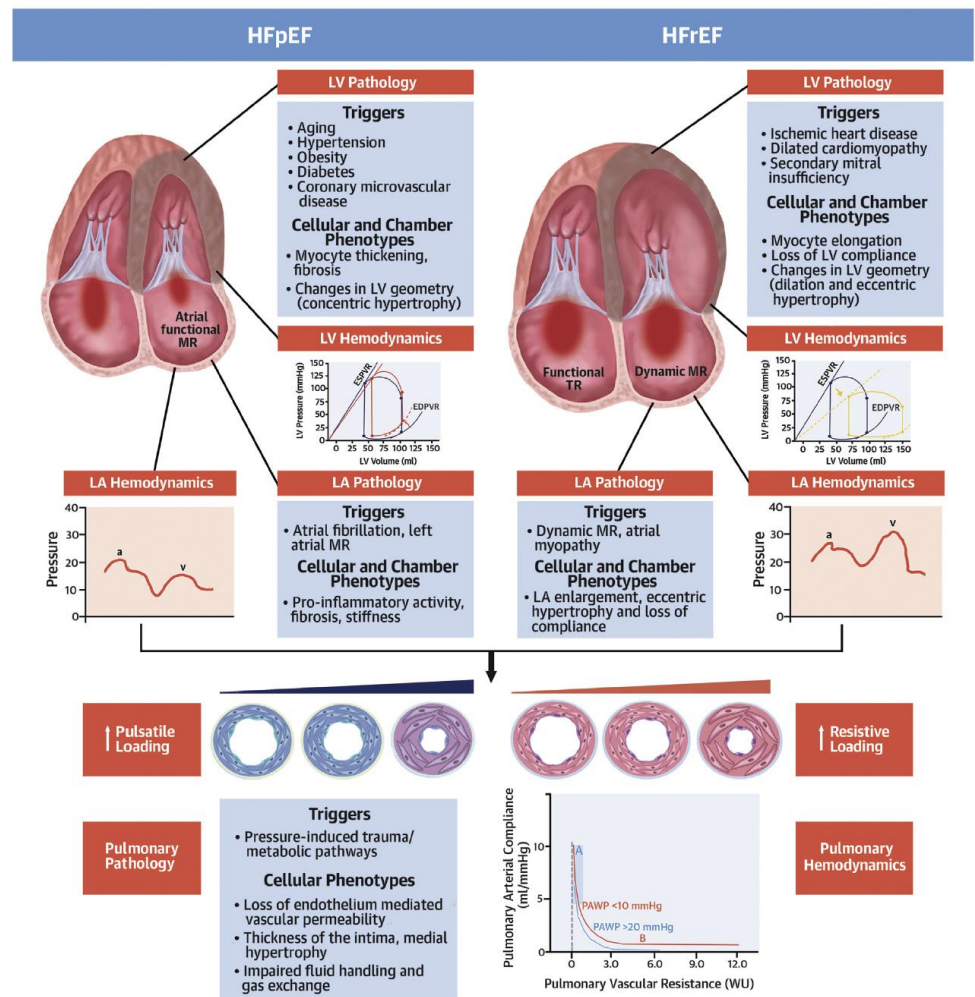
# Pulmonary Hypertension in HFpEF and HFrEF

## JACC Review Topic of the Week

Marco Guazzi, MD, PhD,<sup>a,b</sup> Stefano Ghio, MD,<sup>c</sup> Yochai Adir, MD<sup>d</sup>

J Am Coll Cardiol, 2020;76(9):1102-1111

- In HF, development of PH is an unfavorable clinical turning point in the natural history of the disease.
- Although HFpEF and HFrEF exhibit a similar pulmonary hemodynamic profile and outcomes, there are major differences in underlying causes, cardiac remodeling, and comorbidities.
- There are also different triggers and molecular pathways for pulmonary vascular injury and remodeling in HFpEF versus HFrEF.



# Pre- or post-capillary PH? Building a pre-test probability before RHC...

**Table 23** Patient phenotyping and likelihood for left heart disease as cause of pulmonary hypertension

Feature	PH-LHD unlikely	Intermediate probability	PH-LHD likely
Age	<60 years	60–70 years	>70 years
Obesity, hypertension, dyslipidaemia, glucose intolerance/ diabetes	No factors	1–2 factors	>2 factors
Presence of known LHD	No	Yes	Yes
Previous cardiac intervention	No	No	Yes
Atrial fibrillation	No	Paroxysmal	Permanent/persistent
Structural LHD	No	No	Present
ECG	Normal or signs of RV strain	Mild LVH	LBBB or LVH
Echocardiography	No LA dilation E/e' <13	No LA dilation Grade <2 mitral flow	LA dilation (LAVI >34 mL/m <sup>2</sup> ) LVH Grade >2 mitral flow
CPET	High VE/VCO <sub>2</sub> slope No EOv	Elevated VE/VCO <sub>2</sub> slope EOv	Mildly elevated VE/VCO <sub>2</sub> slope EOv
cMRI	No left heart abnormalities		LVH LA dilation (strain or LA/RA >1)

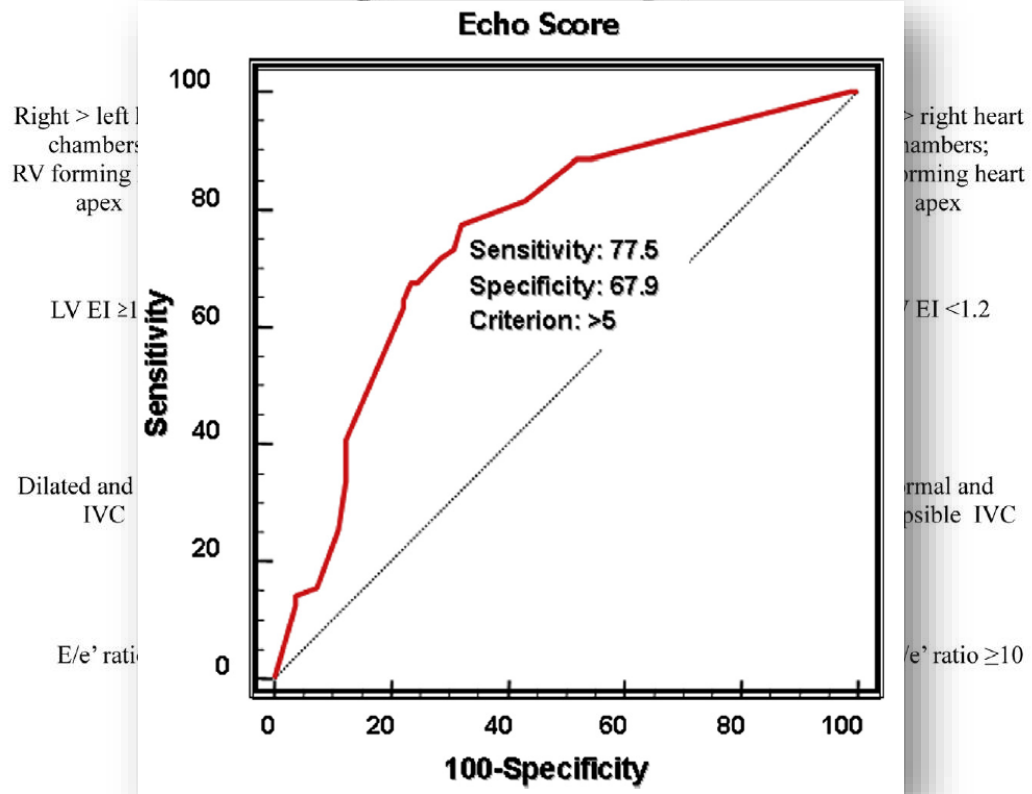
# Echocardiographic Prediction of Pre- versus Postcapillary Pulmonary Hypertension

Michele D'Alto, MD, PhD, Emanuele Romeo, MD, PhD, Paola Argiento, MD, PhD, Adriana Pavelescu, MD, PhD, Christian M lot, MD, PhD, Antonello D'Andrea, MD, PhD, Anna Correria, MD, Eduardo Bossone, MD, PhD, Raffaele Calabr , MD, Maria G. Russo, MD, and Robert Nacije, MD, PhD, *Naples, and Salerno, Italy; Brussels, Belgium*

J Am Soc Echo, 2015;28:108-15

- 152 patients
- echo and RHC **within 1 hour**

**Right phenotype**

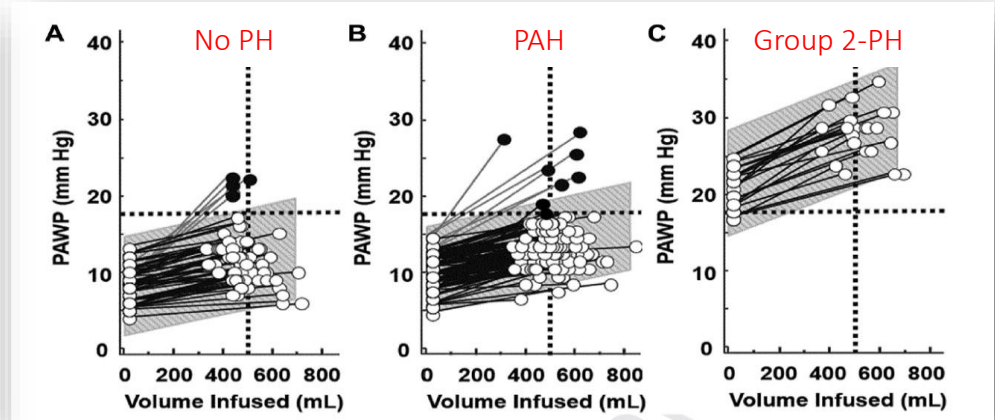
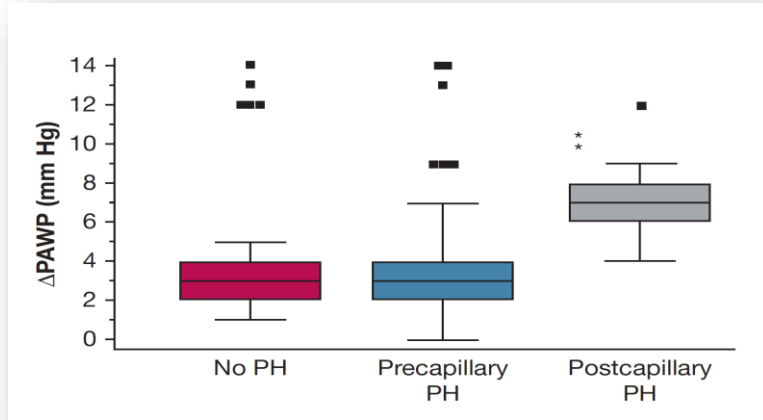


**Left phenotype**

# Clinical Relevance of Fluid Challenge in Patients Evaluated for Pulmonary Hypertension

D'Alto M. et al, CHEST 2017; 151(1):119-126

212 patients consecutive patients  
RHC with measurements before and after rapid infusion of 7 ml/kg of saline in 5-10'.



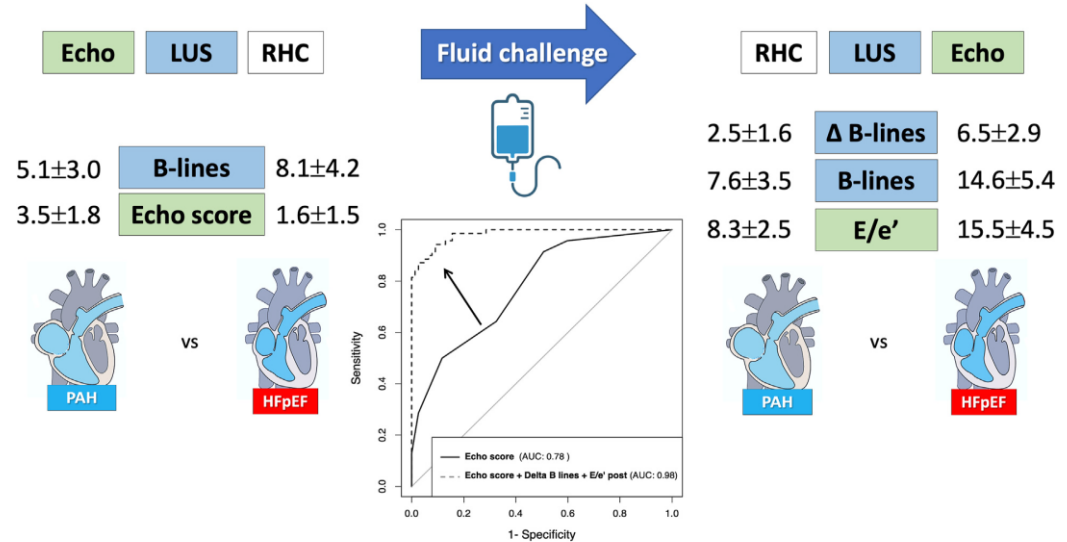
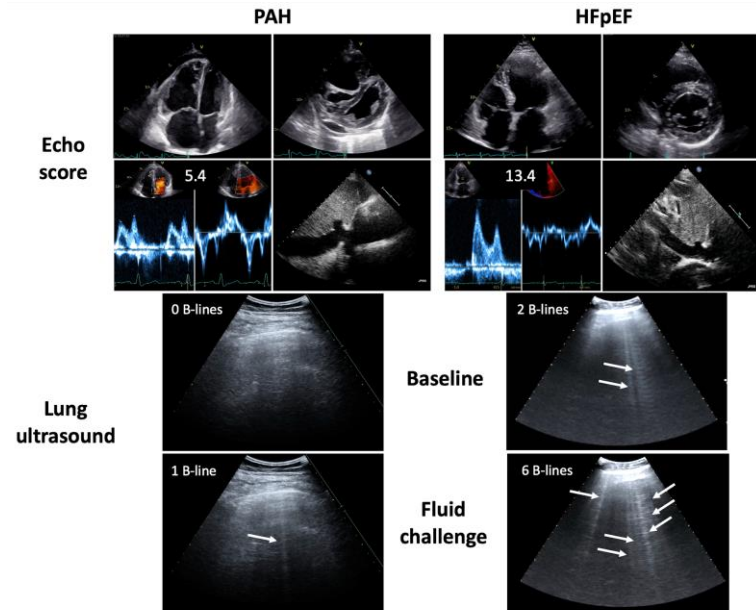
## Conclusion:

A cut-off value of 18 mmHg allows to re-classify 6-8% of patients with pre-capillary PH or normal hemodynamics at baseline.

# Lung Ultrasound, Echocardiography, and Fluid Challenge for the Differential Diagnosis of Pulmonary Hypertension

Michele D'Alto, MD, PhD, Biagio Liccardo, MD, Marco Di Maio, MD, Carmen Del Giudice, MD, Emanuele Romeo, MD, PhD, Paola Argiento, MD, PhD, Francesca Renon, MD, Andrea Vergara, MD, Alessandro Di Vilio, MD, Eleonora Caiazza, MD, Eduardo Bossone, MD, PhD, Gaetano Rea, MD, Antonello D'Andrea, MD, PhD, Luna Gargani, MD, PhD, Paolo Golino, MD, PhD, and Robert Naeije, MD, PhD, *Naples, Salerno, Nocera Inferiore, and Pisa, Italy; and Bruxelles, Belgium*

J Am Soc Echocard 2023



Improved diagnostic accuracy of PAH vs HFpEF by combination of Echo score with post fluid challenge Delta B lines and E/e' post fluid challenge

# PAH vasodilator therapy for HFpEF?

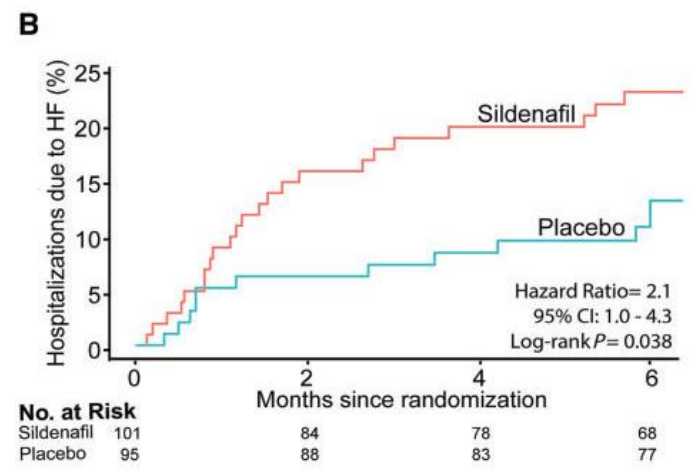
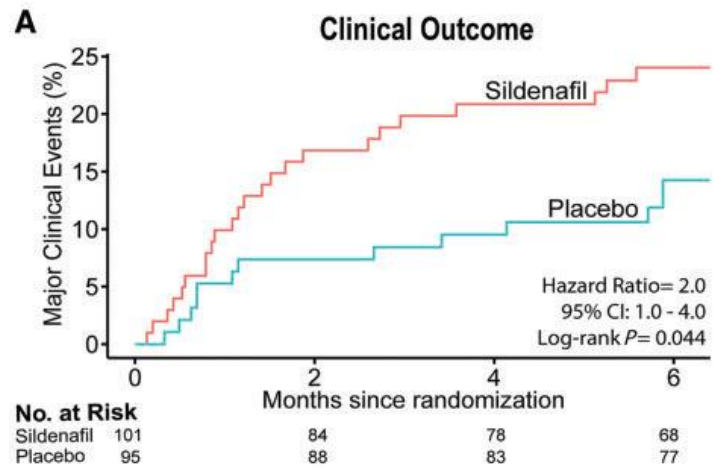




# Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial

Javier Bermejo<sup>1\*</sup>, Raquel Yotti<sup>1</sup>, Rocío García-Orta<sup>2</sup>, Pedro L. Sánchez-Fernández<sup>3</sup>,  
 Eur Heart J 2018;39:1255–1264

- Multicentric, randomized, and placebo-controlled
- **Successful valve replacement or repair procedure**
- **Precapillary PH (mPAP  $\geq$ 30mmHg, PAWP  $\leq$ 15 mmHg)**
- Sildenafil 40 mg x 3 (n: 104) vs placebo (n: 96)



**Conclusion** Treatment with sildenafil in patients with persistent PH after successfully corrected VHD is associated to worse clinical outcomes than placebo. Off-label usage of sildenafil for treating this source of left heart disease PH should be avoided.

# Current Trials in Pulmonary Hypertension and Heart Failure

Study	Study Drug	N	Duration	Population	Primary endpoint	Result
<b>Guazzi</b> <sup>1</sup>	Sildenafil	44	12 mo	HFpEF	HD, RV performance	<b>Improvement in PVR and exercise</b>
<b>Guazzi</b> <sup>2</sup>	Sildenafil	32	52 W	HF rEF	Exercise oscillatory breathing, PVR	<b>Improvement in EOB, PVR and FC</b>
<b>LEPHT</b> <sup>3</sup>	Riociguat	201	16 W	HF rEF	Change in mPAP at rest from baseline to week 16	No significant effect on mPAP compared with pbo
<b>Hoendermis</b> <sup>4</sup>	Sildenafil	52	12 W	HFpEF	Change in mPAP from baseline to week 12	No reduction in mPAP or improvement in other variables
<b>BADDHY</b> <sup>5</sup>	Bosentan	40	12 W	HFpEF	Pilot study 6MWD, echocardiography	<b>Premature discontinuation, favors placebo</b>
<b>MELODY-1</b> <sup>6</sup>	Macitentan	48	12 W	HF with LVEF $\geq$ 30%	Proportion of subjects with significant fluid retention or worsening in FC	<b>Main endpoint more frequently met on macitentan (+10%)</b>
<b>HELP HF</b> <sup>7</sup>	Levosimendan	37	up to 6W	HF with LVEF $\geq$ 40%	Exercise PCWP	No reduction in exercise PCWP Improved 6MWD

# Recommendations for PH associated with left heart disease

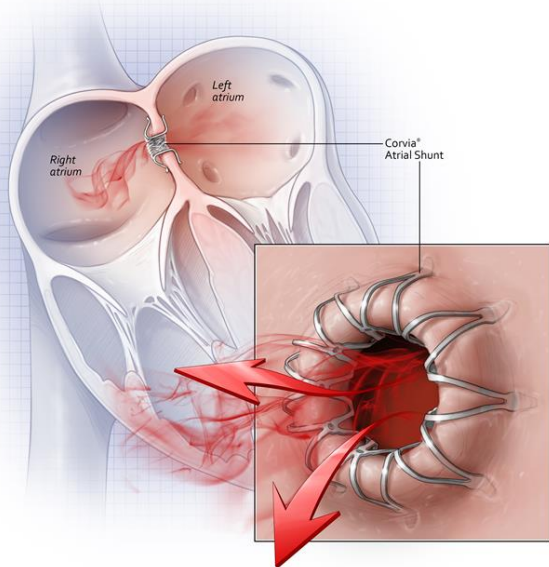
Recommendations	Class	Level
In patients with LHD and CpcPH with a severe pre-capillary component (e.g. PVR >5 WU), an individualized approach to treatment is recommended	I	C
When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended	I	C
In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH	IIb	C
Drugs approved for PAH are not recommended in PH-LHD	III	A

## General management of PH in HFpEF

- Understand pathophysiology (of HFpEF and PH)
- Do not harm!
- Individualized treatment of PH-HFpEF – Phenotyping
- Sequential approach

Underlying condition	Treatment
Diabetes	Optimize therapy Weigh loss
Systemic hypertension	Optimize therapy
Atrial fibrillation	Rhythm control or optimal rate control
Coronary artery disease	Therapy, revascularization (percutaneous, surgical)
Mitral or aortic disease	Percutaneous or surgical treatment
Left heart failure	Optimize therapy: betablockers, MRA, ARNI, SGLT2 inhibitors, iron suppl, CRT...

# A glimpse into the future: Inter Atrial Shunt Devices and Implantable Pressure Sensors in HFpEF



PATIENT TRANSMISSION



SECURE WEBSITE



CLINICAL REVIEW

cardiomems®



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HEART FAILURE SYSTEM



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# Conclusion

A clear definition of post-capillary PH is available: **phenotype the patient!**

**PH and right ventricular dysfunction** represent an **unfavorable turning point** in left heart failure.

**PAH active drugs don't work** in postcapillary PH: **optimize the treatment of the underlying disease!**