Heart failure and pulmonary hypertension: how to access, how to manage?

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Introduction

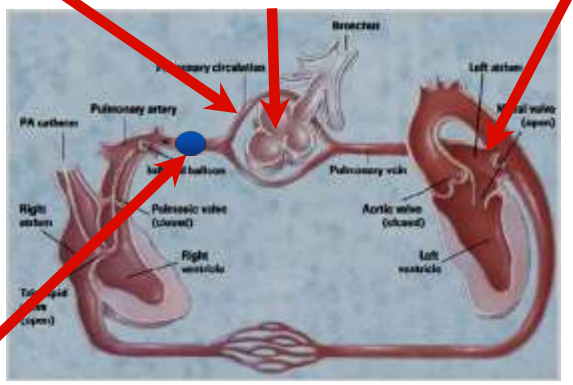
- Pulmonary hypertension is a common hemodynamic complication of heart failure.
- Among the various PH groups, heart failure (HF) represents by far the most common form of PH~ 65–80%.
- When PH and RV dysfunction accompany HF, the impact on functional capacity and prognosis are ominous.

WHO Classification of Pulmonary Hypertension

1. Pulmonary Arterial Hypertension

2. Left Heart Disease

3. Chronic Hypoxemia



4. Thromboembolic

5. Miscelaneous
-Sarcoid, fibrosing mediastinitis

Pulmonary hypertension (PH)

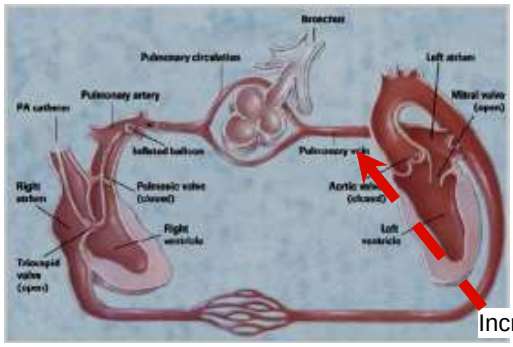
- PH: mean pulmonary artery pressure

  (mPAP) ≥25 mmHg.

- Based on the left-sided filling pressure [LVEDP, LAP,PAWP], the haemodynamic definition further distinguishes
  - **pre-capillary PH (PAWP ≤15 mmHg),**
  - **post-capillary PH (PAWP>15 mmHg).**

Relationship of HF and PH

- Passive Congestion (Elevated PAWP)



Increased LVEDP (PAWP)

Pre - Capillary vs Post - Capillary PH

Classification of PH due to left heart disease.

- **Heart failure with preserved EF (HFPEF)**
  - –Hypertensive heart disease
  - –Diabetic CMP
  - –Hypertrophic (-obstructive) CMP
  - –Restrictive/infiltrative CMP
  - –Ischemic diastolic dysfunction
- **Heart failure with reduced EF (HFREF)**
  - –Ischemic CMP
  - –Dilatative CMP
- **Valvular heart disease**
  - –Mitral valve stenosis/insufficiency
  - –Aortic valve stenosis/insuffciency
- **Others**
  - –Constrictive pericarditis
  - –Tri-atrial heart

Prevalence and significance of PH -heart failure

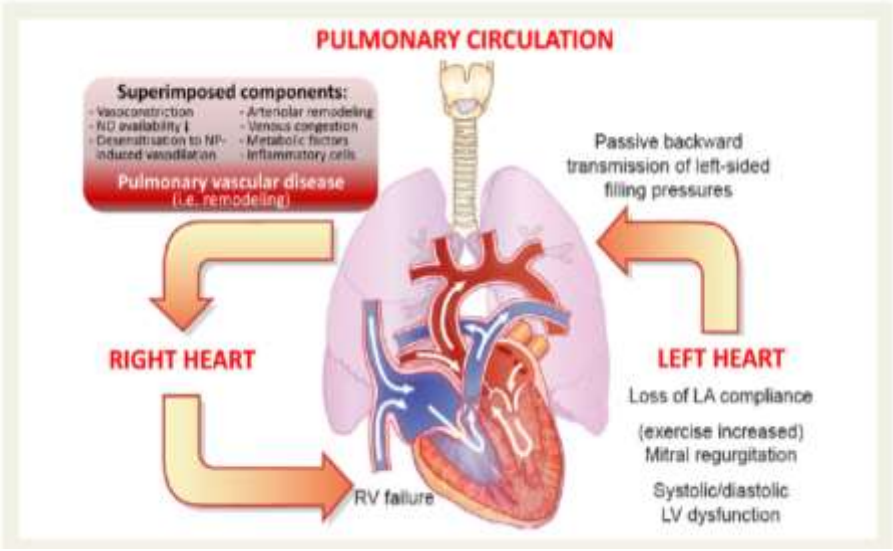
- In HFrEF: 40 and 75%.
- In HFpEF: 36 and 83%.
- The presence and extent of PH and RV dysfunction are associated with disease progression, decreased exercise tolerance, and an unfavorable outcome

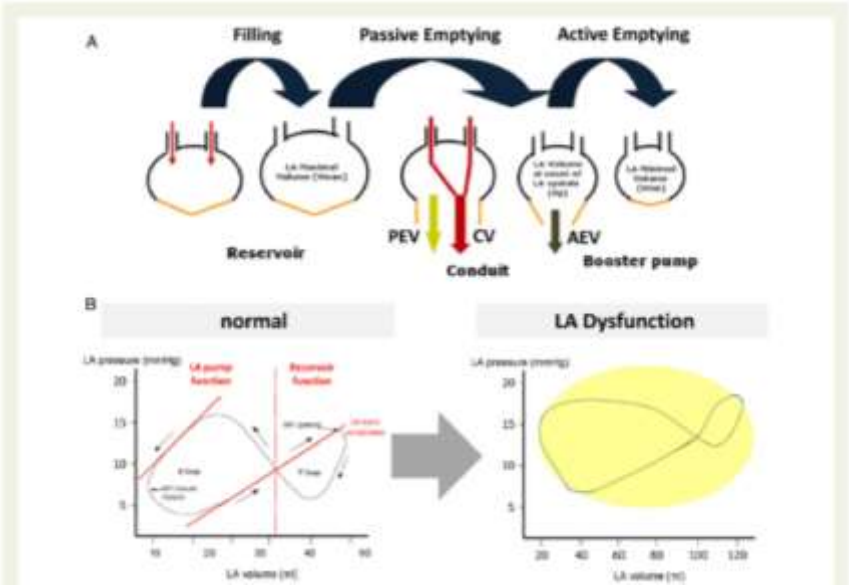
Prevalence and significance of PH_ heart failure

- Pulmonary artery systolic pressure (PASP) estimated by echocardiography strongly predicted all-cause and cardiovascular mortality independently of known predictors of outcome
- Haemodynamic predictors of poor survival in HF include an increased PAWP, mean PAP, and PVR, and a reduced PA compliance/capacitance

Pathobiology of PH_ heart failure

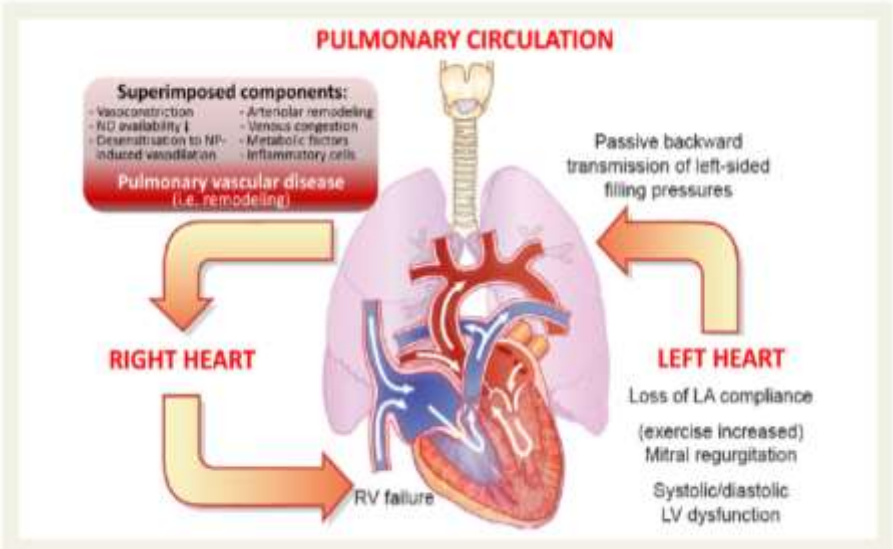
- The pathobiology of PH in left HF is complex and highly heterogeneous, and remains incompletely understood
- Pulmonary hypertension primarily results from the passive backward transmission of elevated left-sided filling pressures, which occur as a consequence of systolic or diastolic LV dysfunction.
- functional mitral regurgitation (MR) will result in elevations of LAP and PAP, which usually worsen during exercise.





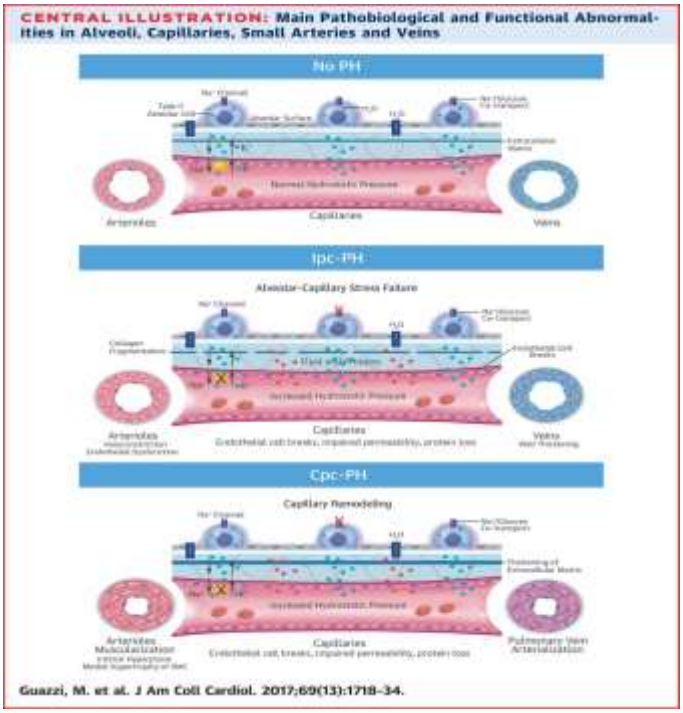
Pathobiology of PH_ heart failure

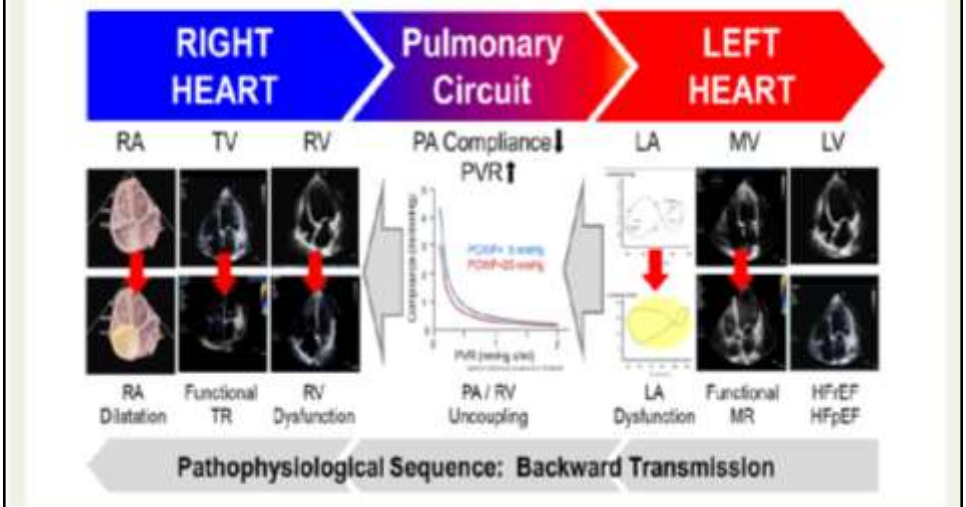
- LA dysfunction relates to symptom onset in patients with HFpEF.
- In addition to its pathophysiological significance, LA dysfunction may also determine treatment responses to targeted PH therapies in patients with LHD, since lowering of PVR and increased pulmonary blood flow may lead to increased PAWP and pulmonary oedema in patients with reduced LA compliance.



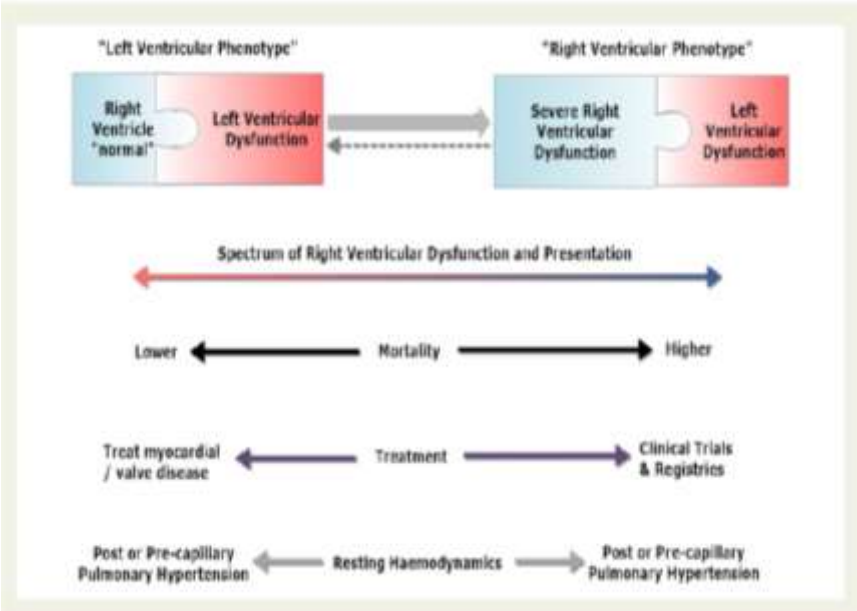
Pathobiology of PH_ heart failure

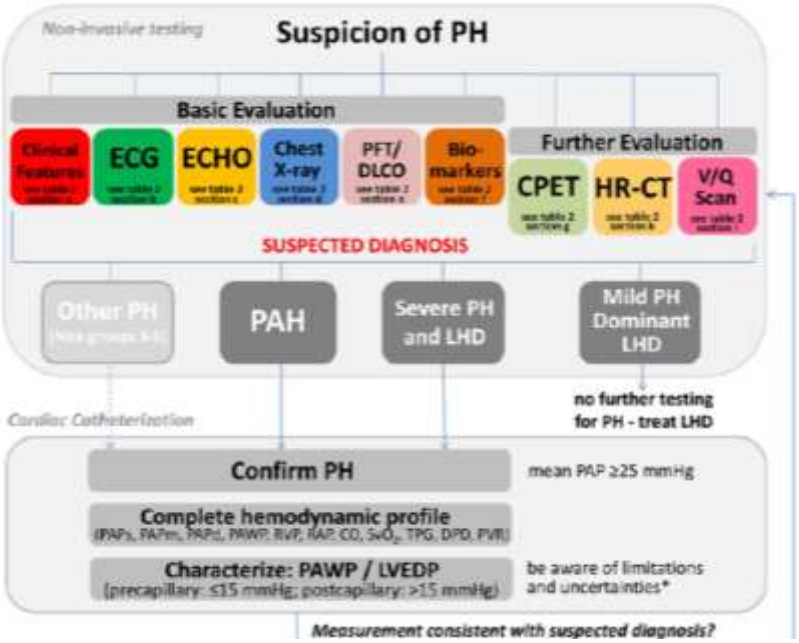
- In the systemic circulation, vascular compliance is mainly determined by the **aorta.**
- In pulmonary circulation , arterial compliance in the lung is distributed over the entire pulmonary vascular bed, so that resistance (R) and compliance (C) are predominantly determined by **the small resistance vessels.**
- Hence, pulmonary arteriolar remodeling mainly contributes to the increase in PVR and reduced PA compliance in Cpc-PH.

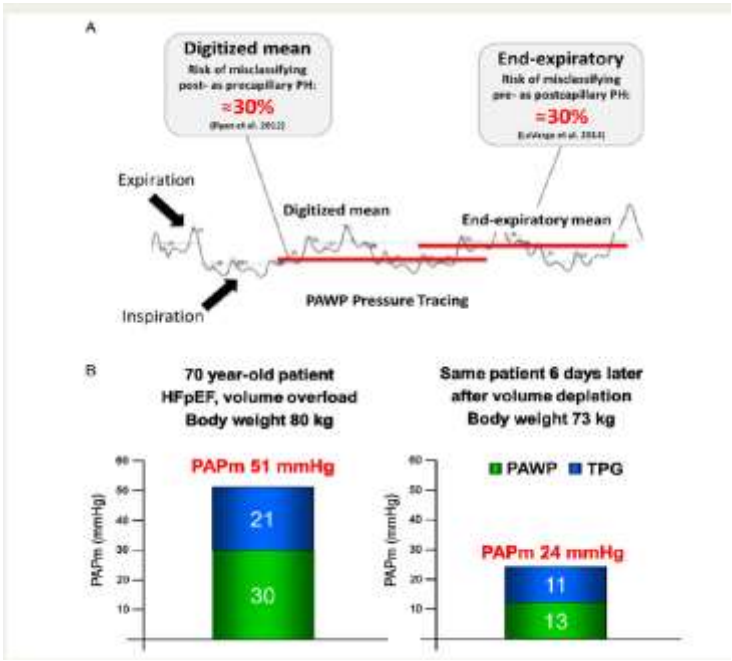

CENTRAL ILLUSTRATION: Main Pathobiological and Functional Abnormalities in Alveoli, Capillaries, Small Arteries and Veins
No PH
Arterioles
Capillaries
Veins
Ipc-PH
Alveolar-Capillary Stress Failure
Cpc-PH
Capillary Remodeling
Guazzi, M. et al. J Am Coll Cardiol. 2017;69(13):1718–34.

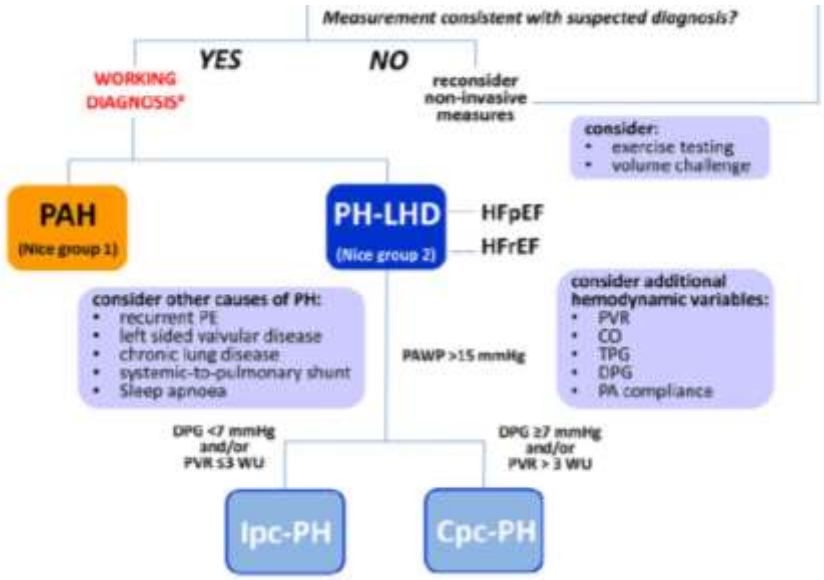

RIGHT HEART
Pulmonary Circuit
LEFT HEART
RA
TV
RV
PA Compliance
PVR
LA
MV
LV
RA Dilatation
Functional TR
RV Dysfunction
PA / RV Uncoupling
LA Dysfunction
Functional MR
HFrEF HFpEF
Pathophysiological Sequence: Backward Transmission

- Why some patients develop severe PH and RV dysfunction whereas others do not, remains limited.
  - (i) the susceptibility for pulmonary vascular disease (due to genetic factors and/or environmental stressors and/or comorbidities)
  - (ii) the factor ‘time’




Non-invasive testing
Suspicion of PH
Basic Evaluation
Clinical Features
ECG
ECHO
Chest X-ray
PFT/ DLCO
Bio-markers
Further Evaluation
CPET
HR-CT
V/Q Scan
SUSPECTED DIAGNOSIS
Other PH
PAH
Severe PH and LHD
Mild PH Dominant LHD
no further testing for PH - treat LHD
Cardiac Catheterization
Confirm PH
mean PAP ≥25 mmHg
Complete hemodynamic profile
(PAPs, PAPm, PAPd, PAWP, RVP, RAP, CO, SvO2, TPG, DPD, PVR)
Characterize: PAWP / LVEDP
(precapillary: ≤15 mmHg; postcapillary: >15 mmHg)
be aware of limitations and uncertainties*
Measurement consistent with suspected diagnosis?


A
Digitized mean
Risk of misclassifying post- as precapillary PH:
≈30%
End-expiratory
Risk of misclassifying pre- as postcapillary PH:
≈30%
Expiration
Digitized mean
End-expiratory mean
Inspiration
PAWP Pressure Tracing
B
70 year-old patient
HFpEF, volume overload
Body weight 80 kg
Same patient 6 days later
after volume depletion
Body weight 73 kg
PAPm 51 mmHg
PAWP
TPG
21
30
PAPm 24 mmHg
11
13
PAPm (mmHg)



Pulmonary hypertension (PH)

- The diastolic pressure gradient (DPG)= diastolic PAP –PAWP
  - less dependent of stroke volume and loading conditions,
  - correlate with pulmonary vascular remodeling in PH-LHD.
- Isolated post-capillary PH (Ipc-PH):DPG is <7 mmHg
- Combined post- & pre-capillary PH (Cpc-PH):DPG is ≥7 mmHg

Results of non-invasive diagnostic tests may be suggestive of either pulmonary arterial hypertension or pulmonary hypertension associated with left heart disease

	Suggestive of PAH (Nice group 1)	Suggestive of PH-LHD (Nice group 2)
a. Clinical features	Younger age, familial cases, bendopnea[a], risk factors for PAH: CTD, CHD, severe liver disease, portal hypertension, HIV	Older age, hypertension, diabetes, CAD, BMI >30, pulmonary congestion, history of pulmonary oedema, orthopnoea
b. ECG	RV hypertrophy, right axis, RV strain	LV hypertrophy (Sokolow–Lyon index: S in V1 + R in V6), left axis, atrial fibrillation
c. ECHO[b]	No signs of LHD, PASP elevated, RV > LV, RV hypertrophy/dysfunction (TAPSE), RVOT notching[c], small LA, dilated IVC	Enlarged LA, LV hypertrophy, signs of systolic (EF) and/or diastolic (E/A, DT, E/E') LV dysfunction, valvular disease
d. Chest X-ray	Enlarged right heart chambers, dilated PA, peripheral PA pruning	Pulmonary congestion, Kerley B lines, pleural effusions, enlargement of left heart chambers
e. PFT/DLCO	Normal/mild obstructive spirometry, normal or moderately decreased DLCO[d], low p_aCO_2 (≤36 mmHg)[e]	Normal/obstructive spirometry, normal DLCO (may be decreased due to comorbid COPD), high p_aCO_2 (>36 mmHg)[e]
f. Biomarkers	BNP/NTproBNP elevated (not discriminate between Groups 1 and 2)	BNP/NTproBNP elevated (not discriminate between group 1 and 2)
g. CPET	Low $P_{ET}CO_2$ at AT, decreasing during exercise; high VE/VCO_2, increasing during exercise	$P_{ET}CO_2$ at AT normal or slightly lowered, not decreasing during exercise, VE/VCO_2 not increasing during exercise
h. HR-CT	To diagnose or rule out parenchymal lung disease (not discriminate between Groups 1 and 2)	To diagnose or rule out parenchymal lung disease (not discriminate between Groups 1 and 2)
i. V/Q scan	To diagnose or rule out CTEPH (not discriminate between Groups 1 and 2)	To diagnose or rule out CTEPH (not discriminate between Groups 1 and 2)

[a]Bendopnea is typical in PAH, but may be found in HFrEF, particularly when associated with RV dysfunction and elevated RAP as described in Ref. 44.

Treatment of pulmonary hypertension in heart failure

I- Treatment of left heart disease

- Optimized treatment of the underlying LHD including medical treatments (reaching the target dosages) and interventional therapies (e.g. CRT, ICD, LVAD, MitraClip) usually helps to lower left-sided filling pressure and is always the primary aim in HF patients

Repair of mitral regurgitation in HF

- In patients with HFrEF, functional MR is common, may represent the main cause of PH, and leads to increased mortality.
- Repair of the mitral valve: Mitral Clipping or Cardio-Band lead to substantial improvement of pulmonary haemodynamics, including ↓mean PAP and PAWP& ↑cardiac index
- Percutaneous mitral valve repair: improve clinical symptoms, exercise capacity, quality of life, and HF-associated hospitalizations in HF patients.

II- Targeted treatment of PH_ heart failure

- Targeted therapies approved for the treatment of PAH include endothelin receptor antagonists (ERAs), prostanoids, phosphodiesterase type 5 inhibitors (PDE5i), and stimulators of soluble guanylate cyclase (sGC).
- **None of these compounds are approved for the treatment of PH-LHD.**

Comparative effectiveness of sildenafil for pulmonary hypertension due to left heart disease with HFrEF

Rong Jiang[1,4], Lan Wang[1,4], Chang-Tai Zhu[2], Ping Yuan[1,4], Bigyan Pudasaini[3], Qin-Hua Zhao[1], Su-Gang Gong[1], Jing He[1], Jin-Ming Liu[1] and Qing-Hua Hu[1]

There is no cure for pulmonary hypertension due to left heart disease (PH-LHD), but the rationale for using sildenafil to treat pulmonary arterial hypertension with heart failure with reduced ejection fraction (HFrEF) has been supported by short-term studies. We performed a meta-analysis to evaluate the effectiveness of sildenafil for PH-LHD with HFrEF. A systematic literature search of PubMed, EMBASE and the Cochrane Central Register of Controlled Trials was conducted from inception through October 2014 for randomized trials and for observational studies with control groups, evaluating the effectiveness of sildenafil to treat PH-LHD with HFrEF. Sildenafil therapy decreased pulmonary arterial systolic pressure both at the acute phase and at the 6-month follow-up (weighted mean difference (WMD): −6.03 mm Hg, $P=0.02$; WMD: −11.47 mm Hg, $P<0.00001$, respectively). Sildenafil was found to reduce mean pulmonary artery pressure (WMD: −3 mm Hg, $P=0.0004$) and pulmonary vascular resistance (WMD: −60.0 dynes cm^{-5}, $P=0.01$) at the 3-month follow-up. Oxygen consumption at peak significantly increased to 3.66 ml min^{-1} kg^{-1} ($P<0.00001$), 3.36 ml min^{-1} kg^{-1} ($P<0.00001$) and 2.60 ml min^{-1} kg^{-1} ($P=0.03$) at 3, 6 and 12 months, respectively. There were significant reductions in ventilation to CO_2 production slope of −2.00, −4.68 and −7.12 at 3, 6 and 12 months, respectively ($P<0.00001$). Sildenafil was superior to placebo regarding left ventricular ejection fraction at the 6-month follow-up (WMD: 4.35, $P<0.00001$), and it significantly improved quality of life. Sildenafil therapy could effectively improve pulmonary hemodynamics and cardiopulmonary exercise testing measurements of PH-LHD with HFrEF, regardless of acute or chronic treatment.

Hypertension Research (2015) **38**, 829–839; doi:10.1038/hr.2015.73; published online 23 July 2015

Summary of recently completed and ongoing clinical trials in pulmonary hypertension associated with left heart disease

Drug	n	Start	End	Duration	Primary endpoint	Secondary endpoints
HF with reduced EF						
Riociguat LEPHT[40]	201	Results available		16 weeks	Change in mPAP from baseline	Haemodynamic and echocardiographic variables, biomarker levels, safety, pharmacokinetics
Sildenafil SI-HF (NCT01616381)	210	9/2012	6/2014	24 weeks	Patient Global assessment (MWD	QoL, Kansas city questionnaire, safety
Tadalafil PITCH-HF (NCT01910389)	2102	Study terminated Febuary 2014[a]		Up to 54 months	Time to CV death or 1st HF hospitalization	Biomarkers levels, exercise capacity, QoL, safety
HF with preserved EF						
Sildenafil RELAX[41]	216	Results available		24 weeks	Change in peak VO_2 from baseline	Exercise capacity, clinical status, QoL, safety
Sildenafil Hoendermis et al.[44]	52	Results available		12 weeks	Change in mPAP from baseline	Change in PAWP, cardiac output, peak VO_2
Riociguat DILATE[73]	49	Results available		16 weeks	Change in mPAP from baseline	Haemodynamic and echocardiographic variables, biomarker levels, safety, pharmacokinetics
HF with EF >35%						
Macitentan MELODY-1 (NCT02070991)	60	5/2014	10/2015	12 weeks	Safety and tolerability (Fluid retention)	PVR, haemodynamics, changes in TPG and DPG, echocardiographic variables (RV function)

Conclusion

- PH associated with left heart failure (HF) represents by far the most common form of PH.
- It is important to establish a precise diagnosis and classification of PH before treatment decisions are made.
- PH and RV dysfunction are worse prognostic factors in patients with heart disease.
- The efficacy and safety of targeted PH therapies in HF remain unproven.

Thank you…