Schweizerische Arbeitsgruppe für Pulmonale Hypertonie SAPH
Groupe Suisse sur l'Hypertension Pulmonaire GSHP
Gruppo Svizzero sull'Ipertensione Polmonare GSIP
Swiss Group for Pulmonary Hypertension SGPH

Symposium Romand d'HTAP – Genève 20 septembre 2012

Cœur gauche et HT(A)P

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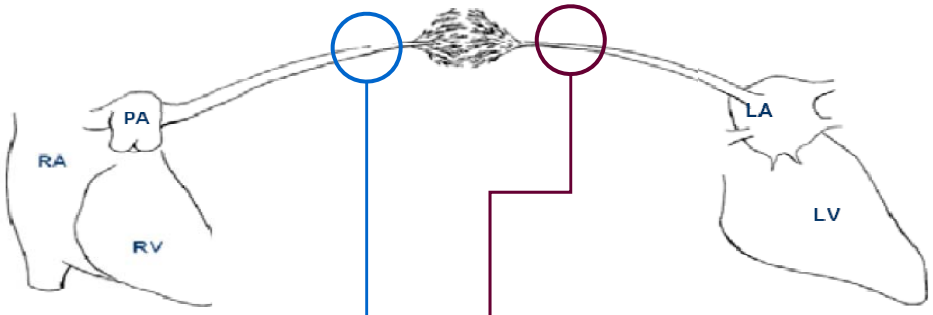
Pulmonary hypertension in left heart diseases

- **Definition, causes and scope of the problem**
- **What are the main drivers of PH in LHD and how to define 'out-of-proportion PH?**
- **Treatment of PH in LHD: what we know and what we should do**

Haemodynamic classification of PH



Pre-capillary PH

- **Ppa ≥25 mmHg**
- **Pcwp <15 mmHg**
- **N or reduced CO**
- **All but Group 2**

Post-capillary PH

- **Ppa ≥25 mmHg**
- **Pcwp ≥15 mmHg**
- **N or reduced CO**
- **Only Group 2**

Passive **Ppa-Pcwp ≤12 mmHg**

Reactive **Ppa-Pcwp >12 mmHg**

Adapted from Galiè N, et al. *Eur Heart J* 2009;30:2493–537; Galiè N, et al. *Eur Respir J* 2009;34:1219–63.

Left-sided heart diseases leading to PH

Left ventricular systolic dysfunction

- Ischemic
- Non ischemic → Familial/idiopathic dilated CM
  Valvular/volume overload (regurgitation or stenosis)

Left ventricular diastolic dysfunction

- Restrictive, constrictive CM
- Hypertensive, hypertrophic CM
- Diastolic dysfunction of the elderly?

Reduced left atrial compliance

Oudiz R. *Clin Chest Med* 2007;28:233–41.

Prevalence of PH in left heart diseases

Increases with disease severity[1]

- Up to 60% in LV dysfunction
- Most of all severe mitral valve disease
- Up to 65% symptomatic aortic stenosis

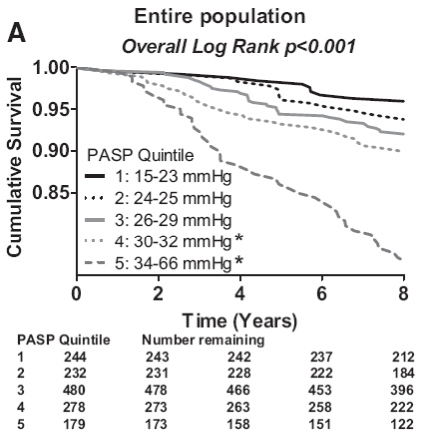
HF with preserved ejection fraction (HF-pEF)

- Up to 44% of all HF patients have preserved EF[1]
- HF-pEF is frequent in patients with metabolic syndrome (MS)[2,3]
- Echo-derived studies suggest that sPAP is increased up to 47 + 17 mmHg[4,5]

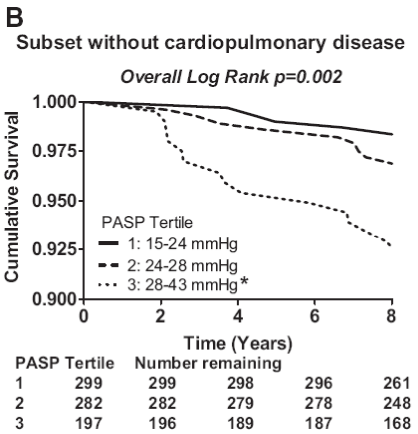
1. Galiè N, et al. *Eur Heart J* 2009;30:2493–537. 2. Wong CY, et al. *Am J Cardiol* 2005;96:1686–91. 3. de las Fuentes L, et al. *Eur Heart J* 2007;28:553–9. 4. Klapholz M, et al. *J Am Coll Cardiol* 2004;43:1432–8. 5. Neuman Y, et al. *Int J Cardiol* 2008;127:174–8.

Age-associated increases in PAPs in a population study

- Random sample of Olmsted county survey
- N=2,042 with 1,413 (69%) having measurable TR jets
- Predictive factors of increased PAPs were age, ↑ PP and E/e'



PASP Quintile	Number remaining				
1	244	243	242	237	212
2	232	231	228	222	184
3	480	478	466	453	396
4	278	273	263	258	222
5	179	173	158	151	122

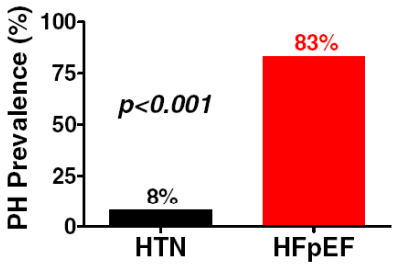


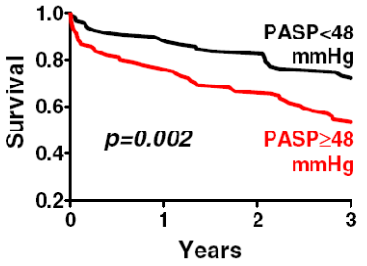
PASP Tertile	Number remaining				
1	299	299	298	296	261
2	282	282	279	278	248
3	197	196	189	187	168

Adapted from Lam C. *Circulation* 2009;119:2663—70.

Pulmonary hypertension in HF with preserved EF

- **Community-based study**
- **N=244 HF-pEF followed by echocardiography**
- **PH defined as PAPs >35 mmHg from TRV**



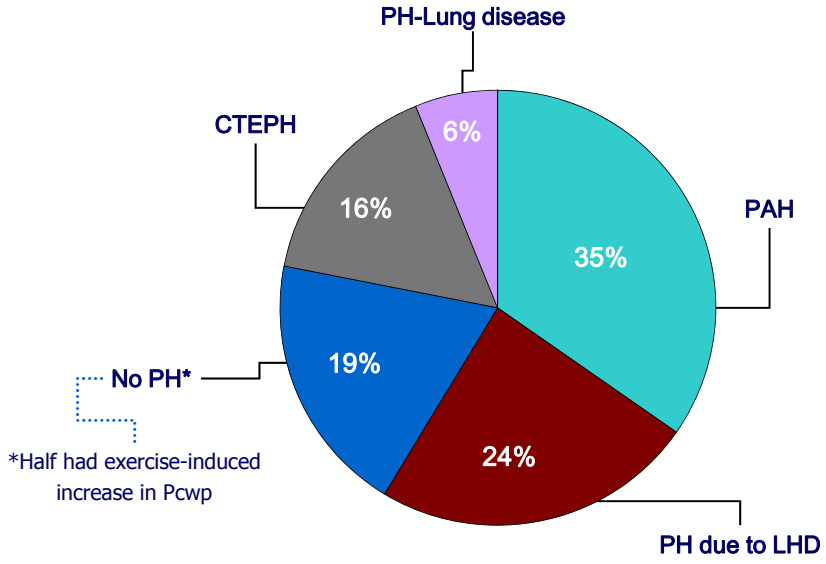


Number remaining				
PASP<48 mmHg	98	86	80	44
PASP≥48 mmHg	105	78	67	38

Adapted from Lam C, et al. *J Am Coll Cardiol* 2009;53:1119–26.

Distribution of the diagnosis @ Erasme

N=196 patients assessed for PH (2006–2009)



Adapted from Vachiery JL. *Pulmonary Hypertension Yearbook 2009.* Benelux edition. pp 39-50.

Pulmonary hypertension in left heart diseases

- Definition, causes and scope of the problem
- **What are the main drivers of PH in LHD and how to define 'out-of-proportion PH?**
- Treatment of PH in LHD: what we know and what we should do

What drives PH in left heart diseases?

- In the linear model, resistance is the key determinant of the pulmonary circulation.

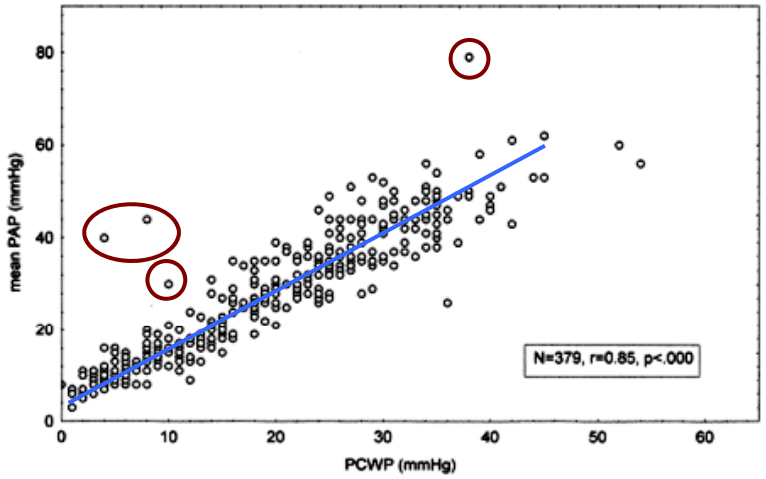
PVR = (Ppa – left atrial pressure)/Q

Ppa = (PVR × Q) + left atrial pressure

Increased left side filling pressure drives pulmonary hypertension in LHD

Is the mechanism of PH purely passive?

In heart failure, an increased Pcwp accounts for the development of pulmonary hypertension…



…in most but not all cases

Ghio S, et al. J Am Coll Cardiol 2001;37:183–8.

What determines the reactive component of PH?

- Local and systemic effects of neurohumoral activation (angiotensin II, cytokines)
- Endothelial dysfunction plays a major role in the loss of local control of pulmonary vascular tone

NO-dependent vasodilation is impaired and ET-1 activity is enhanced in PH due to heart failure

- ET-1 blood level increases in PH, correlates with haemodynamic changes
- Phenotypic changes in ET receptors (A/B), promoting vasoconstriction and vascular growth

Porter TR, et al. *J Am Coll Cardiol* 1993;22:1418–24; Ben Driss A, et al. *Circulation* 2000;101:2764–70; Moraes DL, et al. *Circulation* 2000;102:1718–23.

Mechanism of pulmonary hypertension in Group 2 is led by increased LA filling pressure

Loss of LA compliance
diastolic dysfunction

- **Passive increase in pulmonary pressure**
- **Superimposed reactive component**

Endothelial dysfunction
(ET-1 and NO pathways)

Vascular remodelling (no plexiform lesions)

Decreased vascular compliance
Blunted response to vasodilators

Significant pulmonary vascular disease
RV failure

CHEST Original Research
PULMONARY HYPERTENSION

Association of the Metabolic Syndrome With Pulmonary Venous Hypertension

N=122 patients referred for PH (9/2004 to 12/2005)
Prevalence of MS in both PAH and PH-LVD
Compare haemodynamic and clinical characteristics

- **n=39 PAH** — **31.9%**
- **n=28 PH-LVD** — **23%**
  - **6 valvular diseases (excluded)**
  - **22 preserved ejection fraction**
- **n=23 no PH** — **18.9%**

Robbins IM, et al. *Chest* 2009;136:31–6.

Clinical characteristics

	PAH n=35	PH-LHD n=17	P-value
Female gender, %	83	77	0.711
Age, yr	47.9 ± 14.1	55.7 ± 12.1	0.077
Body mass index (kg/m²)	29.2 ± 8.4	36.8 ± 9.1	0.003
Body mass index >30 (kg/m²)	31	77	0.002
WHO FC, % class 3 or 4	77	71	0.735
Anorexigen use, %	20	41	0.181
Diabetes mellitus, %	20	59	0.005
Hypertension, %	54	94	0.004
Hyperlipidaemia, %	17	47	0.043
Coronary artery disease, %	3	35	0.003
Left atrial dilatation, %	10	77	0.001

70.6% of PH-LHD had >3 features of the MS (>90% had at least one) vs only **20.0%** of PAH (P<0.001; OR, 9.6; 95% CI, 2.5 to 36.4)

Robbins IM, et al. *Chest* 2009;136:31–6.

Haemodynamic characteristics

	PAH n=35	PH-LHD n=17	P-value
Heart rate (beats/min)	81 ± 14	68 ± 10	0.003
mPAP (mmHg)	53 ± 10	45 ± 17	0.041
PCWP (mmHg)	10 ± 4	20 ± 6	<0.001
Cardiac index (l/min/m²)	2.4 ± 1.1	3.0 ± 1.7	0.010
PVR (units)	10.8 ± 4.7	4.4 ± 2.9	<0.001
PAPd-PCWP (mmHg)	26 ± 9	12 ± 9	<0.001

All had increased PVR
Diastolic gradient was found elevated in both group
No report on the number of disproportionate PH in LHD group

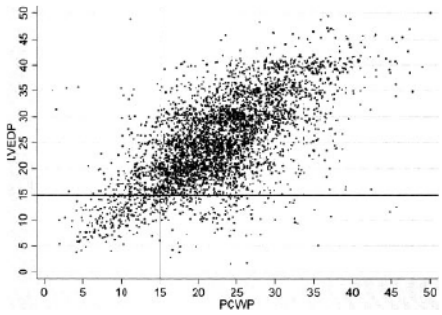
Robbins IM, et al. *Chest* 2009;136:31–6.

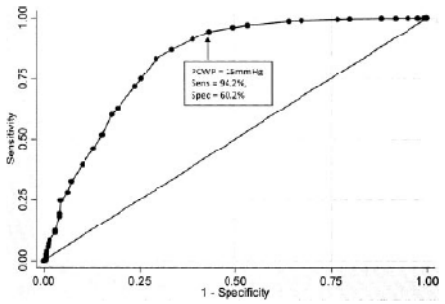
Misclassification of Pulmonary Hypertension Due to Reliance on Pulmonary Capillary Wedge Pressure Rather Than Left Ventricular End-Diastolic Pressure

Scott D. Halpern, MD, PhD; and Darren B. Taichman, MD, PhD, FCCP

N=11,000 (single center) – >90% with right and left cath

14.8% diagnosed as PAH – 53.8% reclassified if LVEDP used vs PCWP
PCWP underestimated LVEDP by 2.9 mmHg





Adapted from Halpern SD and Taichman DB. *Chest* 2009;136:37–43.

What is 'out-of-proportion' PH in LHD?

- **Confusion created by an heterogenous terminology**
  - Proportionate (to Pcwp) or passive PH
  - Reactive PH
  - Out of proportion
  - Unresponsive
  - Fixed or irreversible PH
- **Three specific clinical situations to be addressed in PH due to LHD**
  - High Pcwp – low/normal PVR
  - High Pcwp – elevated PVR
  - Low Pcwp – elevated PVR

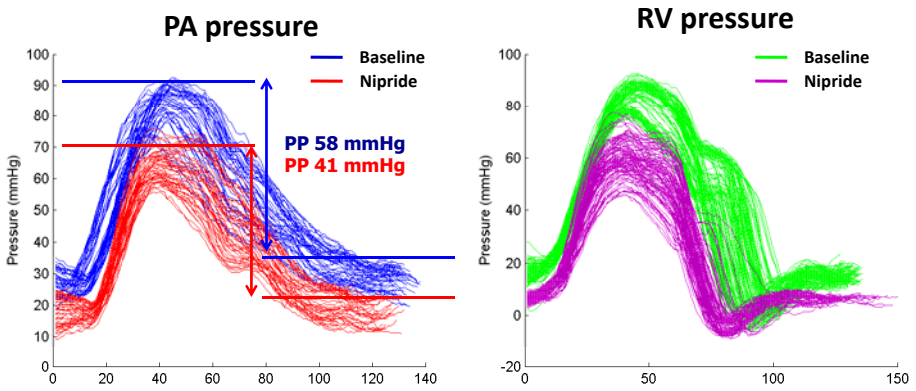
Which variable better reflects pulmonary vasculopathy ?

What are the characteristics of such variable ?

- **Should reflect active changes of the pulmonary circulation – pulmonary vascular disease**
- **Must be less dependent (or the least dependent) on changes of PCWP**
- **Should be less influenced by blood flow and stroke volume**
- **Should reflect changes in compliance, and take into account the distensibility of the PAs**

Effect of NPS on PAP in severe PH due to HF-pEF

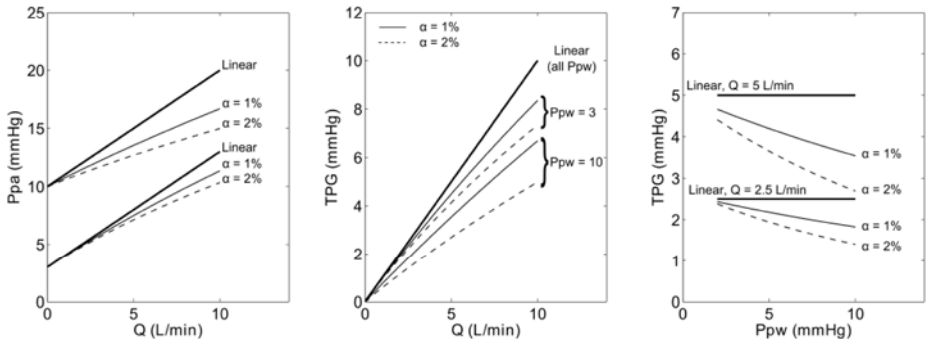
All measured PA and RV pressures



- NPS decreased pulse pressure, through a larger change in PAPs
- PAPd was less sensitive to change, but was poportional to a drop in Pcwp by 10 mmHg.
- TPG appears to be affected by changes in pressure and flow

TPG: a variable under influence !

- Pulmonary arteries are distensible, with α = 1-2% per mmHg
- Distensibility influences Ppa at higher pressures

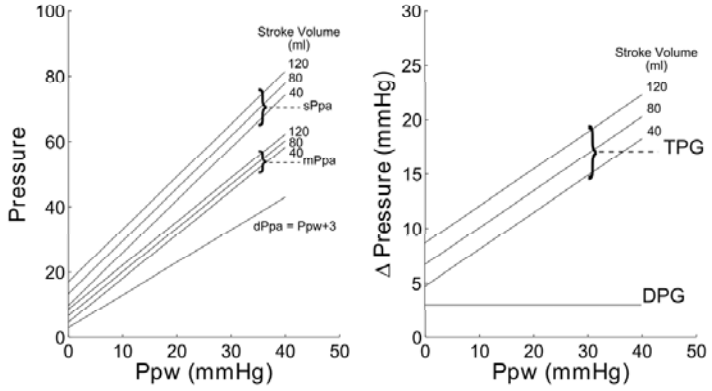


TPG is influenced by CO, PCWP and distensibility

R Naeije, JL Vachiery, P Yerly, R Vanderpool. ERJ Express. August 30, 2012 doi: 10.1183/09031936.00074312

DPG: better to detect pulmonary vascuopathy ?

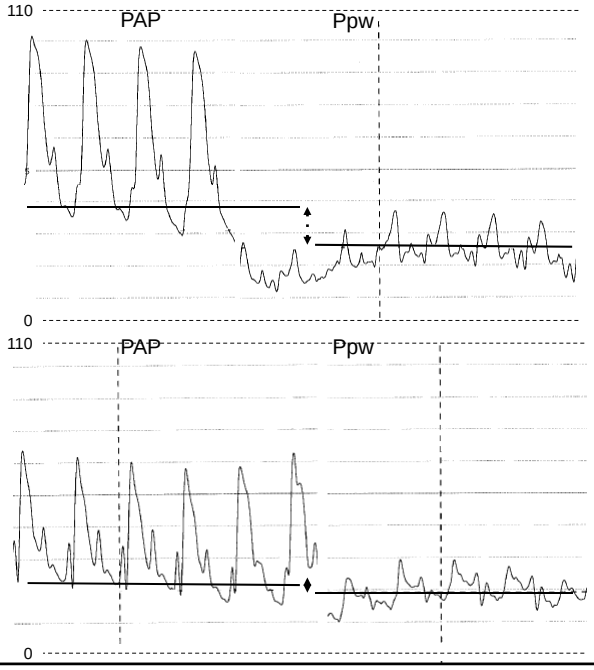
- Effect of PCWP on pulmonary pressures at different SV
- Example of a 1:1 transmission of PCWP to diastolic PAP



DPG is not influenced by SV at any given level of SV

R Naeije, JL Vachiery, P Yerly, R Vanderpool. ERJ Express. August 30, 2012 doi: 10.1183/09031936.00074312

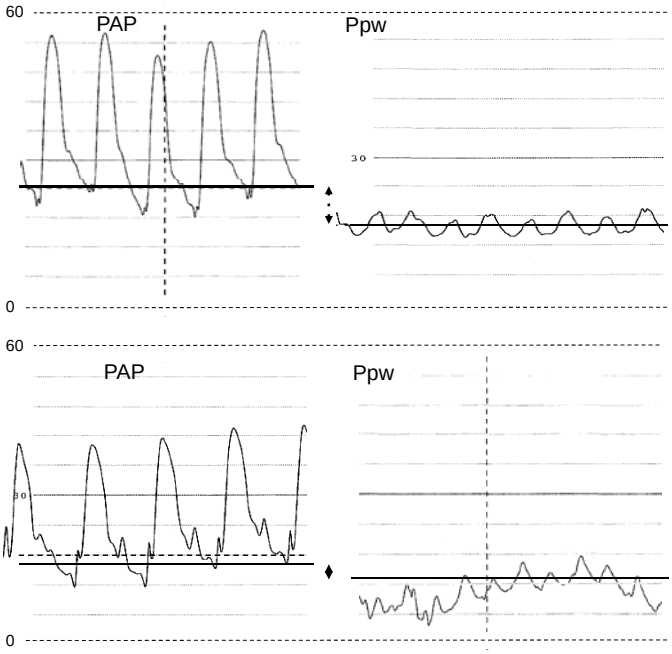
Normalization of DPG, but not TPG, under NPS in HF



Baseline
PAP: 101 / 41 - 61 mmHg
Ppw: 28 mmHg
CO: 4.5 L/min
TPG : 33 mmHg
DPG: 13 mmHg
PVR : 7.33 Wood units

NPS 170 ng / '
PAP: 69 / 24 - 39 mmHg
Ppw: 21 mmHg
CO: 6.06 L/min
TPG : 18 mmHg
DPG : 3 mmHg
PVR : 2.72 Wood units

Normalization of DPG, but not TPG, under NPS in HF



Baseline
PAP: 56 /24- 35 mmHg
Ppw: 16 mmHg
CO: 4.9 L/min
TPG : 19 mmHg
DPG : 8 mmHg
PVR : 3.9 Wood units

NPS 40 ng/ '
PAP: 44 /18- 27 mmHg
Ppw: 13 mmHg
CO: 5.1 L/min
TPG : 14 mmHg
DPG : 5 mmHg
PVR : 2.74 Wood units

Detecting vasoreactivity in Group 2 PH?

Agent	Route	Dosage	Side effects
Nitrates	Sublingual Oral IV	0.8–5 mg 5 mg 2–10 ng/kg/min	Hypotension, headache
Sodium nitroprusside	IV	1 µg/kg/min	Hypotention
Inhaled NO	Face mask	20–80 ppm	Increased left filling pressures
Prostaglandin E1	IV	0.01–0.3 µg/kg/min	Hypotension, flushing, nausea, jaw pain
Epoprostenol	IV	2 – 8 ng/kg/min	
Milrinone	IV	0.375-0.75 µg/kg/min	Hypotension
Dobutamine	IV	4–10 µg/kg/min	Tachycardia
Nesiritide	IV	2 µg/kg bolus and 0.01 µg/kg/min infusion	Hypotension

Maybe useful in some situations (pre transplant) but no set guidelines

Adapted from Natale ME and Pina IL. *Curr Opin Cardiol* 2003; 18:136–40.

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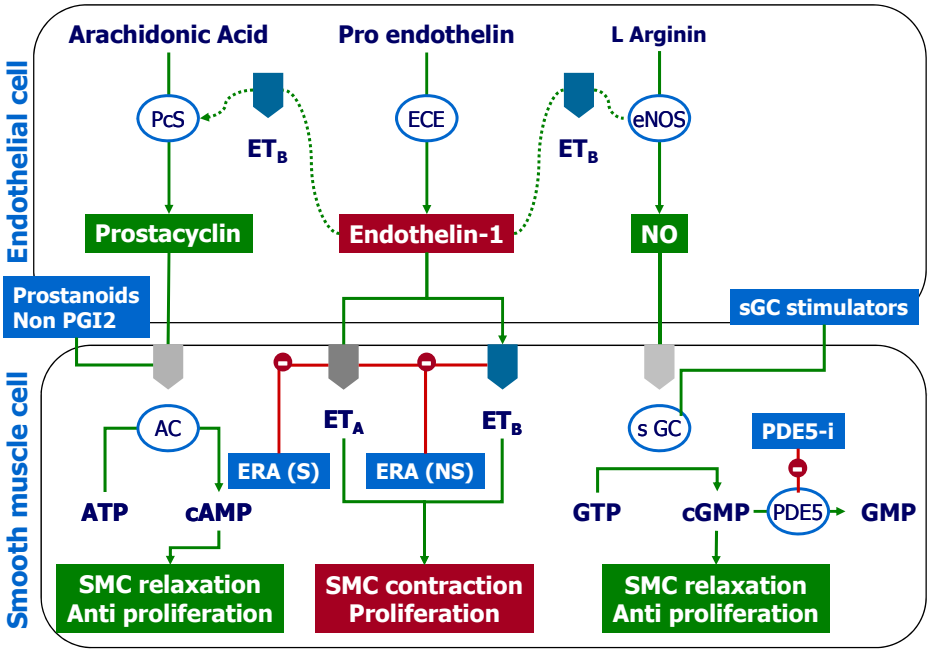


Vachiéry JL. Adv Ther. 2011;28:251-69

PAH therapies in heart failure
A good rationale and encouraging initial results...

Prostaglandins and prostacyclin derivates

- **Improved haemodynamics during short term administration of iloprost[1], PGE_1[2,3] and PGI_2[4]**
- **Epoprostenol improves exercise tolerance in patients with moderate to severe HF[5]**

Endothelin-1 receptor antagonists

- **Acute studies supporting a favourable role of ET-1 blockade in HF, with nonselective (bosentan[6,7]) or ET_A selective (darusentan[8], sitaxentan[9,10]) drugs**

1. Braun S, et al. *Int J Cardiol* 2007;115:67–72; 2. Dzau VJ, et al. *Heart Fail* 1986;2:6–13; 3. von Scheidt W, et al. *J Heart Lung Transplant* 2006;25:1070–6; 4. Kieler-Jensen N, et al. *J Heart Lung Transplant* 1993;12:179–84; 5. Sueta CA, et al. *Am J Cardiol* 1995;75:34–9; 6. Mulder P, et al. *Circulation* 2000;102:491–3; 7. Bauersachs J, et al. *Cardiovasc Res* 2000;47:142–9; 8. Kiowski W, et al. *Lancet* 1995;346:732–6; 9. Spieker LE, et al. *J Am Coll Cardiol* 2000;35:1745–52; 10. Sütsch G, et al. *Circulation* 1998;98:2262–8.

PAH therapies in heart failure …and (very) depressing long-term effects

Drug/trial	Patients	Design	Primary Endpoint	Results
Epoprostenol Califf, Shah FIRST[1,2]	N=471 Severe HF	1:1, event-driven 4 ng/kg/min (mean)	Survival	**Early termination (trend to decreased survival)**
Bosentan Packer REACH-1[3]	N=174 Severe HF	2:1, 26 weeks 500 mg BID	Change in clinical state	**Early termination**
Kalra ENABLE[4]	N=1,613 Severe HF	1:1, 18 months 125 mg BID	Mortality + hosp	**No effect**
Darusentan Lüscher HEAT[5]	N=179 NYHA III	3:1, 3 weeks 30, 100, 300 mg	Haemod (Pcwp/CO)	Increased CO No change Pcwp
Anand EARTH[6]	N=642 NYHA II–IV	5:1, 6 months 10, 25, 50, 100, 300 mg	LV changes (MRI) + events	**No effect**

1. Califf RM, et al. *Am Heart J* 1997;134:44–54; 2. Shah MR, et al. *Am Heart J* 2001;141:908–14. 3. Packer M, et al. *J Card Fail* 2005;11:12–20; 4. Kalra PR, et al. *Int J Cardiol* 2002;85:195–7. 5. Lüscher TF, et al. *Circulation* 2002;106:2666–72. 6. Anand I, et al. *Lancet* 2004;364:347–54.

PDE5 inhibitors in heart failure: studies in PH

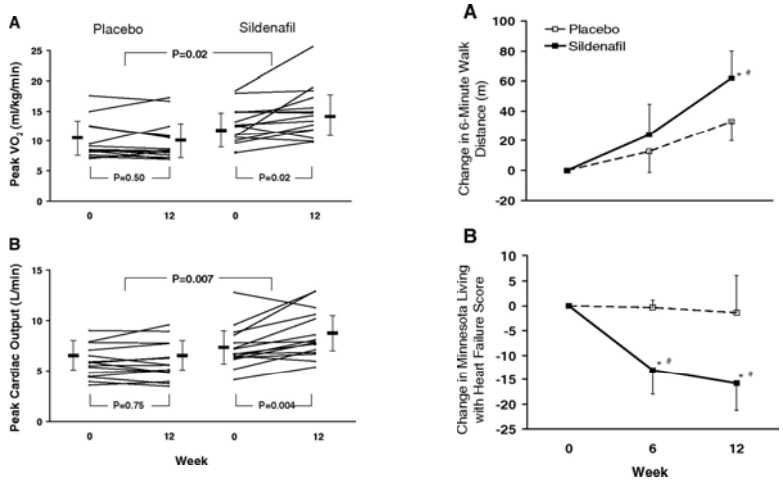
- **Significant acute effects of single doses of sildenafil (25–100 mg)**
  - **Reversibility of PH in pre-transplant setting[1–3]**
  - **Haemodynamic variables at rest[4,5] and exercise[5]**
  - **Exercise capacity (peak VO_2)[4,5]**
- **Chronic use of sildenafil in "systolic" HF to treat erectile dysfunction appears to be safe[4]**

2 monocentric placebo-controlled studies

1. **Improvement (HD, exercise tolerance) sustained >12 W, change in PVR driven by CO (25–75 mg TID)[6]**
2. **Sustained at 6 months (exercise) with sildenafil 50 mg TID[7]**

1. Gomez-Sanchez M, et al. *Eur J Heart Fail* 2004;6:615–17; 2. Jabbour A, et al. *Eur J Heart Fail* 2007;9:674–77; 3. Lepore JJ, et al. *Chest* 2005;127:1647–53; 4. Bocchi EA, et al. *Circulation* 2002;106:1097–103; 5. Lewis GD, et al. *Circulation* 2007;115:59–66; 6. Lewis GD, et al. *Circulation* 2007;116:1555–62; 7. Guazzi M, et al. *J Am Coll Cardiol* 2007;50:2136–44.

Sildenafil Improves Exercise Capacity in Systolic Heart Failure and "Secondary" Pulmonary Hypertension



PVR decreased by 20% (p=0.02), mainly driven by an improvement in CO (no change in Ppa)

Lewis et al Circulation. 2007;116:1555

Heart Failure

Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction

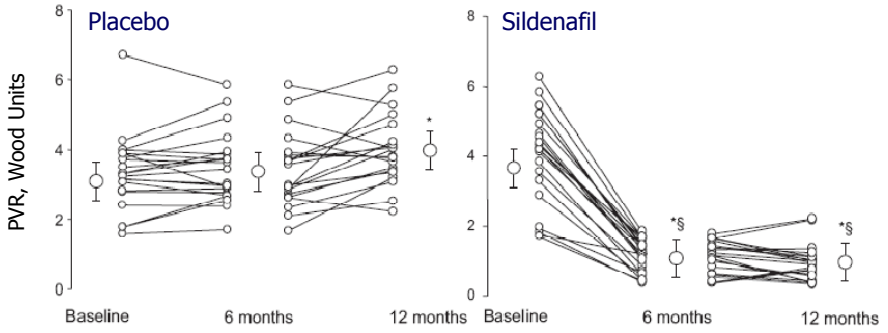
A Target of Phosphodiesterase-5 Inhibition in a 1-Year Study

- **Single center, randomisation sildenafil 50 mg tid vs placebo**
- **Patients screened for HF-pEF and RVSP ≥40 mmHg (N=94)**
- **75 eligible – N=44 included**

	Placebo (n=22)	Sildenafil (n=22)
Age, y (range)	73 (53–79)	72 (62–81)
Male sex, n	18	17
BMI, kg/m²	30.2 ± 8.9	31.8 ± 11.5
RAP, mmHg	23.1 ± 5.5	23.0 ± 4.6
mPAP, mmHg	36.8 ± 5.1	39.0 ± 5.0
PCWP, mmHg	21.9 ± 2.0	22.0 ± 2.5
PAPd-Pcwp, mmHg	**~8**	**~10**
TPG, mmHg	**14.5 ± 2.3**	**16.2 ± 1.6**
PVR, WU	**3.27 ± 0.9 3**	**3.88 ± 1.38**
CI, l/min/m²	2.33 ± 0.64	2.39 ± 0.59

Guazzi M, et al. *Circulation* 2011;124:164–74.

Long-term effects of sildenafil on PH in HF-pEF



@ 12 mo	Placebo	Sildenafil
mPAP, mmHg	39.6 ± 4.7	20.8 ± 3.3*†
PCWP, mmHg	21.9 ± 2.0	17.8 ± 1.9*†
TPG, mmHg	**17.9 ± 1.7**	**3.3 ± 1.8*†**
PVR, WU	**3.96 ± 1.03***	**1.00 ± 0.56*†**
CI, l/min/m²	2.32 ± 0.56	2.51 ± 0.51†‡
PAPd-PCWP	~11 mmHg	~0 mmHg

* †P<0.01 vs baseline; ‡ §P<0.01 vs corresponding placebo value

Adapted from Guazzi M, et al. *Circulation* 2011;124:164-74.

IPAH vs Group 2 PH – Things to consider

The group of patients with LHD/HF is more heterogenous

- Older subjects, male predominance
- More comorbidities (metabolic syndrome)*
- Polymedication (higher risk of side effects)

No large RCT has been performed so far in PH due to HF

- Similar pattern was observed, ie short term positive results based on good rationale, but unconfirmed long term
- PH has not been an inclusion criterion in large trials, with the exception of PDE5-i monocentric trials

A better definition of PH in LHD is desirable

- Definition of « disproportionate PH » based on transpulmonary gradient is arbitrary and the wording may be misleading
- « Pulmonary vascular disease », based on the diastolic (PAPd-Pcwp) gradient may help identifying the right target

*Robbins IM, et al. *Chest* 2009;136:31–6; Guazzi M et al. *Circulation* 2011;124:164–74.

Ongoing Phase II trials in PH in heart failure

Drug	N	Centers	Start	End	Duration	Primary endpoint	Secondary endpoints
HF due to systolic dysfunction							
Riociguat **LEPHT (BAY63-2521)**	201	111	**Recruitment completed**		16 W	Mean PAP	**Adverse events, PK, PVR, NT-pro BNP**
HF with preserved ejection fraction							
Sildenafil (RELAX)	120	15	**01/2009**	**?**	12 W	Peak VO_2	**PVR, BNP, AE**
Riociguat **DILATE (BAY63-2521)**	48	7	**07/2010**	**8/2012**	16 W	Mean PAP	**Adverse events, PK, PVR, NT-pro BNP**

What should be the endpoint in a Phase III trial ?
Clincal worsening ?

Data obtained using search terms on http://www.clinicaltrials.gov. Accessed April 12th, 2012.

Table 31 Recommendations for PH due to left heart disease

Statement	Class[a]	Level[b]
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease	I	C
Patients with 'out of proportion' PH due to left heart disease (*Table 3*) should be enrolled in RCTs targeting PH specific drugs	IIa	C
Increased left-sided filling pressures may be estimated by Doppler echocardiography	IIb	C
Invasive measurements of PWP or LV end-diastolic pressure may be required to confirm the diagnosis of PH due to left heart disease	IIb	C
RHC may be considered in patients with echocardiographic signs suggesting severe PH in patients with left heart disease	IIb	C
The use of PAH specific drug therapy is not recommended in patients with PH due to left heart disease	III	C

[a]Class of recommendation.
[b]Level of evidence.

Galiè N, et al. Eur Heart J 2009;30:2493–537.

PH and RV dysfunction play a critical role in left heart diseases

- Increased RV afterload is a major determinant of exercise intolerance in heart failure[1]
- PH and RV dysfunction have a significant impact on morbidity and mortality in HF and valvular heart diseases[2-4]
- Endothelial dysregulation plays a role in the development of severe pulmonary hypertension (ET-1, NO and PGI$_2$ pathways)[5,6]

1. Butler J, *et al. J Am Coll Cardiol* 1999;34:1802–6; 2. Stobierska-Dzierzek B, *et al. J Am Coll Cardiol* 2001;38:923–31 3. Ghio S, *et al. J Am Coll Cardiol* 2001;37:183–8; 4. Ben-Dor I, et al. Am J Cardiol 2011;107:1046 –1051; 4. Goldstone A, et al. Am J Cardiol 2011;107:755–760; 5. Ben Driss A, *et al. Circulation* 2000;101:2764–70; 6. Moraes DL, *et al. Circulation* 2000;102:1718–23.

Ongoing Phase III trials in PAH

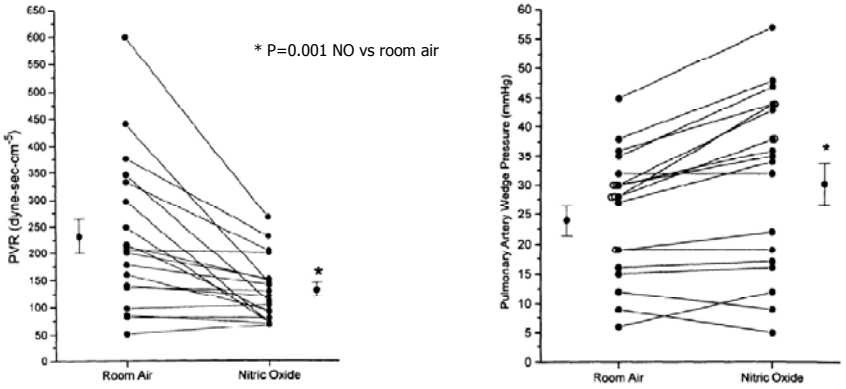
Drug	N	Centers	Start	End	Duration	Primary endpoint	Secondary endpoints
UT15 C **Freedom C²**	313	73	**Results available 24th August 2011 (press release)**		16 W	6MWD	**TTCW, Borg, DF index, Symptoms, WHO FC, NT-pro-BNP, QOL**
Imatinib **IMPRES (QTI571)**	200	91	**Results available presented at ERS Amsterdam 2011**		24 W	6MWD	**TTCW, haemodynamics, Borg, PK (DDI)**
Macitentan **Seraphin (ACT-064992)**	742	153	**Recruitment completed Results 2012**		Event-driven	TTCW	**6MWD, WHO FC, time to death or hospitalization for PAH**
Riociguat **PATENT (BAY63-2521)**	462	173	**Recruitment completed**		12 W	6MWD	**TTCW, PVR, NT-pro BNP, WHO FC, Borg, QOL**
Selexipag **GRIPHON (ACT-293987)**	670 (1170)	139	**12/2009**	**8/2013**	Event-driven	TTCW	**6MWD, Borg, other secondary & exploratory efficacy endpoints in patients with PAH**

Data obtained using search terms on http://www.clinicaltrials.gov. Accessed April 12th, 2012.

Cardiovascular Effects of Inhaled Nitric Oxide in Patients With Left Ventricular Dysfunction

Evan Loh, MD; Jonathon S. Stamler, MD; Joshua M. Hare, MD;
Joseph Loscalzo, MD, PhD; Wilson S. Colucci, MD

- **N=19 with HF stable on therapy**
- **Invasive haemodynamics (base – NO 80 ppm)**



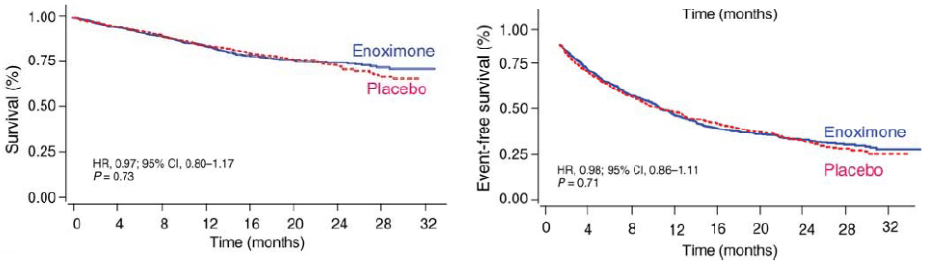
Change in PVR was accounted for by the combination of an increase in PCWP and a decrease in CO with no effect on mPAP!

Adapted from Loh E, et al. *Circulation* 1994;90:2780–5.

PDE-3 inhibition in Heart Failure

- **Very good rationale, as strong as for the use of targeted therapy in Group II pulmonary hypertension**
- **3 drugs tested in RCTs milrinone[1], vesnarinone[2] and enoximone[3-4]**

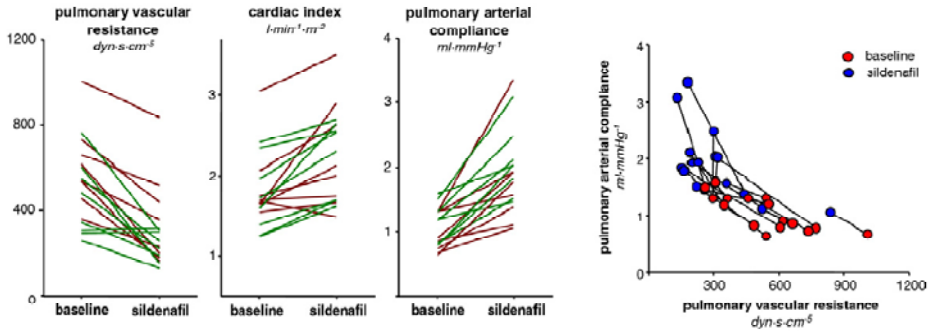
The ESSENTIAL trial [4] (n=1854)



1. Packer M et al. N Engl J Med 1991;325:1468–1475. 2. Cohn JN et al. N Engl J Med 1998; 339 :1810–1816. 3. Uretsky et al. Circulation 1990;82:774–780. 4. Metra M et al. Eur Heart J 2009 30, 3015–3026

Acute effects of sildenafil on PH in HF

N=22 with PVR >200 vs 24 matched controls
Before and after single dose of sildenafil 40 mg
"Reversibility" testing with PGE_1 in patients
Does sildenafil uncover more reversibility ?



Non reversible on PGE_1
Reversible on PGE_1

Melenovski V, et al. *J Am Coll Cardiol* 2009;54:595–600.