Case-based discussion of Pulmonary hypertension Due to left heart disease

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## Guidelines on PH - LHD

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group(s)</th>
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<td>PAWP &gt; 15 mmHg</td>
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<td>Isolated post-capillary PH</td>
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<td>(Ipc-PH)</td>
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<td>Combined post-capillary and pre-capillary PH (Cpc-PH)</td>
<td>DPG ≥7 mmHg and/or PVR &gt;3 WU</td>
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*Humbert M et al, EHJ 2015*
Pulmonary hypertension associated with left heart disease

Is it always so straight-forward.....?
Case 1: Mr J-C N, 67 years

- Heavy smoker (45 PY), with GOLD I COPD (FEV1 70% predicted)
- High blood pressure controled by Losartan and paroxystic AF anticoagulated
- Alcool abuse
- Obstructive sleep apnea well treated
- Tumor of the pharynx needing investigation
- Progressive dyspnea until stage 3 in 2014 with progressive edema ans ascites
- NT-proBNP 23’000 nL
- 6MWD 260 m
Case 1: Mr J-C N, years

Excentricity index 0.53
Notched pulmonary flow
Mitral flow A>E

Max TR vel: 4.5 m/s
RV/RA gradient: 81 mmHg
Case 1: Mr J-C N, years

AP: 100/50-67 mmHg
PAWP: 35 mmHg
DPG: 15 mmHg
RAP: 24 mmHg
CI: 2.8 L/min/m²
PVR: 5.9 WU

Cpc-PH
Pulmonary hypertension associated with left heart disease: Can we rely on PCWP?

Single center study, N = 3926 subjects with PH and simultaneous right and left heart catheterization.

Should we perform a left heart cath in patients with PCWP >15 mmHg?

ROC curve for LVEDP > 15 mmHg:
- Sens: 94.2%
- Spec: 60.2%

Case 1 : Mr J-C N, years

LVEDP 35 mmHg, well matched with PAWP

LVEDP equalizes RVEDP ?!
Case 1: Mr J-C N, years

Differential diagnosis of LVEDP / RVEDP equalization

Constrictive pericarditis?

- PAP very high, no systolic interference, no dissociation between PAWP and LVEDP
- No pattern of constrictive pericarditis at echo

Our hypothesis

- In PH, RV filling pressure rises in response to RV adaptation through Starling mechanism leading to hypervolemia
- Septal interference occurs when RVEDP reaches LVEDP, with D-shape septal deformation at echo.
- Pre-capillary PH with severe right heart decompensation and hypervolemia could increase RVEDP and hence LVEDP and PAWP >15mmHg.

→ Restoration of normo-volemia should also restore normal PAWP-LVEDP.
Case 1: Mr J-C N, years, after 14.5 kg weight loss

PAP: 80/30-47 mmHg  PAWP: 13 mmHg  RAP: 9 mmHg  CI: 3.1 L/min/m²  PVR: 5.2 WU

Precapillary PH after deloading!
Case 1: Mr J-C N

No element for severe lung disease

No element for left heart disease after volume deloading

No element for CTEPH at V/Q scan

Final diagnosis: idiopathic PAH

Combination therapy with ERAs and PDE5i

Follow-up:
- NYHA 2 at six months, NT-proBNP 5800 ng/L, 6MWD: 380 m
- Finally pharynx neoplasm on radiotherapy
Guidelines on PH - LHD

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1” any pre-capillary PH with severe RV/LV interference ??

Humbert M et al, EHJ 2015
Conclusions case 1

- Elevated PAWP alone may not be enough to incriminate intrinsic left heart disease in the mechanism of pulmonary hypertension

- In case PAWP does not reflect clinical judgement, left heart catheterization may be necessary to confirm left heart involvement

- Left heart cath alone may be not enough for understanding and simultaneous right and left heart cath may help

- Severe ventricular interdependence may be a cause of misclassification of group 2 pulmonary hypertension

- Right / left interference is a possible mechanism of elevated PAWP only in severely hypervolemic patients and needs to be demonstrated by volume deloading
Case 2 : Mr PS, 49 years

The difficult management of Cpc-PH
Case 2 : Mr PS, 49 years

- Former heavy smoker with dyslipidemia
- Large infero-postero-lateral myocardial infarction in 2006 → late lary PCI of a dominant circonflex coronary artery
- NSTEMI in 2011 with LAD PCI
- Progressively severe heart failure becoming end-stage in 2014
  - Persistent NYHA class 3 despite optimal therapy
  - Peak VO2 : 12.6 mL/kg/min; VE/ VCO2 slope 43
  - Progressive kidney failure (cratinine 140)

Hospitalization for pre-heart transplantation listing investigations
Echocardiography
Initial right heart catheterization

No significant lung disease on PFT / chest CT
No CTEPH on scintigraphy
Well treated obstructive sleep apnea

AP : 85/38-54 mmHg
PAWP : 26 mmHg
TPG : 28 mmHg
DPG : 12 mmHg
CO : 4.5 L/min
PVR : 6.2 WU

Cpc-PH
Very high risk for heart transplantation

TPG > 14 mmHg or PVR > 3 = relative CI to heart transplantation

Costard-Jackle A, JACC 1992

Mehra et al, ISHLT guidelines 2006 and 2016, JHLT 2006 and 2016
Vasoreactivity testing

- Unique to heart transplant candidates evaluation, not validated in standard PH-LHD
- Goal: unload the left ventricle, lower PAWP and assess TPG and PVR reversibility
- Protocol: no standard protocol, most use nitroprusside with SBP > 85 mmHg

61 HTx candidates with TPG > 12 and PVR > 2.5 WU → vasoreactivity testing

29% didn’t achieve reversibility (PVR < 2.5 WU and TPG < 12 mmHg) → not listed

71% with reversibility
- 1 year post HTx mortality 22%
- 1 year post HTx mortality 14% with no PH (p=ns)

Vasoreactivity testing with Nitroprusside 120 µg/kg/min

BP : 90/60-72 mmHg
AP : 67/30-42 mmHg
PAWP : 17 mmHg
TPG : 25 mmHg
DPG : 13 mmHg
CO : 4.8 L/min
PVR : 5.2 WU

Persistent Cpc-PH
What to do?

<table>
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<tr>
<th>Recommendations</th>
<th>Classa</th>
<th>Levelb</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease)</td>
<td>I</td>
<td>B</td>
<td>396</td>
</tr>
<tr>
<td>It is recommended to identify other causes of PH (i.e. COPD, sleep apnoea syndrome, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD</td>
<td>I</td>
<td>C</td>
<td>396</td>
</tr>
<tr>
<td>It is recommended to perform invasive assessment of PH in patients on optimized volume status</td>
<td>I</td>
<td>C</td>
<td></td>
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<td>Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH centre for a complete diagnostic workup and an individual treatment decision</td>
<td>IIa</td>
<td>C</td>
<td></td>
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<tr>
<td>The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation</td>
<td>III</td>
<td>C</td>
<td>396</td>
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<tr>
<td>The use of PAH-approved therapies is not recommended in PH-LHD</td>
<td>III</td>
<td>C</td>
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Optimal therapy
Limitations by hypotension
No COPD, no PE, no CTEPH
OSA already treated

Optimal volume status

Individual treatment decision

Humbert M et al, EHJ 2015
Pulmonary hypertension associated with left heart disease:

Superimposed pulmonary vascular disease

- ↑ ET-1 production
- ↑ ET-1 rec A and B
- Impaired NO-dependent vasodilation
- Decreased eNOS activity

- Smooth muscle cells constriction
- Smooth muscle cells proliferation
- Vascular remodelling
- Superimposed component of pulmonary vascular disease to passive PH, defined as mixed PH.

Treatment of PH-LHD with specific PAH therapy:

Risk of cardiogenic pulmonary edema

19 patients with stable HF on therapy

Inhaled NO (80 ppm) during invasive HD

* P=0.001 NO vs room air

Loh E. Circulation. 1994;90:2780-2785
**Treatment of PH-LHD with specific PAH therapy:**

**Trials with ERAs and prostacyclins**

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<table>
<thead>
<tr>
<th>Drug, year [ref.]</th>
<th>Study acronym/identifier</th>
<th>Subjects n</th>
<th>Patient characteristics</th>
<th>Design</th>
<th>Primary end-point</th>
<th>Key results</th>
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<tr>
<td><strong>Epoprostenol 1996 [51]</strong></td>
<td>FIRST</td>
<td>471</td>
<td>Severe heart failure, WHO FC IIIb-IV</td>
<td>1:1 randomisation Event-driven Mean dose 4 ng·kg⁻¹·min⁻¹</td>
<td>Survival</td>
<td>Early termination (trend to decreased survival in treated group)</td>
</tr>
<tr>
<td><strong>Bosentan 2002 [50]</strong></td>
<td>ENABLE</td>
<td>1613</td>
<td>Severe heart failure, WHO FC IIIb-IV</td>
<td>1:1 randomisation 18-month duration 125 mg twice daily</td>
<td>Mortality and hospital stays</td>
<td>No effect Early risk of worsening heart failure necessitating hospitalisation due to fluid retention with treatment</td>
</tr>
<tr>
<td><strong>Bosentan 2005 [49]</strong></td>
<td>REACH-I</td>
<td>370</td>
<td>Severe heart failure, WHO FC IIIb-IV</td>
<td>1:1:1 randomisation 26-week duration 500 mg twice daily via rapid or slow infusion</td>
<td>Change in clinical status</td>
<td>No effect Early termination (safety concerns)</td>
</tr>
<tr>
<td><strong>Darusentan 2002 [56]</strong></td>
<td>HEAT</td>
<td>179</td>
<td>Chronic heart failure, WHO FC III</td>
<td>1:1:1 randomisation 3-week duration Doses of 30, 100 and 300 mg daily</td>
<td>Haemodynamics (change in PAWP/cardiac index)</td>
<td>Increased cardiac index No change in PAWP</td>
</tr>
<tr>
<td><strong>Darusentan 2004 [52]</strong></td>
<td>EARTH</td>
<td>642</td>
<td>Chronic heart failure, WHO FC II-IV</td>
<td>1:1:1:1 randomisation 6-month duration Doses of 10, 25, 50, 100 and 300 mg</td>
<td>LVEF changes by MRI and clinical events</td>
<td>No effect</td>
</tr>
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Melody-1 closed, results not released yet

*Farber H and Gibbs S, ERR 2015*
And PDE-5 inhibitors?

Safety

• No major side effects in patients with Sildenafil (No death, No increase in hospitalisations for acute heart failure), no increase in PCWP, more headaches, more flushes

Efficacy

Guazzi M et al. JACC 2007; 50 : 2136-44


Wu X, Eur J Heart Fail 2014

Patient started on progressive doses of Sildenafil under tight clinical control
Hemodynamics on Sildenafil 3 x 20 mg /day, at 4 months

AP: 47/22-30 mmHg    PAWP: 18 mmHg    TPG: 12 mmHg    DPG: 4 mmHg    CO: 4.8 L/min    PVR: 2.4 WU

Patient listed for heart transplantation
Acute heart failure at 9 months

Role of sildenafil in acute decompensation?

What to do now?
Role of Sildenafil in acute decompensation?

Acute HD effect of Sildenafil

Ghofrani et al, JACC 2004

No more HD effect after 6 months

Guazzi et al, Circulation 2011
What to do now?
Hemodynamics under LVAD assistance

AP: 35/15-22 mmHg
PAWP: 9 mmHg
CO: 5.5 L/min
PVR: 2.5 WU

Is LVAD the best therapy for cpc-PH?
Effect of LVAD on pulmonary haemodynamics

But ad odd with:

- Cost (~150'000 CHF)
- 2 years survival 60-78%
- Complications
  - bleeding
  - thrombosis
  - infections

Patel C, JHLT 2014.

Kutty R et al, Eur J Cardiothor Surg 2013
Conclusions case 2

Cpc-PH is a rare complication of heart failure, probably especially in severe HF.

The mainstay of therapy is optimization of HF therapy (inotropes?), volume optimization and co-morbidities (COPD, OSA) treatment.

PAH-specific therapy is not recommended in cpc-PH.

- Lack of evidence
- Potentially harmful

Particular situations (like bridging to HTx candidacy) may require particular measures.

- PAH specific therapy only in expert centers
- LVAD therapy to be considered