Role of Imaging in Pulmonary Hypertension

Management of residual pulmonary hypertension in patients with prosthetic valve

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Onasis Cardiac Surgery Center
Pulmonary Hypertension
Define Lesion

Mean PAP > 25 mmHg
PVR ≥ 3 Wu

Post-Capillary PH

MV Disease

AoV Disease

PCWP > 15 mmHg
MVR - Residual PH
real life case

RV-RA PG: 79 mmHg
Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation.
Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation.
Pulmonary Hypertension in Patients Undergoing TAVR

Brunilda Alushi. J Am Coll Cardiol Img 2018
Persistence of Severe PAH After TAVR
Incidence and Prognostic Impact

A total of 990 consecutive patients were enrolled in 6 high-volume centers and analyzed.

Patients Divided Into 3 Groups According to PH:
- **Group 1**: sPAP, <40 mm Hg
- **Group 2**: sPAP, 40–60 mm Hg
- **Group 3**: sPAP, ≥60 mm Hg

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (346 Patients)</th>
<th>Group 2 (426 Patients)</th>
<th>Group 3 (226 Patients)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA III–IV, n (%)</td>
<td>242 (70)</td>
<td>315 (74)</td>
<td>191 (88)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF &lt;30%, n (%)</td>
<td>24 (7)</td>
<td>34 (8)</td>
<td>40 (20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>69 (20)</td>
<td>93 (22)</td>
<td>70 (32)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

RHC
pre & post LVAD
RA - RV pressure

**Pre LVAD**
- RAP mean: 17 mmHg
- RV: 81 / 17 mmHg

**Post LVAD**
- RAP mean: 13 mmHg
- RV: 53 / 9 mmHg
Pre LVAD

PAP: 70/51/ 59 mmHg
PWCP: 40/39/ 37 mmHg
PVR: 7.3 WU

Post LVAD

PAP: 51/20/ 33 mmHg
PWCP: 14/15/ 12 mmHg
PVR: 4.5 WU
> adenosine 2.5 WU
Hemodynamic algorithm for the diagnosis of a high-risk subgroup of “out-of-proportion” PH.

The pulmonary circulation in Isolated post-capillary (Ipc-PH) & Combined pre-post capillary (Cpc-PH)

Effect of inhaled NO on RV afterload

RV afterload
Histologic analyses of lung specimens. Representative Trichrome stains of lung sections


Table 3—Semiquantitative Morphometric Analysis of Pulmonary Vascular Lesions

<table>
<thead>
<tr>
<th>Vessel Morphology</th>
<th>Postcapillary PH (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TPG ≤ 12 mm Hg (n = 20)</td>
</tr>
<tr>
<td>Vessels with medial hypertrophy, %</td>
<td>50.6 ± 40.6</td>
</tr>
<tr>
<td>No. myocytes/vessel wall, mean</td>
<td>31.3 ± 19.1</td>
</tr>
<tr>
<td>Vessels with intimal fibrosis, %</td>
<td>3.9 ± 7.5</td>
</tr>
<tr>
<td>Vessels with adventitial fibrosis, %</td>
<td>0.6 ± 2.3</td>
</tr>
<tr>
<td>Vessels occluded, %</td>
<td>7.5 ± 23.1</td>
</tr>
<tr>
<td>Patients with plexiform lesions, No. (%)</td>
<td>0</td>
</tr>
</tbody>
</table>

iPAH = idiopathic pulmonary arterial hypertension; TPG = transpulmonary gradient. See Table 1 for expansion of other abbreviations.
Histopathology of pulmonary vessels in PH due to left heart disease

A, Medial hypertrophy with intimal and adventitial proliferation of a small pulmonary artery.
B, Medial hypertrophy with intimal and adventitial proliferation of a small pulmonary vein.
C, Recanalized fibrotic thrombus in arterioles.

Robert Naeije et al. Circ Heart Fail. 2017;10:e004082
PPM following MVR >> Residual PAH

Graphs showing the relationship between indexed mitral valve effective orifice area and systolic PA pressure, and net atrioventricular compliance and systolic PA pressure. The graphs demonstrate a negative correlation with linear regression equations and correlation coefficients.
Impact of prosthesis-patient mismatch on TR & PH following MVR

- At follow-up, the prevalence of fTR ≥ 2+ (57% vs. 22%; p = 0.0001), and PH (62% vs. 24%; p < 0.0001) were significantly higher in patients with PPM.

- On multivariable regression analysis, EOAi (p < 0.0001) and LV ejection fraction (p < 0.0001) were independently associated with PH decrease after MVR.

**Management of pulmonary hypertension in left heart disease**

1. There is no new evidence supporting the use of PAH therapies in PH-LHD, due in part to the absence of studies specifically stratifying patients for PH and/or targeting this specific condition.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</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>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>The use of PAH-approved therapies is not recommended in PH-LHD</td>
<td>III</td>
<td>C</td>
<td>396</td>
</tr>
</tbody>
</table>

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
## Completed RCTs Using Prostanoids and Endothelin Receptor Antagonists in HF

<table>
<thead>
<tr>
<th>Drug/Author Year</th>
<th>Study Acronym (Ref. #)</th>
<th>Patients</th>
<th>Design</th>
<th>Primary Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol Califf 1996</td>
<td>FIRST (31)</td>
<td>n = 471 Severe HF</td>
<td>1:1 randomization event-driven mean dose 4 ng/kg/min</td>
<td>Survival</td>
<td>Early termination (trend to decreased survival in treated group)</td>
</tr>
<tr>
<td>Bosentan Packer</td>
<td>REACH-1 (29)</td>
<td>n = 174 Severe HF</td>
<td>2:1 randomization 26-week duration 500 mg bid</td>
<td>Change in clinical state</td>
<td>Early termination (drug-induced fluid retention in the treated group)</td>
</tr>
<tr>
<td>Kalra 2002</td>
<td>ENABLE (30)</td>
<td>n = 1,613 Severe HF</td>
<td>1:1 randomization 18-month duration 125 mg bid</td>
<td>Mortality + hospital stays</td>
<td>No effect</td>
</tr>
<tr>
<td>Darusentan Lüscher 2002</td>
<td>HEAT (33)</td>
<td>n = 179 NYHA III</td>
<td>3:1 randomization 3-week duration doses of 30, 100, 300 mg</td>
<td>Hemodynamic (changes in PAWP/CO)</td>
<td>Increased CO No change in PAWP</td>
</tr>
<tr>
<td>Anand 2004</td>
<td>EARTH (32)</td>
<td>n = 642 NYHA II–IV</td>
<td>5:1 randomization 6-month duration doses 10, 25, 50, 100, 300 mg</td>
<td>LV changes by MRI + clinical events</td>
<td>No effect</td>
</tr>
</tbody>
</table>
Effect of Nitroglycerin Inhalation on Patients with Pulmonary Hypertension Undergoing Mitral Valve Replacement Surgery

Nitroglycerin inhalation produces a significant reduction in both mean pulmonary artery pressure and pulmonary vascular resistance in patients after mitral valve operations without reducing mean arterial pressure and systemic vascular resistance.

Nurgul Yurtseven et al. Anesthesiology 2003; 99:855–8
The significance of natriuretic peptide in treatment of pulmonary hypertension after mitral valve replacement

- SAP, PAP and PWCP decreased 1 hour after prostaglandin E1 treatment and rebounded after treatment discontinuation.
- PAP & PWCP in the natriuretic peptide group decreased 3 hours after treatment and there was no evidence of hemodynamic rebound.

Nesiritide Acutely Increases Pulmonary and Systemic Levels of NO in Patients With Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Invasive Hemodynamics</th>
<th>Postcapillary PH</th>
<th>$P$ value</th>
<th>Precapillary PH</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>$-10 \pm 7$</td>
<td>.003</td>
<td>$-13 \pm 8$</td>
<td>.002</td>
</tr>
<tr>
<td>RA mean, mm Hg</td>
<td>$-52 \pm 28$</td>
<td>&lt;.0001</td>
<td>$-15 \pm 24$</td>
<td>.08</td>
</tr>
<tr>
<td>PA mean, mm Hg</td>
<td>$-29 \pm 11$</td>
<td>&lt;.0001</td>
<td>$-2 \pm 10$</td>
<td>.54</td>
</tr>
<tr>
<td>PCW mean, mm Hg</td>
<td>$-39 \pm 13$</td>
<td>&lt;.0001</td>
<td>$+10 \pm 106$</td>
<td>.16</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>$+25 \pm 23$</td>
<td>.009</td>
<td>$+15 \pm 20$</td>
<td>.022</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>$-31 \pm 23$</td>
<td>.012</td>
<td>$-9 \pm 11$</td>
<td>.08</td>
</tr>
<tr>
<td>SVR, dynes·s·cm⁻⁵</td>
<td>$-28 \pm 23$</td>
<td>.043</td>
<td>$-23 \pm 16$</td>
<td>.014</td>
</tr>
</tbody>
</table>

Nitric Oxide in Pulmonary Arteries

- Baseline: p=0.010
- 30-minutes: p=0.44
- Total Cohort: p=0.0093

cGMP in Pulmonary Arteries

- Baseline: p=0.0002
- 30-minutes: p=0.0016
- Total Cohort: p<0.0001
Proposed mechanism of enhanced NO production with nesiritide therapy

- Nesiritide binds to natriuretic peptide receptors (NPR) A and B, which activate particulate guanylate cyclase (p-GC).
- P-GC catalyzes the conversion of GTP to cGMP, which then activates ATP-sensitive potassium channels leading to vasodilation.
- Exogenous or endogenous nitric oxide (NO) diffuses into vascular smooth muscle cells and activates soluble guanylate cyclase (s-GC), which also converts GTP to cGMP.
Adjunctive Sildenafil for the Treatment of Pulmonary Hypertension After MVR

Case Report

33 years female
Severe MR
Worsening HF
NYHA III-IV

- RAP: 20 mm Hg,
- RVSP: 130 mm Hg,
- SPAP 120 mmHg,
- Mean PAP 66 mm Hg,
- PWCP: 35 mm Hg mean
- PVR: 6 Wood units.

- After 48 hours of treatment with IV diuretics (torsemide 5 mg/h), nesiritide 0.01 μg/kg/min, + Inhaled nitric oxide;
  + MVR
  - SPAP: 60 mm Hg
  - PVR: 3.6 Wood units.

- After 3 months of treatment with SILDENAFIL 20 mg * 3 times/ daily
  - SPAP: 40 mm Hg
  - PVR: 2 Wood units.

Successful treatment of severe combined post- and precapillary pulmonary hypertension in a patient with idiopathic restrictive cardiomyopathy

Satomi Ishihara. Pulmonary Circulation 2018
ΣΥΜΠΕΡΑΣΜΑΤΙΚΑ

▪ Η παθογένεια και παθοφυσιολογία της παραμένουσας μετά χειρουργικής καρδιακών βαλβίδων Πνευμονικής Υπέρτασης είναι πολυπαραγοντική.

▪ Είναι κλινικά σημαντική διότι υποθηκεύει το προσδόκιμο των ασθενών.

▪ Η αντιμετώπισή της δεν είναι τεκμηριωμένη και σίγουρα δεν είναι μονόδρομος.

▪ Ωφείλουμε ως κλινικοί ιατροί να σταθμίζουμε την συμμετοχή του κάθε παράγοντα στην εμφάνισή της πνευμονικής υπέρτασης και να θεραπεύουμε αναλόγως!!
ΕΥΧΑΡΙΣΤΩ για τη συμμετοχή μου & για την προσοχή σας!!
Right heart catheterisation

- Diagnostic gold standard

Characteristic intracardiac pressure waveforms during passage through the heart:

- RA
- RV
- PA
- PCW

Pressure readings:
- 40 mmHg
- 20 mmHg
# Haemodynamic definitions of pulmonary hypertension

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics*</th>
<th>Clinical group(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>$PAP_m \geq 25$ mmHg</td>
<td>All</td>
</tr>
<tr>
<td>Pre-capillary PH</td>
<td>$PAP_m \geq 25$ mmHg $PAWP \leq 15$ mmHg</td>
<td>1. Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. PH due to lung diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Chronic thromboembolic PH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>$PAP_m \geq 25$ mmHg $PAWP &gt; 15$ mmHg</td>
<td>2. PH due to left heart disease</td>
</tr>
<tr>
<td>Isolated post-capillary PH (Ipc-PH)</td>
<td>$DPG &lt; 7$ mmHg and/or $PVR \leq 3$ WU*</td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Combined post-capillary and pre-capillary PH (Cpc-PH)</td>
<td>$DPG \geq 7$ mmHg and/or $PVR &gt; 3$ WU*</td>
<td></td>
</tr>
</tbody>
</table>

$CO =$ cardiac output; $DPG =$ diastolic pressure gradient (diastolic $PAP - mean~PAWP$); $mPAP =$ mean pulmonary arterial pressure; $PAWP =$ pulmonary arterial wedge pressure; $PH =$ pulmonary hypertension; $PVR =$ pulmonary vascular resistance; $WU =$ Wood units.

*aAll values measured at rest; see also section 7.*

*bAccording to Table 4.*

*Wood Units are preferred to dynes.s.cm$^{-5}$.**

European Respiratory Journal 2015 46: 603-975;
Inhaled Prostacyclin, Nitric Oxide, and Nitroprusside in Pulmonary Hypertension After Mitral Valve Replacement

- Inhaled prostacyclin and NO are effective in the treatment of postoperative PH in patients with MV stenosis undergoing MV surgery.
- Both drugs improve CO and reduce mean PAPA, PVR, and TPG.

High-Risk Mitral Valve Surgery: Perioperative Hemodynamic Optimization with Nesiritide (BNP)

- 14 pts with A) Severe MR
  B) Impaired LV function (EF<50%),
  C) PH (PA systolic > 45 mm Hg).
- Loading dose of 2 mcg/kg,
- Continuous infusion of 0.01 mcg/kg/min IV uptitrated to max 0.03 mcg/kg/min.

![Graph showing changes in pulmonary artery pressures and central venous pressure during treatment with brain-type natriuretic peptide (n = 14). ▲ = pulmonary arterial; ■ = pulmonary capillary wedge pressures; ▲ = central venous pressure.]

<table>
<thead>
<tr>
<th></th>
<th>Baseline BNP</th>
<th>Entry to OR</th>
<th>Before ICU discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>88 (84–92)</td>
<td>81 (76–85)</td>
<td>79 (76–82)</td>
</tr>
<tr>
<td>Cardiac index (L/m²/min)</td>
<td>2.1 (1.9–2.3)</td>
<td>1.9 (1.7–2.2)</td>
<td>2.5 (2.3–2.7)</td>
</tr>
<tr>
<td>PA systolic (mm Hg)</td>
<td>63 (58–66)</td>
<td>38 (34–42)</td>
<td>44 (41–47)</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>30 (27–32)</td>
<td>15 (12–17)</td>
<td>16 (14–18)</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>13 (11–15)</td>
<td>6 (5–8)</td>
<td>8 (7–9)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>86 (82–89)</td>
<td>81 (78–85)</td>
<td>83 (80–85)</td>
</tr>
</tbody>
</table>