Διαγνωστικές και θεραπευτικές προκλήσεις στην πνευμονική υπέρταση με βάση τα τελευταία δεδομένα

Χρόνια θρομβοεμβολική πνευμονική υπέρταση: επεμβατική αντιμετώπιση ή φαρμακευτική αγωγή;

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Chronic thromboembolic pulmonary hypertension (CTEPH)

- CTEPH is symptomatic PH with persistent perfusion defects after 3-6 months of adequate anticoagulation
- CTEPH is a disease with
  - a mechanical component judged amenable to surgery or BPA (obstruction of elastic PA)
  - and variable small vessel disease in non-occluded areas (remodelling in small muscular PA)
Mechanisms of pulmonary hypertension in CTEPH

- Obstruction of proximal pulmonary arteries (main, lobar, segmental) by organized fibrotic clots
- Obstruction of more distal pulmonary arteries (sub-segmental and more distal, up to 3 mm diameter) by fibrotic clots
- Distal pulmonary vasculopathy with histological findings similar to IPAH (thickening of small PA wall from 0.1 to 0.5 mm diameter)

These different lesions may be associated with a highly variable weight in a same patient
CTEPH revised treatment algorithm

CTEPH diagnosis
Continue lifelong anticoagulation

Treatment assessment by an expert CTEPH team

Operable
Pulmonary endarterectomy (treatment of choice)

Non-operable
Targeted medical therapy with or without BPA

Persistent/recurrent symptomatic pulmonary hypertension

1 Multidisciplinary: PEA surgeon, PH expert, BPA interventionalist and radiologist
2 Expert center defined: > 50 PEA, >100 BPA sessions per year
3 BPA without medical therapy can be considered in selected cases

Rationale for PEA

- Complete removal and clearance of PA obstructions
- Reduces pulmonary arterial pressure
- Improve pulmonary perfusion, oxygenation, RV function and dead space ventilation
- Improve *life expectancy and quality of life*

Mayer E, *et al.* *Eur respir Rev* 2010; 19:64-76;
PEA significantly improves the long-term prognosis of CTEPH patients compared with non-operated patients.


Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
Results From an International Prospective Registry

CTEPH Patients

- In-operable 36%
- Operable 64%

57% - Treated with Pulmonary Thromboembolectomy

Patients with predominantly distal disease that is not surgically accessible

PEA contraindicated due to prognostically significant comorbidity

In some centres medical therapy and BPA are initiated concurrently

Patients with persistent or residual PH post-PEA

Patients who are ‘high-risk’ due to extremely poor haemodynamics prior to PEA

When is medical therapy for CTEPH appropriate?

Randomized controlled trials (RCTs) in CTEPH

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Patients (n)</th>
<th>Inoperable / Persistent PH post PEA (%)</th>
<th>Study duration</th>
<th>Primary endpoint</th>
<th>Primary EP met</th>
<th>Secondary EP met</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENEFIT</td>
<td>Bosentan¹</td>
<td>157</td>
<td>72 / 28</td>
<td>16 weeks</td>
<td>6-MWD PVR</td>
<td>No Yes</td>
<td>(TTCW) No</td>
</tr>
<tr>
<td></td>
<td>Sildenafil²</td>
<td>19</td>
<td>53 / 47</td>
<td>12 weeks</td>
<td>6-MWD</td>
<td>No</td>
<td>(PVR) Yes</td>
</tr>
<tr>
<td>CHEST-1</td>
<td>Riociguat³</td>
<td>261</td>
<td>72 / 28</td>
<td>16 weeks</td>
<td>6-MWD</td>
<td>Yes</td>
<td>(PVR) Yes (TTCW) No</td>
</tr>
<tr>
<td>MERIT-1</td>
<td>Macitentan⁴</td>
<td>80</td>
<td>100 / 0</td>
<td>24 weeks</td>
<td>PVR</td>
<td>Yes</td>
<td>(6-MWD) Yes</td>
</tr>
</tbody>
</table>

- 4 RCTs showed beneficial effects of PAH medications on hemodynamics in inoperable CTEPH but only 2 demonstrated an improvement in 6-MWD
- No effect on TTCW
- Only one approved medical therapy (riociguat) for inoperable CTEPH or residual postoperative PH

Comparison of MERIT-1, CHEST-1 and BENEFIT:
Changes in 6MWD for patients with inoperable CTEPH*

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in 6MWD (m) Comparator arm</th>
<th>Change in 6MWD (m) Active arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERIT-1 (week 24)</td>
<td>Placebo including background therapy: 1.0</td>
<td>Macitentan including background therapy: 35.0</td>
</tr>
<tr>
<td>BENEFiT (week 16)²</td>
<td>Placebo: -4.5</td>
<td>Bosentan: 3.7</td>
</tr>
</tbody>
</table>

*Excludes subgroups of patients from CHEST-1 and BENEFIT with persistent/recurrent CTEPH after PEA

Why is important to keep mPAP < 30 mmHg in CTEPH patients

Figure 2. Cumulative survival curves according to the initial $P_{PA}$. Dotted line represents predicted survival among men 40-50 years old.


CTEPH Survival

Figure 1. Kaplan-Meier estimates for patients with CPE based on magnitude of mPAP. ● = nonsurvivors with mPAPs > 30 mm Hg ($n = 13$); ▲ = nonsurvivors with mPAPs < 30 mm Hg ($n = 3$).

Lewczuk et al CHEST 2001; 119:818–823
Comparison of MERIT-1, CHEST-1 and BENEFIT:
Changes in mPAP and PVR for patients with inoperable CTEPH*

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in PVR (WU)</th>
<th>Active arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERIT-1&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>Macitentan including background therapy: -2.6 (-16%)</td>
</tr>
<tr>
<td>CHEST-1&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>Riociguat: -3.2 (-29%)</td>
</tr>
<tr>
<td>BENEFiT&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>Bosentan: -1.6 (-24%)</td>
</tr>
</tbody>
</table>

*Excludes subgroups of patients from CHEST-1 and BENEFIT with persistent/recurrent CTEPH after PEA

Survival from date of diagnosis in not-operated, medically treated and not-treated CTEPH patients

What is Balloon Pulmonary Angioplasty (BPA)?

• BPA is an interventional treatment that uses a balloon catheter to dilate pulmonary stenosis or obstruction.

• BPA was first developed in the field of pediatric cardiology for treating congenital stenotic pulmonary arteries.

• The first attempt to treat inoperable CTEPH case by BPA was performed in 1988.
Balloon Pulmonary Angioplasty (BPA)

Selective PAG  Balloon dilatation  Post BPA
Relation between pulmonary vascular obstruction and pulmonary resistance in APE

Only minor improvement in pulmonary vascular obstruction could significantly decrease PAP.

### The most representative results with BPA in the management of patients with inoperable CTEPH

<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>Pts</th>
<th>Procedures</th>
<th>Baseline mPAP (mmHg)</th>
<th>mPAP post BPA (mmHg)</th>
<th>Mean change (%)</th>
<th>Baseline PVR (WU)</th>
<th>PVR post BPA</th>
<th>Mean change (%)</th>
<th>n of deaths</th>
<th>Mortality/procedures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreassen (2013)</td>
<td>20</td>
<td>73</td>
<td>45±11</td>
<td>33±10</td>
<td>-27</td>
<td>8.8±4.0</td>
<td>5.9±3.6</td>
<td>-33</td>
<td>2/2.7</td>
<td></td>
</tr>
<tr>
<td>Kurzyna (2017)</td>
<td>56</td>
<td>157</td>
<td>50.7±10.8</td>
<td>35.6±9.3</td>
<td>-30</td>
<td>10.3±3.7</td>
<td>5.9±2.8</td>
<td>-43</td>
<td>3/1.9</td>
<td></td>
</tr>
<tr>
<td>Velázquez (2016)</td>
<td>21</td>
<td>75</td>
<td>52.4±13</td>
<td>37.8±10</td>
<td>-28</td>
<td>10.4±4</td>
<td>5.5±2</td>
<td>-47</td>
<td>1/1.3</td>
<td></td>
</tr>
<tr>
<td>Olsson (2017)</td>
<td>56</td>
<td>266</td>
<td>40±12</td>
<td>33±11</td>
<td>-18</td>
<td>7.4±3.6</td>
<td>5.5±3.5</td>
<td>-26</td>
<td>1/0.4</td>
<td></td>
</tr>
<tr>
<td>Mizoguchi (2012)</td>
<td>68</td>
<td>255</td>
<td>45.4±9.6</td>
<td>24±6.4</td>
<td>-47</td>
<td>11.8±4.6</td>
<td>4.1±1.9</td>
<td>-65</td>
<td>1/0.4</td>
<td></td>
</tr>
<tr>
<td>Kimura (2016)</td>
<td>67</td>
<td>405</td>
<td>39.3±11.0</td>
<td>20.0 ± 4.2</td>
<td>-49</td>
<td>9.7 ± 6.8</td>
<td>3.4±1.5</td>
<td>-65</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>Inami (2016)</td>
<td>103</td>
<td>350</td>
<td>41</td>
<td>21</td>
<td>-49</td>
<td>8.7</td>
<td>2.7</td>
<td>-69</td>
<td>1/0.3</td>
<td></td>
</tr>
<tr>
<td>Ogo (2016)</td>
<td>80</td>
<td>385</td>
<td>42±11</td>
<td>25±6</td>
<td>-40</td>
<td>11±5.3</td>
<td>5.1±2.3</td>
<td>-54</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>Kawakami (2016)</td>
<td>97</td>
<td>500</td>
<td>45.1±10.8</td>
<td>23.3±6.4</td>
<td>-48</td>
<td>12±5.7</td>
<td>3.9±1.9</td>
<td>-68</td>
<td>4/0.8</td>
<td></td>
</tr>
<tr>
<td>Aoki (2017)</td>
<td>84</td>
<td>424</td>
<td>38 ± 10</td>
<td>25 ± 6</td>
<td>-34</td>
<td>7.3 ± 3.2</td>
<td>3.8±1.0</td>
<td>-45</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>Ogawa (2017)</td>
<td>308</td>
<td>1408</td>
<td>43.2±11.0</td>
<td>24.3±6.4</td>
<td>-44</td>
<td>10.7±5.6</td>
<td>4.5±2.8</td>
<td>-58</td>
<td>8/0.6</td>
<td></td>
</tr>
</tbody>
</table>

mPAP -15...-7 mmHg  
PVR  -5... -2 WU

mPAP -21...-13 mmHg  
PVR  -8... -3.5 WU

More powerful results with BPA

Medical Therapy and Balloon Angioplasty for Inoperable Chronic Thromboembolic Pulmonary Hypertension: A Systematic Review and Meta-analysis

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Forest plot for haemodynamic outcomes of observational studies on medical therapy and BPA for CTEPH (A) mPAP, (B) PVR.
Efficacy and safety of BPA: The 1st Multicenter Registry

308 patients, 1408 procedures, 7 institutions

Figure 2. Long-term survival after balloon pulmonary angioplasty (BPA). A, Survival from the initial BPA procedure in all registry patients (n=308). B, Survival from the last BPA procedure in patients for whom BPA was terminated (n=249).

Figure 6. Balloon pulmonary angioplasty (BPA) results from a multicenter registry. (Cited from Ogawa A, et al.43) Parameters before BPA (n=308), immediately after final BPA (n=249), and at follow-up (n=196) were compared. World Health Organization functional class (WHO FC, A), mean pulmonary arterial pressure (mPAP, B), cardiac index (CI, C), and pulmonary vascular resistance (PVR, D) were significantly improved immediately after final BPA, and the improvement was maintained at follow-up.

Ogawa et al. Circ Cardiovasc Qual Outcomes. 2017;10
Long term survival after BPA at Okayama medical center (Nov 2004 – Mar 2017, n=329)

- In hospital death: 8 cases
- Deaths during follow up: 17 cases
  - Suicide: 4 cases
  - Malignancy: 3 cases
  - Pneumonia: 2 cases
  - Right heart failure: 2 cases
  - Respiratory failure: 1 case
  - Myocardial infarct: 1 case
  - Others: 4 cases

Patients at risk: 329 276 237 193 128 81 47 8 3
Kaplan-Meier curves showing outcome from diagnosis.

5 lesion types are recognized in CTEPH patients

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description of Type</td>
<td>Ring-Like Stenosis</td>
<td>Web</td>
<td>Subtotal</td>
<td>Total Oclusion</td>
<td>Tortuous</td>
</tr>
<tr>
<td>Number, n</td>
<td>248</td>
<td>1235</td>
<td>342</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td>Bifurcation lesion, n (%)</td>
<td>248 (100)</td>
<td>1092 (88.4)</td>
<td>301 (88.0)</td>
<td>61 (91.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Distribution (upper/middle or lingular/lower)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right lung, n</td>
<td>103/7/46</td>
<td>215/172/367</td>
<td>64/42/118</td>
<td>6/16/24</td>
<td>5/3/9</td>
</tr>
<tr>
<td>Left lung, n</td>
<td>29/0/63</td>
<td>61/22/398</td>
<td>13/6/99</td>
<td>0/2/19</td>
<td>6/1/20</td>
</tr>
<tr>
<td>Used balloon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size, mm</td>
<td>4.0 (1.5–6)</td>
<td>3.5‡ (1.5–8)</td>
<td>3.5‡ (1.25–7)</td>
<td>4.0 (1.5–8)</td>
<td>2.0‡ (1.5–4.5)</td>
</tr>
<tr>
<td>Inflated pressure, atm</td>
<td>12 (2–22)</td>
<td>8‡ (2–18)</td>
<td>10 (2–20)</td>
<td>12 (3–18)</td>
<td>10 (2–16)</td>
</tr>
<tr>
<td>Success, n (%)</td>
<td>248 (100)</td>
<td>1219 (98.7)</td>
<td>236§ (86.5)</td>
<td>35 (52.2)</td>
<td>28 (63.6)</td>
</tr>
<tr>
<td>Complication, n (%)</td>
<td>4 (1.6)</td>
<td>27 (2.2)</td>
<td>53* (15.5)</td>
<td>4 (6.0)</td>
<td>19 (43.2)</td>
</tr>
<tr>
<td>Type of complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon injury, n</td>
<td>3</td>
<td>7</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wire injury/perforation, n</td>
<td>0</td>
<td>12</td>
<td>41</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Dissection of vessels, n</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are presented as the median and the range. DRD indicates distal reference diameter; %DS, percent diameter stenosis; MLD, minimal lumen diameter; PRD, proximal reference diameter; QVA, quantitative vascular analysis; and RD, reference diameter.
Tailored management of CTEPH according to the type of lesions

Proximal fibrotic lesions:
Main, lobar, segmental pulmonary arteries

Distal fibrotic lesions:
Sub-segmental and more distal PA up to 1.5 mm diameter

Small vessels disease (similar to those found in IPAH):
Thickening of small PA wall (0.1 to 0.5 mm diameter)

Med. Rx. (Riociguat)
Combining different treatment modalities in CTEPH

• **Current modalities for the treatment of CTEPH**
  - Surgery (PEA)
  - Angioplasty (BPA)
  - Medical therapy (PAH-targeted drugs: riociguat / others?)

• **Combined modalities**
  - PEA + medical treatment
    - before surgery (“bridging therapy” ??)
    - after surgery (“persistent PH”)
  - BPA + medical treatment
  - PEA + BPA (+ medical treatment?)
    - ”rescue BPA” after surgery
    - “hybrid approach”
  - Combination of PAH-targeted medications
CTEPH IS A CURABLE DISEASE WITH MAINLY A MECHANICAL COMPONENT AND THE SOLUTION IS INTERVENTION TO RESTORE BLOOD FLOW