Clinical and Hemodynamic Features of Scleroderma Patients with Pulmonary Venous Hypertension Versus Pulmonary Arterial Hypertension

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Disclosures

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Background

• Pulmonary arterial hypertension (PAH) is seen in up to 12% of patients with Systemic Sclerosis (SSc.)
• PAH is a leading cause of scleroderma-related deaths.
• Pulmonary hypertension (PH) in SSc patients can also occur due to pulmonary venous hypertension or due to lung disease.

World Health Organization (WHO) Classification of Pulmonary Hypertension (PH)

Based on shared pathologic and clinical features, as well as therapeutic approach.

– Group 1 – Pulmonary Arterial Hypertension (PAH)
  • mPAP ≥ 25 mmHg
  • PCW ≤ 15 mmHg
– Group 2 – PH owing to left heart disease, pulmonary venous hypertension (PVH)
– Group 3 – PH owing to lung diseases or hypoxemia, (PH-ILD)
– Group 4 – PH owing to chronic thromboembolic disease.
– Group 5 – PH owing to unclear multifactorial mechanisms.

Objective – Compare PVH and PAH

• The objective of this analysis is to describe SSc patients with PVH (WHO 2) and compare them with SSc patients with PAH (WHO 1)
Pulmonary Hypertension Assessment Registry Of Scleroderma (PHAROS)

- Multicenter, observational, prospective, longitudinal cohort study of patients at high risk of developing PH and those who have newly diagnosed PH.
- Specific Aims
  1. To understand the natural history of pulmonary hypertension in systemic sclerosis.
  2. To evaluate the course of disease progression in patients with systemic sclerosis and early pulmonary hypertension.
  3. To collect blood and cells for specific markers of PHT to test for surrogate markers of PHT and PHT progression.

Entry Criteria

Patients >18 years of age with a diagnosis of SSC

- **Pre-PH**: DLCO <55% predicted or FVC/DLCO ratio >1.6 or PASP on echocardiogram > 40 mmHg
- **PH**: diagnosed by RHC (mean PAP ≥ 25 mmHg) within 6 months.

Study Design

Observational Study

1. **Baseline**: demographic, clinical and laboratory data including antibodies, BNP, PFTs, Echo, and 6 minute walk test
2. **Biannual**: patient questionnaires, 6 minute walk, medication/hospital, clinical history
3. **Yearly**: PFTs, echo, BNP, labs
4. **RHC**: performed as clinically indicated according to local protocols

Methods

- Patients in PHAROS with PH (mPAP ≥ 25 mmHg) were categorized by WHO criteria.
- Patients with a normal PCWP≤15 mmHg on initial RHC were classified as Group 1.
- An elevated PCWP>15 mmHg defined Group 2 patients.
- Patients with ILD as defined by a forced vital capacity (FVC) <65% predicted and/or significant fibrosis on chest CT with a normal PCWP were included in group 3, and are not included in this analysis.
- Descriptive and univariate analysis with Mann-Whitney and Fischer-Exact tests was performed.

Results

- As of June 2011, there were 197 patients in the PHAROS database with Pulmonary Hypertension
  - PAH/WHO 1 = 127 – 15 of whom entered PHAROS as pre-PH
  - PVH/WHO 2 = 32 – 9 of whom entered PHAROS as pre-PH

Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>PAH (n=127)</th>
<th>PVH (n=32)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (median, range)</td>
<td>61.00 (34, 84)</td>
<td>55.50 (35, 78)</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Disease Duration</strong> (median, range)</td>
<td>7.32 (0.02, 43.2)</td>
<td>6.9 (0.2, 19.2)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>84% ♂</td>
<td>70% ♂</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td>83% Caucasian</td>
<td>60% Caucasian</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>SSc Subtype (%)</strong></td>
<td>72% Limited</td>
<td>41% Limited</td>
<td>0.003</td>
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</table>

- 9% Black
- 8% Other
- 27% Black
- 13% Other
Autoantibodies

<table>
<thead>
<tr>
<th></th>
<th>PAH (n=120)</th>
<th>PVH (n=30)</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>Anti-centromere</td>
<td>44 (37%)</td>
<td>6 (20%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Anti-Scl70</td>
<td>8 (7%)</td>
<td>6 (20%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Isolated nucleolar</td>
<td>27 (23%)</td>
<td>7 (23%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Other</td>
<td>41 (34%)</td>
<td>11 (37%)</td>
<td>0.67</td>
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</table>

Baseline BNP

<table>
<thead>
<tr>
<th></th>
<th>PAH (n=51)</th>
<th>PVH (n=14)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Range)</td>
<td>164 (14, 5534)</td>
<td>281 (0, 996)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Echocardiographic Data

<table>
<thead>
<tr>
<th></th>
<th>PAH (n=118)</th>
<th>PVH (n=27)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic PAP - mmHg</td>
<td>60 (31, 46)</td>
<td>49 (17, 38)</td>
<td>0.005</td>
</tr>
<tr>
<td>Ejection Fraction - %</td>
<td>60 (45, 82)</td>
<td>60 (25, 77)</td>
<td>0.49</td>
</tr>
<tr>
<td>Left Atrial Diameter – cm</td>
<td>3.7 (2.4, 6.3)</td>
<td>4.1 (2.1, 5.2)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Left Atrial Diameter

- The left atrial diameter (LAD) was not always increased in PVH patients.
- PVH: LAD was ≥ 4.0 cm on echo in 13/32 (40.6%)
- PAH: LAD was ≥ 4.0 cm on echo in 50/127 (39.3%)
- There was no correlation between the LAD and PCWP or PCWP and BNP.

Pulmonary Function Test Data

<table>
<thead>
<tr>
<th></th>
<th>PAH (n=114)</th>
<th>PVH (n=26)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced Vital Capacity – % predicted, median (range)</td>
<td>81.7 (43, 123)</td>
<td>65.4 (27, 99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diffusion Capacity - % predicted, median (range)</td>
<td>38.9 (14, 98)</td>
<td>36.5 (13, 97)</td>
<td>0.40</td>
</tr>
<tr>
<td>FVC/DLCO Ratio</td>
<td>2.02 (0.95, 6.08)</td>
<td>1.69 (0.46, 2.96)</td>
<td>0.03</td>
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Right Heart Catheterization Data

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<thead>
<tr>
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<th>PVH (n=32)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Artery Systolic Pressure – mmHg</td>
<td>55 (30, 119)</td>
<td>46 (36, 87)</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean PAP – mmHg</td>
<td>35 (25, 75)</td>
<td>32.5 (26, 60)</td>
<td>0.11</td>
</tr>
<tr>
<td>PCWP – mmHg</td>
<td>10 (2, 17)</td>
<td>21 (16, 35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR – dyn·s·cm⁻⁵</td>
<td>368 (106, 999)</td>
<td>189.3 (56, 828)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Overlap

Some PAH pts had evidence of PVH on either repeat RHC or on exercise RHC.
- 8/34 Group 1 patients who underwent repeat RHC were seen to have a PCWP >15.
- 8/22 Group 1 patients undergoing exercise RHC the PCWP was ≥18.

Conclusions

- PVH pts differ from PAH pts in several ways. They are more likely to be:
  - African American
  - Male
  - Diffuse cutaneous Subtype
  - anti-Scl70 positive
  - Slightly younger

Conclusions

- In SSc, an increased pulmonary artery pressure is not always pulmonary \textit{arterial} hypertension.
- The RHC is critical in making this diagnosis since the echo can not determine the PCWP.
- The PVR is useful in distinguishing the groups.
- There is evidence for some degree of PVH in a significant percentage of patients with PAH.
- How these categorizations affect the prognosis of PH patients will be further studied in the long-term follow-up of the PHAROS cohort.