Detection and Management of Pulmonary Hypertension in Connective Tissue Disease

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Disclosures

CSL Behring: Research
Kinemed: Research
Medimmune: Research
Novartis: Consultant/Research
Sanofi Aventis: Research
United Therapeutics: Research/Consultant

FDA unapproved drugs and off-labeled drug use will be discussed

INACTIVE
Actelion: Research/Lecture
Amira: Consultant/Research
Asahi-Kasei Pharma Corp: Research
Biogen-Idec: Research
Bristol-Myers-Squibb: Research/Consultant
Eiger Biopharmaceuticals: Research/Consultant
Genzyme: Consultant
Hoffman-La Roche: Research
ImClone: Research/Consultant
Mediquest: Consultant/Research
Millenium: Research
Orion: Consultant
Otsuka: Research/Consultant
Pfizer: Research
Messages of Lecture

• Patients with CTD and scleroderma are at risk to develop pulmonary vascular disease
• Pulmonary Hypertension is a life threatening complication
• Diagnostic studies can detect PH early and provide prognostic information
• Therapy exist that can improve quality of life and perhaps survival

High Prevalence and poor survival
Aggressive therapy of mild disease may improve outcome
What are the Causes of PH?

Vascular Disease
Arteries 500µm
PAH

Parenchymal Disease
PH

Left Heart Disease
PH

PVOD
Emboli
Apnea

Mixed causes occur
Pulmonary arterial hypertension (PAH)
The World Health Organization (WHO) classification of pulmonary hypertension (PH), is defined:

A mean pulmonary artery pressure (mPAP) ≥25 mmHg with a pulmonary vascular resistance (PVR) ≥3 Wood units....

Absence

- Significant left-sided disease (pulmonary capillary wedge pressure ≤15 mmHg)
- Parenchymal lung disease (FVC <60%; mPAP<35 mmHg at rest)
- Chronic thromboembolic disease.

As a consequence of the high prevalence of both left heart disease and interstitial lung disease in CTD, the accurate diagnosis of PAH is particularly challenging.
Right heart catheterization (RHC)

- RHC should be performed in all cases in which PAH is suspected
- RHC confirms the presence of PH
- RHC enables a specific diagnosis of PAH to be established, and eliminates other cardiac (post-capillary) and the degree of right heart dysfunction.
Pulmonary Hypertension in CTD

- Scleroderma (8-12%)
  - Annual incidence of PAH in patients with systemic sclerosis of 0.61 per 100 patient years.
- Systemic Lupus Erythematosus (0.5-14%)
- MCTD (? : Survey RHC 3.4%)
- Myositis (?: Anti-synthetase RHC: 7.9%)
- Rheumatoid Arthritis (? Low: ECHO 27.5%)
- Sjogrens syndrome (?Low: ECHO 23%)

Hachulla Arth Rheum 2005 & 2009
Hass C. Lupus 2008; Gunnarson Rheumatology 2013
Kobak autoimmune dis 2014; Keser Scan J Rheum 2004
Mortality Data

- **Surveys of survival SSc-PAH:**
  - 1 year: 81-90%
  - 2 year: 78%
  - 3 year: 52-56%

- **Prognostic factors:**
  - Age, male, functional class, pulmonary vascular resistance, stroke volume, pulmonary compliance, measures of **right heart** function, GFR
Compared to patients with idiopathic PAH (IPAH), patients with CTD-PAH have:

- A higher mortality
- A lower 6-minute walk distance (6MWD)
- Higher B-type natriuretic peptide
- Worse right ventricular function
- More left heart dysfunction
- Lower lung function
- More pericardial disease

876 CTD-PAH vs. 1,935 IPAH in review of 11 RCT

Less effective:
6 minute walk and clinical worsening.

Rhee et al Arth & Rheum 2015
Age (older)
Pulmonary venule involvement
Right ventricular disease (pro BNP)
Left systolic and diastolic disease
Interstitial lung disease (ILD)
Multisystem (co-morbid)
Immune Process: Auto antibodies
• While therapy may be associated with improved survival in PAH compared with historical controls, the prognosis for patients with ILD-associated PH is particularly grim.
  – 1 year survival 82% versus 87%
  – 2 year survival 46% versus 79%
  – 3 year survival 39% versus 64%

Survey over 4 years of 59 patients

Mathai et al A&R 2008
Factors Predicting Outcome

• World Health Organization functional class (WHO FC)symptoms
• The 6MWT is a simple way to measure submaximal exercise tolerance
• Echocardiography
  – The tricuspid annular plane systolic excursion (TAPSE)
• Cardiac magnetic resonance imaging (CMR)

Mathai J. Rheum 2011
Hagger D. Rheumatology 2009
Why Screen?

• High prevalence and poor outcome of PAH scleroderma (30% of deaths)

• Usual presentation NYFC III or IV

Patients identified with SSc-PAH via a screening program have milder disease and superior survival (73% vs. 25%) than those patients who presented with symptomatic disease

Humbert et al Arth Rheum 2011
When to start Screening?

- Late complication (?): 9-14 years
- Scleroderma
  - A study of 78 consecutively diagnosed systemic sclerosis-PAH patients reported the onset of PAH <5 years from the onset of systemic sclerosis in 55% of patients
    - Older at Dx of SSc
    - Same in I-SSc and D-SSc
  
- PAH is almost as common in diffuse skin disease as it is in limited skin disease

Start screening in every patient at first encounter
How to Screen?

Characterize the patients risk factors

- Asymptomatic early in PAH
- Dyspnea and fatigue are nonspecific
- Multisystem disease may mask PAH
- Physical Examination challenging to detect PAH
- Exclude other causes of symptoms
Risk Factors and predictors of PAH in scleroderma

- Late age onset of scleroderma
- Limited scleroderma
- Severe Raynaud phenomenon
- Numerous telangiectasias
- Low Diffusing Capacity
- Pro-brain natriuretic peptide (NT- proBNP)
- Auto-antibody associations (nucleolar)
  - Anti-Centromere
  - Anti-U1 RNP
  - Anti- fibrillarin (Anti-U3 RNP)
  - Anti-Th/To
  - Anti- B23
Risk Factors: Age

• 274/790 (38.6%) patients
  – 114 mild (ERVSP 36-45 mmHg)
  – 66 moderate (ERVSP 46-55 mmHg)
  – 92 severe (ERVSP >56 mmHg)

• 52% increase in risk for every 10 years of age at disease onset

• RR = 2.30 (95% CI; 1.32 to 3.99) for late age onset (>60 years versus < 60 years)

Schachna et al. Chest 2003
Pulmonary Function Testing (PFT)

Retrospective Case control study:
106 patients with PAH versus 106 without PAH

- Patients with PAH had a mean DLCO of 52% of predicted 4.5 years prior to the diagnosis of PAH.

- Ratio of forced vital capacity to diffusion capacity (%FVC/%DLCO) > 2.0 by PFT.

Steen V et al Arthritis Rheum 2003
Diffusing Capacity

A decreasing DLCO is an excellent predictor of the subsequent development of isolated PH in scleroderma.

A DLCO of >80% may exclude PAH

Steen V et al A&R 2003

Hachulla E Chest 2009
Relationship between mean pulmonary pressures (mPAP) on cardiac catheter and corrected DLCO in 85 SSc patients without significant pulmonary fibrosis.

D. Mukerjee et al. Rheumatology 2004;43:461-466
ECHO: Screening for PH/PAH

- ECHO is the most effective screening tool

<table>
<thead>
<tr>
<th>Peak tricuspid regurgitation velocity (m/s)</th>
<th>Presence of other echo ‘PH signs’a</th>
<th>Echocardiographic probability of pulmonary hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.8 or not measurable</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>≤2.8 or not measurable</td>
<td>Yes</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2.9–3.4</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>2.9–3.4</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>&gt;3.4</td>
<td>Not required</td>
<td>High</td>
</tr>
</tbody>
</table>

Galie et al  Euro Heart Jour 2015
Relationship between systolic pulmonary pressures on cardiac catheter and echocardiographically determined tricuspid gradient (echo TG) in 137 patients.

$R^2 = 0.4515$

D. Mukerjee et al. Rheumatology 2004;43:461-466
<table>
<thead>
<tr>
<th>A: The ventricles&lt;sup&gt;a&lt;/sup&gt;</th>
<th>B: Pulmonary artery&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C: Inferior vena cava and right atrium&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle/ left ventricle basal diameter ratio &gt;1.0</td>
<td>Right ventricular outflow Doppler acceleration time &lt;105 msec and/or midsystolic notching</td>
<td>Inferior cava diameter &gt;21 mm with decreased inspiratory collapse (&lt;50 % with a sniff or &lt;20 % with quiet inspiration)</td>
</tr>
<tr>
<td>Flattening of the interventricular septum (left ventricular eccentricity index &gt;1.1 in systole and/or diastole)</td>
<td>Early diastolic pulmonary regurgitation velocity &gt;2.2 m/sec</td>
<td>Right atrial area (end-systole) &gt;18 cm&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>PA diameter &gt;25 mm.</td>
<td></td>
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Galie et al  Euro Heart Jour 2015
Echocardiography (ECHO)

Survey of 681 patients with serial ECHOs

Compare to the group with stable RSVP there was an increased risk of developing PH with increasing per year RVSP estimated by ECHO:

1-1.99 mmHg per year  HR = 1.52 (0.80, 2.89)
2-2.99 mmHg per year  HR = 3.22 (1.70, 6.11)
3-3.99 mmHg per year  HR = 4.24 (2.14, 8.41)
4 plus mmHg per year  HR = 6.54 (4.10, 10.4)
Exercise Studies

- Exercise TTE with >20 mmHg increase in RSVP had RHC confirmation of PH in 81%.

  Steen et al Chest 2008

- Given both the marked age-dependency of “normal” mPAP threshold on exercise and the paucity of robust data supporting its clinical relevance.
Biomarkers: Predicting risk of PH

- Natriuretic peptides
  - brain natriuretic peptide (BNP)
- Endothelin-1
- Uric acid
- Troponin T
- Nitric oxide
- Asymmetric dimethylarginine
- cGMP
- D-dimer
- Serotonin
- Plasma von Willebrand factor
- I CAM
- Anti-beta 2 glycoprotein
- Endoglin

Soluble VEGF receptor 1 (sFlt-1)
Placental growth factor (PIGF)

Are growth factors are potential biomarkers for PH in patients with scleroderma

McMahan Arthr Res Ther 2015

Warwick et al Eur Respir J 2008
N-terminal pro-brain natriuretic peptide (NT-proBNP)

- proBNP levels were significantly higher in SSc patients with PAH (n=68) than in those without PAH (n=41; P=0.0002)

- proBNP was also found to be predictive of survival:
  - For every order of magnitude increase in proBNP levels among patients with PAH, there was a 4-fold increase in the risk of death

Williams MH et al Eur Heart J 2006
Mathai Eur Respir J. 2010
How to Screen?

• Systematic yearly screening
  – ItinerAIR screening algorithm
  – Australian algorithm
  – DETECT algorithm

Hachulla et al Rev Med Interne 2004
Thakkar et al Arthritis Res Ther 2012
Coghlan et al Ann Rheum Dis 2013
ItinerAIR screening algorithm

• All patients with SSc, regardless of symptoms but without severe pulmonary function abnormalities:
  
  – **Echocardiography**: Patients with a peak TR jet velocity of $>3$ meters/second or a peak TR jet velocity of $>2.8$ meters/second accompanied by unexplained dyspnea undergo RHC to confirm the presence of PAH

  False positive rate: 30.7%

Hachulla et al  Rev Med Interne 2004
Hachulla et al  Arthritis Rheum  2009
Australian algorithm

- N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥ 210 pg/ml
- DLCO less than 70% with FVC%/DLCO% of ≥ 1.8
  - Similar sensitivity
  - Higher negative predictive value (NPV)
  - Better Specificity and positive predictive value (PPV)

than the ERS/ESC guidelines

Thakkar et al Arthritis Res Ther 2012
Thakkar et al Arthritis Res Ther 2013
DETECT Study algorithm

- 466 systemic sclerosis patients enriched for an increased risk of PAH (>3 years from diagnosis of systemic sclerosis with DLCO <60%)

- A total 2 step score determines whether right heart catheterization is required:
  - First score based on 6 non-echocardiographic variables
  - Second score based on right atrial area and tricuspid regurgitant velocity is then added

- Less false negatives (missed cases) than an approach using echocardiography alone (4% versus 29%)

Coghlan et al  Ann Rheum Dis 2013
Recommendations

• All patients with scleroderma should be screened for PAH
• Patients with MCTD or CTD with features of scleroderma should be screened
• Screening is not recommended for asymptomatic patients with other CTDs (SLE, RA, Sjogren’s, Myositis)
• PFT with DLCO (high)
• Transthoracic echocardiogram (TTE) (high)
  – Yearly (define group)
  – New signs or symptoms (high)
• NT-proBNP (moderate)
How to Screen?

**ECHO, PFT & HRCT scan**

- eRVSP < 45 mmHg
- DLCO > 55%
- No unexplained dyspnea
- No cardiac disease
- HRCT normal

**Follow**

- eRVSP > 45 mmHg or TV 3.0-3.5 m/sec
- eRVSP 35-40 mmHg with Dyspnea
- DLCO < 55% with normal FVC & TLC
- Declining DLCO (>15-20%)

**Right Heart catheterization**

± Exercise, ± Vasodilator challenge

**Exclude other causes of PH**

- Thromboembolic disease
- Pulmonary venous hypertension (Left heart disease)
- Hypoxemic pulmonary disease (COPD, Sleep anpea, ILD)
Borderline PAH on RHC

• Mean pulmonary arterial pressures of 21-24 mmHg

• A study of 228 patients observed progression to PAH in 31% of such patients at subsequent right heart catheterization

• Patients with borderline pressures require careful monitoring. PAH may occur as early as 14 months.

Valerio et al Arth Rheum 2013
Bae et al Ann Rheum Dis 2012
• While specific therapies for PAH have been studied in randomized clinical trials that have included patients with SSc-PAH, there has been only one study conducted exclusively in patients with SSc-PAH.
  – Before treatment era: 3 year survival 35%
  – Survival rates improved with early intervention

Mathai 2015
Goals of Treatment

- **Functional Class**
  - Improve Class Status I or II

- **Pro BNP**
  - Obtain normal levels

- **Exercise Capacity (6 minute walk)**
  - 3 to 6 month intervals [33 to 24 meters]

- **RV function**
  - Echo (TAPSE) or CMR

- **Cardiopulmonary Hemodynamics**
  - Repeat RHC

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“Goal oriented therapy”
Re-evaluate at 3-6 month intervals: improves outcome

Mortality

6 MWT did not associate with Hemodynamic studies in PAH –Scleroderma
{Sanges et al Ann Rheum Dis 2015}
General Measures

- Supplemental oxygen (90% with rest, exercise, sleep)
- Diuretic therapy (RV overload)

- Anticoagulation
  - A recent large retrospective study regarding the utility of anticoagulation in SSc-PAH reported a strong trend towards worse outcomes in SSc-PAH patients treated with anticoagulation compared to those not treated (HR 1.82; 95% CI 0.94-3.54, p=0.08)  
    (Olsson Circulation 2014)

- Exercise (low grade aerobic)
- Supportive Care
  - Vaccine
  - Family support
Anti-inflammatory

- In SLE or MCTD there is reported response to cyclophosphamide and prednisone

- No good response recorded in scleroderma

- Trial of Rituximab underway in SSc-PAH

Sanchez Chest 2009
Treatment Options

• Current PAH-specific therapies target 3 pathways:
  - prostacyclin
  - endothelin-1
  - nitric oxide

Studies suggest a less marked response to PAH therapy in CTD-PAH
Intravenous Prostaglandins
- Epoprostenol, Iloprost, Treprostinil

Subcutaneous
- Treprostinil

Inhaled
- Iloprost
- Treprostinil

Oral Prostaglandins
- Iloprost, Cisaprost, Beraprost, Treprostinil

IV 12 week Epoprostenol improved exercise tolerance, quality of life, improved functional class

Badesch Ann Intern Med 2000
Management

• Phosphodiesterase type 5 (PDE-5) inhibitors
  • Sildenafil (Mild side effects; 20 mg tid)
  • Tadalafil (mild side effects; once daily)

• Endothelin receptor antagonists (ERA)
  • Bosentan (reversible elevated transaminases 10%)
  • Macitentan (dual ERA a&b; Hgb fell in 4.3 %)
  • Ambrisentan (less liver toxicity; edema)

• Soluble guanylate cyclase stimulator
  • Riociguat (enhances cGMP; CTEPH; Not with PDE-5)
Management

• There is no consensus as to which oral agent should be used as initial therapy

Calcium Channel Blockers are not of benefit in SSc-PAH: consider negative inotropic effect on heart.
Combination therapy is shown to improve exercise capacity and hemodynamics and decrease the risk of clinical worsening, but did not show a significant improvement in mortality.

There is no consensus as to the specifics or order of combination therapy.
Inhaled Agents + Oral Agent

- Combination studies with inhaled agents (iloprost and treprostinil) and various oral therapies have shown some improvement in symptoms, functional capacity, and time to clinical worsening, however, disaggregated data for CTD-PAH have not been reported.

McLaughlin AM J Respir Crit Med 2006 and J AM Coll Cardiol 2010
Simonneau Ann Intern Med 2001
Therapy for PAH

Right Heart catheterization

PAH confirmed
Resting mean PAP ≥ 25 mmHg
or Exercise PAP ≥ 30 mmHg and PCW ≤ 15 mmHg

- Functional class I/II
  - PDE5i or ERA

- Functional class III
  - PDE5i or ERA

- Functional class IV
  - IV or SC Prostacyclin

Unchanged or Failure

- PDE5i plus ERA
  - PDE5i plus ERA
    - add prostacyclin (inhaled, Oral or IV)

Lung Transplant referral
• 2-year survival was shown to be comparable (64%) among patients receiving lung transplant for SSc, interstitial lung disease, or IPAH (Schachua Arth Rheum 2006)

• No difference in 1 year survival in patients with SSc-PAH compared to those with other forms of PAH (Bernstein ET Arth Rheumatol 2015)
Future Therapy

- Selexipag (PGI2 receptor)
- Growth factors (Kinase Inhibitors)
- Serotonin
- RhoKinase
- Anti-inflammatory
- Immunosuppression
Thank You

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Johns Hopkins Scleroderma Center

hopkinsscleroderma.org
Pulmonary Hypertension in CTD

- Pulmonary arterial hypertension (PAH) is a common complication of connective tissue diseases (CTD) particularly scleroderma.
- When complicating CTD PAH significantly worsens survival and is a leading cause of death in these patients.
- Methods are available for early detection and therefore early intervention.
- Standard PAH-specific therapy is not as effective in CTD-associated PAH compared to IPAH.
- There is a need for a better understanding of underlying mechanisms of CTD associated.
Summary

• Echocardiography (plus) is recommended for patients with scleroderma even if asymptomatic
• Same screening for symptomatic patients with other CTDs
• RHC is recommended in all cases of PAH related CTD before specific treatment
• Anti-coagulation is decided on individual case
• Treatment plan is same for IPAH and CTD
RHC Recommendations: Scleroderma

• Annual clinical assessment, TTE and PFT
• ERVSP > 40 mmHg and /or DLco ≤50% with FVC >85%
• And/or a fall in DLco of > 20% in previous year
• Or unexplained dyspnea especially in the of a normal HRCT scan, PFT and V/Q scanning.
Prostaglandin + ERA or PD5

• Combination of bosentan added to intravenous epoprostenol did not show significant improvement in symptoms or functional capacity.

• Combination of sildenafil and epoprostenol demonstrated an improvement in exercise capacity, hemodynamics, and time to clinical worsening.

Humbert Eur Respir J 2004
Simonneau Ann Intern Med 2008
ERA plus PD5

- Compass 2 (Bosentan + Sildenafil)
  - No improvement in composite endpoint of clinical worsening
    [McLaughlin Eur Respir J 2015]

- ATENA -1 (Amberisentan + Sildenafil)
  - Improvement in hemodynamics and exercise capacity
    [Oudiz Chest abstract 2011]

- Ambition trial (Amberisentan + Tadalafil)
  - Improved pro BNP and 6 MWT in CTD
    [Coghlan Ann Rheum Dis 2015; Galie NEJM 2015; Hassoun Am J Respir Crit Care Med 2015]

- Inhaled Iloprost + bosentan
  - Improved functional class and time to clinical worsening.
PAH confirmed by RHC

General measures

Lower-intermediate risk
Functional class II or III

Monotherapy

Oral Combination

High risk
Functional Class IV

Oral plus IV prostacycline

Measure 3-6 months

Inadequate response

Double or triple Combination

Inadequate response

Comfort Care

Lung Transplant