Pulmonary hypertension in the connective tissue diseases pathogenesis, clinical features and therapeutic options in 2006

Ronald A. Asherson
MD (Hon), FRCP, MD, FACP, FCP, FACR
Sorrento Italy November 2006

Dramatic new developments in past few years

• Genetic mapping of 2q31-q32 locus in familial PAH
• PAH with viral illnesses viz HIV and other environmental “trigger” factors; e.g., drugs such as fenfluramine
• Importance of pulmonary endothelial cell enzymes in causation of PAH
• Identification of new therapeutic areas; e.g., endothelin-1 antagonists

Pulmonary hypertension in fact represents the response of the pulmonary arterial vasculature to many and varied stimuli
Pulmonary hypertension
in the connective tissue diseases pathogenesis, clinical features and therapeutic options in 2006
Prof. Ronald A. Asherson

Pulmonary hypertension
Sustained elevation of pulmonary arterial pressure
to > 25 mm Hg at rest or > 30 mm with exercise
Mean pulmonary-capillary wedge pressure
and left ventricular end-diastolic pressure < 15 mm Hg

Epidemiology and pathophysiology
Early natural history of the condition is not completely known
May exist without symptoms and may remain asymptomatic for years
Usually presents late in the course of the connective tissue disease
Characterized by vascular remodeling and pulmonary arteriopathy

Diagnostic and treatment challenges
Making the diagnosis of PAH
Classifying the type of pulmonary hypertension present
Identifying the high risk patient
Deciding on the type of therapy
Management and assessing outcomes of therapy
Pulmonary hypertension in the connective tissue diseases pathogenesis, clinical features and therapeutic options in 2006
Prof. Ronald A. Asherson

Revised World Health Organization classification of pulmonary hypertension
Venice 2003

Group I
Pulmonary arterial hypertension
• Idiopathic (primary) and familial;
Portal hypertension with collagen vascular diseases
• Others e.g., HIV; Drugs/toxins; Glycogen storage;
Splenectomy HHT; Hemoglobinopathies, myeloproliferative diseases

Group II
Pulmonary venous hypertension:
Left atrial/ventricular disease; Valvular disease

Group III
Hypoxic; e.g., COPD, interstitial lung disease,
sleep-disordered breathing; Alveolar hypoventilation;
High altitude exposure

Group IV
Thromboembolic and thrombotic (proximal, distal)

Group V
Miscellaneous: sarcoid, lymphangiomatosis, schistosomiasis

Functional assessment
Two classifications

New York Heart Association classification

Class 1. No symptoms with ordinary physical activity
Class 2. Symptoms with ordinary activity
Class 3. Symptoms with less than ordinary activity;
Marked limitation of activity
Class 4. Symptoms with any activity or even at rest

WHO organization functional classification 1973
Essentially similar but more detailed

Class I
No limitations

Class II
Slight limitation of physical activity only;
Ordinary physical activity causes undue dyspnoea or fatigue,
chest pain or near syncope

Class III
Marked limitation of physical activity;
Comfortable at rest; Less than ordinary activity causes undue dyspnoea
or fatigue; Chest pain or near syncope

Class IV
Inability to carry out physical activity
without symptoms; RHF; Dyspnoea/tachypnoea may be present at rest
Main difference between the two classifications is the inclusion of patients with syncope as functional class IV in the WHO classification.

Pathogenesis

There is an imbalance of vascular effectors:

- Prostacyclin/thromboxane A2 balance shifted towards thromboxane A2; Metabolites of prostacycline decreased; Prostacycline synthetase also decreased in small and medium sized arteries
- Endothelin-1 levels increased; A potent vasoconstrictor which stimulates proliferation of smooth muscle cells in arterioles
- Nitric oxide synthesis (catalyzed by nitric oxide synthetase decreased) decreased
- Serotonin (vasoconstrictor) increased
- Vasoactive intestinal peptide levels decreased
- Decreased vascular endothelial growth factor
These vascular effectors, in addition to playing important roles in the vasoconstriction of blood vessels seen in PHT, are also important in the smooth muscle cell proliferation, hypertrophy and hyperplasia as well as the disordered angiogenic responses which underlie the formation of the plexiform lesions.

There is desynchronous production and release of the endothelial vasoactive factors mentioned. Abnormalities of other regulatory molecules, e.g., vascular endothelial growth factor, also contribute to this process. These all act to produce characteristic fibromuscular changes seen in vessel walls.

It should be stressed that endothelial cell dysfunction/injury is the primary problem. Genetic and immunological factors now known to play important roles in the development of PHT.
In summary

- Characteristic histopathological picture is:
  Fibromuscular proliferation of the intima of precapillary arteries
  which raises the resistance to pulmonary flow

- There are anatomical and functional abnormalities
  in each layer of the vessel wall

- A deficiency of pulmonary endothelial enzymes elaborating
  vasodilators NO2 and PG12,
  as well as increased expression of vasoconstrictor
  peptide Endothelin-1 exists

What is the role of antiphospholipid antibodies
in the context of pulmonary hypertension?

No problem with their role in thromboembolic PAH

Their significance in patients
with the "primary" type of PAH unclear
A clue from a recent study?

Pulmonary hypertension and systemic sclerosis

Prevalence of anticardiolipin antibodies in SSc is low (8 – 14%).

Important study from France over 10 yr period showed initial aCL negativity but tests became positive with development of PHT.

- Higher prevalence in SSc with PHT (similar to that found in SLE patients with APS and in patients with precapillary PHT irrespective of etiology)
- Significant correlation with von Willebrand factor indicating production of aCL related to endothelial cell injury
- No correlation of levels with severity of PHT!

Conclusions

Therefore APL not the cause but rather an association with the condition?

Antiphospholipid antibody production related to endothelial cell injury!
Significantly reduced CD4+CD25+ (Treg subset) in conditions associated with PAH as well as the occurrence of autoimmune phenomena

Significantly CD4+ reduction in HIV infection where PAH is also encountered (in some APS)

Conditions with CD4 cell defects and PAH include

- SSc*
- SLE*
- Polymyositis
- Sjogren's syndrome
- Hashimoto's thyroiditis

*SSc and SLE associated with reduction in peripheral CD4+CD25+ cells, the putative Treg population

These cells only represent 5 – 10% of the CD4 cell population

However their depletion is sufficient to break self-tolerance and cause autoimmune disease
Autoimmune aspects of pulmonary hypertension

In the early 1980's it was suggested the "idiopathic" primary pulmonary hypertension was perhaps "autoimmune" in its pathogenesis.

Evidence

- High frequency of positive ANF in primary idiopathic PHT
- Essentially similar condition in CTD's; e.g., SLE, MCTD, CREST, RA, Sjogren's syndrome, APS, dermatomyositis, Hashimoto's thyroiditis

PHT may precede the connective tissue disease

30-40% of patients with idiopathic pulmonary hypertension are ANF positive

- 10 – 15% are antiphospholipid antibody positive

Relationship with anti Ku and ssDNA

- 39% have Raynauds +/- ANA positivity

References:

- Isern et al.
- Asherson et al.
- Karaschuk et al.
- Yves Landau et al.
Anticentromere antibody

Usually in CREST Syndrome
Not specific
- Primary biliary cirrhosis
- SSc
- Raynaud's phenomenon
- Myositis
- Morphea
- SLE

PAH is seen increasingly in HIV infection
it has also been reported in HHV-8 and HCV infection
together with other autoimmune phenomena

The incidence of PAH in HIV infection
is 6 – 12 x higher than in the general population

It is related to duration of HIV infection

Relationship to CD4+CD25+ population
unknown at this time

Relationship to AIRE gene

This is a single gene found on chromosome 21
designated as the autoimmune regulator gene
mapping to 21q 22.3
Autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia (APECED) is a condition in which there is a mutation of the AIRE gene leading to loss of function.

The autoimmune effects are adrenal insufficiency and hypoparathyroidism as well as other endocrine abnormalities.

Patient reported with this condition who died from fatal PHT.

PAH reported following splenectomy.

Clinical manifestations:
- Progressive exertional dyspnea
- Exercise intolerance
- Chest pain on exertion
- Syncope
- Inability of a compromised right ventricle to meet the body's demands for CO
- Pulmonic component of the second heart sound
Pulmonary hypertension in the connective tissue diseases pathogenesis, clinical features and therapeutic options in 2006
Prof. Ronald A. Asherson

Signs of pulmonary hypertension

- Elevated jugular venous pressure
- Positive hepatojugular reflex
- Dominant a-wave in JVP (early)
- Prominent v-wave later
- Palpable RV and closing pulmonary valve
- Narrow split S2 and pulmonary ejection snap; Loud P2
- Tricuspid regurgitation SM at LSE
- Cyanosis (shunt)
- Signs of RHF, including edema, hepatomegaly

Many of these signs may be overlooked by the attending physician or rheumatologist at regular routine examinations

- Increased P2
- Left parasternal right ventricular heave
- Elevation of JVP

The screen versions of these slides have full details of copyright and acknowledgements
Electrocardiography might alert the physician as to the presence of PAH.

Transthoracic echocardiography is usually the first definitive study to suggest that an abnormality of the pulmonary vasculature may be present.

### Laboratory tests

Standard laboratory tests are nonspecific.

Immunological tests will be able to detect which of the underlying connective tissue disorders is present.

Tests to detect the presence of an underlying clotting disorder should be performed.

### Predisposing factors in thromboembolic PAH 1

Hemostatic abnormalities

- Detection of antiphospholipid antibodies
- Abnormalities of protein C, S, antithrombin III
- Abnormalities of the fibrinolytic system
Pulmonary hypertension in the connective tissue diseases pathogenesis, clinical features and therapeutic options in 2006
Prof. Ronald A. Asherson

Predisposing factors in thromboembolic PAH 2

• Malignancies
• Atrial septal defects
• Indwelling venous catheters

Lung function testing, high resolution CT scanning, VQ scans, are all important

But
Cardiac catheterization and angiography are the “gold standards” for diagnosis and assessment of severity

Seen particularly in SLE and APS
Histology

Depends on the etiology
- In the primary type the histology is exactly the same as is seen in “primary” idiopathic PAH
- Thromboembolic
- Vasculitis (+/- systemic vasculitis)

Important to remember that secondary vascular occlusions may occur in the primary plexogenic type of PAH

Histological lesions

Primary pulmonary arteriopathy
- Plexiform lesions (+/- thrombosis)
- Thrombotic lesions
- Isolated medial hypertrophy
- Intimal fibrosis and medial hypertrophy
- Isolated arteritis
Examples of vascular pathology

Intimal proliferation in pulmonary hypertension
Poor prognostic factors

- Raynaud’s phenomenon
- Decreased DLCO; low PA oxygen saturation
- High RAP; low stroke volume index
- High mean PA pressure
- Poor RV function

Causes of death

- Right ventricular failure
- Arrhythmia; Sudden death
- Pneumonia
- ARDS
- Thrombotic complications
- Massive venous return postpartum results in RV failure due to reduced pulmonary vascular bed
Prognosis of PAH

Primary PAH median survival was only 2.8 yrs in the US prospective National Registry of 1991

Pregnancy: 50% mortality

SLE: 2 yr mortality > 50%

Pulmonary hypertension patients surviving from year of diagnosis

Pulmonary hypertension in connective tissue disorders

• Systemic lupus erythematosus
• Chronic cutaneous LE
• Antiphospholipid syndrome
• “CREST” syndrome*
• Systemic sclerosis (SSc)
• Rheumatoid arthritis
• Sjogren’s syndrome
• Mixed CTD
• Thyroiditis (?)
• Dermatomyositis

The screen versions of these slides have full details of copyright and acknowledgements
Pulmonary hypertension in the connective tissue diseases may take several forms

“Plexogenic” (resembling primary PAH)
Secondary to
Thromboembolism
Pulmonary fibrosis
Pulmonary vasculitis

In the connective tissue diseases there may be great variations as to which type of PHT predominates in a particular disorder

- Pulmonary fibrosis predominates in SSc
- Plexogenic type more common in CREST (limited) form of SSc
- Antiphospholipid-related (thromboembolic/plexogenic type) more common in SLE-related PHT
- Vasculitis more common in RA (generally very uncommon)

PAH in the connective tissue disorders will now be considered separately
Pulmonary hypertension in SLE

Prevalence 5 - 14%
Mean age at diagnosis 29 yrs (range 18 - 64 yrs)
Mean SLE duration 2 - 4 yrs (range 1 - 11 years)

Quismorio 1984
Asherson 1986 and 1990

Types of pulmonary hypertension in SLE
- Primary pulmonary hypertension*  →
  Indistinguishable from “primary” PHT
Secondary to
- Chronic lupus pneumonitis
- Pulmonary thrombo-embolism*  →
- Pulmonary vasculitis
*Accompanied by antiphospholipid antibodies

Associated with
- Raynaud’s phenomenon
- Renal disease and cytotoxic therapy
- Anti RNP and antiphospholipid antibodies
Not associated with disease activity

Quismorio 1984
Asherson 1990
Pulmonary hypertension and systemic sclerosis

Prevalence varies from 9 – 35%

More common complication in limited SSC (CREST)

- Isolated vasculopathy in limited scleroderma
- Severe fibrosis with secondary PHT
- Pulmonary fibrosis with severe vascular PHT
- Left heart or diastolic dysfunction

Frequency of PAH and fibrosis in 619 SSc patients

PAH from heart involvement

Most common cause of right heart failure is left heart failure

- Diffuse SSC:
  LV failure from primary cardiac involvement (LVEF < 50%)
- Diastolic dysfunction more common in older people, with lung involvement or other heart disease
- Increased diastolic dysfunction in SSC
Echocardiogram doesn’t easily identify diastolic dysfunction

Onset of PAH often delayed for 10 – 15 yrs following other symptoms such as oesophageal dysmotility and Raynaud’s phenomenon

Screening of patients with SSc for PAH

Pulmonary diffusing capacity for carbon monoxide (DLCO); Simple test to perform

Markedly reduced DLCO; common at time of diagnosis of PAH
Use of DLCO

- Serial testing of DLCO may anticipate development of PAH
- Incidence of PAH was 20% within 5 years in patients who had reduced DLCO and increased to 35% in patients with DLCO < 55% of the predicted value in one study
- Progressive decline of DLCO’s seen in patients who would develop PAH over a 10 – 15 yr period

DLCO (% predicted) in patients who developed PAH vs. controls

Mean DLCO, % pred.

Controls (n = 14) Cases (n = 19)

Years prior to PAH

RATIO: FVC% / DLCO% very helpful

Primary vasculopathy:
DLCO ↓ out of proportion to FVC
  e.g., FVC 85%, DLCO 35%

- FVC% / DLCO% ratio > 1.8
- Fibrotic disease: FVC and DLCO ↓ at same rate:
  FVC% / DLCO% < 1.4
- Mixture of fibrosis and vasculopathy:
  FVC% / DLCO% is also > 1.8 but FVC ↓↓
FVC/DLCO ratio between 1.6 – 1.8 may help to identify patients with a higher risk for developing pulmonary vascular disease.

Cardiopulmonary findings in limited SSc with PAH

<table>
<thead>
<tr>
<th></th>
<th>PAH (n=30)</th>
<th>No-PAH (n=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>14.5 yr</td>
<td>10.1 yr</td>
</tr>
<tr>
<td>Fibrosis (x-ray)</td>
<td>25%</td>
<td>32%</td>
</tr>
<tr>
<td>FVC% predicted</td>
<td>85%</td>
<td>83%</td>
</tr>
<tr>
<td>DLCO % predicted</td>
<td>39%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Autoantibodies in PAH cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticentromere</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>Nucleolar ANA</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>Anti-U1 RNP</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Anti-Scl-70</td>
<td>0</td>
<td>13%</td>
</tr>
</tbody>
</table>
Frequency of auto-antibodies in all SSC patients with any type of PAH

- Anti-centromere antibody
- Anti-nuclear antibody
- Anti-polymerase III antibody
- Anti-Scl-70 antibody

Frequency (%)

Embedded image of a bar chart showing the frequency of various auto-antibodies in SSC patients with PAH.

Echocardiography

- Non invasive
- More accessible
- Less expensive than catheterization

But

- Accurate pulmonary arterial systolic pressure measurements not possible
- Right ventricular systolic pressure (RVSP) (a surrogate for PAP) can only be estimated
- Because the RSVP has such a wide range its values are unreliable

Echocardiography may indicate PAH but does not diagnose PAH

- New ECHO methods
- Novel contrast agents
  may improve TR Doppler signals
- Three dimensional ECHO's
  Strain rate imaging
  may increase the sensitivity for detection of RV dysfunction

The screen versions of these slides have full details of copyright and acknowledgements
Risk factors for PAH in systemic sclerosis

- Long standing (>10 yrs), limited SSc, ACA or antinucleolar antibodies
- Diffuse/limited, antinucleolar antibody, shorter disease duration, some fibrosis, but no chronic hypoxia
- DLCO < 60% predicted, and the ratio of FVC% / DLCO% > 1.6
- Echocardiogram: PASP > 40 mmHg
- ↑PASP with exercise

Making diagnosis of PAH

Suspect PAH
Patient subset
Late limited, ACA, antinucleolar Ab, low DLCO, FVC% / DLCO% > 1.6
Echo PASP > 40 mmHg or ↑PASP with exercise
Exclude
Left Heart failure
Pulmonary emboli
Severe fibrosis

Confirm with right heart catheterization

Right heart catheterization still the most accurate measurement of PAH

The screen versions of these slides have full details of copyright and acknowledgements
PAH in SSc associated with significant and disabling dyspnoea and significant mortality

Natural history of elevated PASP in SSc
12% of SSc patients have PASP > 35 mmHg; 3 years later however 65% still with mild to moderate elevations of PASP; 20% have severe PAH and death occurs in 2 years; Risk factors for severe PAH are males, limited scleroderma and increasing PASP’s

Pulmonary hypertension and systemic sclerosis
HLA DRw52 in 94% of patients with SSc and PHT; Only in 64% without PHT; 63% of normal controls
Also higher incidence of DR3 and DR6 antigens in children with PHT
Antiphospholipid antibodies

No correlation between antibodies to β2GP1, vWF and the development of PHT

aCL related to endothelial cell injury and β2GP1 more specific for APS

No association between aCL and thrombotic events in SSc patients

Rheumatoid arthritis and pulmonary hypertension

Uncommon

Distinctly rare with JRA

- Plexogenic type resembling “primary” PHT
- Secondary to pulmonary fibrosis
- Secondary to vasculitis (+/- systemic vasculitis)
- Hyperviscosity syndrome

Thromboembolic PHT not reported

Mild asymptomatic elevations of pulmonary arterial pressures present in 25% - 30% of RA patients according to several series reported; ? Significance
Pulmonary hypertension in the connective tissue diseases pathogenesis, clinical features and therapeutic options in 2006
Prof. Ronald A. Asherson

Sjogren’s syndrome and pulmonary hypertension

- Nineteen cases reported in world literature only
- Mostly in middle aged females
- Frequently associated with Raynaud’s phenomenon
- Usually of primary “plexogenic” type
- None associated with pulmonary fibrosis or vasculitis

Treatment

- Prostacycline derivatives
  - i.v. epoprostenol
  - SC and i.v. treprostenil
  - Inhaled iloprost
- Endothelin receptor antagonists
  - Non-selective; e.g., bosantan
  - Selective; e.g., sitaxsentan
- Phosphodiesterase vs. inhibitors
  - e.g., sildenafil

With new treatments

- Improved survival for patients with IPAH
- But not for other patients with PAH

The screen versions of these slides have full details of copyright and acknowledgements
Approved therapies for SSc and pulmonary hypertension

First:
- Oral agents
- Bosentan: Tracleer 125 mg BID
- Sildenafil: Revatio 20 mg TID alone or in combination

Patients should be monitored with 6 minute walk distance, $O_2$ saturation or with dyspnea questionnaires.

Second: add a prostacyclin;
- Treprostinil (remodulin) sub-cutaneous or inhaled iloprost (ventavis)

Lastly: add continuous i.v. therapy
- Treprostinil (remodulin) i.v.
- Epoprostenol (flolan) i.v.

(Usually need PAH center with nursing coverage to deal with these)

Many new studies with combinations of many of these medications.
Other endothelin antagonists

Inhaled remodulin (twice a day)

Combination therapy

Inhaled nitric oxide - too short acting, less effective in SSc

---

Comments on PAH therapy

- Tracleer:
  Oral medication, liver function abnormalities, edema ($$$$

- Revatio:
  Less effective, tachyphylaxis

- Remodulin:
  Continuous subcutaneous infusions required; severe site reaction in 85% (15% withdrawals)

- Ventavis:
  6x day administration required (cumbersome)

- Flolan:
  Continuous i.v. infusion problems, tachyphylaxis, severe headache and jaw pain limit dose which can be administered

- Remodulin:
  Longer acting, still i.v. administration required

---

New compounds being currently tested

Alefecept
T cell antagonist

Sitaxsentan
Single receptor endothelin antagonist
Pulmonary hypertension in the connective tissue diseases: pathogenesis, clinical features and therapeutic options in 2006

Prof. Ronald A. Asherson

Supportive therapy

Anticoagulation/aspirin
Oxygen
Vasodilators
Diuretics/digoxin
Immunosuppression
Transplantation

Lung involvement in scleroderma is very common and the most frequent cause of scleroderma-related deaths

Careful evaluation of the patient’s risk factors, the FVC, DLCO, FVC/DLCO ratio, the HRCT and the ECHO is needed

Treatment is dependent on what type of lung disease is present

PHT in diffuse SSC

Most frequently secondary to fibrosis

10% prevalence of “vasculopathic” PHT in diffuse SSC [antinucleolar ANA, U3-RNP (African-Americans)]

Vasculopathic PHT rare in anti-Scl-70+ve pts

20% with mild fibrosis only may have marked increased in PA pressures

The screen versions of these slides have full details of copyright and acknowledgements
Pulmonary hypertension in the connective tissue diseases pathogenesis, clinical features and therapeutic options in 2006

Prof. Ronald A. Asherson

Summary of PAH in SSc

- Know the types of PAH in SSc
- Identify the high risk patient
- Make a definite diagnosis of PAH
- Chose when and whom to treat
- Decide when to add new therapies

We can improve outcomes in PAH!

I am indebted to

Prof Virginia Steen
of Georgetown University
Washington, USA

for her assistance with this presentation

The screen versions of these slides have full details of copyright and acknowledgements