

Connective tissue disease related Pulmonary arterial hypertension

DM Seminar:
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PAH in connective tissue diseases

- CTD accounts for 30% of PAH according to US PAH registry.
- Incidence is on rising trend (40% of all cases after 2002, as compared to 28% before 2002)
- Mean age is 55 ± 15 yrs
- Females accounted for 87% of cases
- More severe disease with a lower exercise capacity, a worse functional class, a higher mean pulmonary artery pressure and pulmonary vascular resistance, and lower cardiac index, compared with IPAH

*A UNITED STATES-BASED REGISTRY FOR
PULMONARY ARTERIAL HYPERTENSION: 1982-2006
ERJ Express. Published on September 5, 2007*

PAH in connective tissue diseases

High incidence of PAH: Case reports and series:

- Systemic sclerosis
 - Diffuse SSc
 - Limited SSc
- SLE
- Mixed connective tissue disease
- Sjogren's disease
- Rheumatoid arthritis
- APLA
- Polymyositis / dermatomyositis

Systemic sclerosis

- Pulmonary hypertension may be due to
 1. Pulmonary arteriopathy as seen in PPH
 2. A consequence of interstitial lung disease
 3. Left ventricular diastolic dysfunction
 4. Chronic thromboembolic disease
- The incidence of pulmonary hypertension varies between 6% to 60% of patients with Systemic sclerosis
- But recent studies with Right heart catheterization showed prevalence of around 15%

Ann Rheum Dis. 2003 Nov;62(11):1088-93

Systemic sclerosis

- Prevalence of PAH did not differ in patients with Diffuse SSc or limited SSc (17 Vs 23%) patients with and without ILD (22% Vs 19%)

J Rheumatol. 2007 May;34(5):1005-11

- A 52% increase in risk of PAH was demonstrated for every 10 years of age at disease onset
- Twofold greater risk of PAH (OR, 2.30; CI :1.32 - 3.99) for late-onset (age > or =60 years) vs earlier-onset (< 60 years) disease

Chest. 2003 Dec;124(6):2098-104

SLE

- Pulmonary hypertension is found in 5–14% of all patients with SLE
 - Lupus. 2004;13(7):506-9*
 - Lupus 2000;9: 338–342*
 - Rheumatol Int 1999;18: 147–151*
- Pulmonary circulation may be directly involved in 50% of cases
- Association with other complications including interstitial lung disease or thromboembolic disease in 50% of cases
 - Lupus. 2000;9(5):338-42*
- Mortality rate of 25% to 50% at 2 years from diagnosis of PAH
 - J Rheumatol. 1999 Sep;26(9):1923-9*

SLE

- Presence of Raynauds phenomenon is associated with incidence of PAH.

J Rheumatol. 1999 Sep;26(9):1923-9

Lupus. 2007;16(7):505-8

- Disease activity, organ involvement and anticardiolipin antibodies were not associated with PAH

Lupus. 2004;13(7):506-9

- Increased values of VEGF and P-selectin in patients with long standing PH are related to severe endothelial dysfunction .

- VEGF and P-selectin may constitute new therapeutic targets for PH

Eur J Med Res. 2007 Apr 26;12(4):145-51

Rheumatoid arthritis

- Incidence of pulmonary artery systolic pressure > 30 mm Hg significantly higher in patients with RA (26.7% versus 4.5% in controls; p=0.03)
- 20% of patients had pulmonary hypertension without lung disease or cardiac disease
- A strong correlation between the PAP and the disease duration ($r=0.68$, $p<0.000$)

Int J Cardiol. 2007 Aug 7

- 20 - 27.5% of RA have mild Pulm HTn

Scand J Rheumatol. 2004;33(4):244-5
Rheumatology (Oxford) 2000;39:1320-1325

Other diseases

- Three fourths of patients with MCTD had evidence of pulmonary hypertension

Medicine (Baltimore) 63:92-107, 1984

- Patients with APLA can develop Chronic thromboembolic pulmonary hypertension (CTE-PH).

CTE-PH with APLA fare better than CTE-PH otherwise

Medicina (B Aires). 2007;67(3):225-30

Only a few case reports of PAH in APLA

Z Rheumatol. 2000 ;59(5):334-42

Angiology. 1997 ;48(2):183-7

Natural history

- In SSc, change in Tricuspid gradient measured by ECHO, was $1.34+4.55$ mm Hg/Yr
- Age and presence of ILD were associated with increased risk of progress of TG

Rheumatology (Oxford). 2005 ;44(3):366-71

Prognosis

- 2-year survival in patients with CREST without PAH is 80%, whereas patients with PAH had a 2-year survival of 40%.

Arthritis Rheum 29:515-524, 1986

- 40% survival at 2 years in patients with SSc and PAH compared with higher survival in scleroderma patients without organ failure or with lung involvement (interstitial lung disease)

Br J Rheumatol 35:989-993, 1996

Prognosis

- Patients with PAH-SSc 3.06 times more likely to die than IPAH
- 1 and 3 year survival estimates were 87.8% and 48.9%, respectively, in patients with PAH-SSc and 95.1% and 83.6%, respectively, in those with IPAH.

Arthritis Rheum. 2006;54(9):3043-50

- No difference in survival between patients with SSc PAH with (n=40) and without (n=108) pulmonary fibrosis ($p=0.3$)

Ann Rheum Dis. 2003;62(11):1088-93

- RVSP above 30 mm Hg at diagnosis, mortality was 20% at 20 months

Rheumatology 2001;40(4):453–9

- Raised mRAP (hazard ratio 21), raised mPAP (hazard ratio 20), and low CI (hazard ratio 11) predicted an adverse outcome

Ann Rheum Dis. 2003;62(11):1088-93

Prognosis

- In SLE, mortality rate of 25% to 50% at 2 years from diagnosis of pulmonary hypertension.
- For SLE-PH, the 3-year survival rate was 44.9% and the 5-year survival rate was 16.8%. For IPAH, the 3-year survival rate was 73.4% and the 5-year survival rate was 68.2% ($p=0.02$).

Clin Rheumatol. 2006 ;25(6):866-72

- Multivariate analysis showed that an elevated serum UA (>4.7 mg/dl) as an independent predictor for survival in CTD PAH (hazard ratio, 1.88, 95% CI [1.24- 2.84], $P < 0.01$).

Int Heart J. 2007 Jul;48(4):523-32

Poor prognostic markers

- Advance NYHA functional class.
- Low 6MW distance
- Elevated mean right atrial pressure
- Reduced cardiac index.
- Presence of a pericardial effusion
- Low VO_2 max and low peak exercise systolic and diastolic BP as determined by cardiopulmonary exercise testing
- Elevated brain natriuretic peptide ($> 180 \text{ pg/mL}$).
- In patients with IPAH treated with epoprostenol, persistence of NYHA functional class III or IV status after at least 3 mo of therapy
- Reduced DLCO ($< 45\%$ of predicted)

ACCP guidelines 2004

CTD related PAH is Underdiagnosed

- 909 patients with either scleroderma or MCTD.
- ECHO done and PAH (ERVSP of \geq 40 mm Hg) was detected in 89 patients (82- SSc and 9- MCTD)
- 13.3% patients with SSc or MCTD followed up in a community rheumatology practice setting have undiagnosed elevated ERVSP consistent with PAH.

The UNCOVER study.

Arthritis Rheum. 2005 Jul;52(7):2125-32

Whom to screen

- Limited SSc of >10 years' duration,
- symptoms and/or signs of PAH,
- DLCO <50% predicted,
- a rapid or large fall in DLCO without evidence of ILD

Intern Med J. 2007;37(7):485-94

- DLCO <72% in absence of ILD

J Rheumatol. 2007;34(5):1005-11

- Paricardial thickening of 8mm

Chest. 2007;131(4):988-92

- Raynauds phenomenon preceding PAH by 3 yrs

Semin Arthritis Rheum. 2007;36(6):392-6

- N-TproBNP in excess of 395 pg/mL

Eur Heart J. 2006 Jun;27(12):1485-94

- SSc patients with Age of onset >60 yrs

Chest. 2003 Dec;124(6):2098-104

Screening

ECHO

- RVSP > 36 mm Hg
- RVSP > 25 when associated with dyspnea

} PPV of 60%

Arthritis Rheum. 2005; 52(12):3792-800

- RVSP >45 mm Hg cutoff has high correlation with PAH detected by RHC. But ECHO has low predictive value at any cutoff

Rheumatology (Oxford). 2004 Apr; 43(4):461-6

- Stress ECHO in those with normal study at rest showed elevation of RVSP in SSc (diffuse and limited) and SLE.

Eur Respir J 2002; 19: 571–576

- Patients with lower work capacity had higher post exercise RVSP

Chest 2006; 130:176–181

Screening

- Screening of all patients with SSc for PAH is not standard practice in North America and Europe

Why screening?

- Unfortunately, there is no early symptom or sign of pulmonary hypertension. When patients develop symptoms, they usually suffer from advanced pulmonary hypertension with manifest low cardiac output
- Severe PAH has poor prognosis with high mortality
- Availability of therapeutic options

But

- Natural history of mild PAH not studied prospectively
- Most of the studies used prostacyclins and bosentan and sildenafil in advanced PAH (NYHA class 3,4)

Evaluation

- ECG, CXR, ABG
- Pulmonary function test with DLCO
- Doppler Echo (for follow up and evaluation of treatment)
- HRCT chest / CTPA
- Right heart catherization
- 6 minute walk test (for follow up and evaluation of treatment)

- Anticentromere antibody and anti U3RNP antibody for patients with SSc
- NT pro BNP
- Serum uric acid

Right heart catheterization (RHC)

- Accurate measurements of PAP for diagnosis
 - PAP during exercise
 - Vasodilator challenge
 - Currently it is mandatory to conduct RHC before commencing treatment
- British Cardiac Society Guidelines
Heart 2001;86:11 –13
- Patients with PAH associated with underlying processes, such as scleroderma should undergo acute vasoreactivity testing.
- ACCP guidelines 2004

Right heart catheterization (RHC)

- 32% of patients referred were on calcium channel blocker therapy without proper evaluation
- A positive acute vasodilator response to adenosine occurred only in 2.3 patients (compared with 4.5% in IPAH)
- Not rigorously evaluated for vasodilator response and are receiving potentially harmful therapy with calcium channel blockers.

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N terminal pro BNP

- Amongst SSc PAH patients, NT-proBNP values were significantly correlated with PAP ($r=0.73$, $p=0.003$) and inversely correlated with the SMWD ($r=-0.60$, $p=0.02$)

Int J Cardiol. 2007 14;121(1):135-7

- A 10-fold increase in N-TproBNP level on therapy is associated with a greater than three-fold increase in mortality, and may indicate therapeutic failure in SSc PAH

Eur Heart J. 2006 ;27(12):1485-94

- Cut-off value of 395.34 pg/ml had a sensitivity of 0.69 and specificity of 1.0 for PAH in SSc

Respir Med. 2003 Nov;97(11):1230-6

**Additional biological tool in the evaluation and management
of SSc PAH patients**

Monitoring

- Serial Doppler-echocardiography every 3 to 6 months
- The 6-minute walk test (6MWT) is established as a reproducible simple clinical measure of exercise capacity in PAH; this associates with progression and survival.

Rheum Dis Clin N Am 2003;344 :335–349

- NT- Pro BNP can be used

Functional class and exercise capacity assessed by the 6MW test provide benchmarks for disease severity, response to therapy, and progression

ACCP guidelines 2004

Pathology

- Intimal thickening
- Media hypertrophy
(small and medium sized arteries)
- Plexiform leisons
- 6 (75%) of 8 patients with CTD/PAH showed significant obstructive pulmonary vascular lesions predominating in veins/preseptal venules, as compared with 5 (17.2%) of 29 non CTD/PAH
 - Explain why these patients are less prone to respond to specific pulmonary arterial hypertension

Hum Pathol. 2007;38(6):893-902

Pathogenesis : Vasospasm

- Increased endothelin1 levels in SSc/PAH

J Rheumatol 1994;21(10):1838–44

Am J Med 1995; 99:255-260

Rev Med Interne. 2007;28(6):371-6

- Endothelin1 levels were higher inpatients of SSc/PAH with anti centromere antibodies

Rev Med Interne. 2007;28(6):371-6

- Patients with scleroderma have defective endothelial-dependent vasodilation and this may be related to decreased endothelial nitric oxide synthase (NOS 2). (studied in cutaneous vasculature)

Vasc Med 5:147-158, 2000

Pathogenesis : Vasospasm

Association with Raynaud's phenomenon

- All patients with PAH and CREST had Raynaud's phenomenon whereas 68% without PAH had Raynaud's phenomenon

Arthritis Rheum 29:515-524, 1986

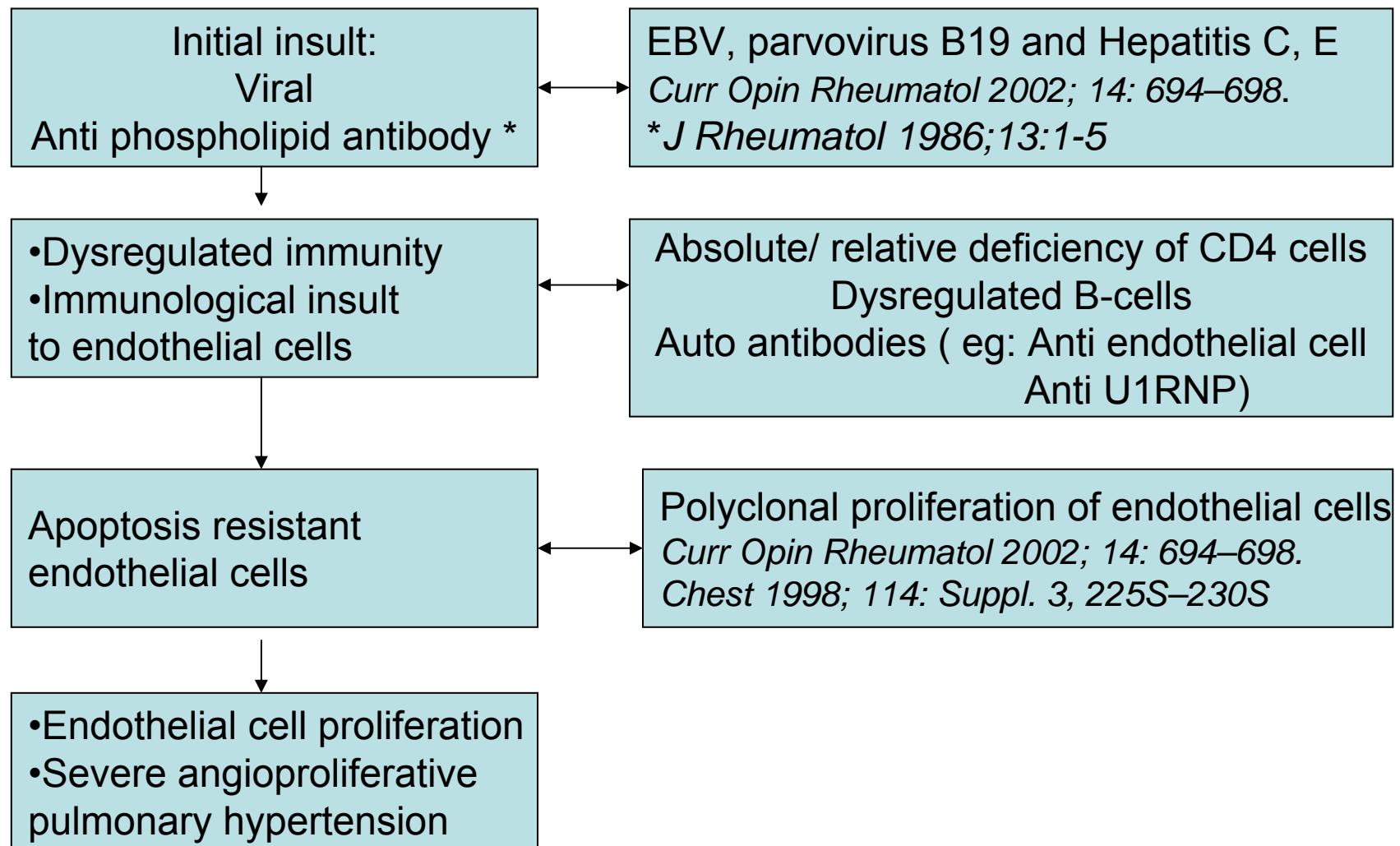
- Up to 75% of patients with PAH and SLE had Raynaud's phenomenon

J Rheumatol 13:1-5, 1986

Reversibility testing on RHC showed positive results in SSc patients when tested with

- Prostacyclin *Arthritis Rheum.* 1998;41(3):466-9
- Nifedipine *Am J Med.* 1991;90(5):541-6

Pathogenesis



Anti endothelial cell antibodies (AECA)

- Present in 40% of patients with diffuse scleroderma and in 13% with CREST and are associated with a higher incidence of pulmonary hypertension.

J Rheumatol 1998;25:462-466

- AECA associated with pulmonary hypertension in SLE.

J Rheumatol 1994;21:2058-2063

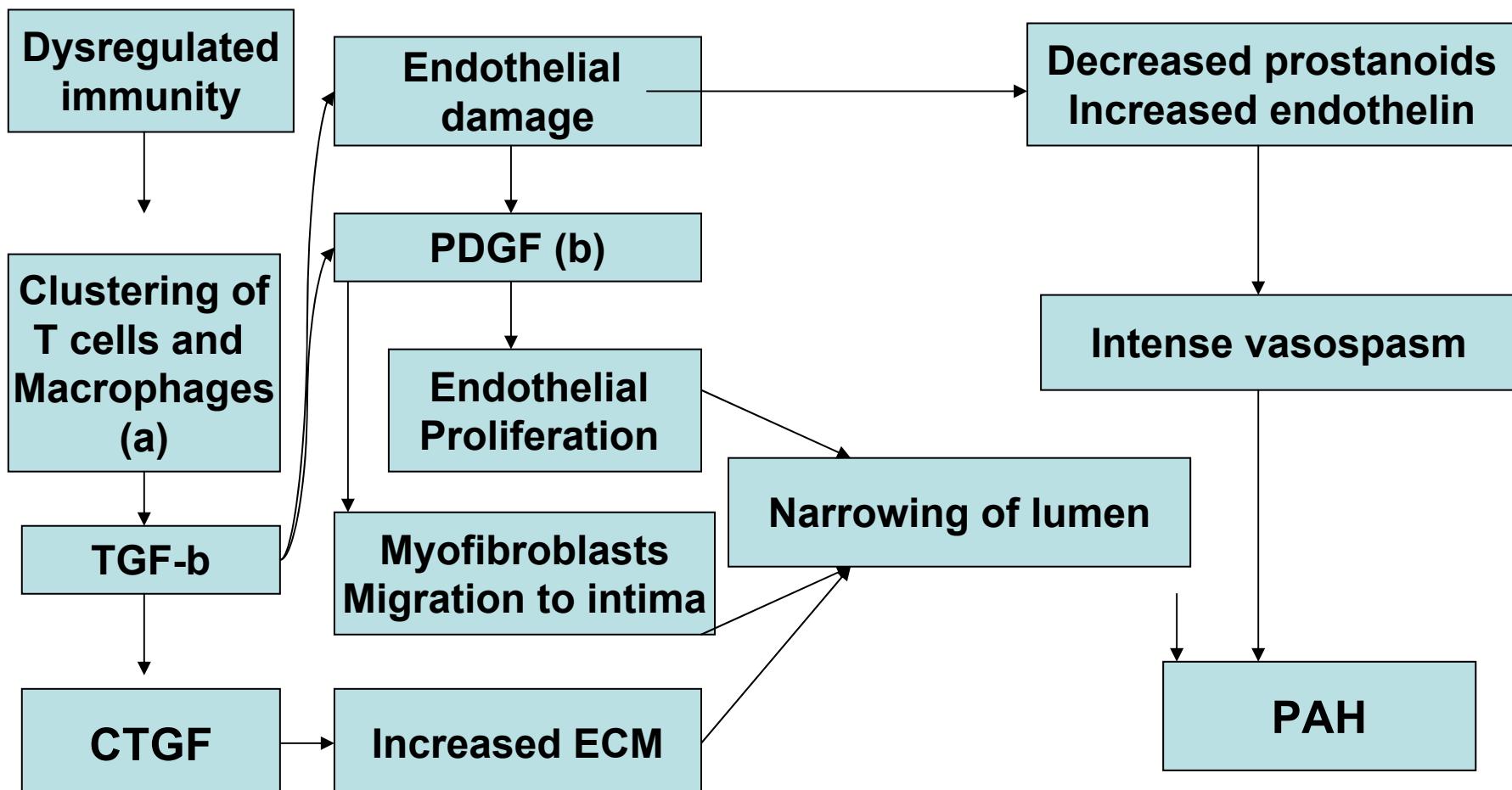
- Apoptosis of pulmonary arterial endothelial cells induced by AECA may be the first step of vascular damage in patients with MCTD

Ryumachi. 2002;42(6):885-94

- In MCTD, presence of AECA and endothelial cell activation may play in the maintenance of obliterative vascular processes

Scand J Immunol. 2006 Jul;64(1):69-76

Pathogenesis



(a) *Hum Pathol* 1997; 28: 434–442

(b) *Rheum Dis Clin North Am* 1996; 22: 675–94.

Role of TGF- β in SSc related PAH

- A smaller number of cases (10) are associated with mutations in the Alk1 (activin receptor like kinase 1) receptor, which is an accessory TGF- β receptor

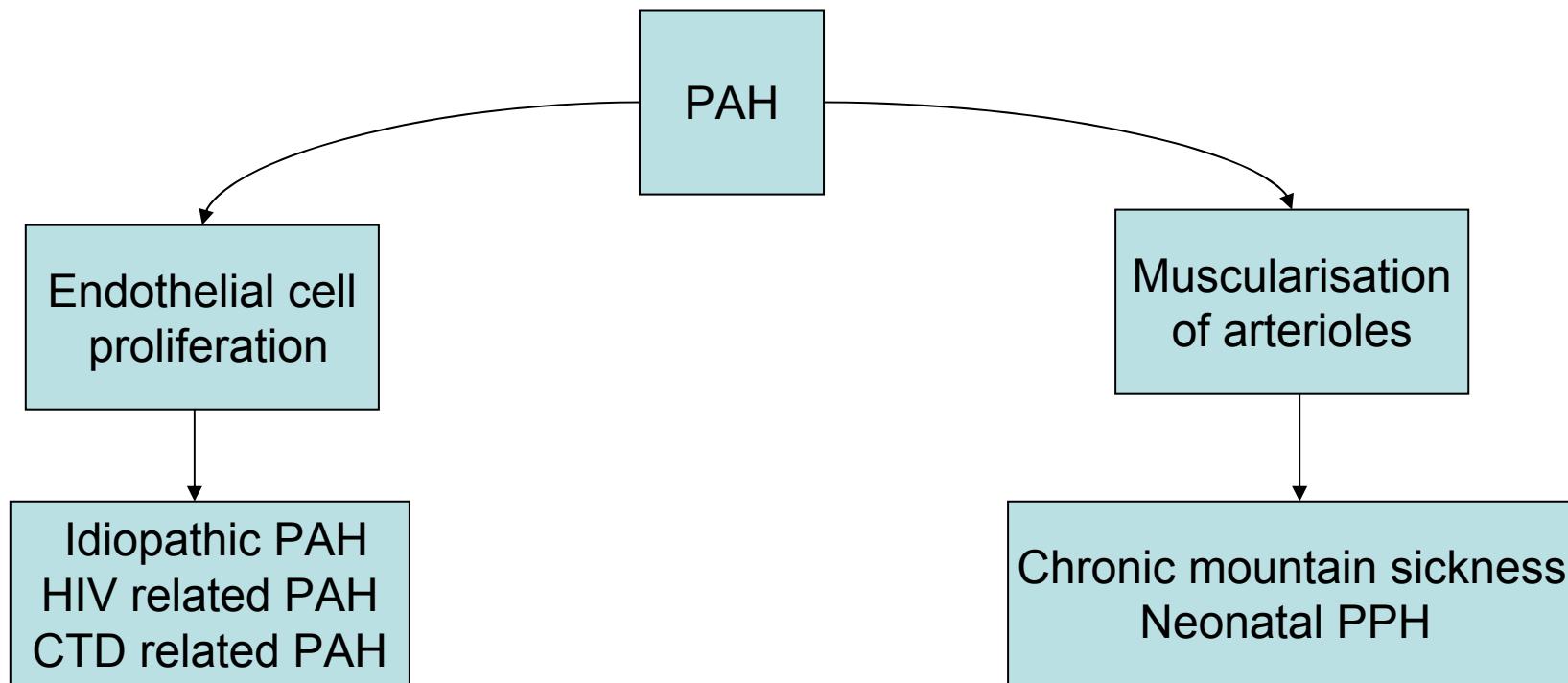
Clin rheumatol 2007;26(6):947-9

- Association between TGFb1 single nucleotide polymorphisms (SNPs) with SSc or its clinical subsets

Ann Rheum Dis 2002;61(8):678–81

**Evidence suggests that alterations in
TGF - β family ligand receptor axis in SSc /PAH**

Primary pulmonary hypertension and CTD related PAH



Severe angioproliferative pulmonary
Hypertension (SAPPH):
Similar pathology, pathobiology and treatment

*Eur Respir J 2005;
26: 1110–1118*

Treatment options

Oxygen
Cautious diuretics
Anticoagulant (INR 2-3)*

Calcium channel blockers

Epoprostenol
Treprostinil
Iloprost
Beraprost

Bosentan
Sitaxsentan

Sildenafil

Immunosuppression

*Eur Respir J 2002; 19: 571–576

Treatment

- Possibly less severely involved vessels may be vasodilated. Short-term benefits may occur in this way.
- It is unlikely that pulmonary arterial spasm is a prominent long term mechanism; some form of structural remodeling is much more likely.
- The endothelin-receptor blockade is antifibrotic
J Invest Dermatol 2001;116(3):417– 25
- Iloprost downregulates expression of a potentially important, downstream profibrotic mediator, connective tissue growth factor
J Clin Invest 2001;108(2):241– 50

Epoprostenol

- RCT of 111 patients with SSc-PAH (70% limited and 30%diffuse) showed improvement in 6MWD (108 mt, p<0.001) and mean pulmonary arterial pressure (5 mm Hg)

Ann Intern Med. 2000 Mar 21;132(6):425-34

- In a case series of 6 SLE patients, mean pulmonary artery pressure decreased by 38 +/- 21% and pulmonary vascular resistance by 58 +/- 12% and all patients of NYHA class 3,4 improved to class 1,2

Chest. 2000 Jan;117(1):14-8

- In SLE, Intermittent EPO infusion did not substantially reduce PASP, it prevented further rise in PAP during the treatment period (N=3)

Ann Acad Med Singapore. 2003 Jan;32(1):118-21

Treprostинil

- Continuous subcutaneous infusion of treprostинil for 12 weeks in patients with 90 patients with PAH associated with CTD improved dyspnea scores, exercise capacity, symptoms of PAH, and hemodynamics (PVR, CI)

Chest. 2004 Aug;126(2):420-7

- 12 week use lead to significant increase in 6MWD by 16 mt ($p = 0.006$) irrespective of etiology (CTD-PAH, IPAH)

Am J Respir Crit Care Med. 2002 15;165(6):800-4

Iloprost

- Anecdotal use in PAH associated with *MCTD*, ^SLE , SSc**

**Rheumatol Int.* 2006 ;26(3):264-9.

^*Lupus.* 1999;8(4):328-31

***Arthritis Rheum.* 1994 ;37(10):1528-33

- Addition of iloprost to bosentan helped in further increase of 6MWD by 26m and associated with improvement in hemodynamics (study included 26 patients of CTD-PAH)

Am J Respir Crit Care Med 2006;174:1257-1263

Bosentan

- Bosentan in doses of 125 mg, has been shown to improve endothelial function assessed by flow mediated dilatation, without effecting other hemodynamic parameters

Arthritis Rheum. 2007 Jun;56(6):1985-93

- The endothelin-receptor blockade is antifibrotic

J Invest Dermatol 2001;116(3):417– 25

Bosentan

- Long-term treatment (1 yr) improved 6MWD and pulmonary haemodynamics (ECHO) in patients with PAH related to with CTD (9 with SSc, 2 with SLE, 2 with MCTD) who initially failed on prostanoids.

Eur J Clin Invest. 2006 ;36 Suppl 3:49-53

- 66 patients with PAH secondary to CTD (mostly SSc and SLE)
- At the end of 16 weeks treatment group had better 6MWD (+19.5 m, 95% ,CI -3.2 to 42.2), whereas placebo group deteriorated (-2.6 m, 95% CI -54.0 to 48.7)

Survival in those receiving bosentan was 85.9% after 1 year and 73.4% after 2 years

Ann Rheum Dis. 2006 ;65(10):1336-40

Bosentan in SSc

- 45 patients, received bosentan as treatment. Had survival 81% and 71% ($p = 0.016$) at one and two years, respectively compared to the historical control group 68% at 1 year and 47% at 2 years.

- PVR remained stable over an average of nine months

Heart. 2006 Jul;92(7):926-32

- 8 patients with diffuse SSc with Interstitial fibrosis and PAH showed improvement in 6MWD and NYHA class

Eur J Clin Invest. 2006 ;36 Sup3:44-8

- In 50 patients with SSc -PAH 1-, 2- and 3-year survival was 82%, 67% and 64%, respectively, vs. approximately 45%, 35% and 28%, respectively in IPAH

Eur J Clin Invest. 2006 ;36 Sup3:10-5

Bosentan in SLE

- In SLE, a small case series of 8 patients revealed, significant increase in 6MWD (+24.8 m, +26.2 m and +62.7 m at three ($P = 0.001$), six ($P = 0.001$) and 12 ($P = 0.01$) months respectively) , Borg dyspnea index and mild improvement in SF-36 at 3,6,9 and 12 months

Lupus. 2007;16(4):279-85

Sitaxsentan and Ambrisentan

- In a post hoc subgroup analysis of 33 patients with CTD, sitaxsentan has shown improvement in 6MWD (20 ± 52 m as compared to decrease by 38 ± 84 in controls) and NYHA functional status

Ann Rheum Dis. 2007 Sep 3; [Epub ahead of print]

- Ambrisentan* and Sitaxsentan[^] have shown favourable results in RCTs which included CTD- PAH in significant proportion (30% of total cases)

**J Am Coll Cardiol 2005;46:529-535*

[^]*J Am Coll Cardiol 2006;47:2049-56*

Sildenafil

- In SLE* and SSc[^] with PAH, anecdotal use of sildenafil (upto dose of 400 mg) has shown beneficial effects (6MWD, PVR)

**Lupus. 2003;12(4):321-3*

**Arch Bronconeumol. 2003;39(10):476-7*

[^]*Rheumatol Int. 2006 Jan;26(3):270-3*

- Addition of sildenafil to bosentan failed to improve NYHA Class and 6MWD in SSc PAH

Eur Respir J. 2007 Mar;29(3):469-75

Immunosuppressive therapy

- Monthly IV bolus of cyclophosphamide, 600 mg/m², for at least 3 months.(22 of 28 patients also received steroids)
- None of the 10 patients with systemic sclerosis responded, while 5 of 12 patients with SLE and 3 of 8 patients with MCTD did respond (remained in NYHA class I or II, with out addition of any other medicine)
- Low baseline PAP NYHA class predict better response

Chest. 2006 Jul;130(1):182-9

- Monthly IV cyclophosphamide (0.5 gm/ sq.mt BSA) for 6 months reduced PAP from 41 to 28 mm Hg and was associated with improvement in NYHA class in patients with SLE-PAH

Lupus. 2004;13(2):105-12

- 7/8 SLE patients with PAH treated with Steroids + Cyclophosphamide responded
Relapses after withdrawl of immunosuppression responded to repeat treatment

J Rheumatol 29: 282-287, 2002

Serotonin antagonists

- The selective serotonin receptor 2 antagonist ketanserin acutely improved pulmonary artery pressure and cardiac output in patients with pulmonary hypertension and systemic sclerosis

J Rheumatol 14:519-524, 1987

- Sarpogrelate, another receptor 2 antagonist, administered orally for 12 months, decreased mean pulmonary arterial pressure and increased right ventricular ejection fraction.

J Int Med Res 28:258-268, 2000

Balloon atrial septostomy

- Has been tried as palliative procedure in SSc related PAH
Exercise capacity was improved and exertional syncope abolished.
BAS improved clinical symptoms and increased the CI

Arthritis Rheum 44:1660-1662, 2001

Thorax. 2003 Sep;58(9):797-800

Lung transplant

- Class 3,4 PAH whose prognosis remains poor despite medical therapy should undergo lung or heart-lung transplantation
- Procedure of choice is a bilateral lung transplant

ACCP guidelines 2004

- Survival in SSc–associated pulmonary hypertension after lung or heart-lung transplantation was not different than primary pulmonary hypertension.

Ann Transplant 5:38-43, 2000

- Anecdotal case reports of single lung transplant in SLE-PAH

J Chin Med Assoc. 2004 May;67(5):248-51.

ACCP guidelines 2004 - Treatment

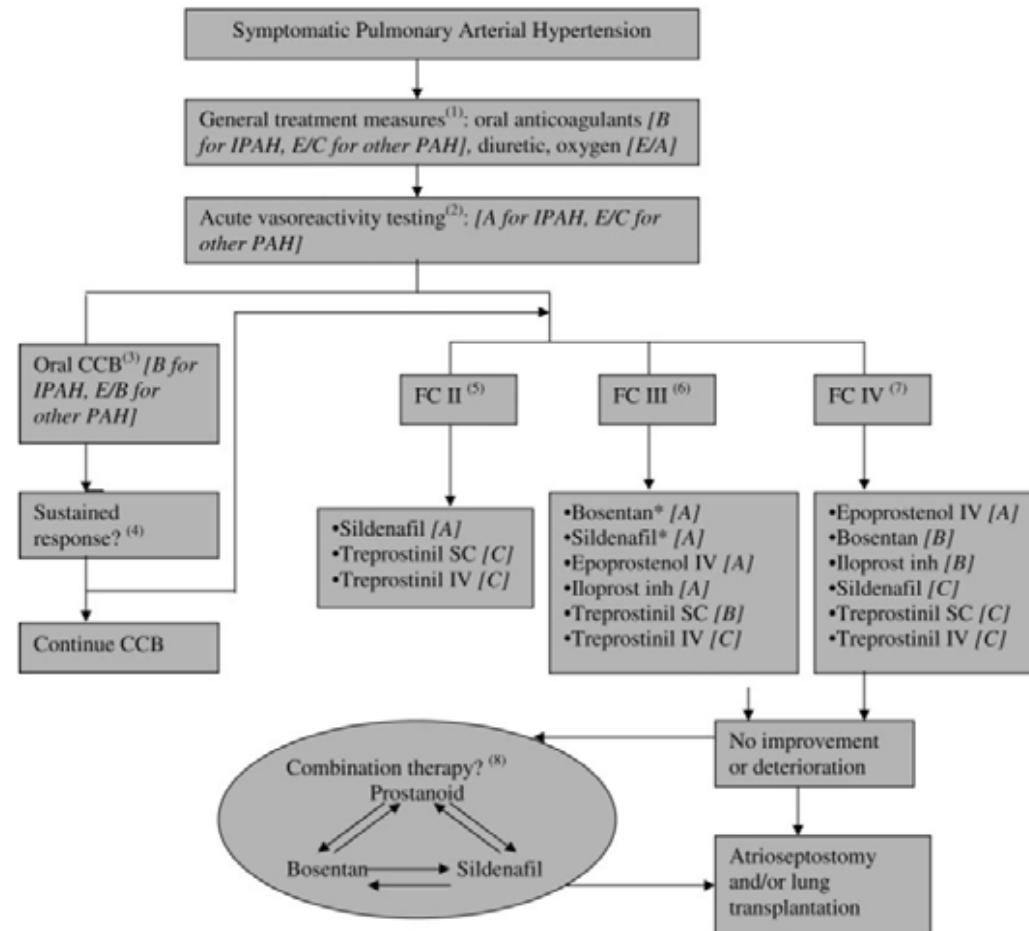
Calcium channel blockers:

- In those who show reversibility during RHC
- Long-acting nifedipine or diltiazem, or amlodipine are suggested.
- Due to its potential negative inotropic effects, verapamil should be avoided.
- Patients should be followed up closely for both safety and efficacy, with an initial reassessment after 3 months of therapy.
- If a patient does not improve to functional class I or II, additional or alternative PAH therapy should be instituted.

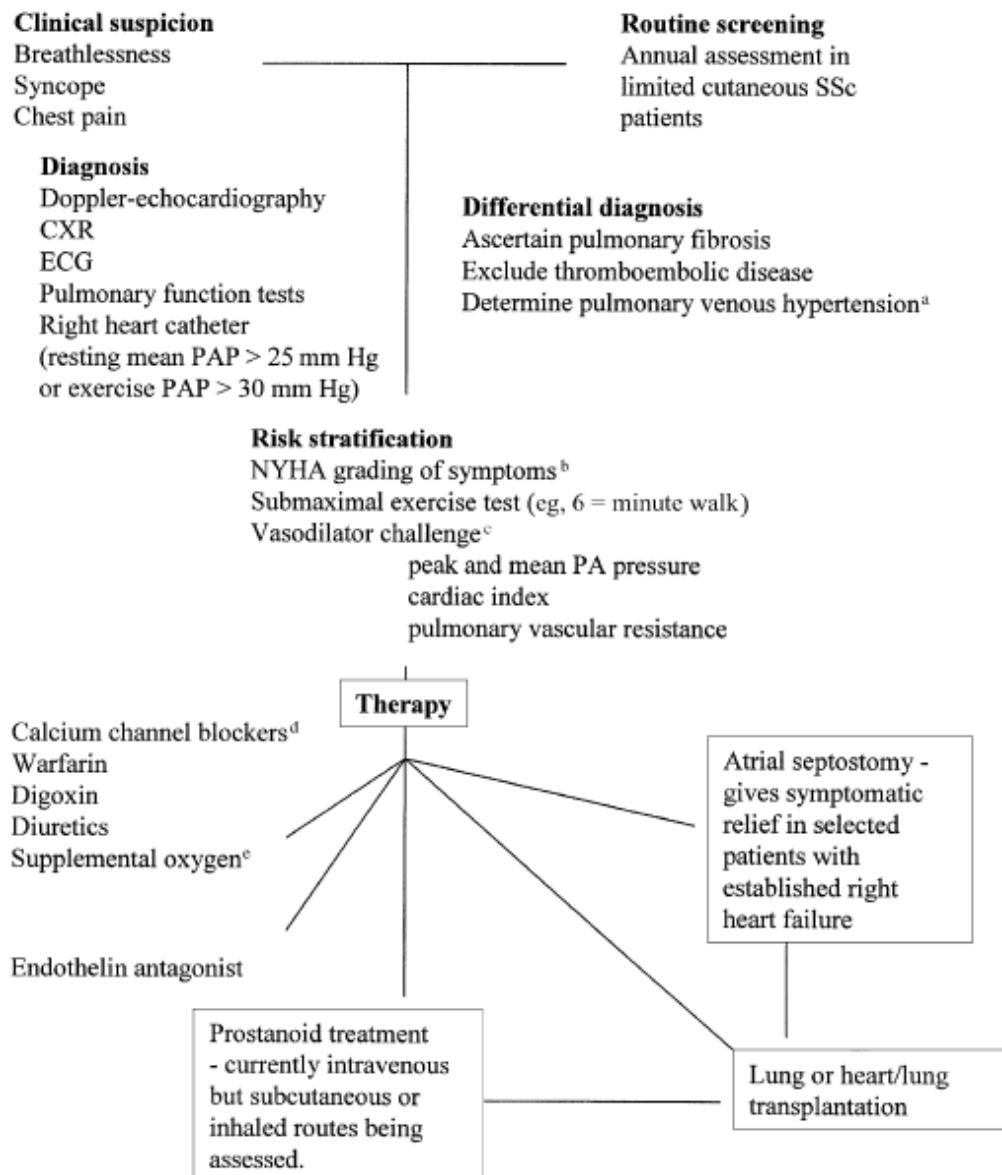
Anticoagulation to be considered

Oxygen to maintain SpO₂ >90%

Update ACCP guidelines 2007 - Treatment



* Not in order of preference.



Unresolved issues

- Whom to screen?
- Screening modality?
- Natural history of mild PAH?
- Effects of treatment of mild PAH?

Conclusions

- Pulmonary arterial hypertension is increasingly being recognised in Systemic sclerosis, SLE, MCTD patients
- Compared to IPAH, patients with CTD- PAH have poor prognosis
- Risk factors and screening algorithms are being evaluated
- Management and treatment options are similar to that of IPAH
- Of all the drugs available, Bosentan has shown significant survival benefit in addition to improvement in symptoms, exercise capacity and hemodynamics
- Natural history of early PAH and impact of treatment in them needs evaluated