# Hypertension pulmonaire et connectivites

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*Société Médicale des Hôpitaux de Paris le 10 octobre 2014*

# Conflicts of interest

- **Consultant**: Actelion, CSL Behring, Cytheris, GSK, LFB Biotechnologies, Lilly, Pfizer
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
- **Financial support (grants)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer

# Updated classif cation of pulmonary hypertension

## Connective tissue diseases

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart diseases
     - 1.4.5 Schistosomiasis
   - 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   - 1'' Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: **chronic hemolytic anemia**, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in **bold**.
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Simmoneau G et al. J Am Coll Cardiol 2013

# Pulmonary arterial hypertension in France : results from a national registry

Humbert M et al. AJRCCM 2006, Feb 2; [Epub ahead of print]

Table 1. Clinical and hemodynamic data at the time of diagnosis of pulmonary arterial hypertension

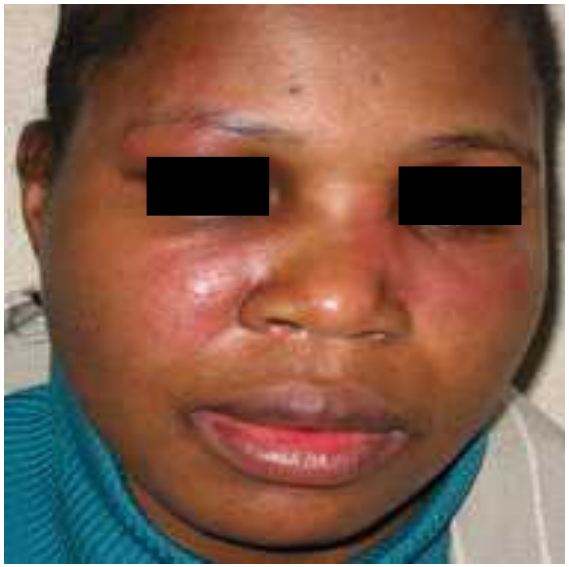
| | All cases | Incident cases | Prevalent cases |
|---|---|---|---|
| **Disease subtype (%)** | | | |
| Idiopathic (n=264) | 39.2 | 40.5 | 38.9 |
| Familial (n=26) | 3.9 | 2.5 | 4.2 |
| Connective tissue diseases (n=103) | 15.3 | 18.2 | 14.6 |
| Congenital heart diseases (n=76) | 11.3 | 4.1 | 12.8 |
| Portal hypertension (n=70) | 10.4 | 14.9 | 9.4 |
| Anorexigens (n=64) | 9.5 | 3.3 | 10.8 |
| HIV infection (n=42) | 6.2 | 9.9 | 5.4 |
| 2 co-existing risk factors (n=29) | 4.3 | 6.6 | 3.8 |

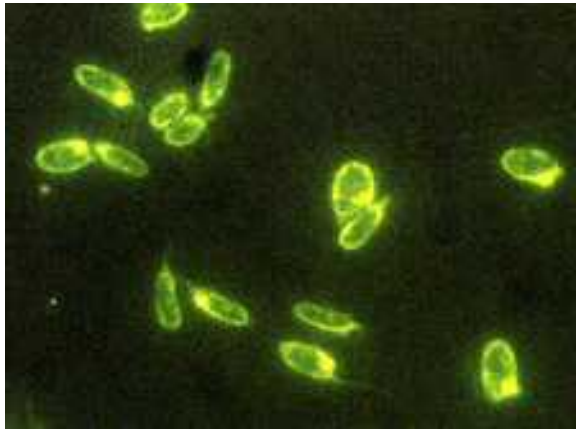
Data expressed as mean ± SD, and range for age

HIV: human immunodeficiency virus; mPAP: mean pulmonary arterial pressure; n=number of cases; NY York Heart Association; PAWP: pulmonary arterial wedge pressure; PVRI: pulmonary vascular resistance in right atrial pressure; SvO2: venous oxygen saturation

*comparisons are for incident versus prevalent cases of pulmonary arterial hypertension

# Classification criteria for SLE (ARA 1982)*





- Malar rash
- Discoid lupus
- Photosensitivity
- Oral or nasal ulcers
- Non erosive arthritis ≥ 2 peripheral joints
- Pericarditis, pleuresis
- Protéinuria ≥ 0,5 g/d
- Seizure or psychosis
- Hemolytic anemia or

Leucopenia < 4000/µl on two occasions *or*
Lymphopenia < 1500/µl on two occasions or
Thrombocytopenia < 100000/µl

- LE cells or

anti-native, double strand DNA or
Anti-Sm *or*
Positive VDRL (negative TPHA) on two occasions at six months intervals

- Abnormal ANA titer in the absence of drug

**4 criteria simultaneous/successive to assess the diagnosis of SLE (sensitivity and specificity of 96%).*

# PAH-SLE: prevalence

| Reference | Number of patients | Definition of PAH | Prevalence |
|---|---|---|---|
| Perez HD 1981 | 43 | Echo | 9.3 % |
| Quismorio FP 1984 | | Echo | |
| Badui E 1985 | 100 | Echo | 9 % |
| Simonson JS 1989 | 36 | syst PAP > 30 mmHg echo | 14 % |
| Winslow TM 1995 | 28 | syst PAP > 30 mmHg echo | 14 (43) % |
| Pan TL 2000 | 786 | syst PAP > 30 mmHg echo | 7.5 % |
| Johnson SR 2004 | 117 | syst PAP > 40 mmHg echo | 14 % |

# Characteristics of 93 SLE patients according to pulmonary hypertension status

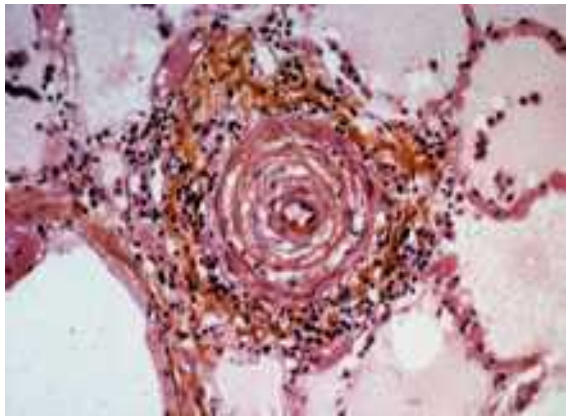
| | No PH group n = 81 | PH group n = 12 | | p* |
|---|---|---|---|---|
| **Demographics** | | | | |
| SLE duration at evaluation, (mean ± SD) years | 9.5 ± 8 | 14 ± 8 | | 0.049* |
| **Clinical,** n (%) | | | | |
| Péricarditis | 22 (27) | 7 (58) | | 0.04* |
| PNS involvement | 3 (4) | 3 (25) | | 0.02* |
| **Antibodies detected,** n (%) | | | | |
| Anti-Sm antibodies | 9 (11) | 5 (42) | | 0.01* |
| Anti-cardiolipin antibodies | 25 (31) | 9 (75) | | 0.007* |

Fois E et al. Clin Exp Rheumatol. 2010 Nov-Dec;28(6):836-41

# SYSTEMIC SCLEROSIS

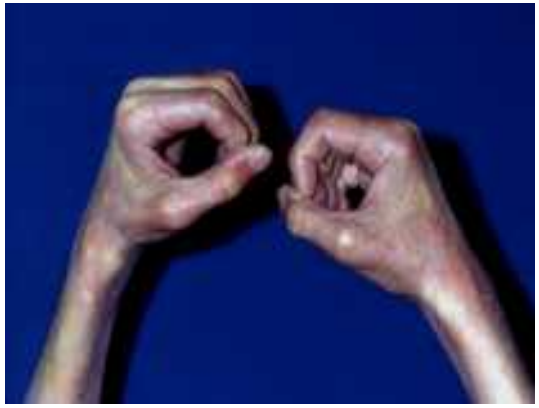
## ➢Vascular hyperreactivity

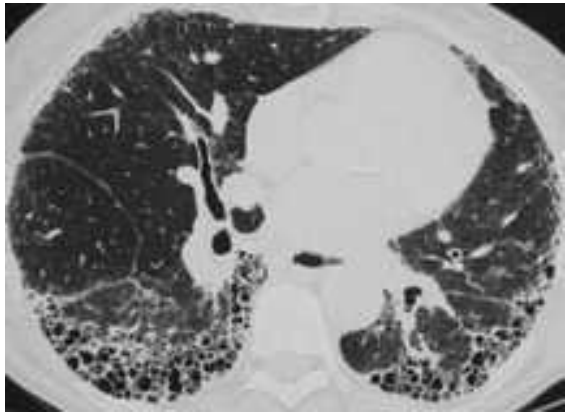
Raynaud's phenomenon
Renal crisis
Pulmonary arterial hypertension



## ➢Fibrosis

Skin
Lung
Bowell
Heart

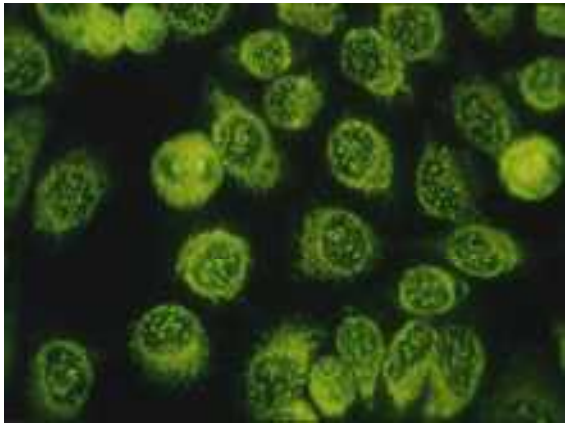


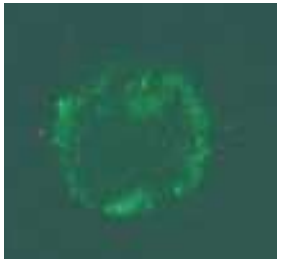


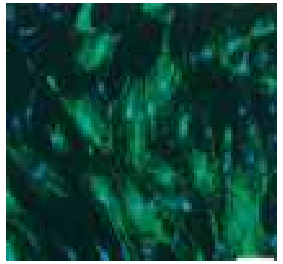
## ➢Autoimmunity

Autoantibodies
- Anti-Scl70
- Anti-centromere
- Anti-ARNPolIII

Ac anti-fibroblasts







# Systemic sclerosis: prevalence

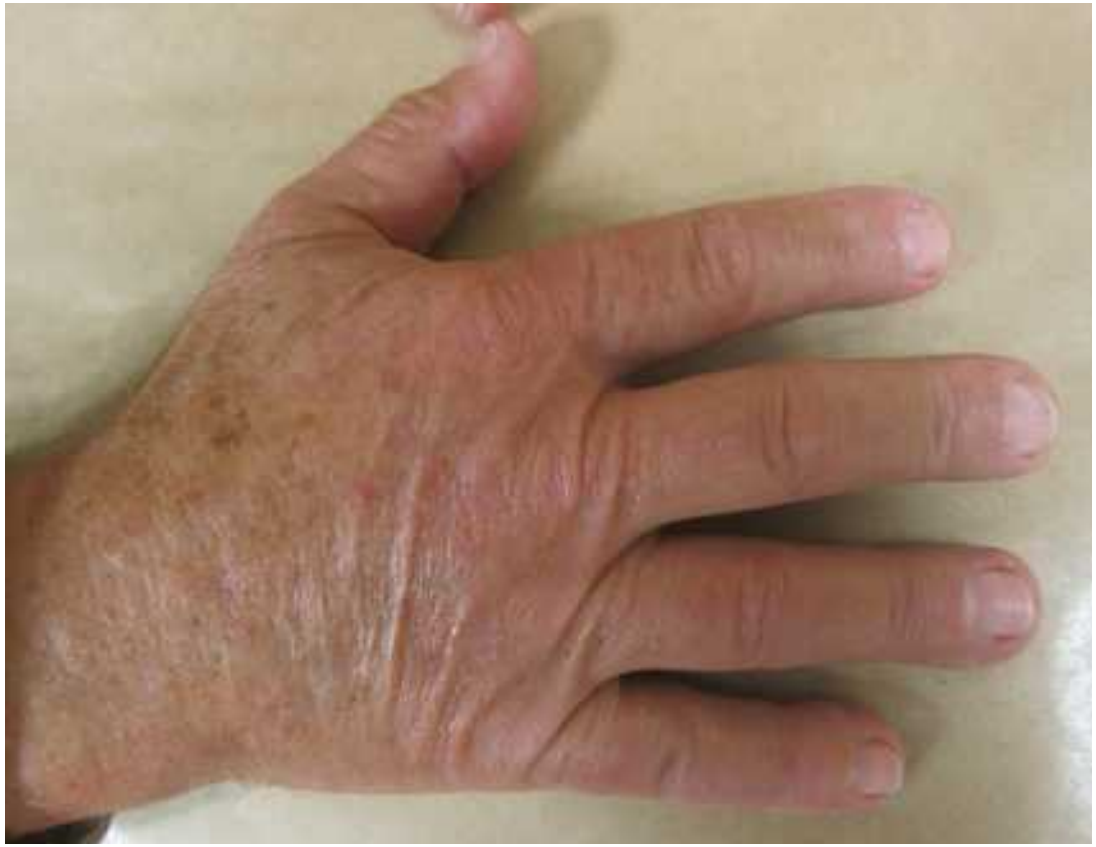
| Authors | States | technique | Prevalence /million |
|---|---|---|---|
| **USA** | | | |
| Michet | Rochester | Hospital | **138** |
| Mayes | Detroit | Multiples sources | **242** |
| Maricq | Caroline du sud | Population | **190-750** |
| **Océanie** | | | |
| Chandran | South Australia | | **147-208** |
| Roberts-Thomson | South Australia | Multiples sources | **233** |
| **Asie** | | | |
| Shinkai | Japon | Public health | **7** |
| Tamaki | Tokyo | Public health | **21-53** |
| **Europe** | | | |
| Silman | West midland | Multiples sources | **31** |
| Asboe-Hansen | Danemark | Hospital | **126** |
| **Le Guern** | **Seine St Denis, France** | **Multiples sources** | **158** |

# 2013 classification criteria for SSc: an ACR/EULAR collaborative initiative (I)

- Skin thickening of the fingers extending proximal to the metacarpophalangeal joints: SSc;
- If that is not present, 7 additive items apply:
  - skin thickening of the fingers,
  - fingertip lesions,
  - telangiectasia,
  - abnormal nailfold capillaries,
  - interstitial lung disease or pulmonary arterial hypertension,
  - Raynaud's phenomenon,
  - SSc-related autoantibodies.

van den Hoogen F et al. Ann Rheum Dis 2013

# Skin thickening of the fingers (I)



Score = 2

Only count higher score

**Puffy fingers**

# Skin thickening of the fingers (II)

Sclerodactily

Score = 4

Only count higher score

# fingertip lesions

Digital ulcers

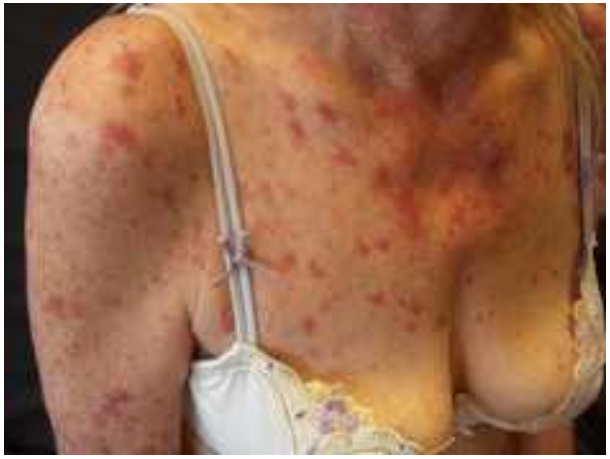
Score = 2

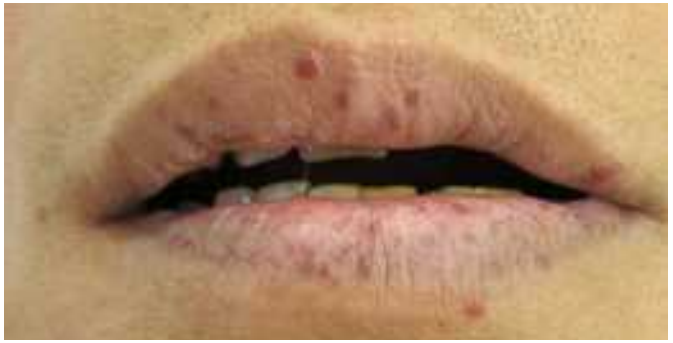
Fingertip pitting scars

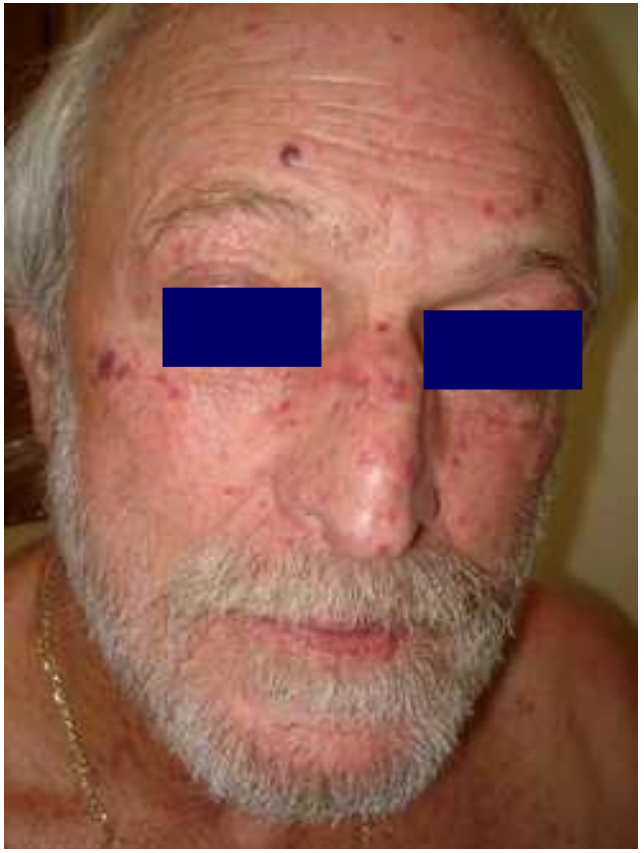
Score = 3

Only count higher score

# telangiectasia



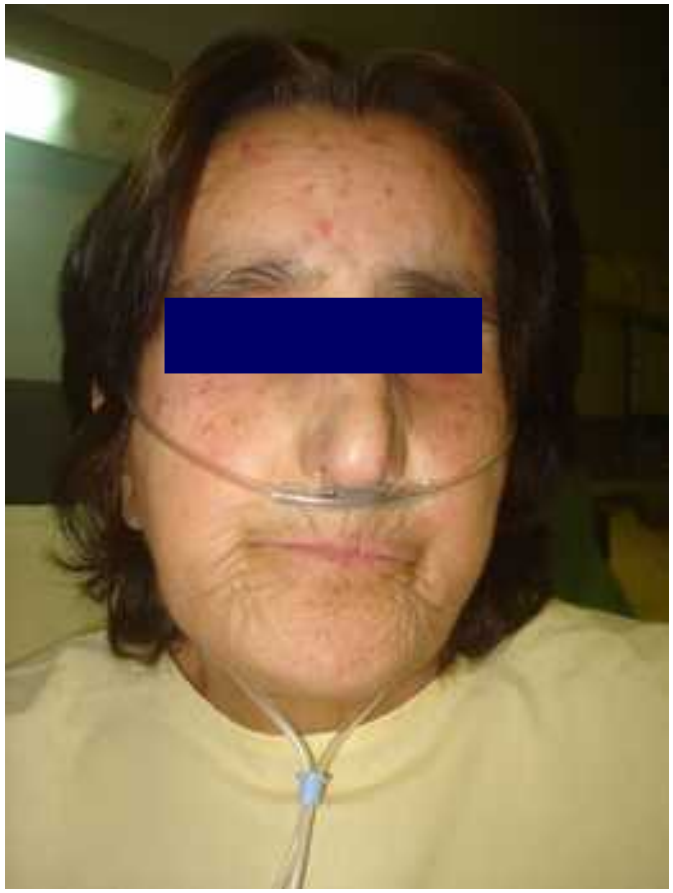


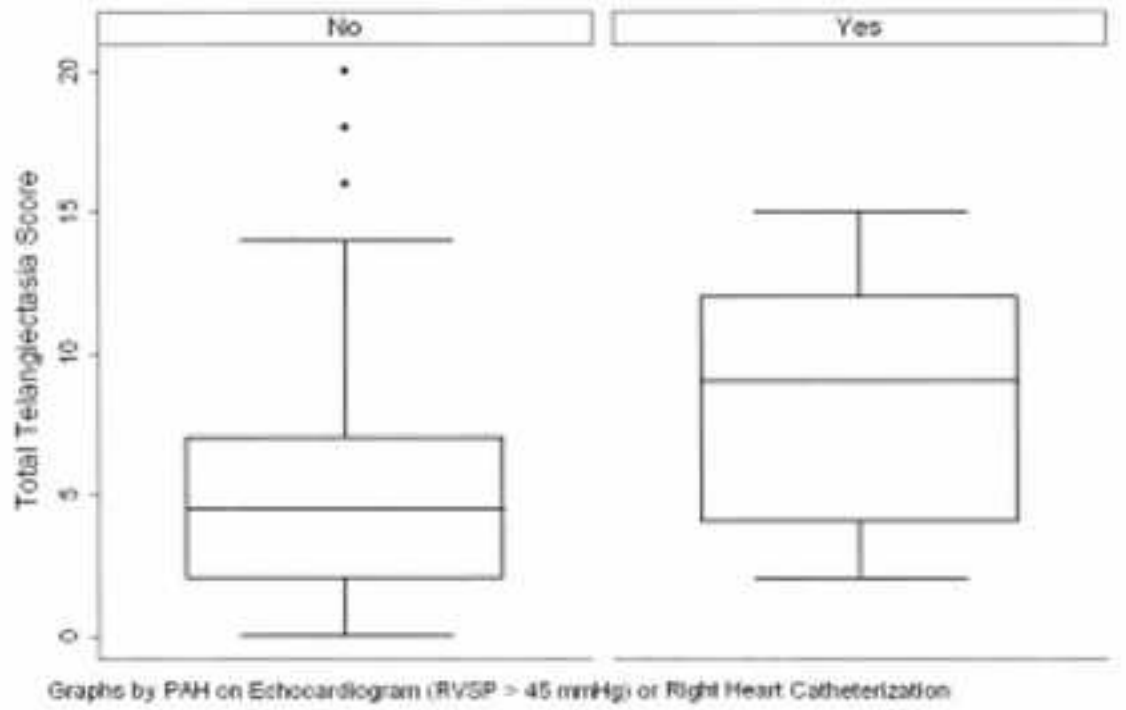


Score = 2

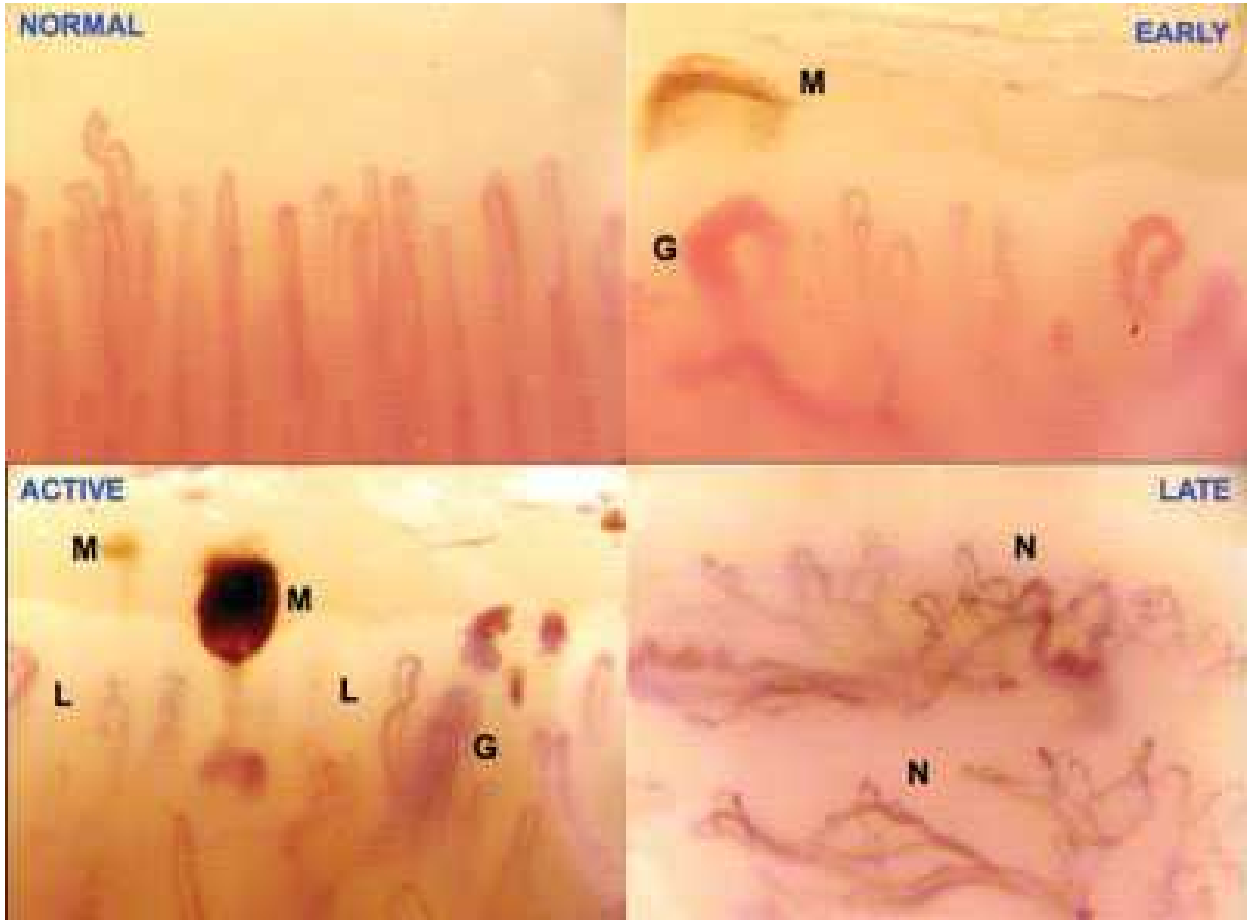
# Telangiectases in Scleroderma: A Potential Clinical Marker of Pulmonary Arterial Hypertension

**Shah et al. J Rheumatol 2010**





# Abnormal nailfold capillaries

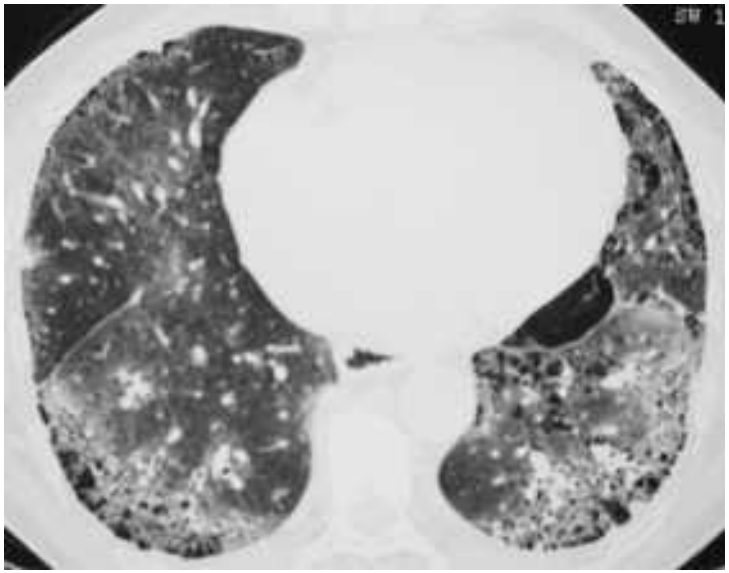



Score = 2

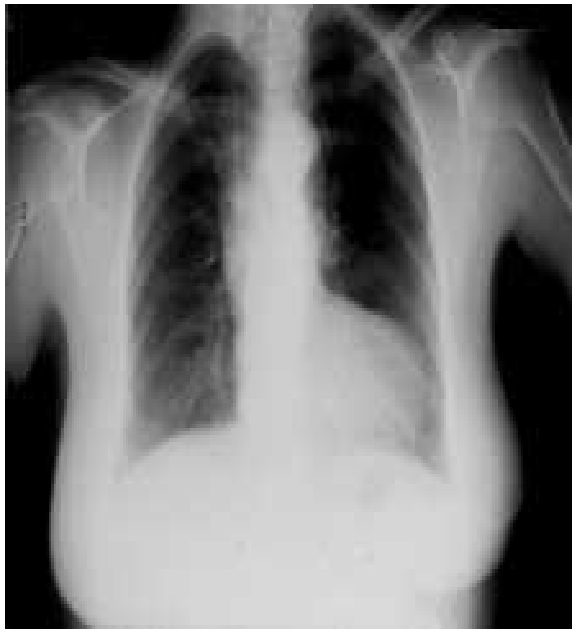
# Interstitial lung disease/pulmonary arterial hypertension

Score = 2

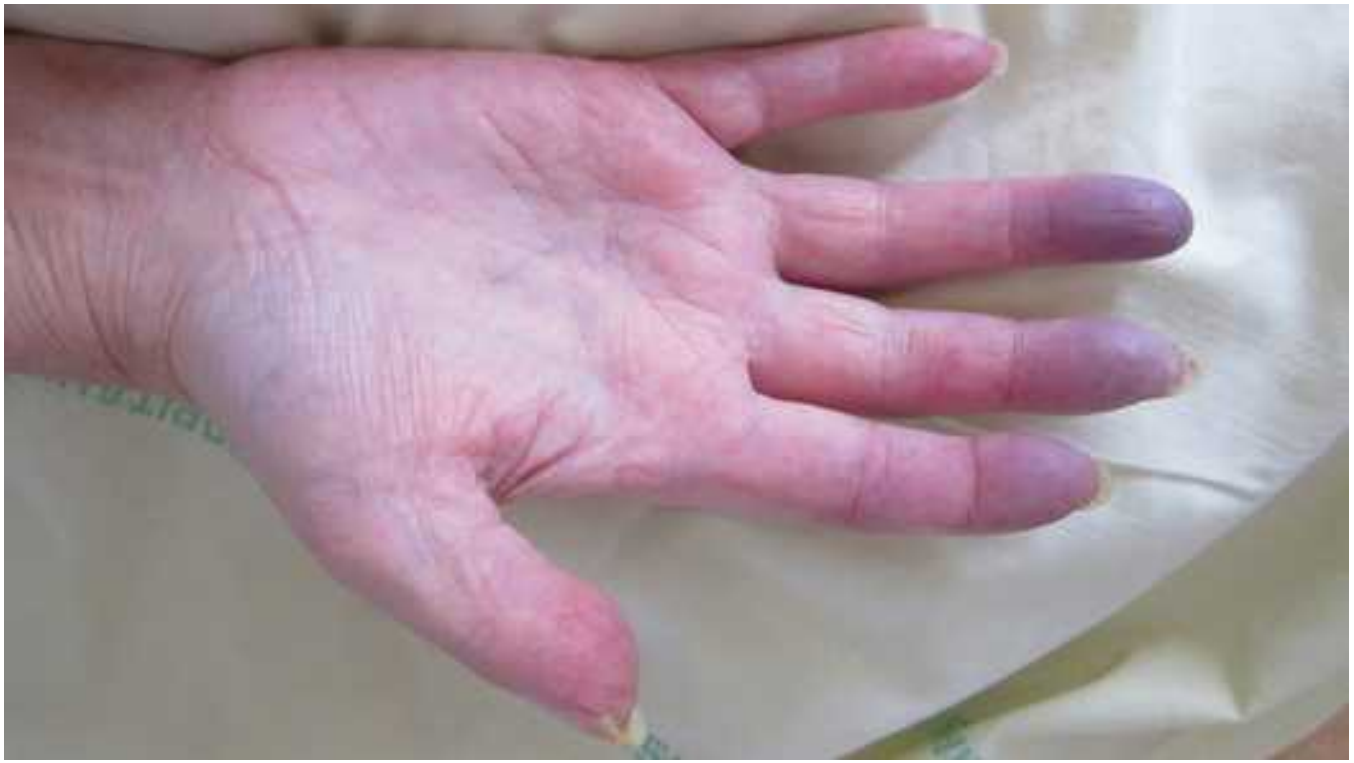
Score = 2



Maximum score = 2



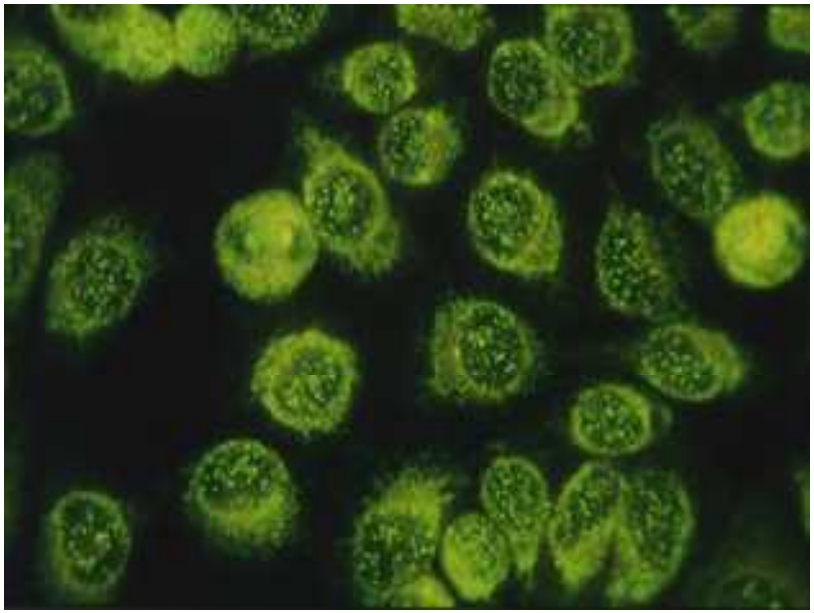
# Raynaud's phenomenon



Score = 3

# SSc-related autoantibodies

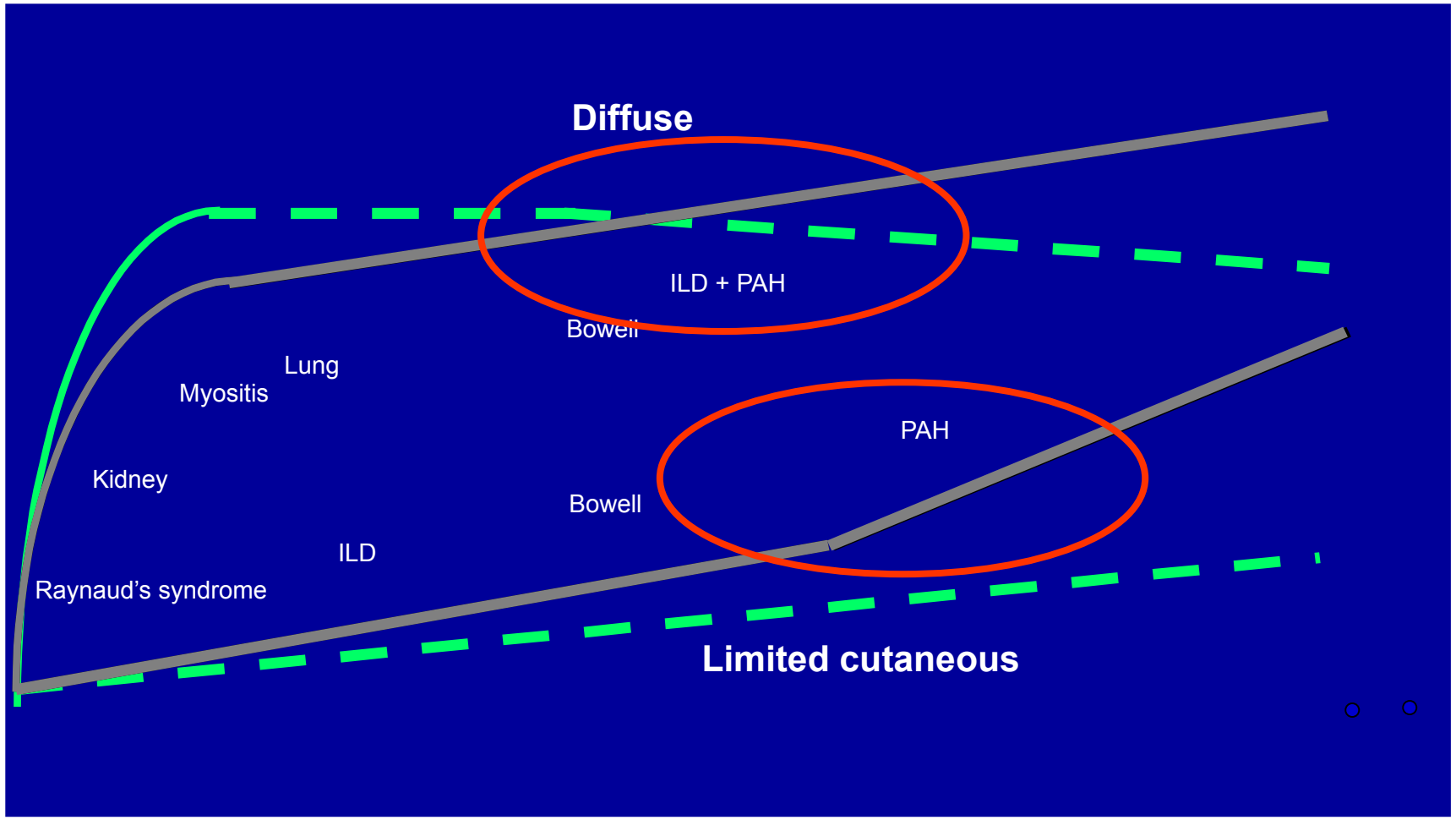
Anti-centromere
Anti-topoisomerase I
Anti-RNA polymerase III



Score = 3

Maximum score = 3

# SYSTEMIC SCLEROSIS : EVOLUTION



# HTAP-ScS: prévalence

| Auteur | Année de publication | Pays | Définition HTAP (cathétérisme cardiaque droit) | Prévalence |
|---|---|---|---|---|
| Mukerjee et al. | 2003 | Royaume Uni | PAPm> 25 mmHg au repos ou > 30 à l'effort et CPC < 14 mmHg | 12% (86/722) |
| Hachulla E, et al. | 2005 | France | PAPm ≥25mmHg au repos, ou ≥30mmHg à l'effort et PCP < 15mmHg | 7,85% (47/599) |
| Vonk, et al. | 2009 | Pays-Bas | PAPm ≥25mmHg au repos et PCP normale | 9,9% (113/1,148) |
| Phung, et al. | 2009 | Australie | PAPm ≥25mmHg au repos, ou ≥30mmHg à l'effort et PCP < 15mmHg et RPV> 240 dyn/s/cm² | 13% (24/184) |
| Avouac, et al. | 2010 | France et Italie | PAPm ≥25mmHg au repos, ou ≥30mmHg à l'effort et PCP < 15mmHg en absence de fibrose pulmonaire | 3,6% (42/1,165) |
| Hsu et al. | 2014 | Amérique du Nord | PAPm ≥25mmHg au repos, ou ≥30mmHg à l'effort et PCP < 15mmHg | 13,9% (35/251) |

Legendre P, Mouthon L. Presse Med 2014

# Pulmonary vascular remodeling in SSc-PAH

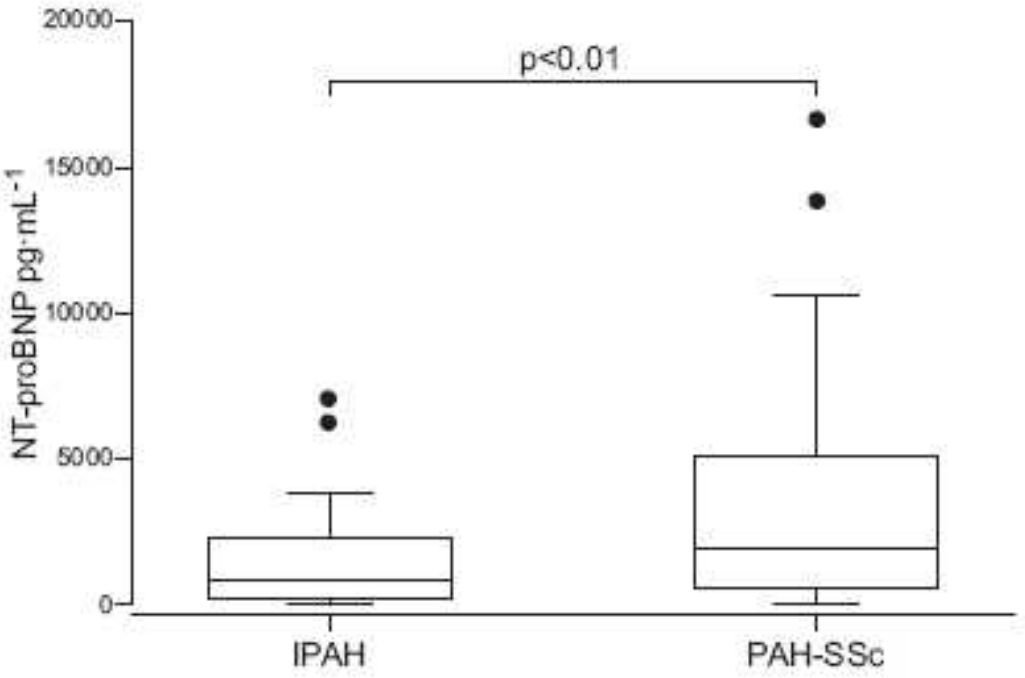
Le Pavec J et al 2010 AJRCCM

# Disproportionate elevation of N-terminal pro-brain natriuretic peptide in SSc-related pulmonary hypertension

Mathai et al. Eur Resp J 2010

NT-proBNP levels are

1) **significantly higher in PAH-SSc than IPAH** despite less severe haemodynamic perturbations,
2) **stronger predictors of survival in PAH-SSc,** suggesting tha t neurohormonal regulation may differ between PAH-SSc and IPAH.

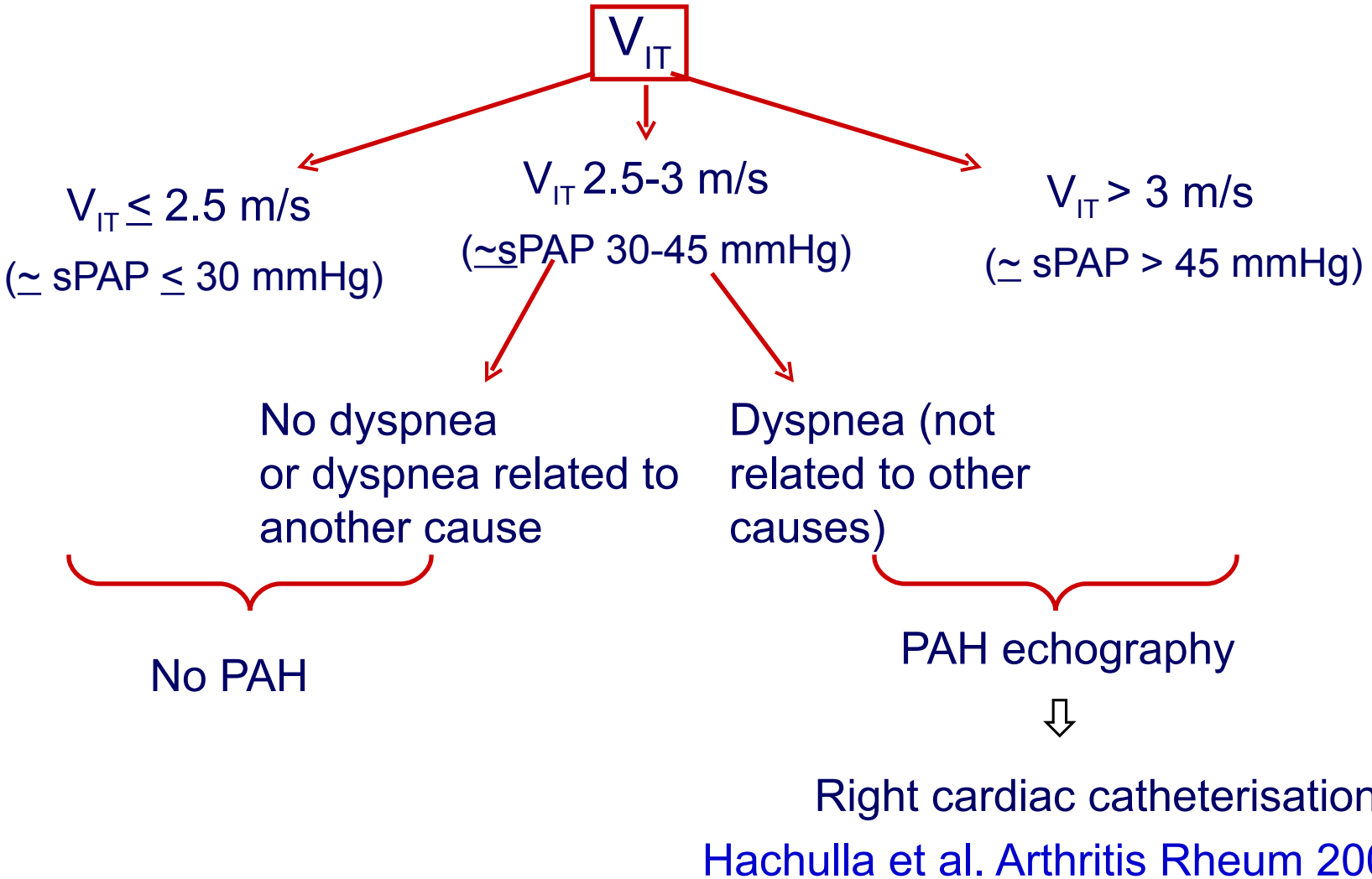



Box and whisker plots of the N-terminal pro-brain natriuretic peptide (NT-proBNP) levels measured in IPAH and PAH-SSc patients.

# PAH-SSc: Prevalence

| Reference | Methodology | Number of patients | SSc profile | PAH definition | PAH prevalence |
|---|---|---|---|---|---|
| RG Ungerer 1983 USA | ▪ Prospective<br>▪Monocentric<br>▪1973 to 1979 | 49 | Proximal SSc and CREST | ▪Mean PAP ≥ 20 mmHg and mean PCP ≤ 12 mmHg (right heart catheterization) | 16% |
| I. Murata 1992 Japan | ▪Prospective<br>▪Monocentric<br>▪1988 to 1991 | 71 | SSc and MCTD | ▪$V_{IT}$ ≥ 2,5 m/s Doppler Echo | 17% |
| R. Battle 1996 USA | ▪Prospective<br>▪Monocentric | 34 | **Diffuse or limited c SSc** | ▪PAPs ≥ 30 mmHg Doppler Echo | 35% |
| ET Koh 1996 Canada | ▪Prospective<br>▪Monocentric<br>▪1978 to 1994 | 344 | **Diffuse or limited cutaneous SSc** | ▪PAPm ≥ 25 and cap m ≤ 12 mmHg upon RHC, or<br>▪Ps VD > 35 mmHg (echo)<br>▪ or RV dilatation, P or T insufficiency, or paradoxical septum motion upon echo | 4,9% |
| AJ MacGregor, 2001 UK | ▪Prospective<br>▪Monocentric<br>▪1992 to 1997 | 152 | **Diffuse or limited c SSc** | ▪PAPs > 30 mmHg Doppler Echo | 13% |
| **D Mukerjee, 2003 UK** | ▪Prospective<br>▪Monocentric<br>**▪1998 to 2002** | **722** | **Diffuse or limited c SSc** | **▪mPAP > 25 mmHg at rest or > 30 at exercise pulmonary capillary < 14 mmHg** | **12 %** |
| **Hachulla et al 2005 France** | ▪Prospective<br>▪Multicentric<br>**▪2002-3** | **599** | **Diffuse or limited c SSc** | **▪mPAP > 25 mmHg at rest or > 30 at exercise pulmonary capillary < 14 mmHg** | **7.85%** |

# Cardiac EchoDoppler
# PAH definition




Hachulla et al. Arthritis Rheum 2005

# Cardiac catheterisation (n=33)

- PAH : 18

- [mPAP > 25 mmHg at rest or > 30 mmHg at exercise with PAwP < 15 mmHg]
  - 25-35 mmHg: 14
  - 35-45 mmHg: 3
  - 45 mmHg: 1
- Post-capillary “venous”pulmonary hypertension: 3 (10%)
- No PAH : 12 => 6 with mPAP > 20 mmHg

Hachulla et al. Arthritis Rheum 2005

# Estimated incidence of pulmonary hypertension during the 3-year followup period*

| | Estimated incidence (no. of cases per 100 patient-years) | 95% CI |
|---|---|---|
| All forms of pulmonary hypertension | 1.37 | 0.74–2.00 |
| Pulmonary arterial hypertension | 0.61 | 0.26–1.20 |
| Among patients with lcSSc | 0.40 | 0.11–1.03 |
| Among patients with dcSSc | 1.25 | 0.34–3.20 |
| Postcapillary pulmonary hypertension | 0.61 | 0.26–1.20 |
| Pulmonary hypertension secondary to pulmonary fibrosis | 0.15 | 0.02–0.55 |

* 95% CI = 95% confidence interval; lcSSc = limited cutaneous systemic sclerosis; dcSSc = diffuse cutaneous systemic sclerosis.

Hachulla et al. Arthritis Rheum 2009

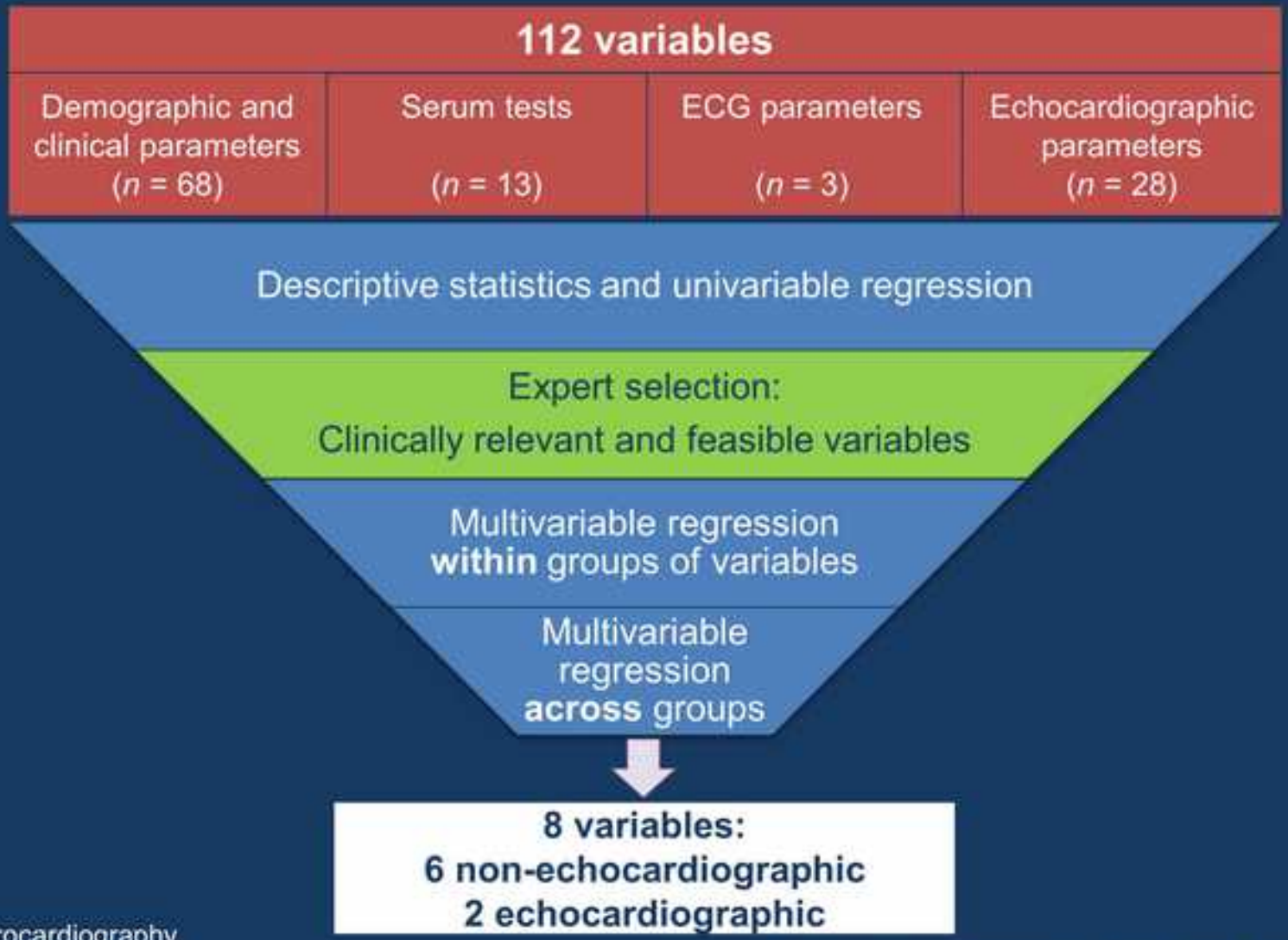
# DETECT study: Main objective

- Prospectively develop an evidence-based screening algorithm for PAH in SSc patients that would
  - Minimise the number of missed PAH diagnoses
  - Optimise the use of diagnostic right heart catheterisation



Coghlan JG, *et al. Ann Rheum Dis* 2013; Epub ahead of print.

# Selection of screening variables in the DETECT study

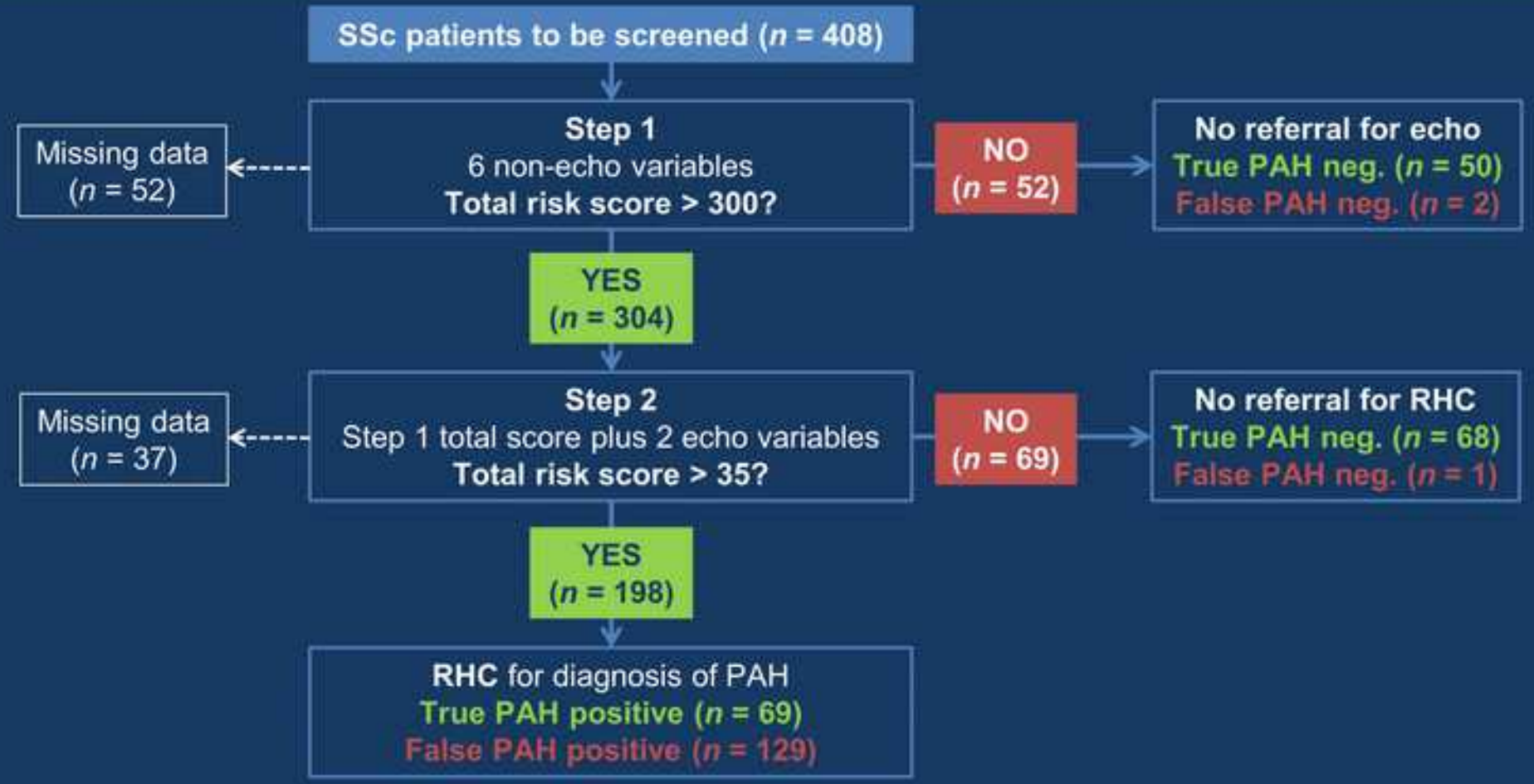



ECG: electrocardiography

*38; 20 October 2013*

Coghlan JG, *et al. Ann Rheum Dis* 2013; Epub ahead of print.

# DETECT: Two-step decision tree performance




For step 1: ROC AUC = 0.844 (95% CI, 0.795, 0.898)
For step 2: ROC AUC = 0.881 (95% CI, 0.824, 0.923)

ROC: receiver operating characteristic; AUC: area under the curve

*39; 20 October 2013*

Coghlan JG, *et al. Ann Rheum Dis* 2013; Epub ahead of print.

# Detect: results

- Six simple assessments in Step 1 of the algorithm determined referral to echocardiography.
  - FVC % predicted/DLCO %predicted
  - Current/past telangiectasia
  - Anti-centromere Abs
  - Serum NT-pro-BNP
  - Serum urate
  - ECG: right axis deviation
- In Step 2, the Step 1 prediction score and two echocardiographic variables determined referral to RHC.
  - Right atrium area
  - TR velocity

Coghlan G, ARD, 2013

# DETECT online PAH risk calculator

DETECT
DETECTion of PAH in SSc

HOME | WHAT IS DETECT? | PAH RISK CALCULATOR | ABOUT SSC AND PAH | SUPPORTING INFORMATION

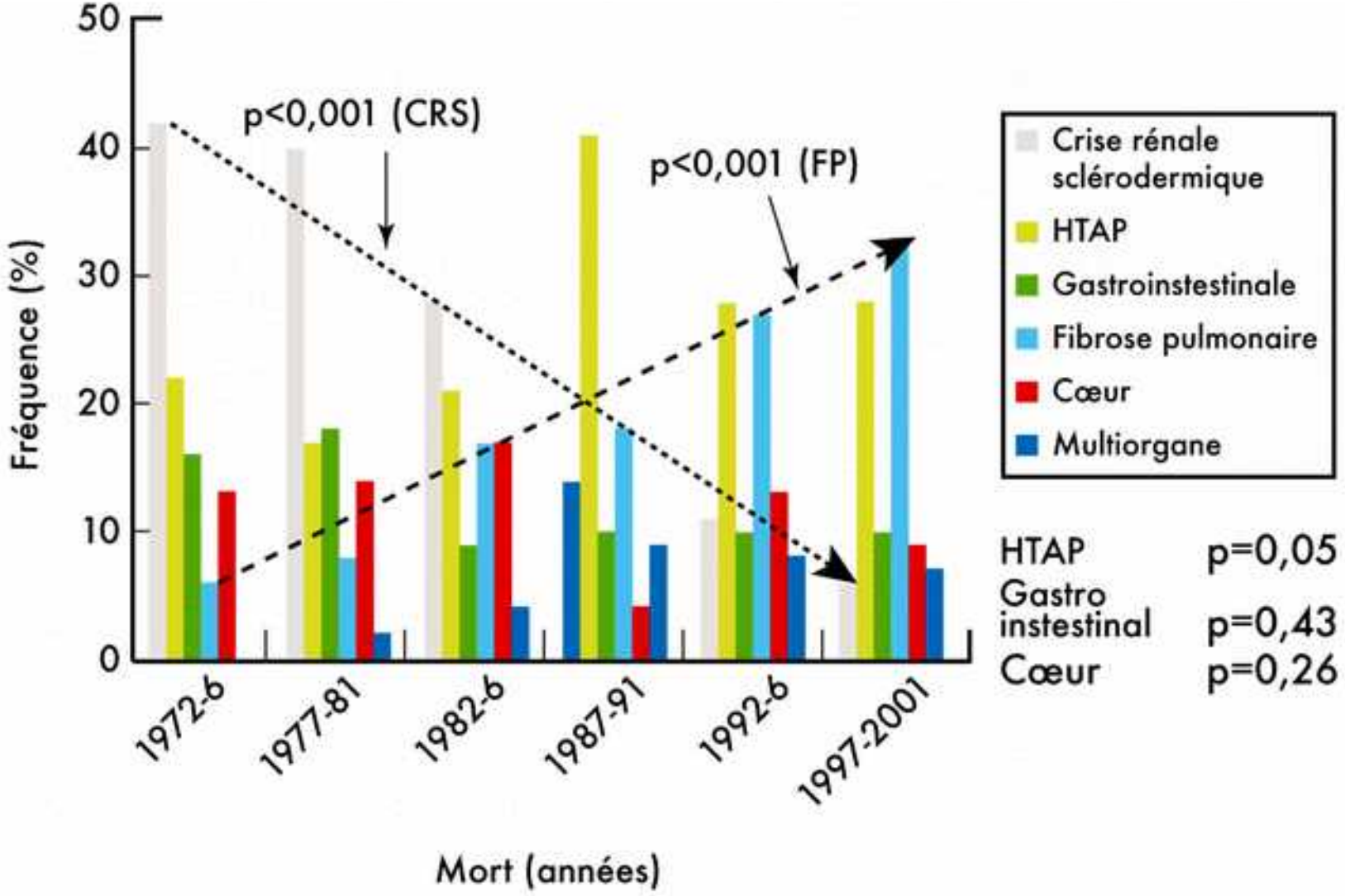
## WELCOME TO THE PAH RISK CALCULATOR

The PAH risk calculator is a tool for all physicians dealing with systemic sclerosis (SSc). The calculator was developed and validated in the DETECT study. The DETECT study was designed and carried out by a group of experts, all of whom are physicians practising in different countries, and was supported by Actelion Pharmaceuticals Ltd.

The calculator was developed for your daily clinical practise. It will help you to identify and diagnose SSc patients with pulmonary arterial hypertension (PAH), which is a serious condition that develops in 8-13% of SSc patients and is the leading cause of death in patients with this disease. The calculator is based on an algorithm with a high sensitivity and specificity and can help you to decide which of your SSc patients should be evaluated using echocardiography, and of those patients who should be referred for right heart catheterization.


START CALCULATOR

# Changes in causes of Systemic Sclerosis related deaths between 1972 and 2001




Steen et Medsger. Ann Rheum Dis 2007

# Causes of death in SSc patients

TABLE 2. Causes of death observed in the total population

| Causes of death, *n* (%) | All patients (*n* = 546) |
|---|---|
| Total number of deaths | 47 (8.6) |
| Scleroderma-related causes of death | 24 (4.4) |
| PAH | 17 |
| Pulmonary fibrosis | 2 |
| Gastrointestinal | 2 |
| Renal crisis | 3 |
| Non-scleroderma-related causes of death | 23 (4.2) |
| Cancer | 8 |
| Infection | 4 |
| Cardiovascular or cerebrovascular atherosclerosis | 2 |
| Other cause | 2 |
| Unknown cause | 7 |

Hachulla et al. Rheumatology 2009

## The impact of comorbidities

- Age
- Myocardial involvement
- Musculoskeletal involvement
- Pulmonary fibrosis
- Pulmonary Veno-Occlusive Disease

# SSc-PAH: why a so bad prognosis?

**Table 3.** Baseline echocardiographic findings*

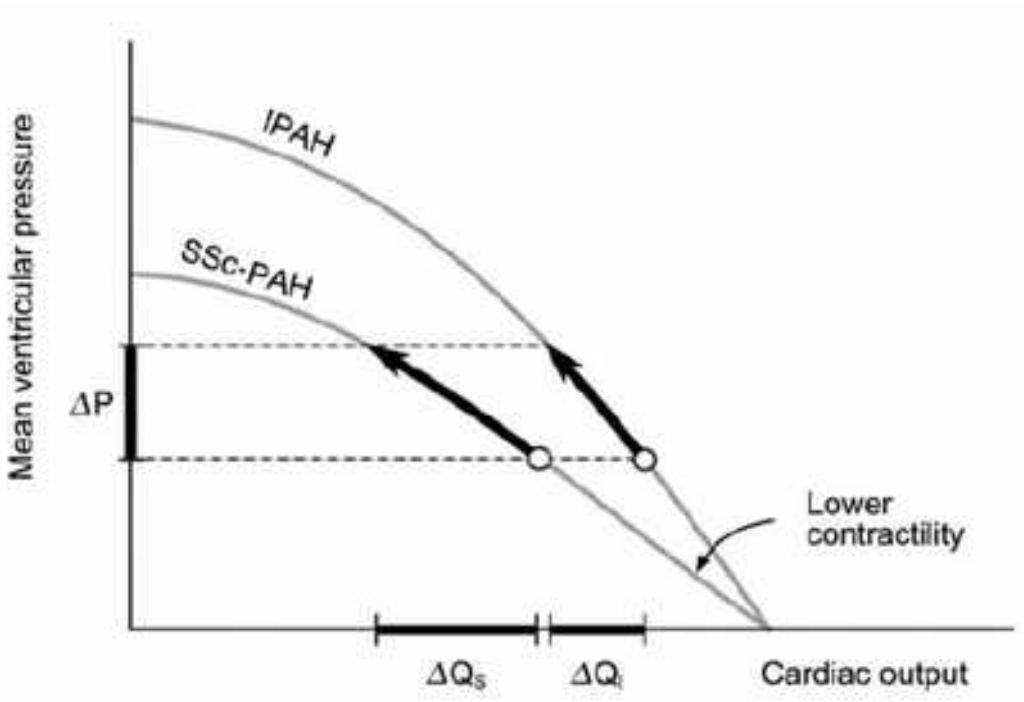
| | IPAH (n = 38) | PAH-Scl (n = 49) | *P* |
|---|---|---|---|
| Right atrial dilation | 31 (81.6) | 36 (73.5) | 0.37 |
| Right ventricular dilation | 34 (89.5) | 39 (79.6) | 0.21 |
| Right ventricular hypertrophy | 7 (18.4) | 5 (10.2) | 0.27 |
| Left atrial diameter, mean ± SEM cm | 3.3 ± 0.2 | 3.8 ± 0.1 | 0.004 |
| Left atrial dilation | 4 (10.5) | 14 (28.6) | 0.039 |
| Left ventricular hypertrophy | 5 (13.2) | 17 (34.7) | 0.022 |
| Left ventricular ejection fraction, mean ± SEM | 57.3 ± 1.6 | 55.7 ± 1.4 | 0.44 |
| Diastolic dysfunction | 5 (13.2) | 16 (32.7) | 0.035 |
| Pericardial effusion | 5 (13.2) | 17 (34.7) | 0.022 |

* Except where indicated otherwise, values are the number (%). See Table 1 for definitions.

- Multivariate analysis, factors associated with increased death:
  - Left ventricular dysfunction
  - Pericardial effusion

Fisher *et al.* Arthritis Rheum 2006

# Right ventricular function in SSc-PAH




- SSc-PAH has a poorer exercise capacity and worse prognosis than those reported in other types of PAH.
- This appears related to a relative RV failure, explained by altered contractility and maybe also decreased pulmonary arterial compliance.

Overbeek *et al.* ERJ 2008

# PAH complicating Pulmonary fibrosis

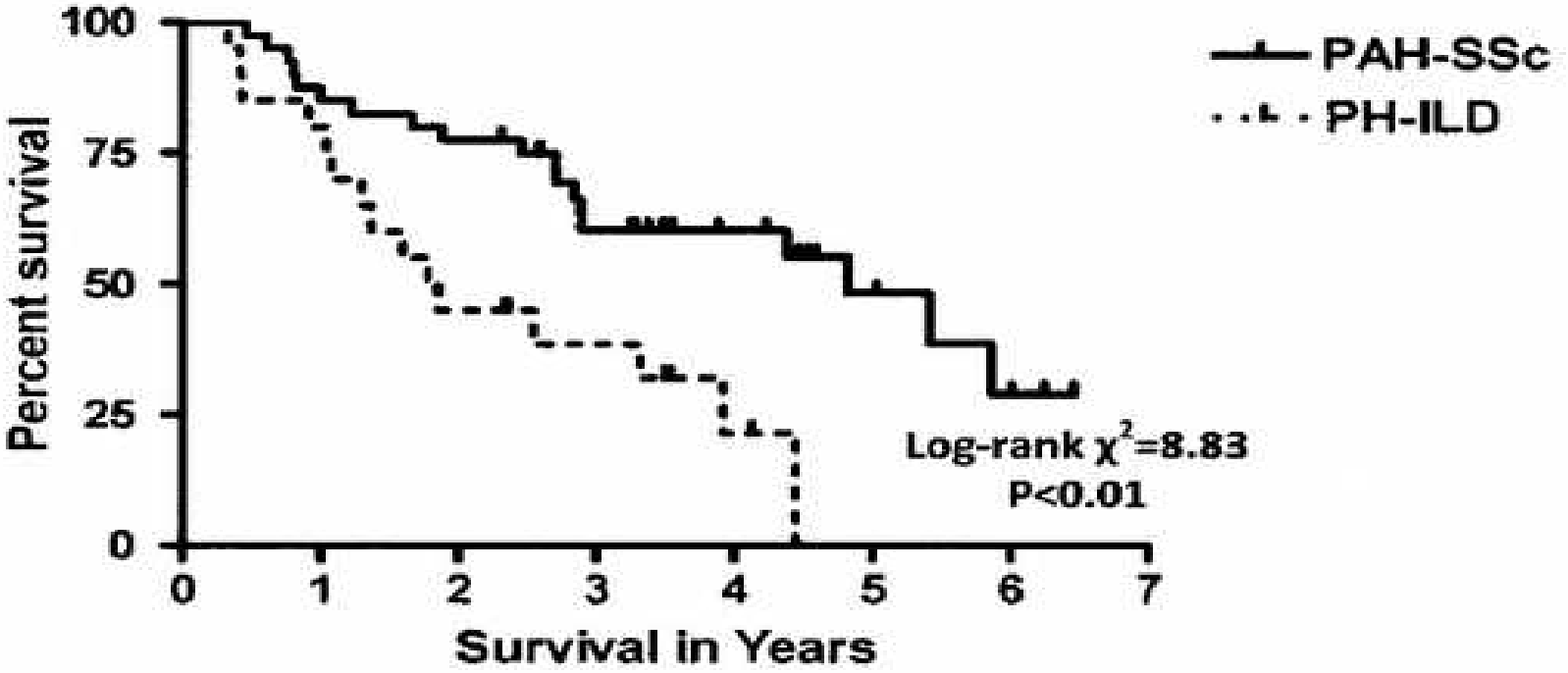
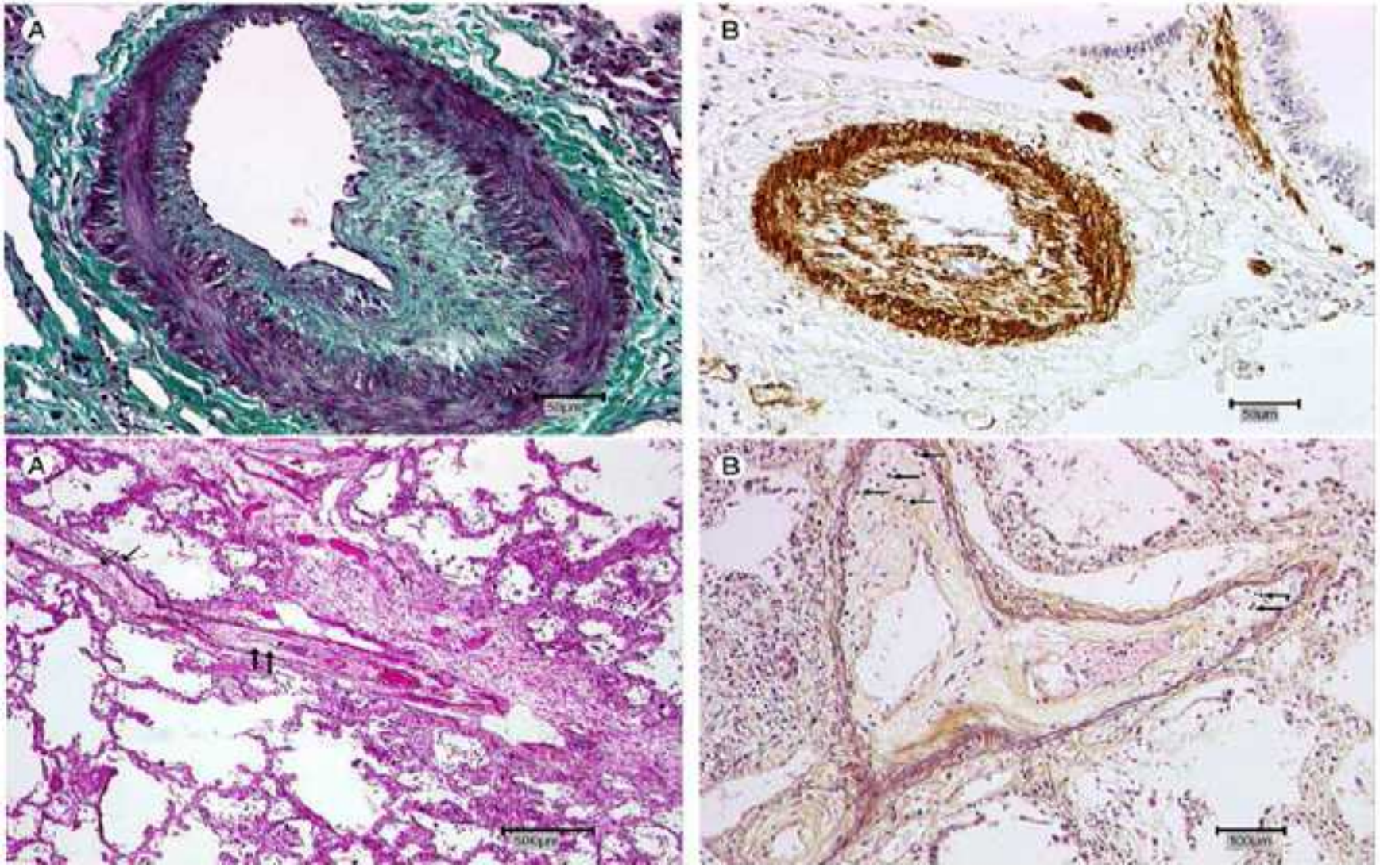



**Figure 1.** Kaplan-Meier survival graph comparing patients with systemic sclerosis (SSc) and pulmonary arterial hypertension (PAH) with those with SSc and interstitial lung disease (ILD)–associated pulmonary hypertension (PH). The x-axis shows years from diagnosis of PH by right heart catheterization.

*Mathai et al,Arthritis Rheum. 2009;60:569---77*

# Fibrous remodeling of the pulmonary venous system in PAH associated with CTD

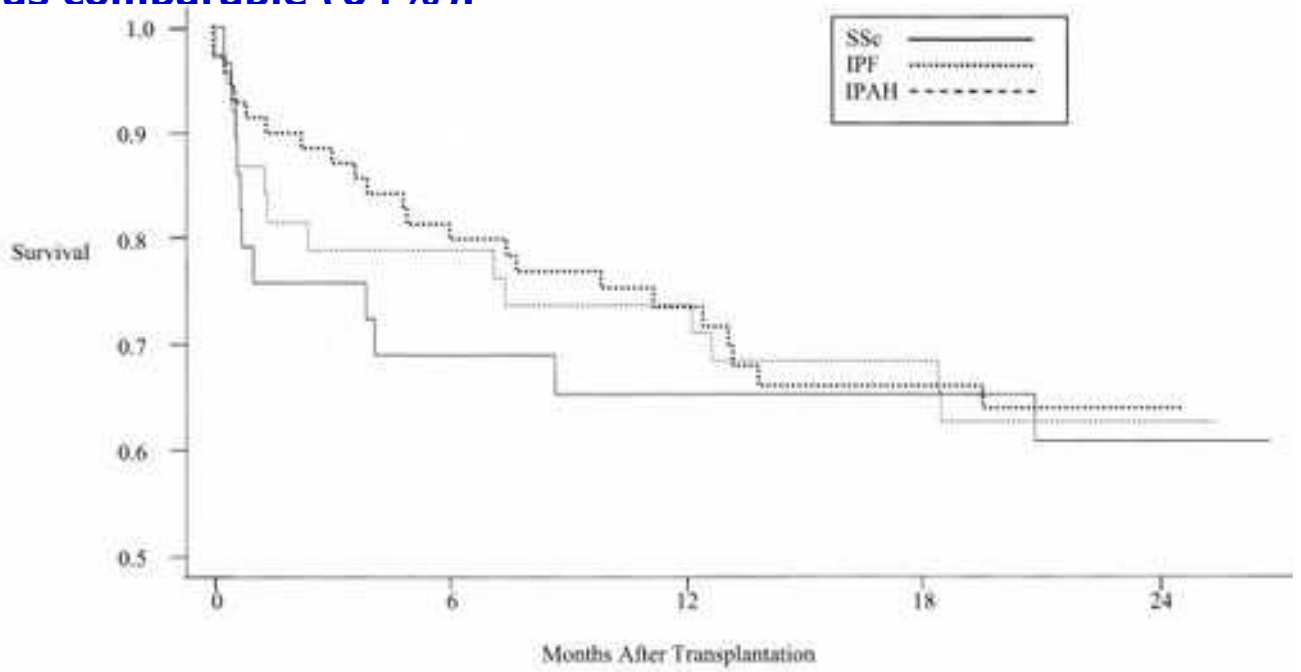


# SSc-PAH: treatment

- Preventive measures
- Conventionnal medical treatment (O2 - diuretics - anticoagulants)
- Calcium chanel blockers
- Epoprostenol continuous infusion
- Endothelin receptor antagonists
- PDE-5 inhibitors/GC stimulators
- Combined treatments
- Lung transplantation

# Lung transplantation

- **29 SSc patients vs 70 patients with IPF and 38 with IPAH**
- **End point: death.**
- **During 2 years of followup, 11 patients with scleroderma (38%), 23 with IPF (33%), and 14 with IPAH (37%) died.**
- **Cumulative survival at 6 months posttransplantation was 69% in the scleroderma group compared with 80% in the IPF group (log-rank P = 0.21) and 79% in the IPAH group (P = 0.38). Cumulative survival at 2 years was comparable (64%).**




Schachna L. et al. Arthritis Rheum 2006

# Some PAH patients with associated CTD may improve with anti-inflammatory agents

- Retrospective analysis of clinical and haemodynamic effects of immunosuppressants given 1st therapy to 28 patients with PAH-CTD
- All patients received monthly intravenous pulse cyclophosphamide (600 mg/m$^2$) during at least 3 months and 22 out of 28 patients received oral prednisone
- 9 (32%) patients were responders (SLE 6/12 and MCTD (3/8). None of the 8 patients with SSc responded
- At 1 year of therapy, “responders” to immunosuppressive therapy were those who could be reclassified in New York Heart Association (NYHA) functional class I or II

*Sanchez et al. Chest 2006*

# A number of patients with PAH improved with anti-inf ammatory agents

- Immunosuppressive therapy in connective tissue disease associated PAH (Sanchez O et al Chest 2006)
- Immunotherapy in SLE and MCDT associated PAH (Jaïs X et al Arthritis Rheum 2008)
- Reversibility of PAH in HIV/HHV8-associated Castlemann disease (Montani et al Eur Respir J 2005)
- PAH: a rare complication of primary Sjogren's syndrome (Launay D et al, (Baltimore) 2007)

# Conclusions

- PAH rare manifestation of SLE
- Treatment: combination of Immunosuppressants and classical PAH treatments.
- 8-12% of SSc patients develop PAH/Incidence 0.6%
- Detection: echocardiography
- Comfirmation: Right heart catheterization (treshold….)
- Detect algorithm: step 1 and step 2
- Prognosis: reserved
- Impact of comorbidities
- New treatments/combined treatments
- Lung transplantation

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