



HTAP liée aux connectivites

Luc Mouthon

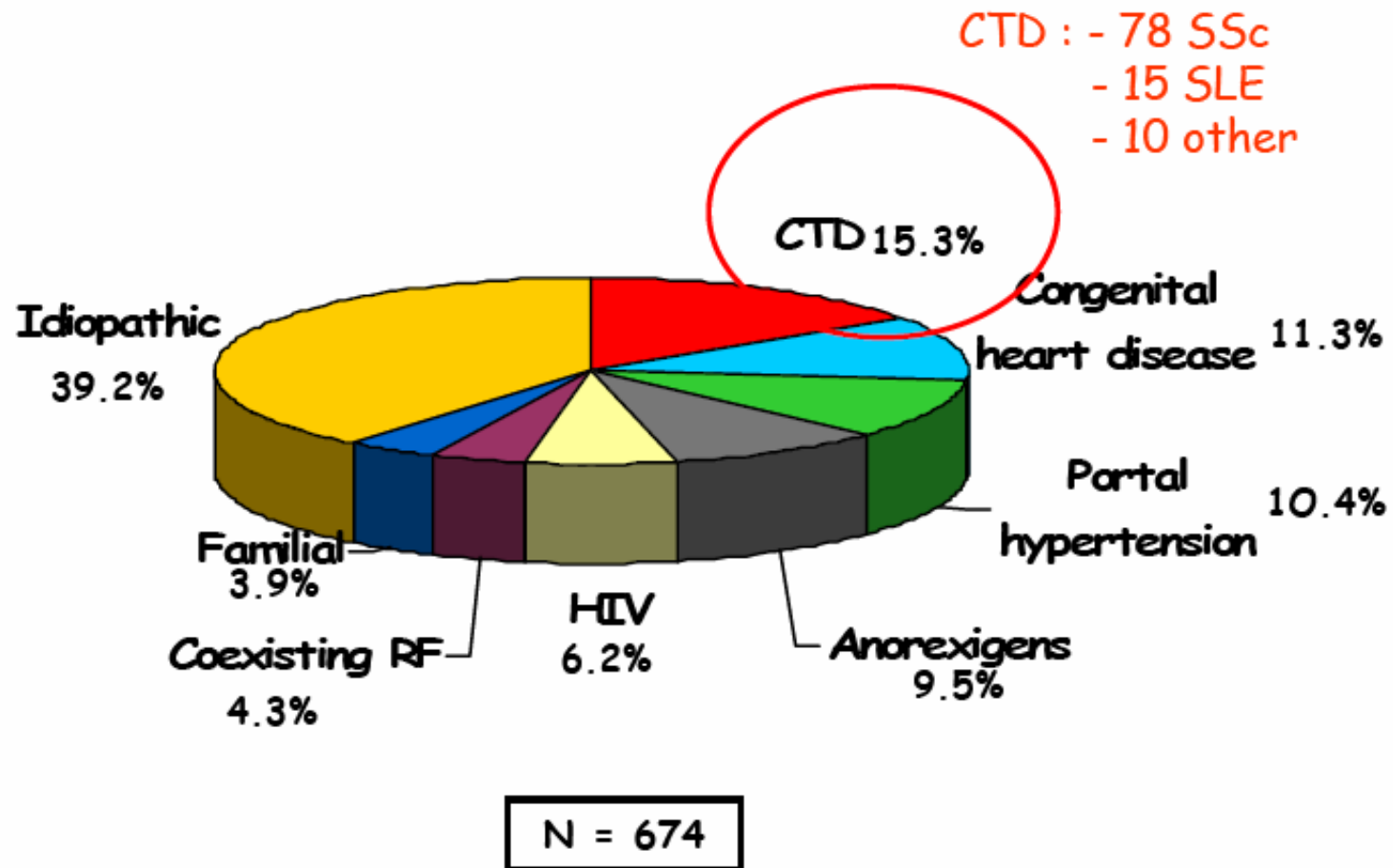
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PAH associée aux connectivites

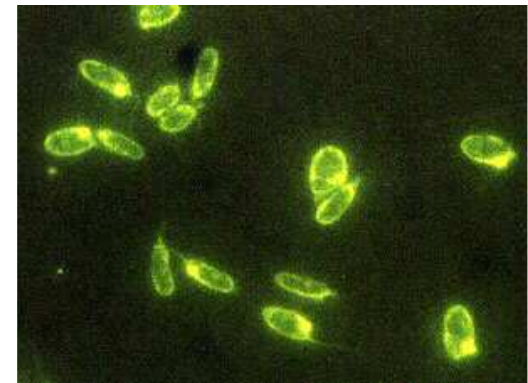
- **Sclérodermie systémique**
- **Lupus érythémateux systémique**
- **Connectivites mixtes**
- **Syndrome de Sjögren**

L'HTAP en France: données du registre national



Critères de classification du LES (ARA 1982)

- Rash malaire
- Lupus discoïde
- Photosensibilité
- Ulcérations orales ou naso-pharyngées
- Arthrite non érosive ≥ 2 articulations périphériques
- Pleurésie ou péricardite
- Protéinurie $\geq 0,5$ g/j ou cylindrurie
- Convulsions ou psychose
- Anémie hémolytique *ou*
Leucopénie $< 4000/\mu\text{l}$ à 2 reprises *ou*
Lymphopénie $< 1500/\mu\text{l}$ à 2 reprises *ou*
Thrombopénie $< 100000/\mu\text{l}$
- Cellules LE *ou*
Anticorps anti-ADN natif *ou* Anti-Sm *ou* sérologie
syphillitique dissociée à 2 reprises en 6 mois
- AAN à un titre anormal en l'absence de drogues
inductrices



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 %

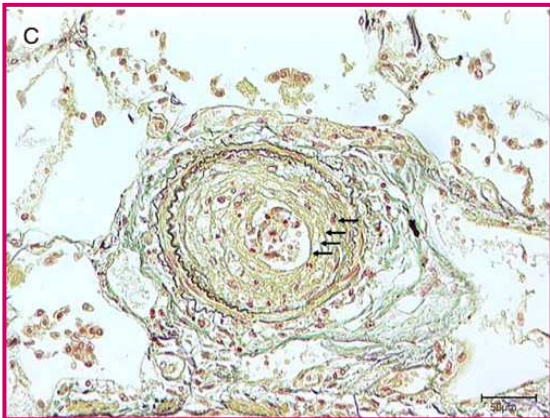
Characteristics of 93 SLE patients according to pulmonary hypertension status

	No PH group n = 81	PH group n = 12		p*
Demographics				
SLE duration at evaluation, (mean \pm SD) years	9.5 \pm 8	14 \pm 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*

SYSTEMIC SCLEROSIS

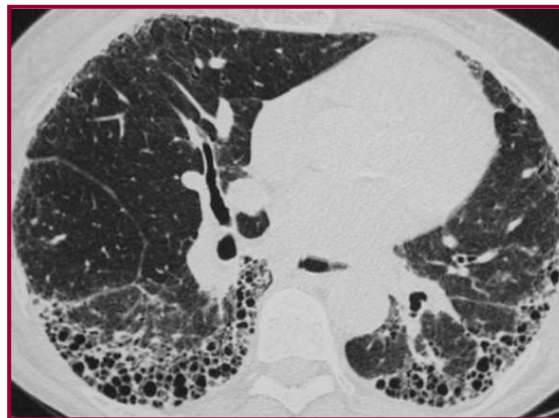
➤ Vascular hyperreactivity

Raynaud's syndrome
Renal crisis
Pulmonary arterial hypertension



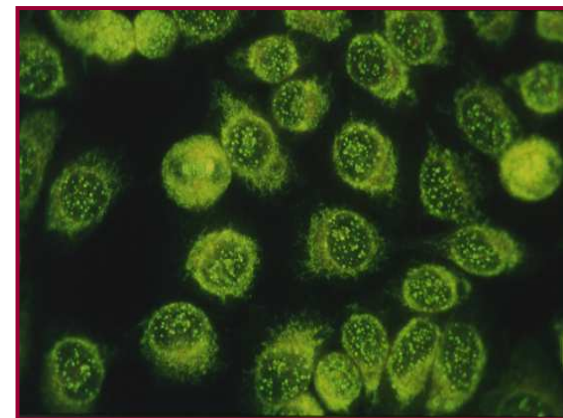
➤ Fibrosis

Skin
Lung
Bowel
Heart



➤ Autoimmunity

Antinuclear Abs
Anti-Scl70
Anti-centromere
Anti-ARNP α III
Anti-fibroblast Abs



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

Idiopathic PAH: When should we think to SSc ?

Extra-thoracic signs that may be helpful:

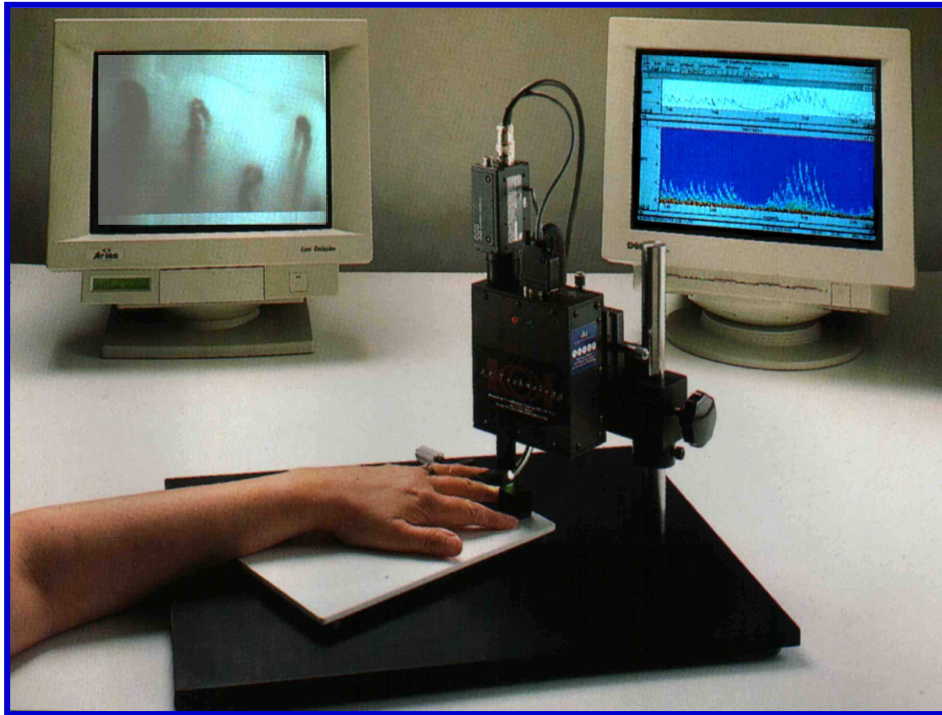
- **Raynaud's syndrome**
- **Esophagus involvement**
- **Skin involvement**
- **SSc related autoantibodies**
- **Megacapillaries**

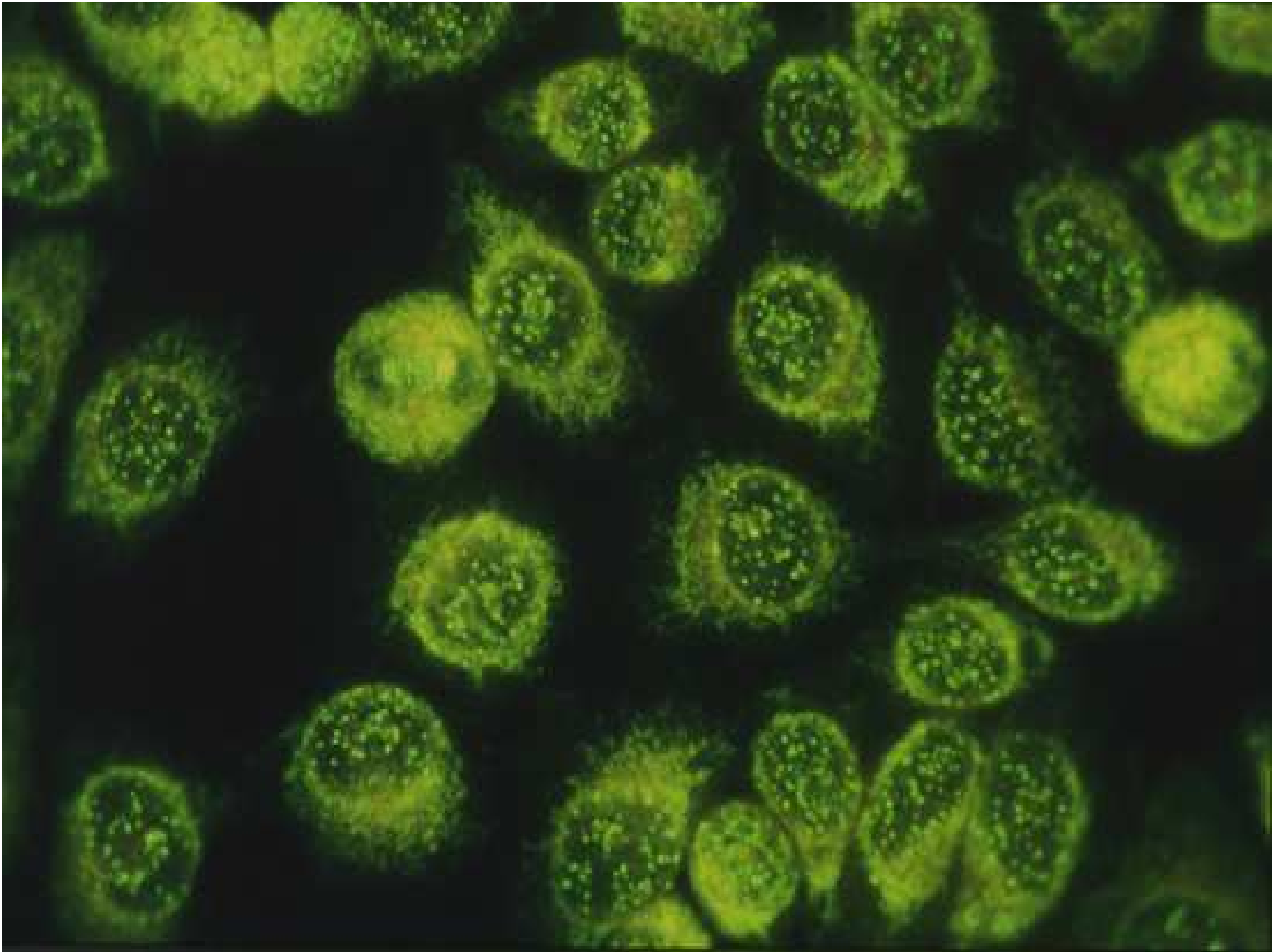




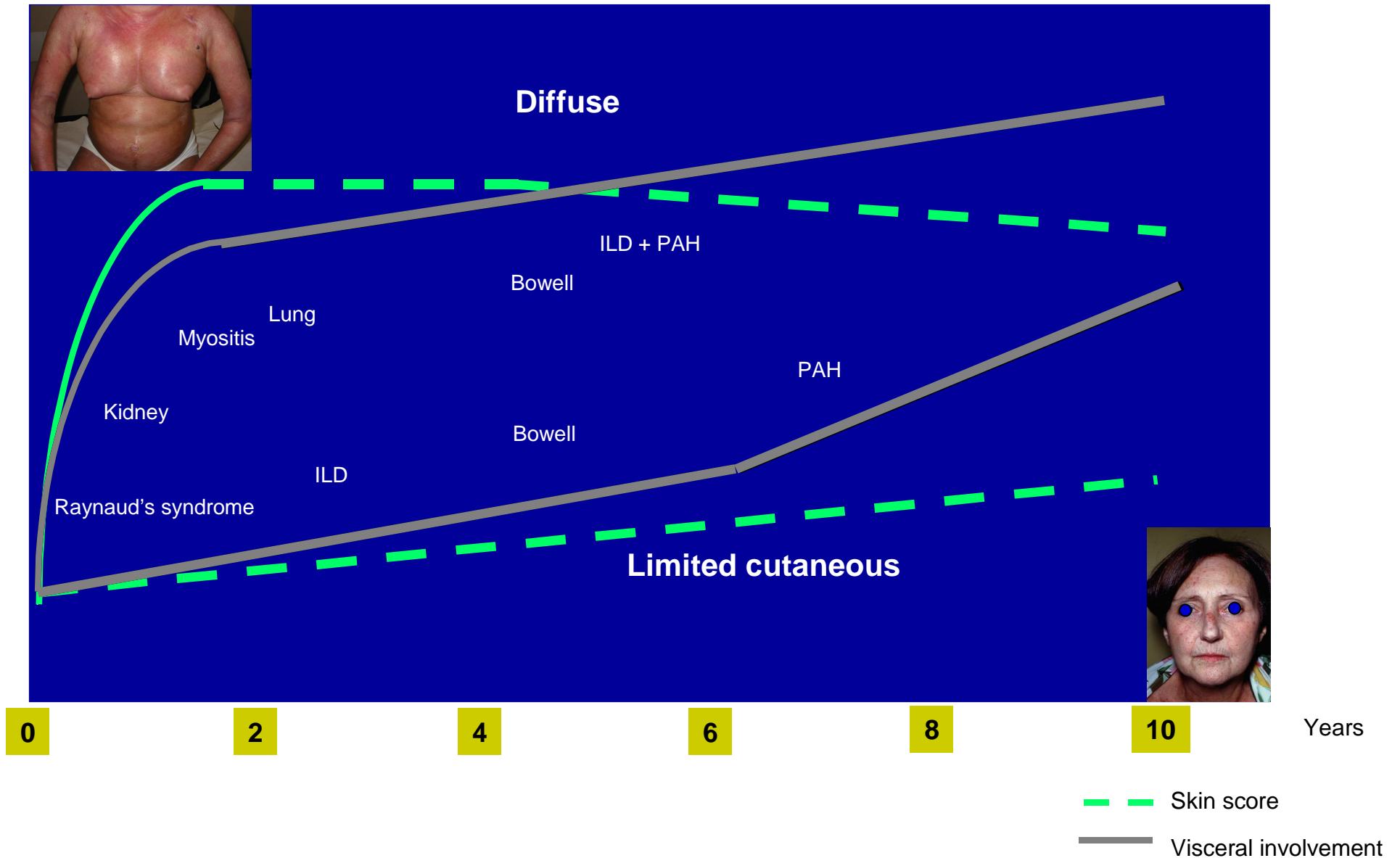


Capillaroscopy





SYSTEMIC SCLEROSIS : EVOLUTION





Is Pulmonary Arterial Hypertension Really a Late Complication of Systemic Sclerosis?

*Eric Hachulla, MD, PhD; David Launay, MD, PhD; Luc Mouthon, MD, PhD; Olivier Sitbon, MD, PhD; Alice Berezne, MD; Loïc Guillevin, MD; Pierre-Yves Hatron, MD; Gérald Simonneau, MD; Pierre Clerson, MD; and Marc Humbert, MD, PhD; for the French PAH-SSc Network**

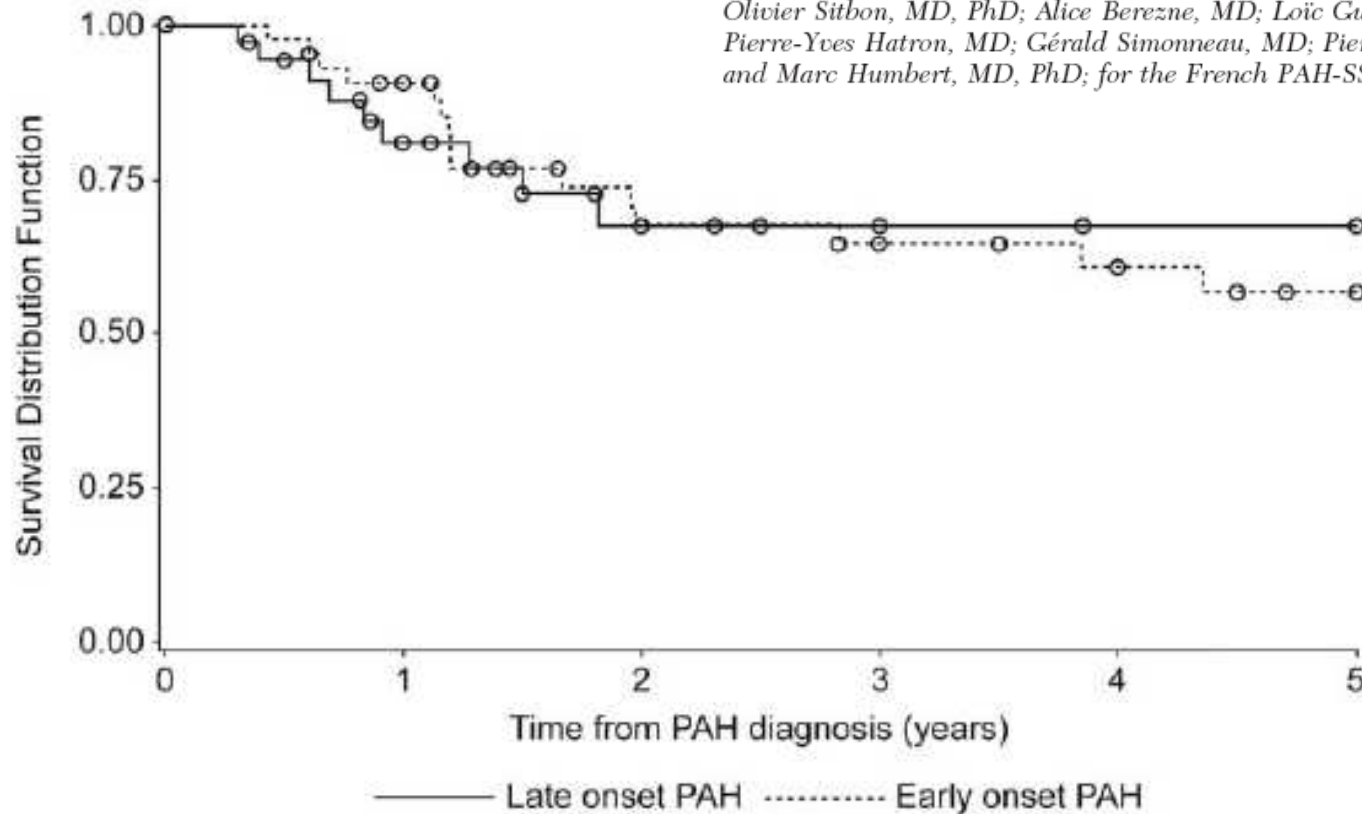
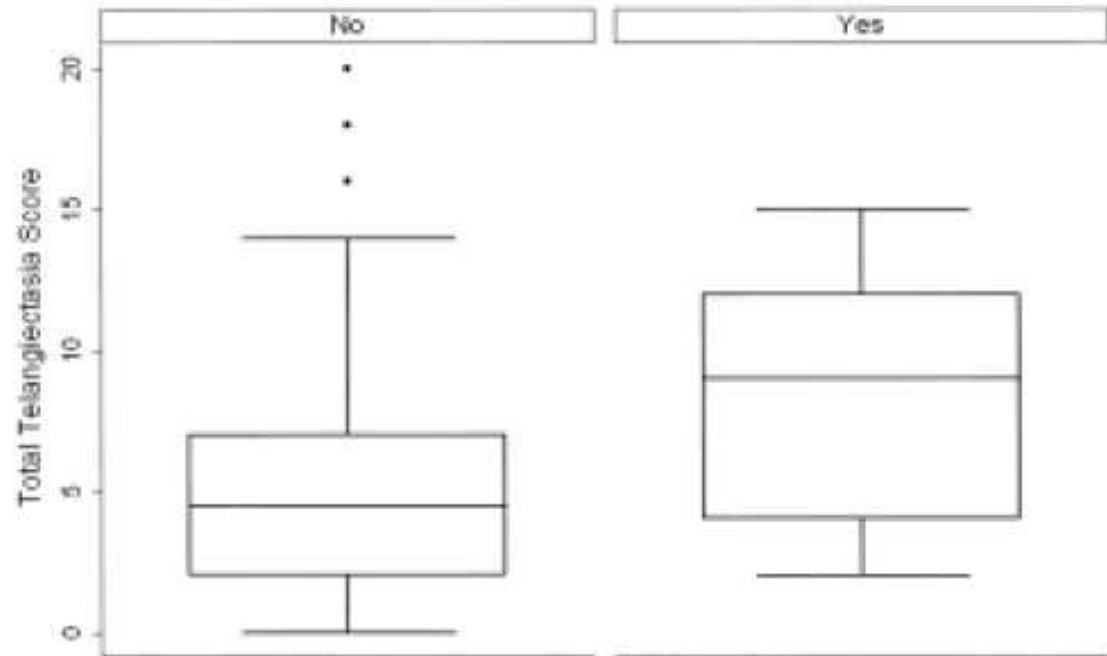


FIGURE 3. Kaplan-Meier estimate of survival from the time of PAH diagnosis according to the delay of occurrence of PAH from SSc diagnosis (n = 78). Early-onset PAH was defined as PAH diagnosed within 5 years of an SSc diagnosis; late-onset PAH was defined as PAH diagnosed > 5 years from the time of SSc diagnosis. Circles represent censored observations.

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

Shah et al. J Rheumatol 2010



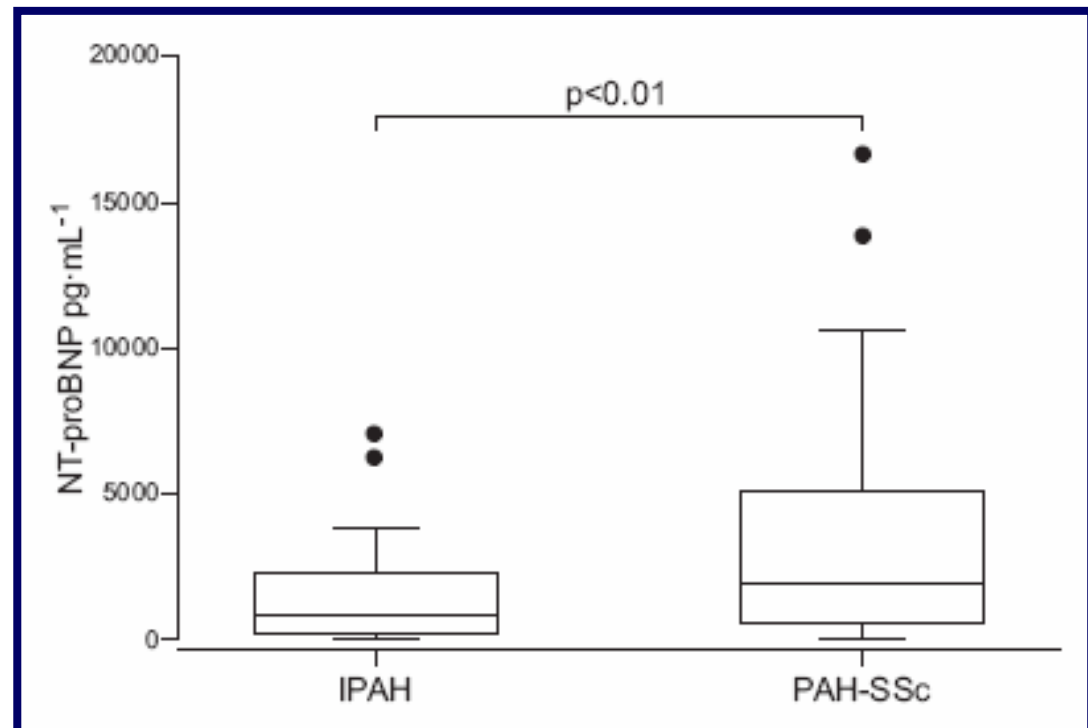
Graphs by PAH on Echocardiogram (RVSP > 45 mmHg) or Right Heart Catheterization

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 that neurohormonal regulation may differ between PAH-SSc and IPAH.

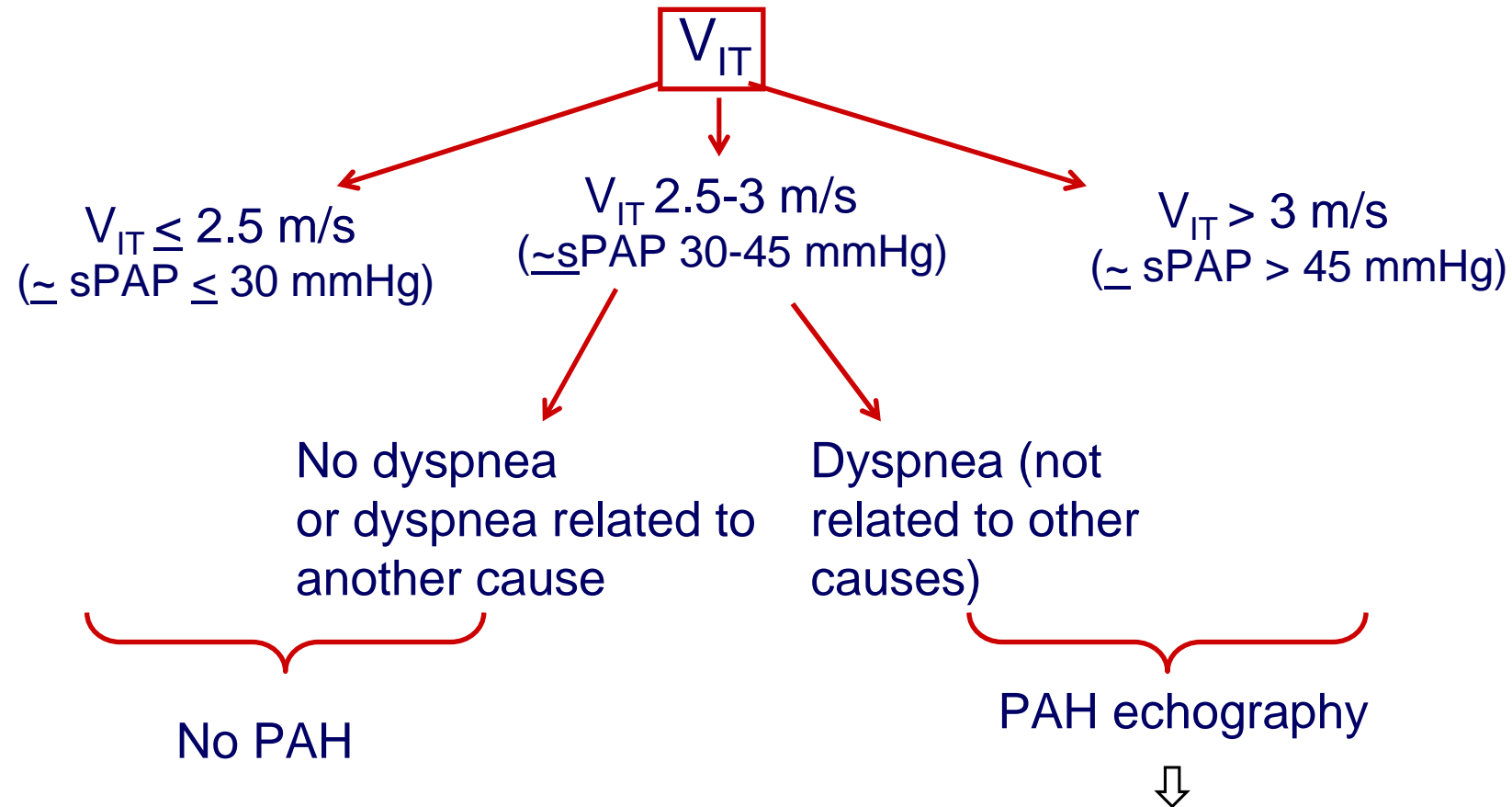


Box and whisker plots of the N-terminal pro-brain natriuretic peptide (NT-proBNP) levels measured in IPAH and PAH-SSc patients.

PAH-SSc: Prevalence

Reference	Methodology	Number of patients	SSc profile	PAH definition	PAH prevalence
RG Ungerer 1983 USA	<ul style="list-style-type: none"> ▪ Prospective ▪ Monocentric ▪ 1973 to 1979 	49	Proximal SSc and CREST	▪ Mean PAP \geq 20 mmHg and mean PCP \leq 12 mmHg (right heart catheterization)	16%
I. Murata 1992 Japan	<ul style="list-style-type: none"> ▪ Prospective ▪ Monocentric ▪ 1988 to 1991 	71	SSc and MCTD	▪ $V_{IT} \geq 2,5$ m/s Doppler Echo	17%
R. Battle 1996 USA	<ul style="list-style-type: none"> ▪ Prospective ▪ Monocentric 	34	Diffuse or limited c SSc	▪ PAPs \geq 30 mmHg Doppler Echo	35%
ET Koh 1996 Canada	<ul style="list-style-type: none"> ▪ Prospective ▪ Monocentric ▪ 1978 to 1994 	344	Diffuse or limited cutaneous SSc	<ul style="list-style-type: none"> ▪ PAPm \geq 25 and cap m \leq 12 mmHg upon RHC, or ▪ Ps VD $>$ 35 mmHg (echo) ▪ or RV dilatation, P or T insufficiency, or paradoxical septum motion upon echo 	4,9%
AJ MacGregor, 2001 UK	<ul style="list-style-type: none"> ▪ Prospective ▪ Monocentric ▪ 1992 to 1997 	152	Diffuse or limited c SSc	▪ PAPs $>$ 30 mmHg Doppler Echo	13%
D Mukerjee, 2003 UK	<ul style="list-style-type: none"> ▪ Prospective ▪ Monocentric ▪ 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	<ul style="list-style-type: none"> ▪ Prospective ▪ Multicentric ▪ 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



Right cardiac catheterisation
Hachulla et al. Arthritis Rheum 2005

Cardiac catheterisation (n=33)

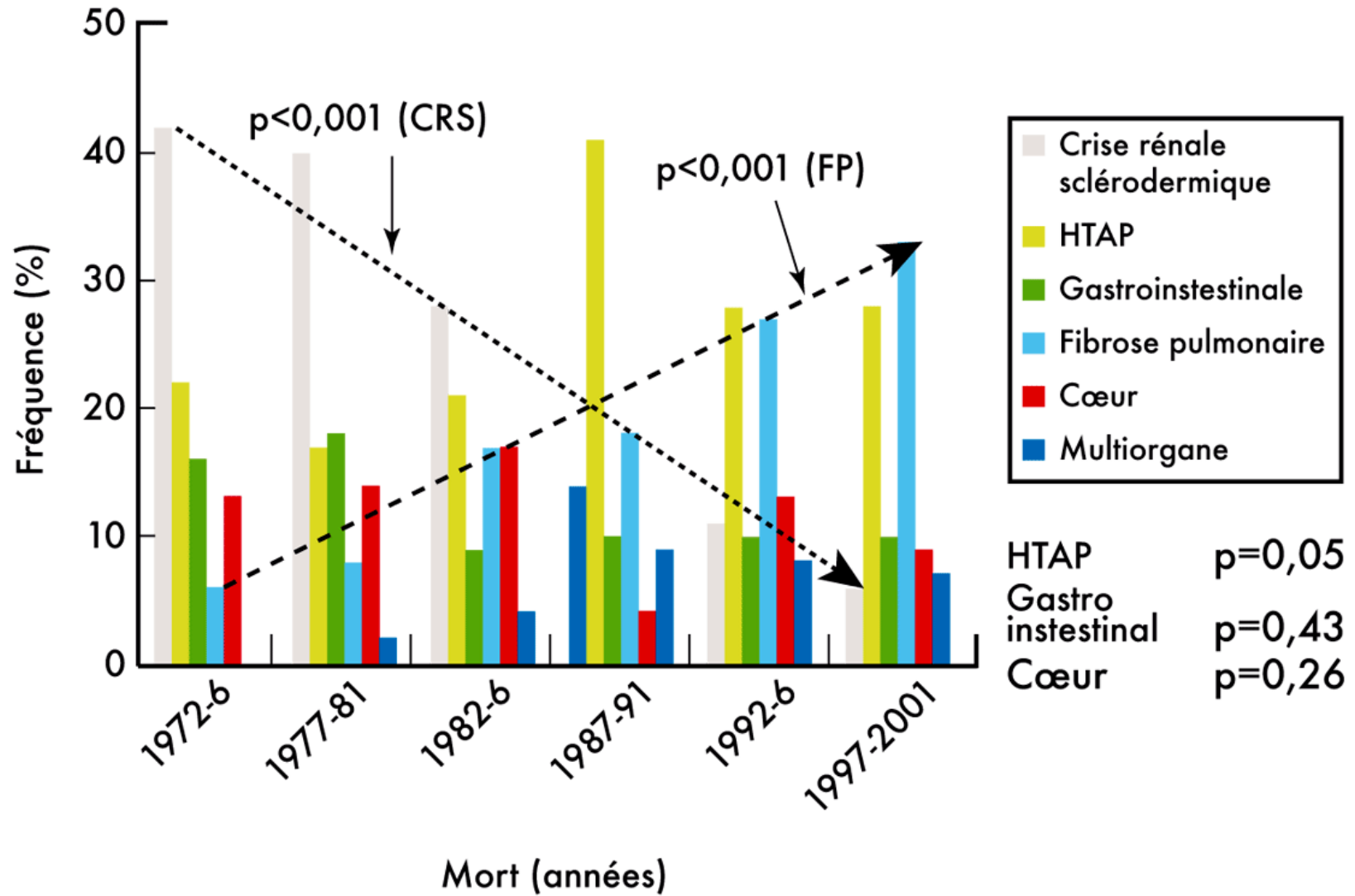
- PAH : 18
- [mPAP > 25 mmHg at rest or > 30 mmHg at exercise with PAwP < 15 mmHg]
 - 25-35 mmHg: 14
 - 35-45 mmHg: 3
 - 45 mmHg: 1
- Post-capillary “venous” pulmonary hypertension: 3 (10%)
- No PAH : 12 => 6 with mPAP > 20 mmHg

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.

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



PAH in SSc: prognosis

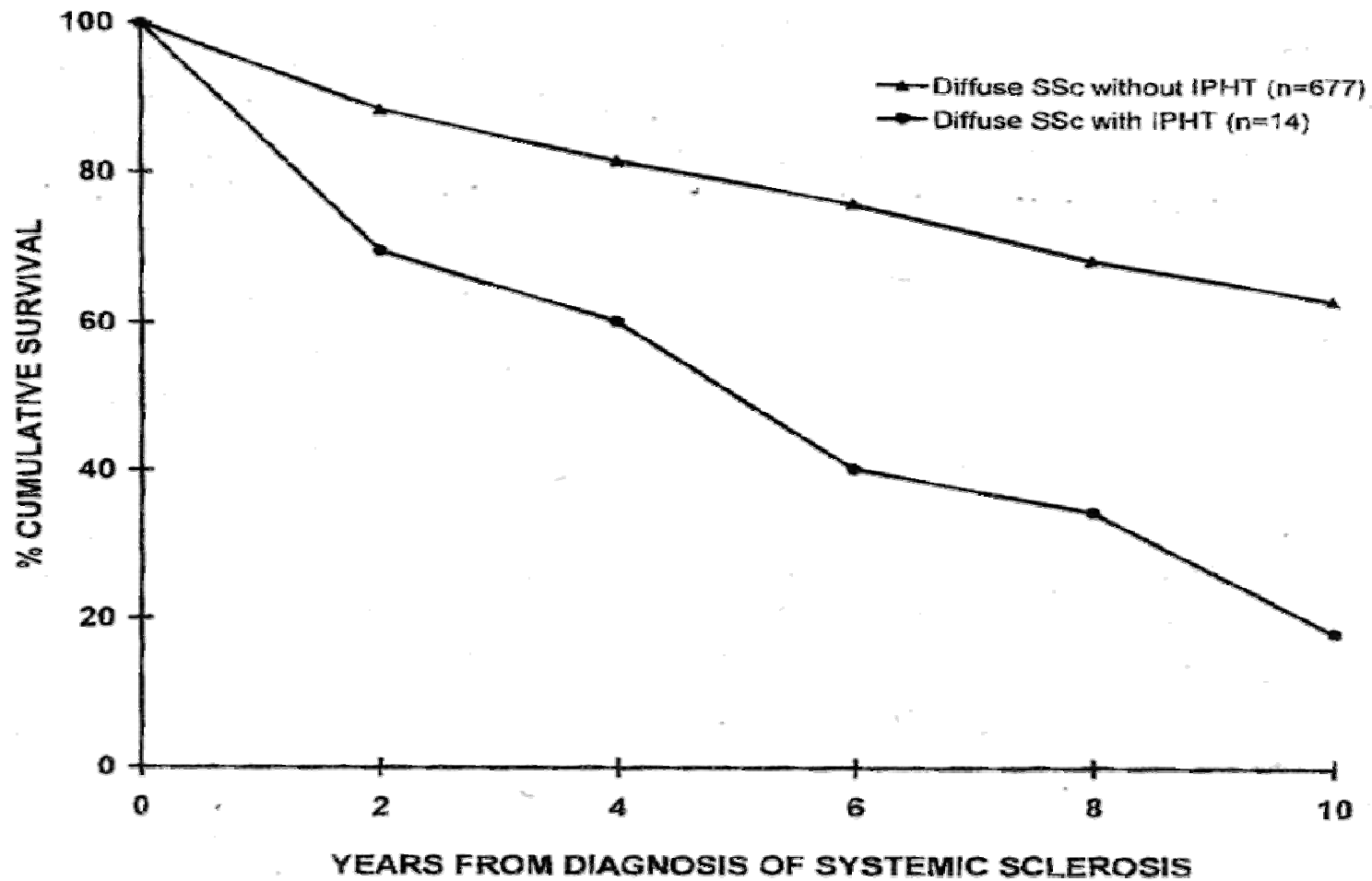
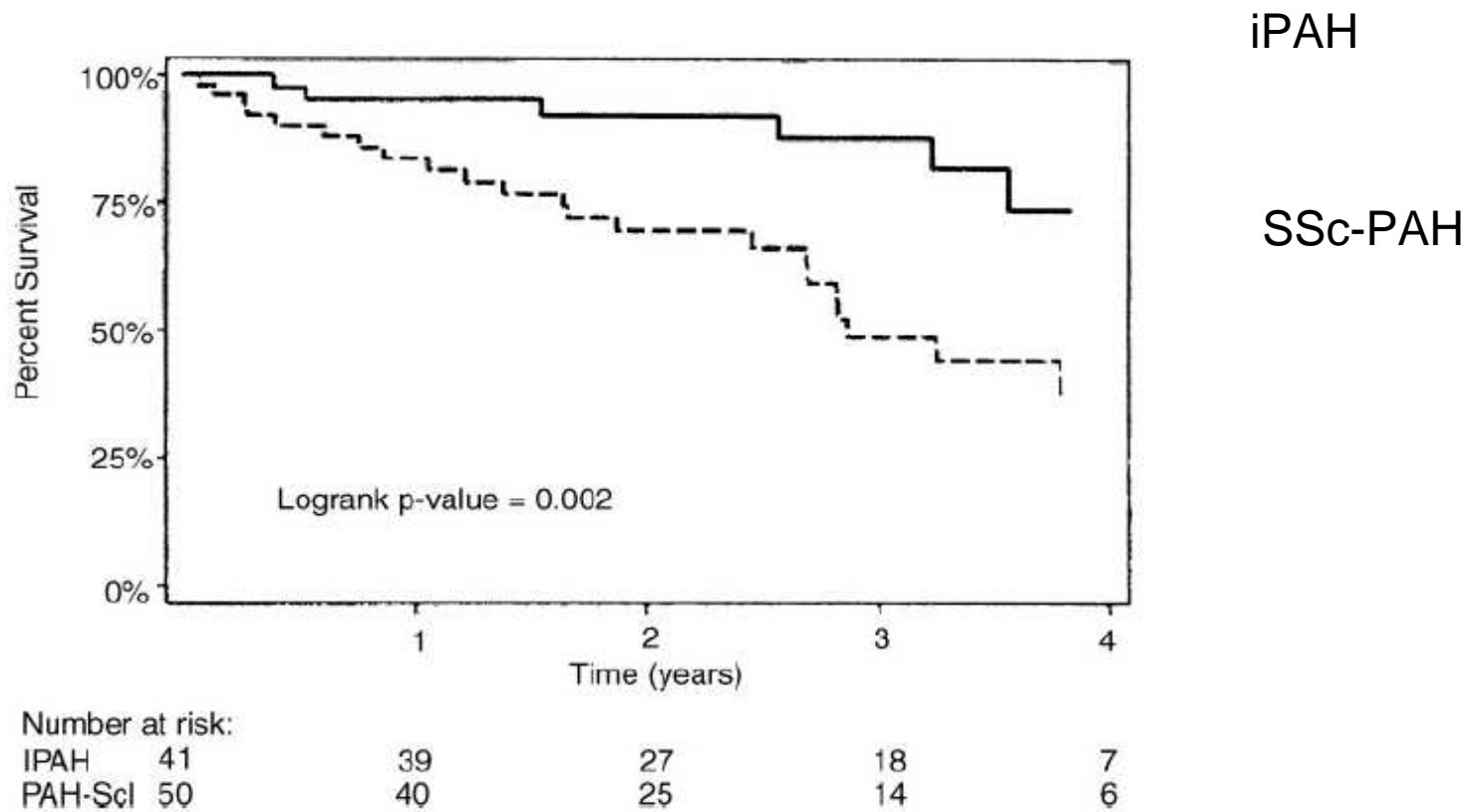


Figure 1. Cumulative survival from diagnosis of SSc in patients with dcSSc with (n = 15) or without (n = 677) IPHT. Patients with IPHT have significantly decreased survival ($p < 0.001$) compared to others with dcSSc.

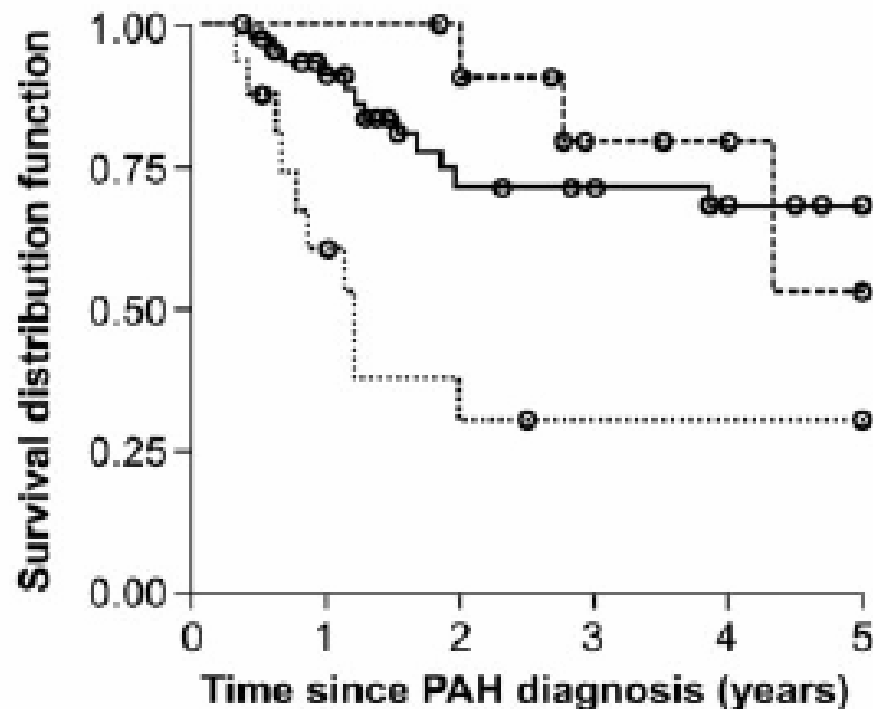
PAH complicating Connective Tissue Diseases



Concise report

Pulmonary arterial hypertension associated with systemic sclerosis in patients with functional class II dyspnoea: mild symptoms but severe outcome

Eric Hachulla¹, David Launay¹, Azzedine Yaici^{2,3,4}, Alice Berezne⁵, Pascal de Groote^{4,6}, Olivier Sitbon^{2,3,4}, Luc Mouthon⁵, Loïc Guillevin⁵, Pierre-Yves Hatron¹, Gérald Simonneau^{2,3,4}, Pierre Clerson⁷ and Marc Humbert^{2,3,4} on behalf of the French PAH-SSc Network*



--- NYHA FC II	M0	M12	M24	M36	M48
Patients at risk	12	12	9	5	3
Censored	–	0	2	3	2
Events	–	0	1	1	0
— NYHA FC III					
Patients at risk	49	38	24	19	16
Censored	–	7	7	5	2
Events	–	4	7	0	1
..... NYHA FC IV					
Patients at risk	16	8	4	3	3
Censored	–	6	0	1	0
Events	–	2	4	0	0

Causes of death in SSc patients

TABLE 2. Causes of death observed in the total population

Causes of death, <i>n</i> (%)	All patients (<i>n</i> = 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

Impact des comorbidités

- Age
- Atteinte myocardique
- Atteinte musculo-squelettique
- Fibrose pulmonaire
- Maladie veino-occlusive pulmonaire

Age

- SSc-PAH patients are typically older compared to iPAH patients at disease onset.
- The specific role of age at time of diagnosis on overall survival remains to be determined in SSc-PAH. ⁽¹⁾
- Late disease onset decreases survival in SSc patients not afflicted with PAH.
- Regarding SSc-PAH, there is only one study suggesting that older patients at time of diagnosis have a worse survival. ⁽²⁾
- A recent multivariate analysis showed that age was not an independent predictor of death, suggesting that age might impact survival only through associated comorbidities. ⁽³⁾

(1) Humbert *et al.* Am J Respir Crit Care Med 2006, Fisher *et al.* Arthritis Rheum 2006, Girgis *et al.* J Heart Lung Transplant 2005, Kawut *et al.* Chest 2003, Verbeek *et al.* Eur Respir J 2008

(2) Jacobsen *et al.* J Rheumatol 2001, Mayes *et al.* Arthritis Rheum 2003

(3) Fisher *et al.* Arthritis Rheum 2006

Myocardial involvement

- Recent studies suggest that clinical evidence of myocardial dysfunction may be present in up to 15 to 35 % of patients with SSc. ⁽¹⁾
- 46 patients SSc patients underwent myocardial biopsies (n = 38) or autopsies (n = 8) ⁽²⁾. Myocardial fibrosis, either minimal or severe, was found in all patients on histological analysis. Myocardial inflammation was identified in 88 % of the patients.
- The presence of clinical cardiac involvement in SSc is a harbinger of poor prognosis and is associated with a 70 % mortality at 5 years. ⁽³⁾
- Left heart abnormalities, such as left ventricular hypertrophy and left atrial dilatation, are common in SSc-PAH. ⁽⁴⁾
- Similarly, non-systolic dysfunction is more prevalent in SSc-PAH than in iPAH. ⁽⁵⁾
- A higher proportion of arrhythmias in PAH related to connective tissue disease (CTD) than in iPAH has also been shown. ⁽⁶⁾

(1) Kahan *et al.* Rheumatology 2009

(2) Wung *et al.* Arthritis Rheum 2008

(3) Medsger *et Masi.* J Chronic Dis 1973

(4) De Groote *et al.* Ann Rheum Dis 2008

(5) Fisher *et al.* Arthritis Rheum 2006

(6) Tongers *et al.* Am Heart J 2007

SSc-PAH: why a so bad prognosis?

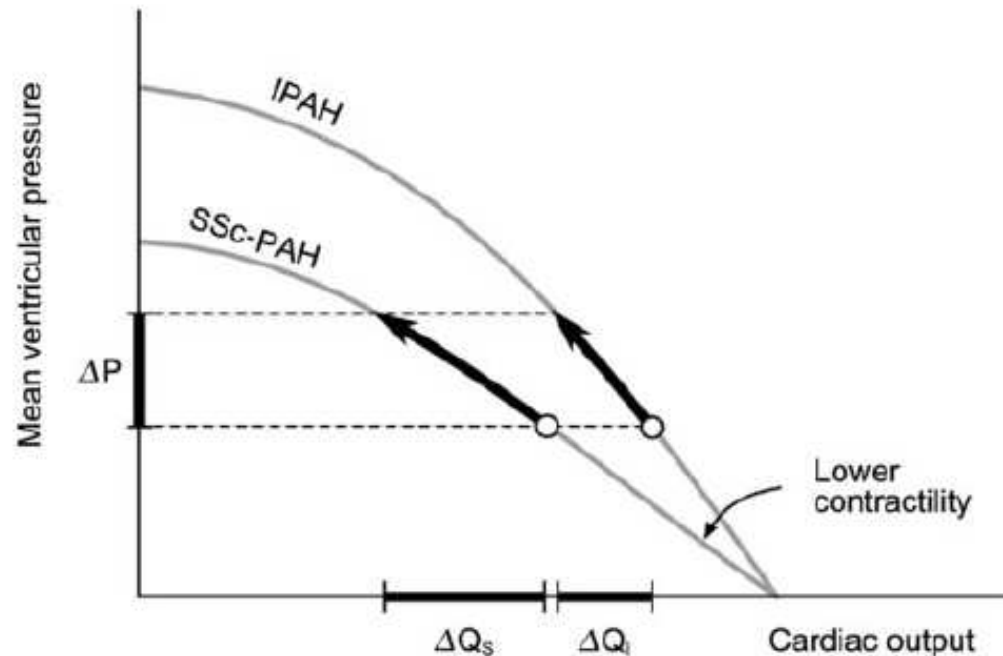
Table 3. Baseline echocardiographic findings*

	IPAH (n = 38)	PAH-Scl (n = 49)	<i>P</i>
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 \pm SEM cm	3.3 \pm 0.2	3.8 \pm 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 \pm SEM	57.3 \pm 1.6	55.7 \pm 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

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.

Musculoskeletal involvement

- Musculoskeletal involvement is frequent in SSc patients.
- Muscle involvement occurs in up to 96 % of cases and correlates strongly with myocardial disease in SSc. ⁽¹⁾
- In an analysis of over 300 SSc patients with skeletal myopathy, diffuse SSc, the presence of pulmonary fibrosis, and male gender tend to be risk factors for development of myopathy. ⁽²⁾
- While the role of musculoskeletal involvement in overall prognosis is unclear, it does impact function, such as the 6 minute walk distance (6MWD) as recently suggested ⁽³⁾, raising very strong doubt about the validity of this functional end-point in SSc-PAH.

(1) Randone *et al.* Best Pract Res Clin Rheumatol 2008

(2) Mimura *et al.* Clin Rheumatol 2005

(3) Garin *et al.* J Rheumatol 2009

Pulmonary fibrosis

- Patients with limited SSc disease will typically develop isolated PAH 10-15 years after the onset of their disease. ⁽¹⁾
- In contrast, patients with diffuse SSc are at greater risk for ILD, usually within the first 5 years after diagnosis ⁽²⁾, but may develop PH at any stage in the course of their disease. ⁽³⁾
- However, while SSc patients with ILD alone have a median survival of 5-8 years ⁽⁴⁾, development of PH (PH-ILD) will shorten survival.
- In a study by Mathai *et al*, PH-ILD was associated with a 5-fold increased risk of death compared to SSc-PAH. ⁽⁵⁾
- Similarly, in a recent large study by Condliffe *et al*, the 3-year survival was significantly worse (28 %) in the group of patients with ILD compared to patients with isolated SSc-PAH (47 %). ⁽⁶⁾

(1) Steen et Medsger. Arthritis Rheum 2003

(2) Steen. Ann Rheum Dis 2003

(3) Chang *et al*. J Rheumatol 2003

(4) Altman *et al*. Arthritis Rheum 1991

(5) Mathai *et al*. Arthritis Rheum 2009

(6) Condliffe *et al*. Am J Respir Crit Care Med 2009

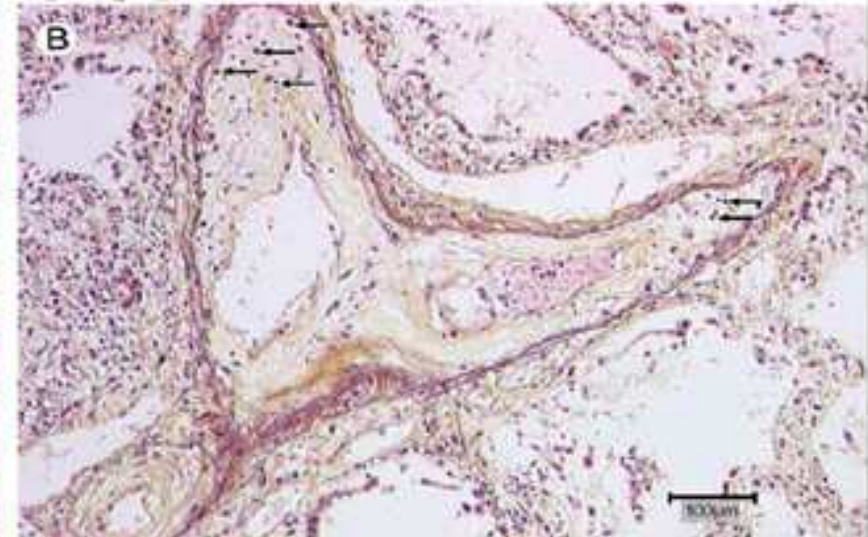
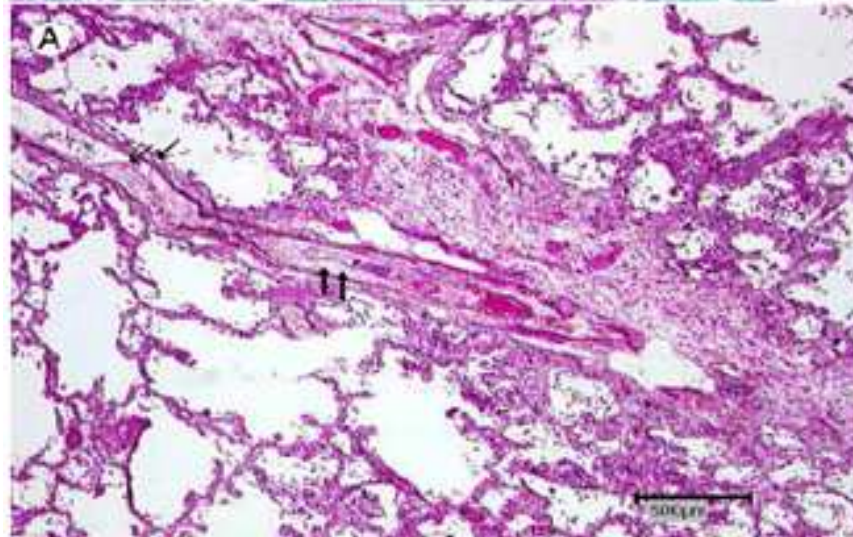
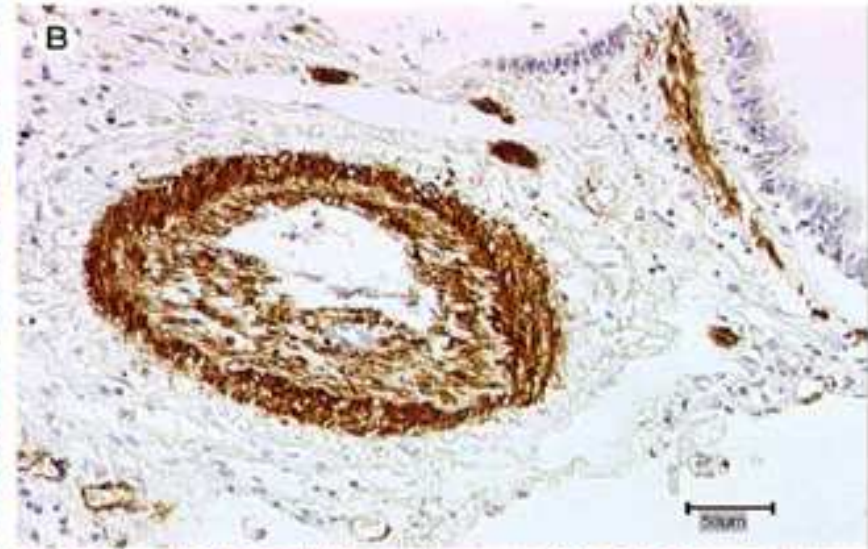
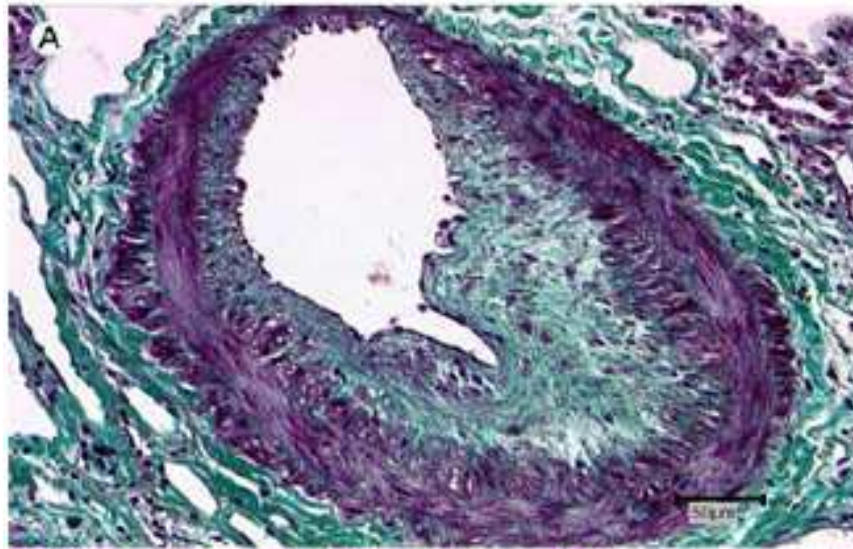
Pulmonary Veno-Occlusive Disease

- PVOD is characterized by intimal proliferation and fibrosis of the intrapulmonary veins and venules, occasionally extending to the arteriolar bed. ⁽¹⁾
- PVOD is an underrecognized cause of PAH in SSc patients. ⁽²⁾
- A recent histological study suggested that SSc-PAH may be characterized by a more frequent involvement of pulmonary veins than previously recognized perhaps explaining in part why these patients are less responsive to specific PAH treatment as compared with iPAH patients. ⁽¹⁾

⁽¹⁾ Dorfmueller *et al.* Hum Pathol 2007

⁽²⁾ Montani *et al.* Eur Respir J 2009

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

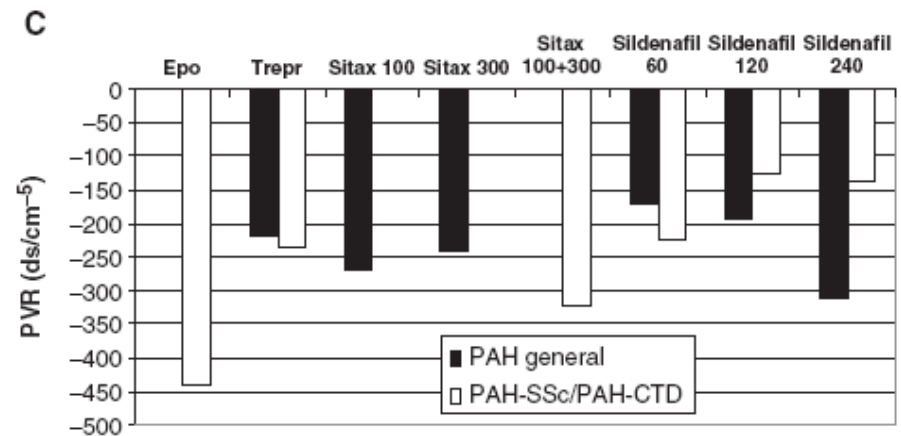
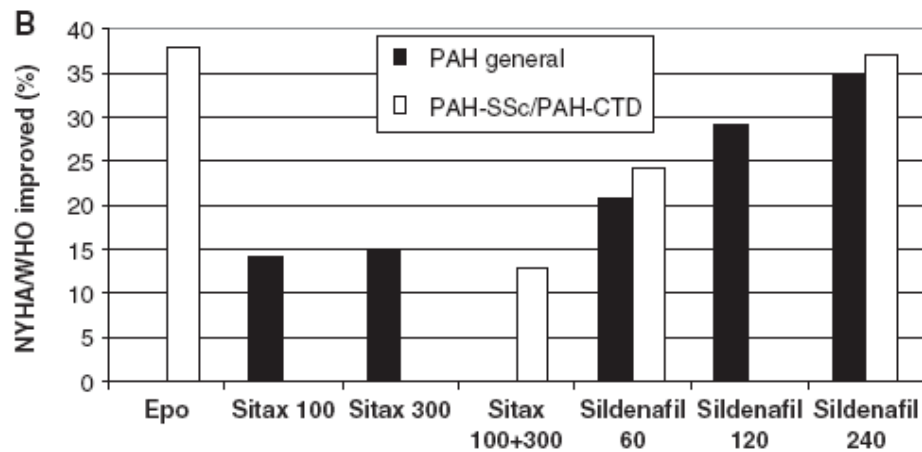
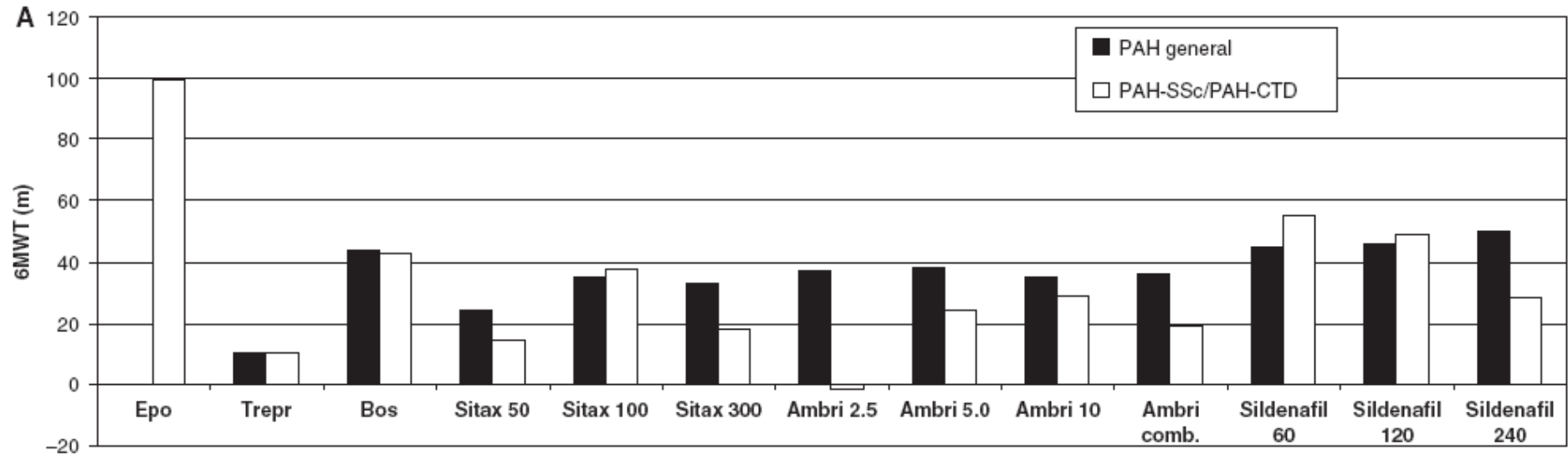


SSc-PAH: treatment

- Preventive measures
- Conventional medical treatment (O₂ - diuretics - anticoagulants)
- Calcium blockers
- Epoprostenol continuous infusion
- Endothelin receptor antagonists
- Lung transplantation
- New strategies

Outcome measures in pulmonary arterial hypertension associated with systemic sclerosis

O. Kowal-Bielecka et al Rheumatology 2008



Mean/median effects of PAH therapies on the 6MWD (A), NYHA/WHO functional class (B) and PVR (C) in the pivotal randomized trials for which data on SSc or CTD subgroups could be retrieved.

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/m²) 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

Conclusions

- 8-12% des patients sclérodermiques développent une HTAP
- Détection: échocardiographie
- Confirmation: cathétérisme droit
- Prognosis: plus mauvais que celui des autres HTAP
- Impact des comorbidités
- Efficacité moindres des traitements de l'HTAP
- Efficacité des Immunosuppresseurs dans 1/3 des cas d'HTAP associées au LES ou aux connectivites mixtes