HIPERTENSIÓN PULMONAR EN LA ESCLERODERMIA

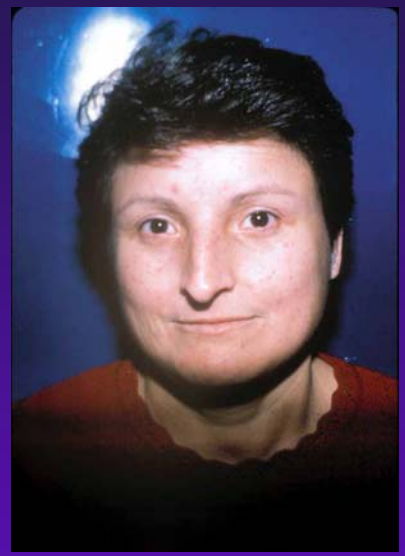
V. Fonollosa Pla – CP. Simeón Aznar

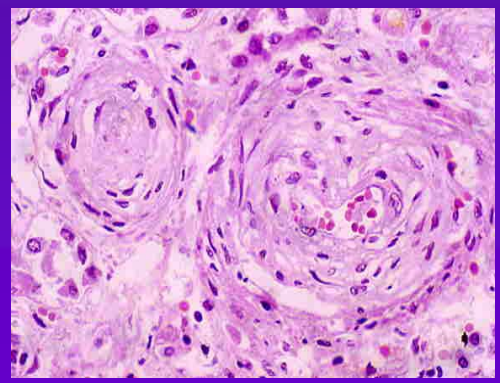
Unidad de Enfermedades Autoinmunes Sistémicas
Servicio de Medicina Interna
Hospital Universitario Vall d'Hebron . Barcelona

Esclerodermia. Hipertensión arterial pulmonar

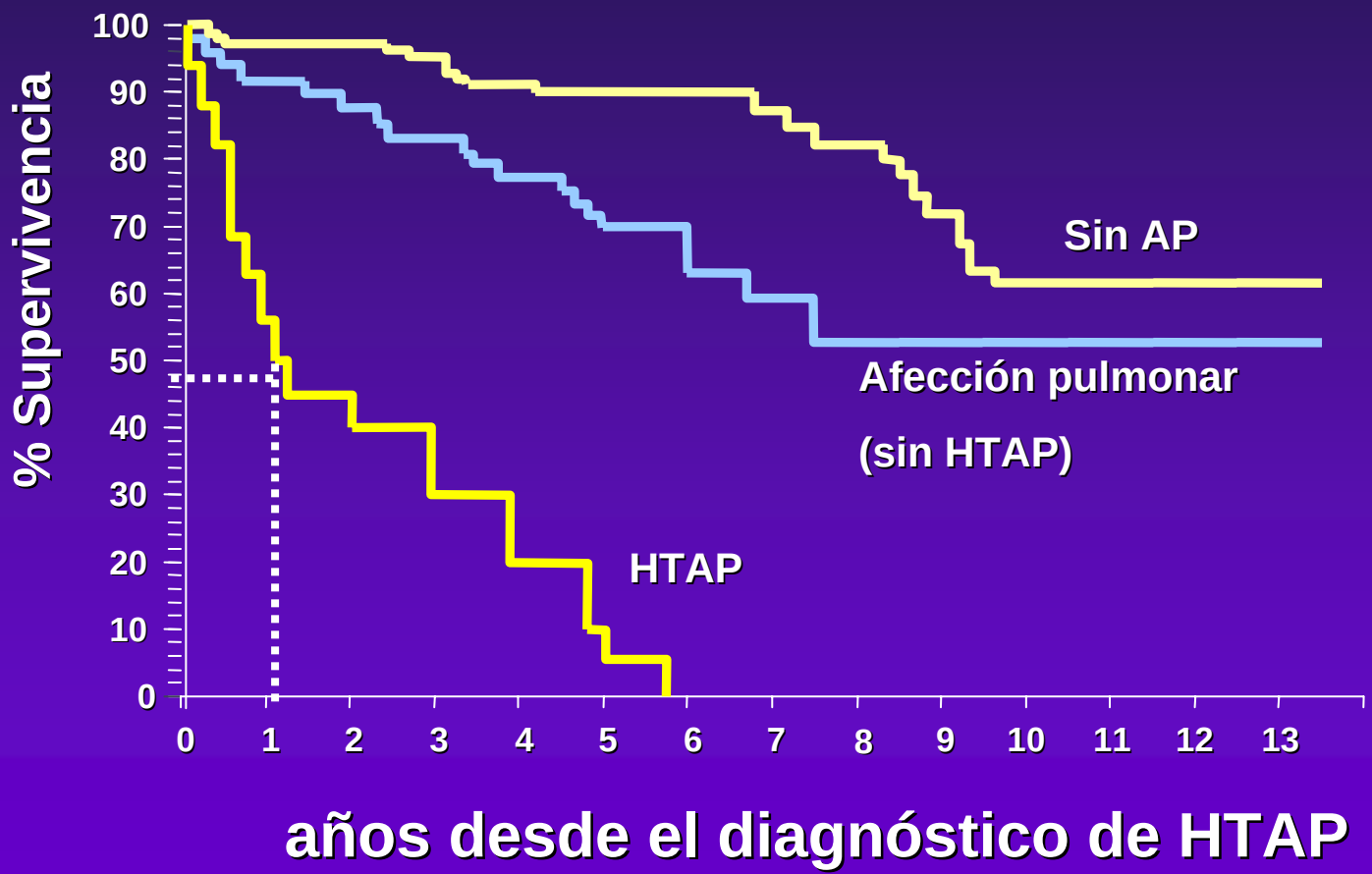
Pulmonary hypertension in the CREST syndrome variant of progresesive systemic sclerosis (Scleroderma). *Salerni et al*, 1977

"El síndrome CREST ***no siempre es benigno*** *ya que después de un curso clínico prolongado puede presentar una progresiva obliteración vascular pulmonar,* ***hipertensión pulmonar y muerte****, en ausencia de fibrosis pulmonar significativa"*



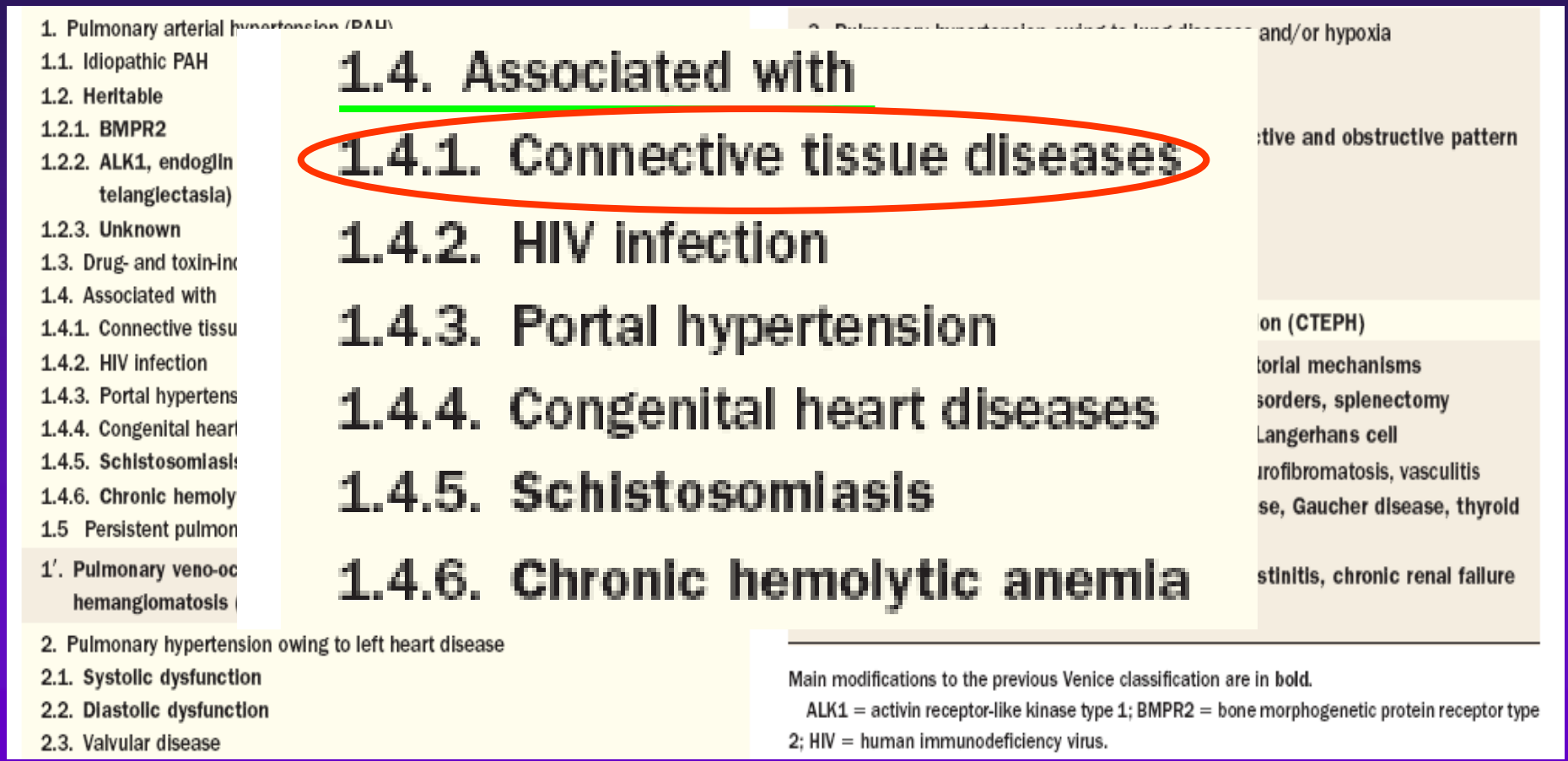


HTAP y supervivencia en la ESC



Koh ET, et al. *Brit J Rheumatol*. 1996;35:989.

Clasificación de la hipertensión arterial pulmonar. Dana Point, 2008

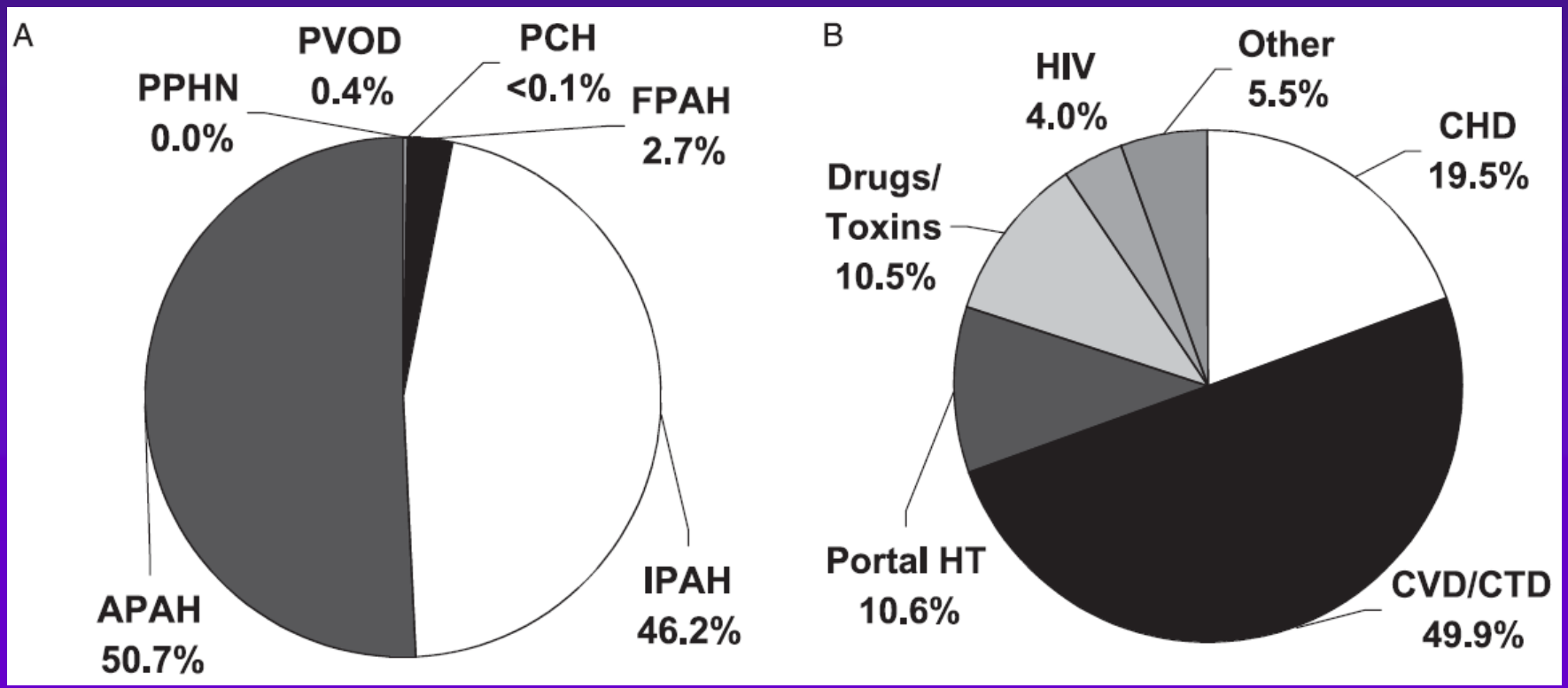


Pulmonary Arterial Hypertension

Baseline Characteristics From the REVEAL Registry

David B. Badesch, MD, FCCP; Gary E. Raskob, PhD; C. Greg Elliott, MD, FCCP; Abby M. Krichman, BS, RRT; Harrison W. Farber, MD, FCCP; Adaani E. Frost, MD, FCCP; Robyn J. Barst, MD, FCCP; Raymond L. Benza, MD; Theodore G. Liou, MD, FCCP; Michelle Turner, MS; Scott Giles, BA; Kathy Feldkircher, PhD; Dave P. Miller, MS; and Michael D.McGoon, MD, FCCP

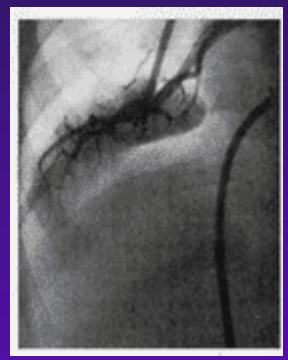
CHEST 2010; 137(2):376–387

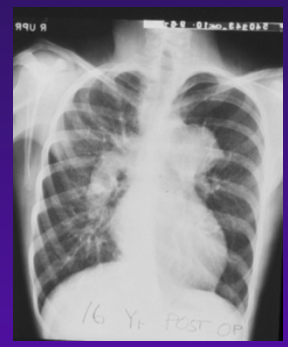


Esclerodermia: prevalencia de la HTAP

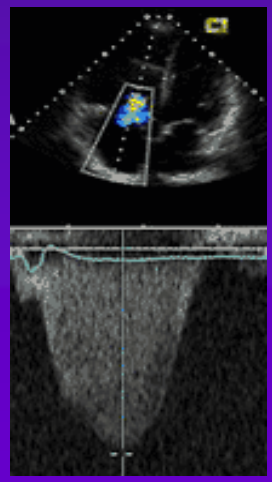
Carr RD et al.: *CREST syndrome. A benign variant of scleroderma*. Arch Dermatol. 1965

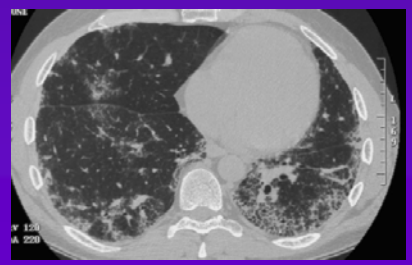
- Salerni RM. 10 casos, 1977
- Ungerer RG. **33%,** 1983
- Koh ET. **4.9%,** 1996
- Battle RW. **35%,** 1996
- Candell J. **14%,** 1996
- MacGregor AJ. **13%,** 2001
- Pope JE. **21-26%,** 2005
- Chang B. **13,6%,** 2006
- Hachulla E. **7,85%**, 2009
- Avouac J. **5-9 %,** 2010

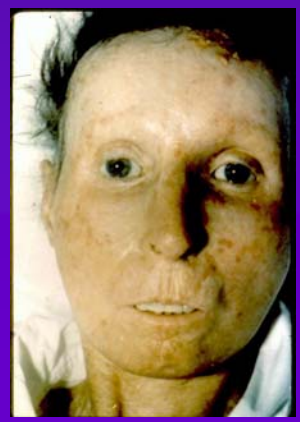




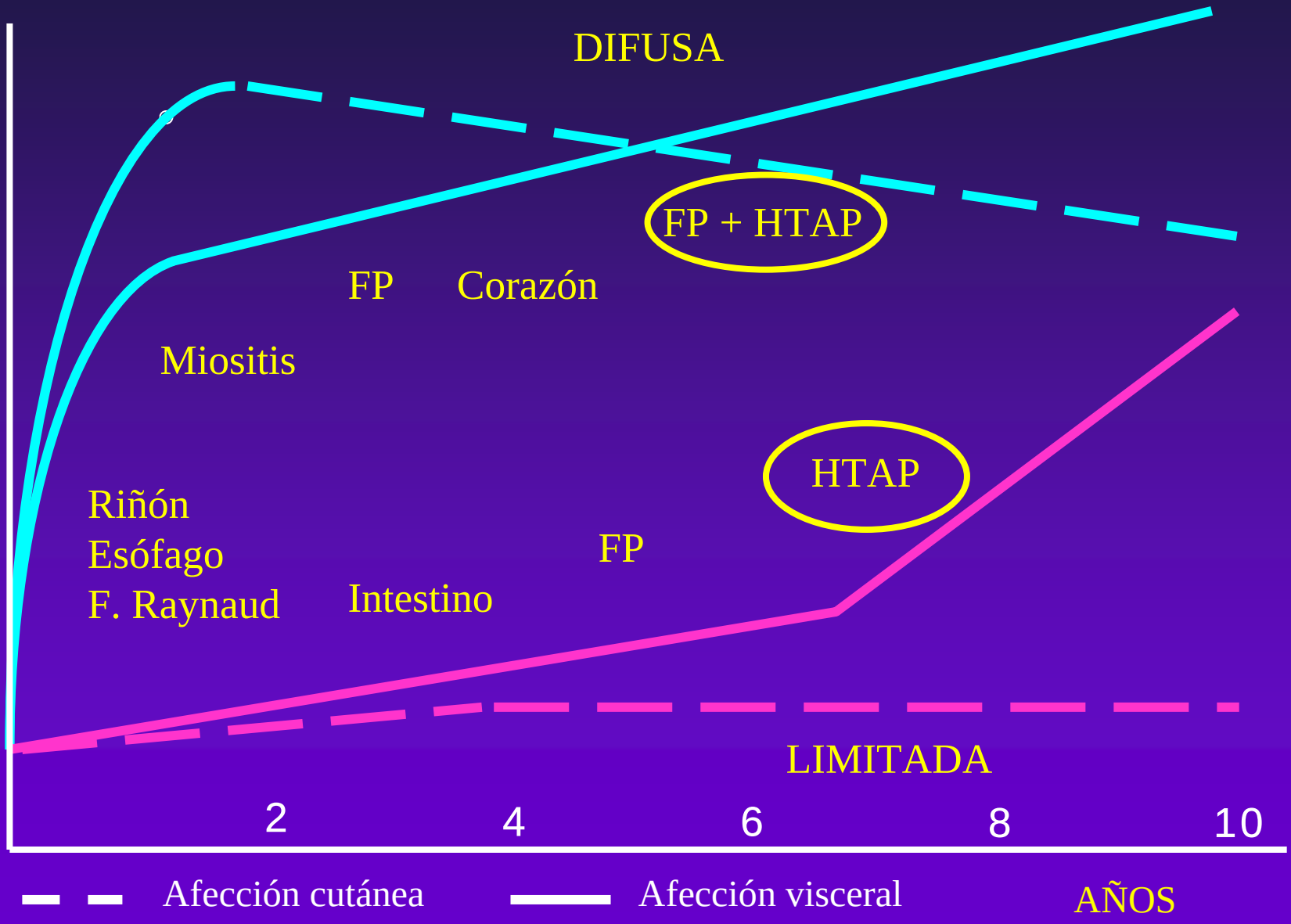
7 – 12 %
Autopsia: 60%







Esclerodermia. Evolución



ESCLERODERMIA. Hipertensión pulmonar

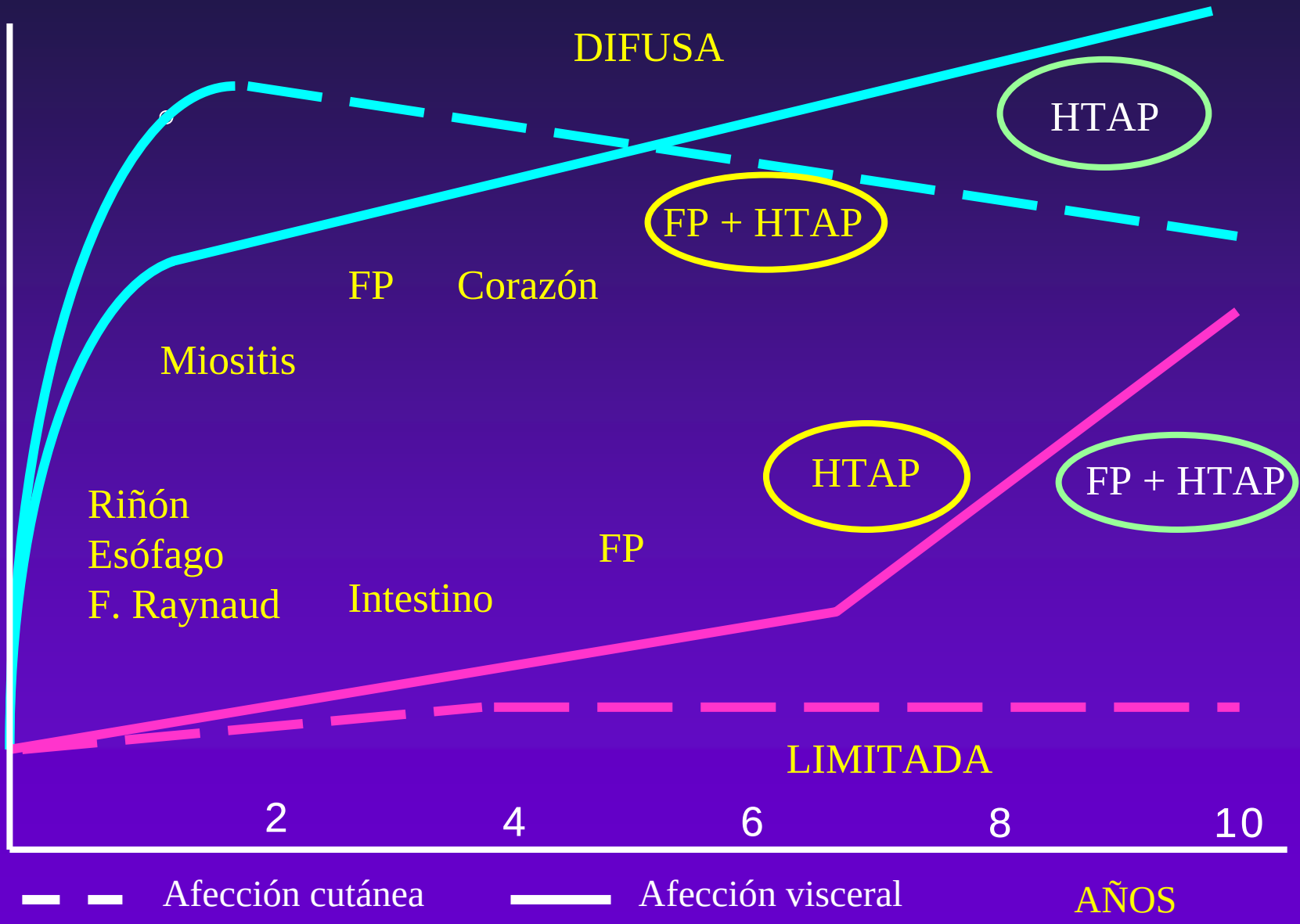
Is Pulmonary Arterial Hypertension Really a Late Complication of Systemic Sclerosis?

*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**

Conclusions: **In contrast to the expected scenario, early-onset PAH occurred in approximately half of SSc patients. Early-onset PAH was as frequent among patients with diffuse SSc as those with limited SSc. Annual screening for PAH should be implemented immediately after SSc diagnosis for all patients.**

(CHEST 2009; 136:1211–1219)

Esclerodermia. Evolución



HTAP en la esclerodermia: factores de riesgo

Forma clínica limitada
Diagnóstico de la enfermedad en edad tardía (>60 a.)
Descenso de la DLCO con CVF normal
Fenómeno de Raynaud grave y de curso prolongado
Pérdida capilar en la capilaroscopia
Anticuerpos anticentrómero
anti-U3-RNP
anti-B23
anti-U1- RNP
Valores elevados de NT-proBNP

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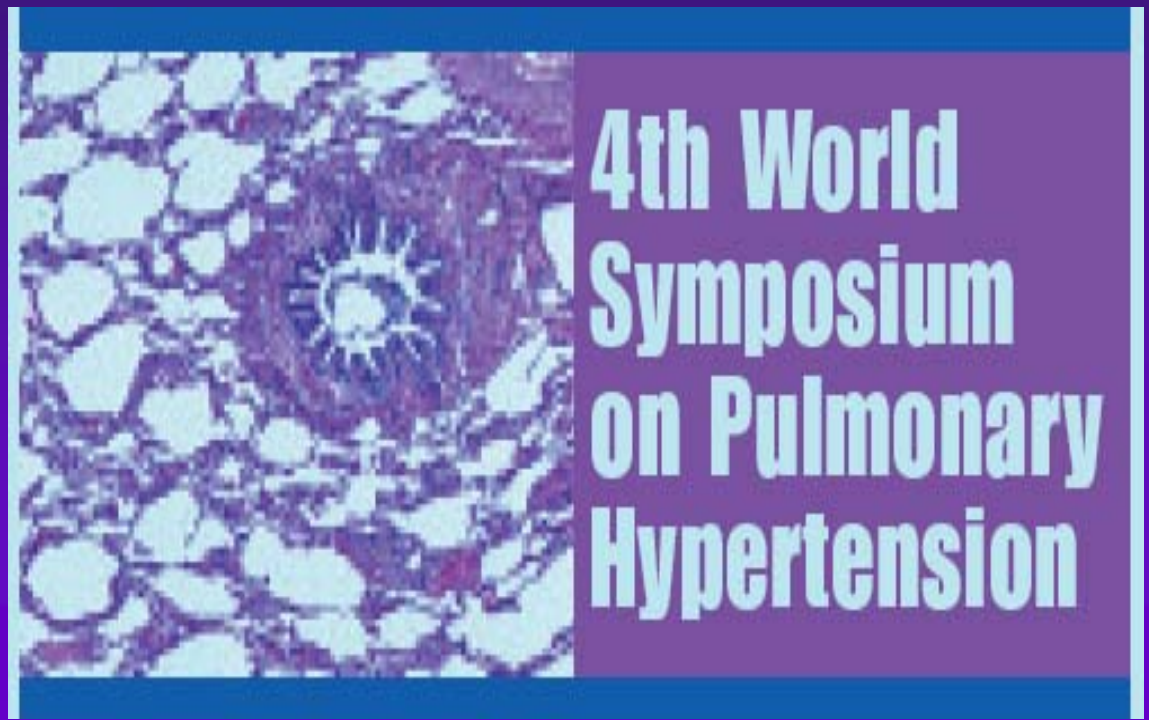
doi:10.1016/j.jacc.2009.04.011

Diagnosis and Assessment of Pulmonary Arterial Hypertension

Recommendations. Based on this literature review, we recommend simplifying the definition of PH, as follows:

- The exercise and PVR criteria should be eliminated.
- A resting mPAP of 8 to 20 mm Hg should be considered normal, based on available evidence.
- The proposed new definition of PH is a resting mPAP ≥25 mm Hg.

Further studies are needed to better determine the natural history of patients with mPAP 21 to 24 mm Hg.



Dana Point (California), febrero 2008

HTAP en la esclerodermia: sospecha diagnóstica

Disnea de causa no manifiesta

Descenso de la DLCO: CVF normal/mínima fibrosis

FVC/DLCO: > 1,6 – 1,8

Por Ecocardiografía Doppler:

- Velocidad de regurgitación tricuspídea > 3 m/sec
- PAPs > 40 mm Hg
- Dilatación de cavidades derechas

Aumento de NT-proBNP

Controles: 6 m – 1 año: Ecocardiograma; PFRs; NT-proBNP
RNM

Rheumatology 2008;47:v33–v35 doi:10.1093/rheumatology/ken306

Screening for PAH in patients with systemic sclerosis: focus on Doppler echocardiography

J. Sánchez-Román[1], C. F. Opitz[2], O. Kowal-Bielecka[3], F. J. García-Hernández[1], M. J. Castillo-Palma[1] and D. Pittrow[4] for the EPOSS-OMERACT Group

TABLE 1. Overview on echo Doppler parameters used for PAH screening in SSc patients

Author	Source	Setting	SSc patients *n*	Doppler parameter primarily used for screening
Murata	Jpn Circ J 1992;56:983	Univ. centre Japan	71	VTR
Battle	Chest 1996;110:1515	Univ. centre USA	34	sPAP ≥30 mmHg
Murata	Chest 1997:111:36	Univ. centre Japan	135	sPAP ≥40 mmHg
Denton	Br J Rheumatol 1997;36:239	Univ. centre UK	33	sPAP ≥30 mmHg
Mukerjee	Ann Rheum Dis 2003;62:1088	Univ. centre UK (mostly)	794	sPAP >35 mmHg (or DL_{CO} <50% predicted, or precipitous fall in DL_{CO} >20% over 1 yr)
Mukerjee	Rheumatology 2004;43:461	Univ. centre UK	137	Tricuspid gradient (range 30–40 mmHg); elevated sPAP
Hachulla	Arthritis Rheum 2005;52:3792	21 Univ. centres France ('ItinérAIR Sclérodermie')	599	VTR ≥3 m/s or VTR 2.5–3 m/s (plus unexplained dyspnoea)
Wigley	Arthritis Rheum 2005; 52:2125	50 Rheumatol. practices USA	669 *de novo*	(Estimated) RVSP ≥40 mmHg
Kiatchoosakun	J Med Assoc Thai 2007;90:2024	Univ. centre Thailand	129	RVSP >36 mmHg
Hsu	J Rheumatol 2008; online first	Univ. centre USA	49	RVSP >47 mmHg (optimal cutpoint compared with RHC)

- SSc patients have a high incidence and prevalence of PAH.
- Despite important limitations, Doppler echocardiography currently represents the screening method of choice according to recent PAH guidelines.
- A RHC is mandatory to confirm the diagnosis.
- A number of predisposing factors may help to identify SSc patients at particularly high risk of developing PAH.

HTAP y esclerodermia: NT- proBNP

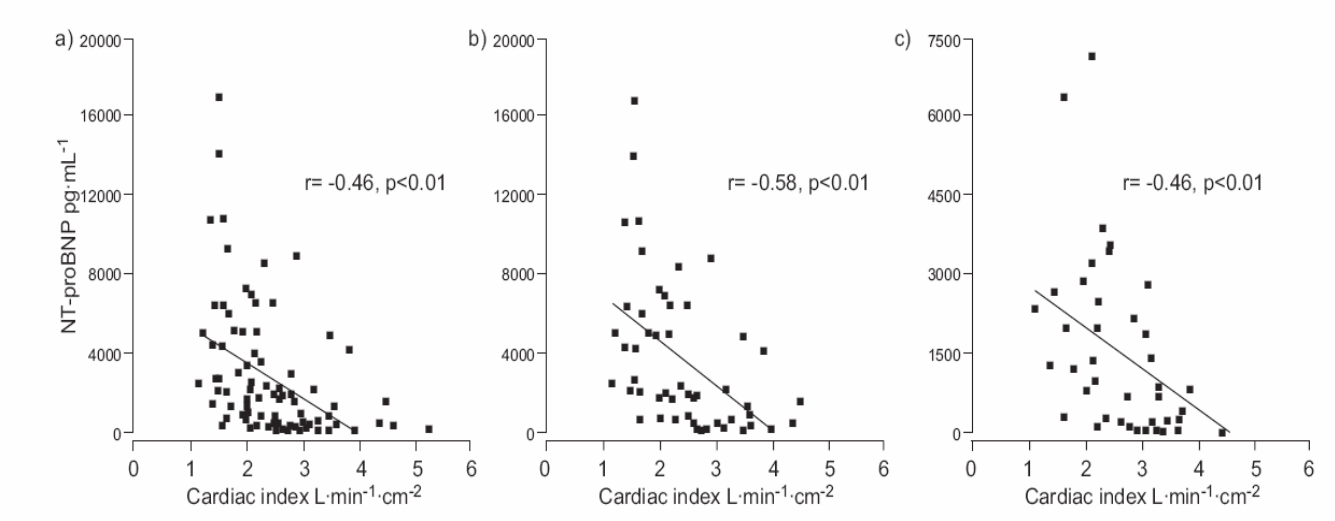
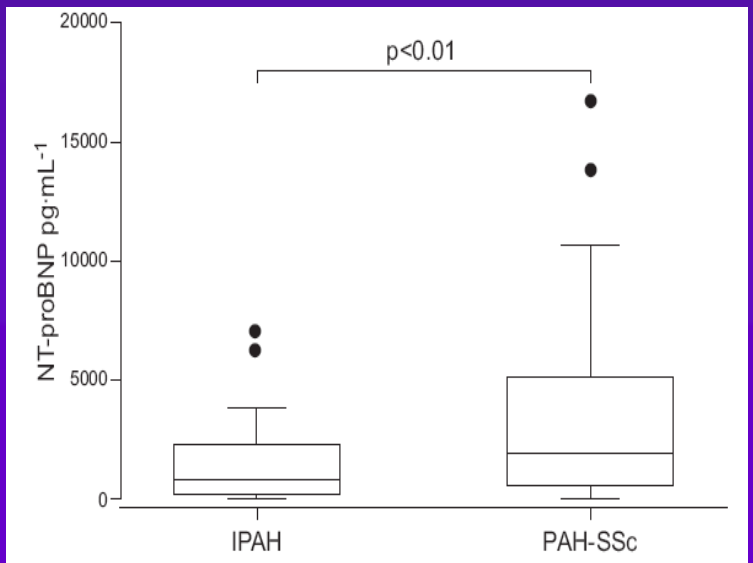
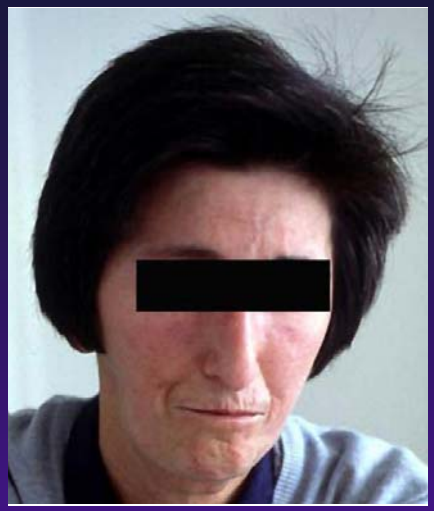


FIGURE 2. Correlations between N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac index in a) the overall cohort, b) pulmonary arterial hypertension related to systemic scleroderma patients and c) idiopathic pulmonary arterial hypertension patients.



In conclusion, in this cohort of patients with PAH, NT-proBNP levels were significantly higher in PAH-SSc subjects compared to IPAH subjects despite similar haemodynamics, suggesting differences in response to cardiac load. Furthermore, NT-proBNP was a strong predictor of survival only in the PAH-SSc group, further emphasising the role of this noninvasive marker in the evaluation of patients with PAH-SSc. Although the

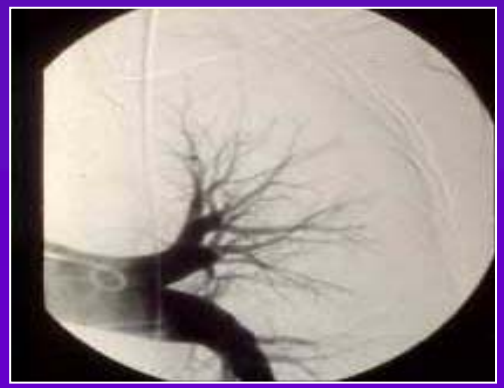
Mathai SC et al. Eur Respr J. 2010;35:95-104

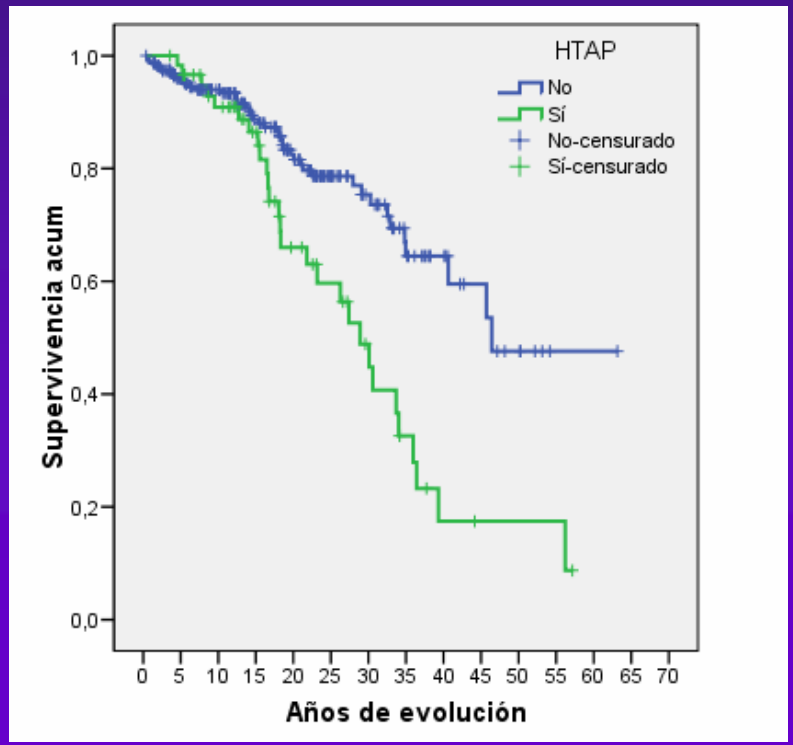


Factores pronósticos	RR	*p*
Esclerodermia difusa	2,730	0,001
Edad de comienzo	1,079	0,0001
Fibrosis pulmonar	2,463	0,003
HTAP	2,802	0,0001
Crisis renal	30,062	0,0001

Esclerodermia
Factores pronósticos

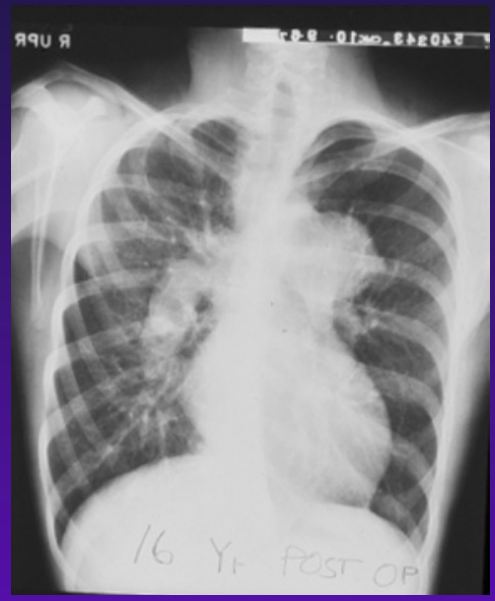
Simeón CP, *Ann Rheum Dis, 1997*
Simeón CP, *Rheumatology, 2003*





ESCLERODERMIA. Hipertensión pulmonar

N= 335 (Hospital Vall d'Hebron)

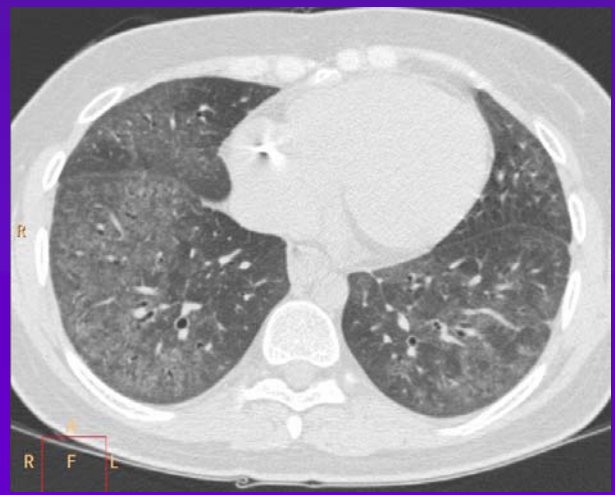


Causas de muerte

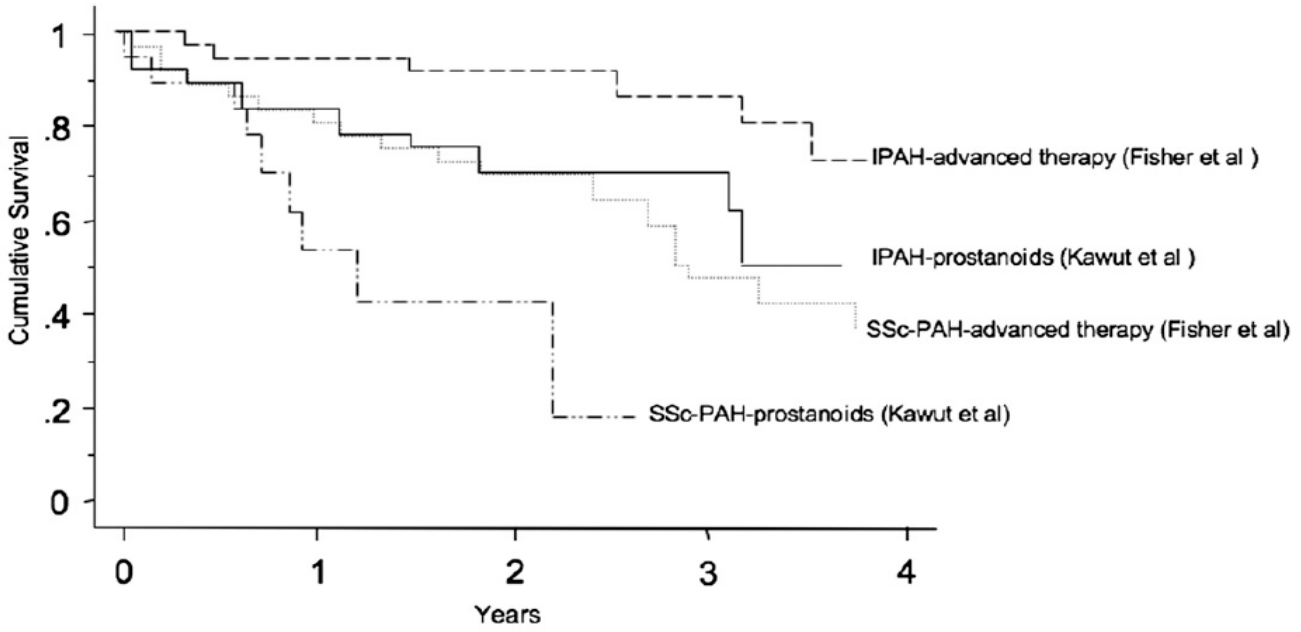
Afección pulmonar : 29 (40 %)

HTA pulmonar aislada: 15
Fibrosis pulmonar + HTAP: 8

Fibrosis pulmonar: 6



HTAP en la esclerodermia: pronóstico



Studies	Kawut et al [6]		Fisher et al [4]	
Period of time	1997-2001		2000-2005	
Patients	IPAH n = 33	SSc-PAH n = 22	IPAH n = 41	SSc-PAH n = 50
First line PAH therapy	Prostanoïds		ERA, PDE5 inhibitors, or prostanoïds according to guidelines	
NYHA FC III-IV, %	-		77.5	64
mPAP, *mmHg*	52 ± 12	48 ± 10	54 ± 1.9	47 ± 1.5
CI, $L.min^{-1}.m^{-2}$	2.1 ± 0.62	2.2 ± 0.54	2.1 ± 0.1	2.2 ± 0.1
PVR, $dyn.s.cm^{-5}$	918 ± 433	755 ± 238	941 ± 88	855 ± 83

Comparison of Baseline Characteristics and Survival Between Patients With Idiopathic and Connective Tissue Disease–related Pulmonary Arterial Hypertension

Maria J. Ruiz-Cano, MD, Pilar Escribano, MD, Rafael Alonso, MD, Juan Delgado, MD, Patricia Carreira, MD, Teresa Velazquez, MD, Miguel A. Gomez Sanchez, MD, and Carlos Sáenz de la Calzada, MD

J Heart Lung Transplant 2009;28:621-7

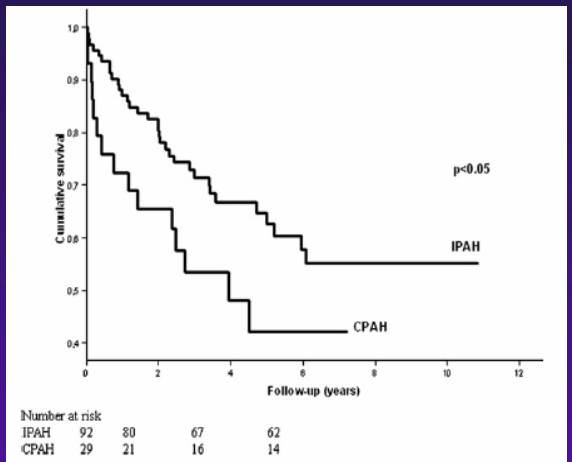


Figure 1. Overall survival in each etiologic group. IPAH: 1-year survival 87%; 3-year survival 71%; 5-year survival 63%. CPAH: 1-year survival 70%; 3-year survival 53%; 5-year survival 42%.

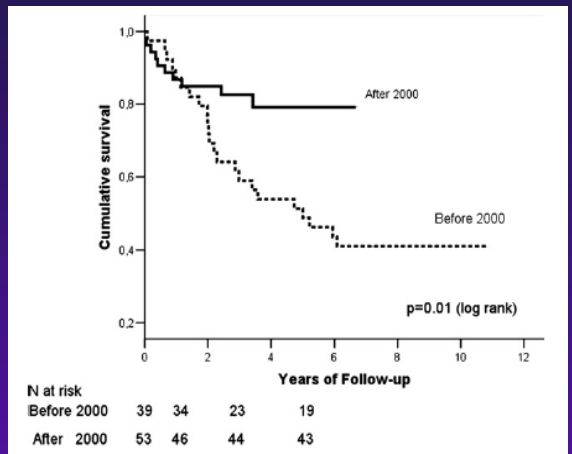


Figure 3. IPAH survival related to treatment era. Historic treatment era: 1-year survival 87%; 3-year survival 59%; 5-year survival 48%. Current treatment era: 1-year survival 87%; 3-year survival 82%; 5-year survival 79%.

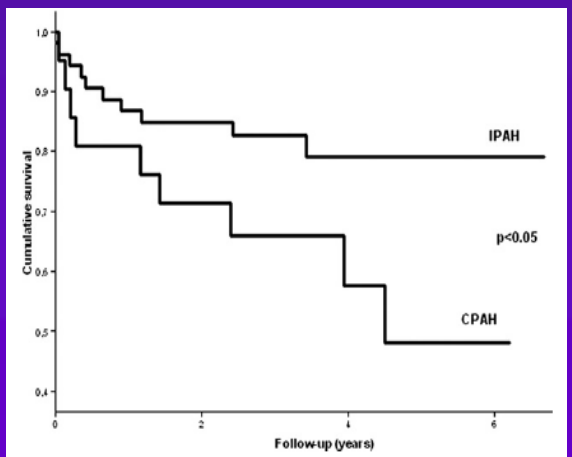


Figure 5. Survival in the current era for each etiologic group. IPAH: 1-year survival 87%; 3-year survival 82%; 5-year survival 79%. CPAH: 1-year survival 81%; 3-year survival 66%; 5-year survival 48%.

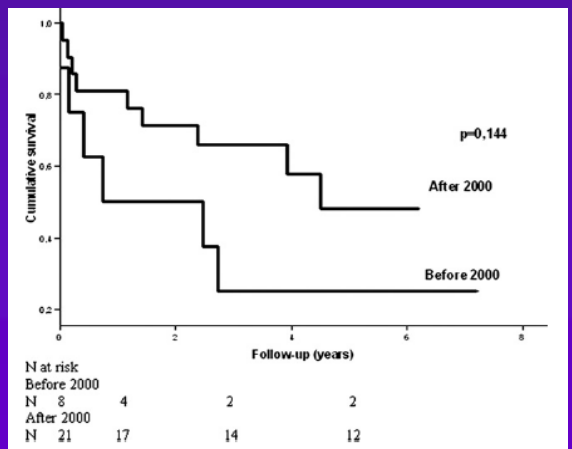
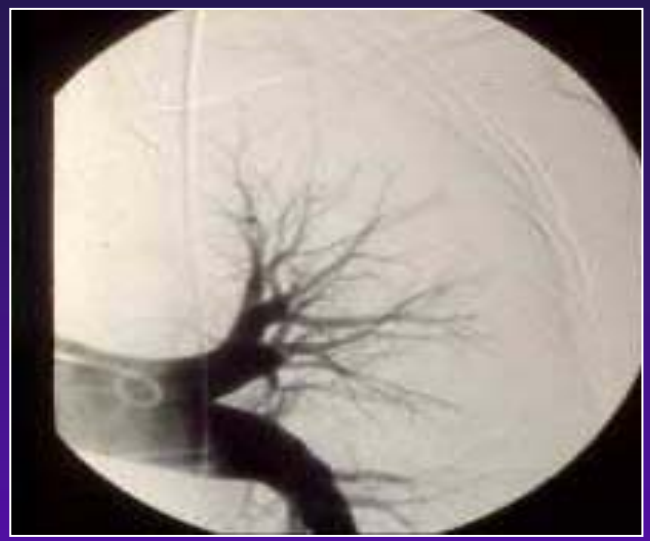
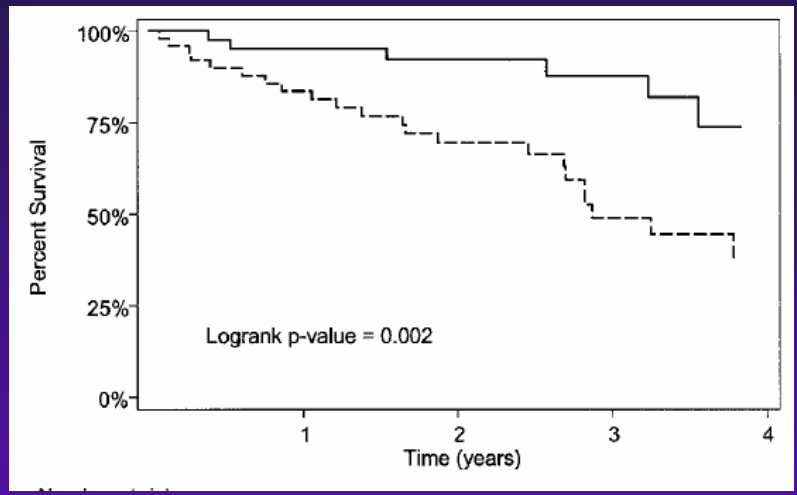


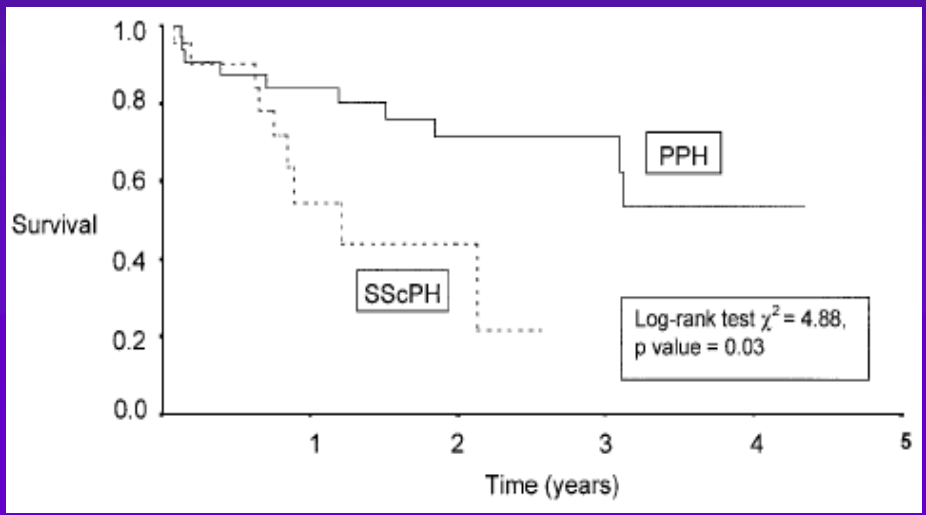
Figure 4. CPAH survival related to treatment era. Historic treatment era: 1-year survival 50%; 3-year survival 25%; 5-year survival 25%. Current treatment era: 1-year survival 81%; 3-year survival 66%; 5-year survival 48%.

Clinical Differences Between Idiopathic and Scleroderma-Related Pulmonary Hypertension





Fisher MR et al. *Arthritis Rheum, 2006*



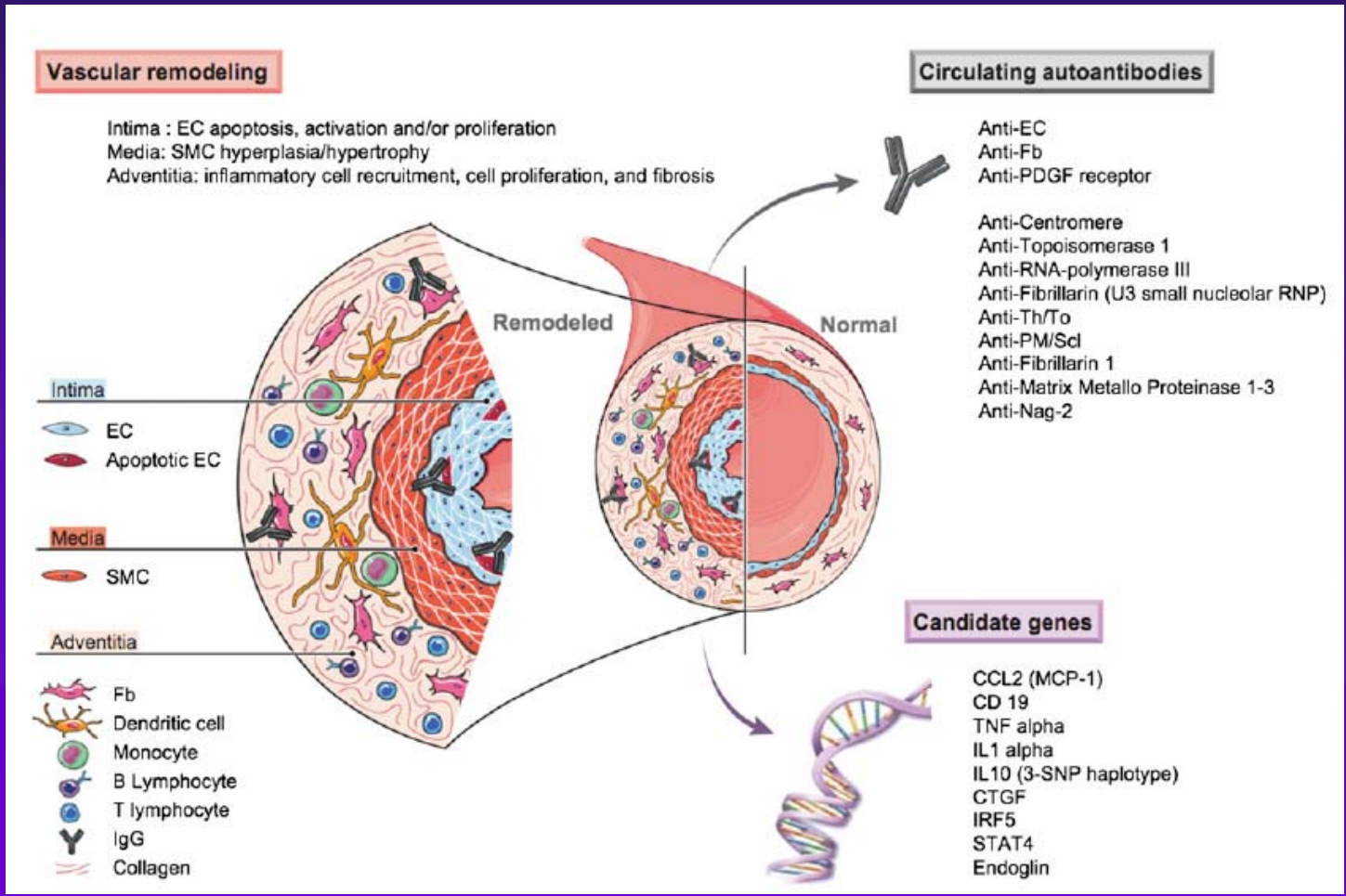
Kawut SM. et al. *Chest*, 2003

Table 2. Baseline right heart catheterization findings*

	IPAH (n = 41)	PAH-Scl (n = 50)	*P*
Right atrial pressure, mm Hg	10.1 ± 0.9	11.2 ± 0.7	0.36
Pulmonary artery systolic pressure, mm Hg	86.4 ± 2.9	75.6 ± 2.4	0.004
Pulmonary artery pressure, mm Hg	54.4 ± 1.9	46.6 ± 1.5	0.002
Pulmonary capillary wedge pressure, mm Hg	12.0 ± 0.8	11.4 ± 0.7	0.59
Cardiac index, liters/ minute/m^2	2.1 ± 0.1	2.2 ± 0.1	0.19
Pulmonary vascular resistance index, Wood units	22.8 ± 1.8	17.5 ± 1.5	0.026

Table 2 Differences in Pulmonary Microvascular Histopathology Between IPAH and Pulmonary Hypertension in Limited SSc (37)

Pathological Findings	IPAH ($N = 11$)	SSc-PH ($N = 8$)	P Value
Plexogenic arteriopathy	10	0	0.001
Intimal fibrosis of the small vessels (arterioles/venules) adjacent to the alveoli	3	8	0.003
Pathological changes resembling pulmonary veno-occlusive disease	0	4	0.02
Intimal fibrosis involving pulmonary venules and interlobular veins	3	7	0.02
Concentric laminar intimal fibrosis in the bronchiolar axial arteries	0	3	—
Loose concentric arterial intimal fibrosis	3	7	0.02



Le Pavec J et al. Am J Resp Crit Care Med. 2010

HTAP y ESCLERODERMIA

Patogenia

HTAP por vasculopatía 1ª
Enfermedad venooclusiva pulmonar
Cardiopatía ventricular izquierda
Hipoxia por vasoespasmo arterial
Microtrombosis
Enfermedad pulmonar intersticial

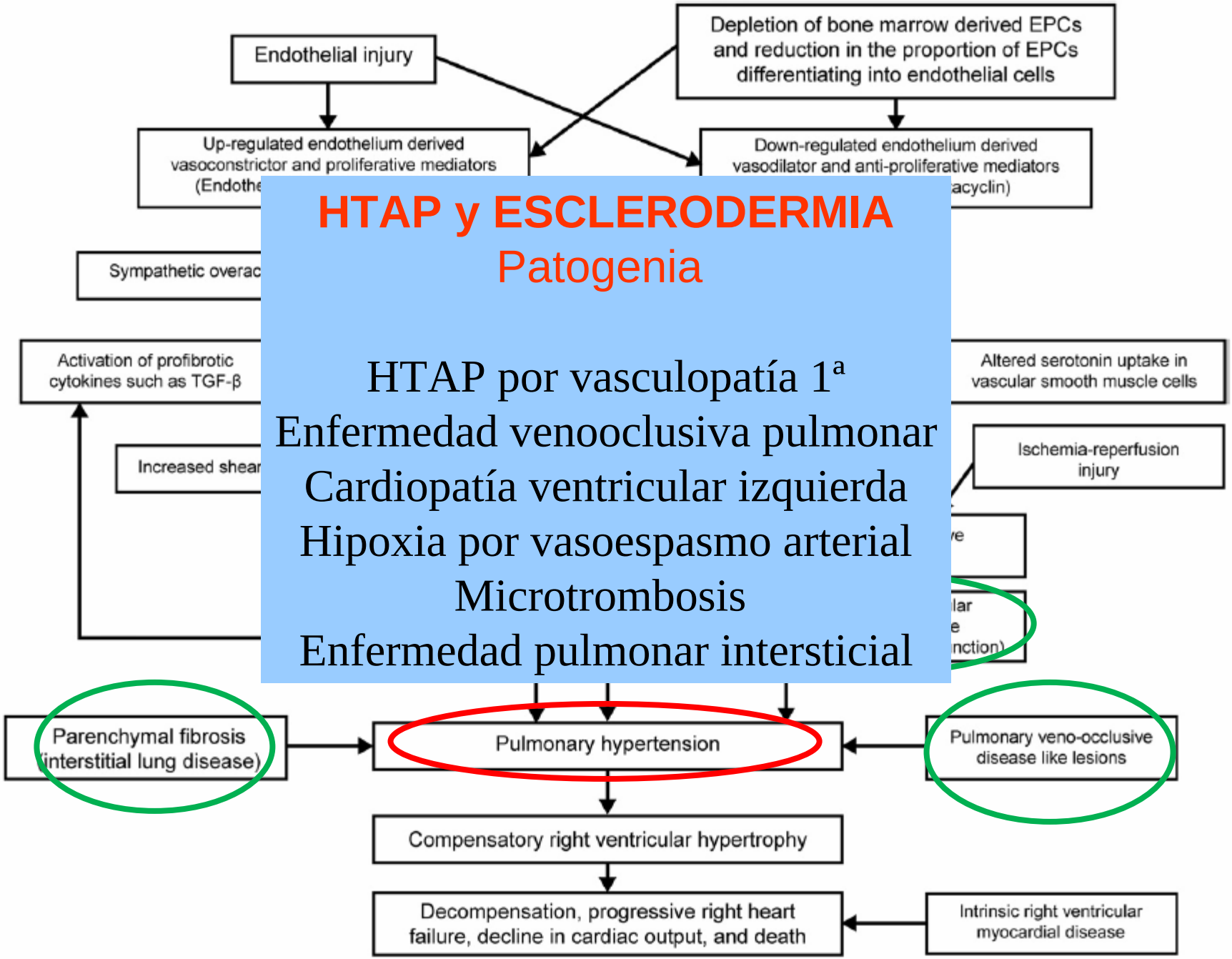
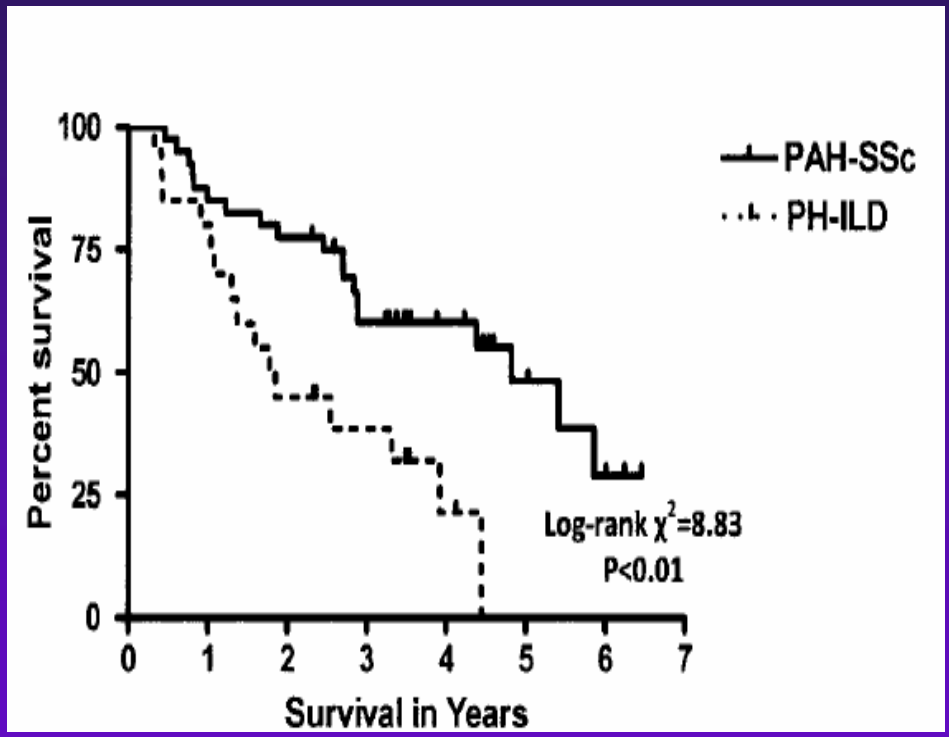


Figure 1 Pathogenesis of pulmonary hypertension in scleroderma. EPC = endothelial precursor cells.

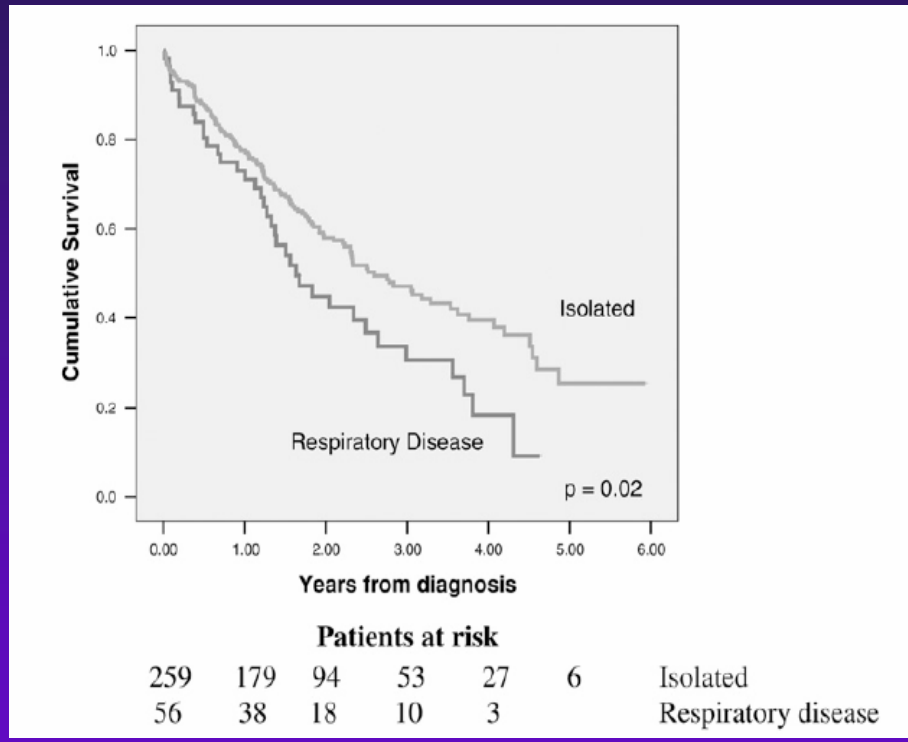
Survival in Pulmonary Hypertension Associated With the Scleroderma Spectrum of Diseases

Impact of Interstitial Lung Disease



Mathai SC. *Arthritis Rheum*. 2009;60:569

Connective Tissue Disease–associated Pulmonary Arterial Hypertension in the Modern Treatment Era



Condliffe R, *Am J Respir Crit Care Med*. 2009;179:151

Table 2. 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

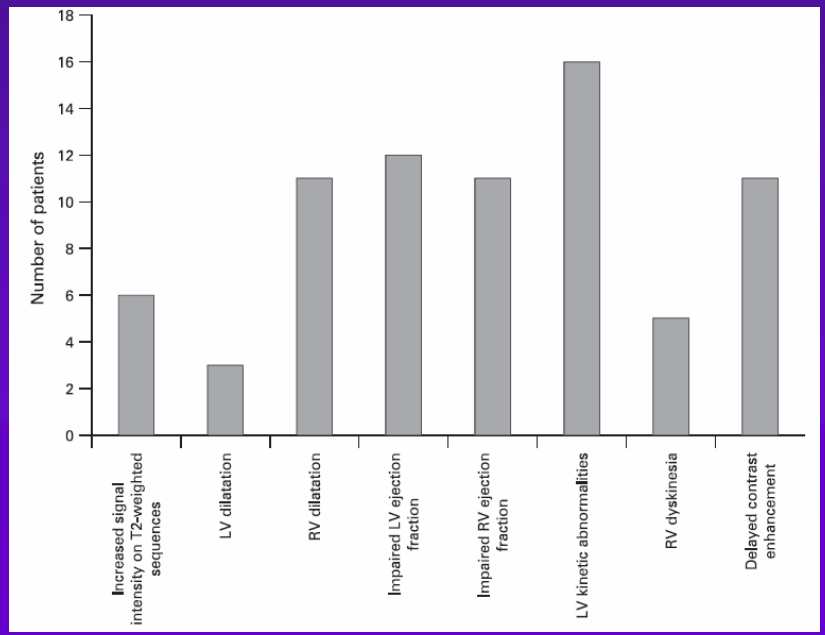
* 95% CI = 95% confidence interval; lcSSc = limited cutaneous systemic sclerosis; dcSSc = diffuse cutaneous systemic sclerosis.

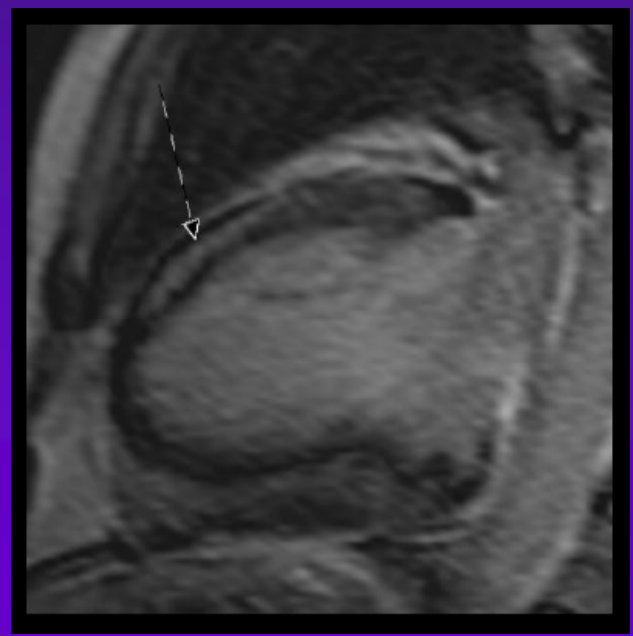
Hachulla E et al. Arthritis Rheum, 2009

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

Fisher MR et al. *Arthritis Rheum*, 2006





Hachulla AL et al. *Ann Rheum Dis*, 2009

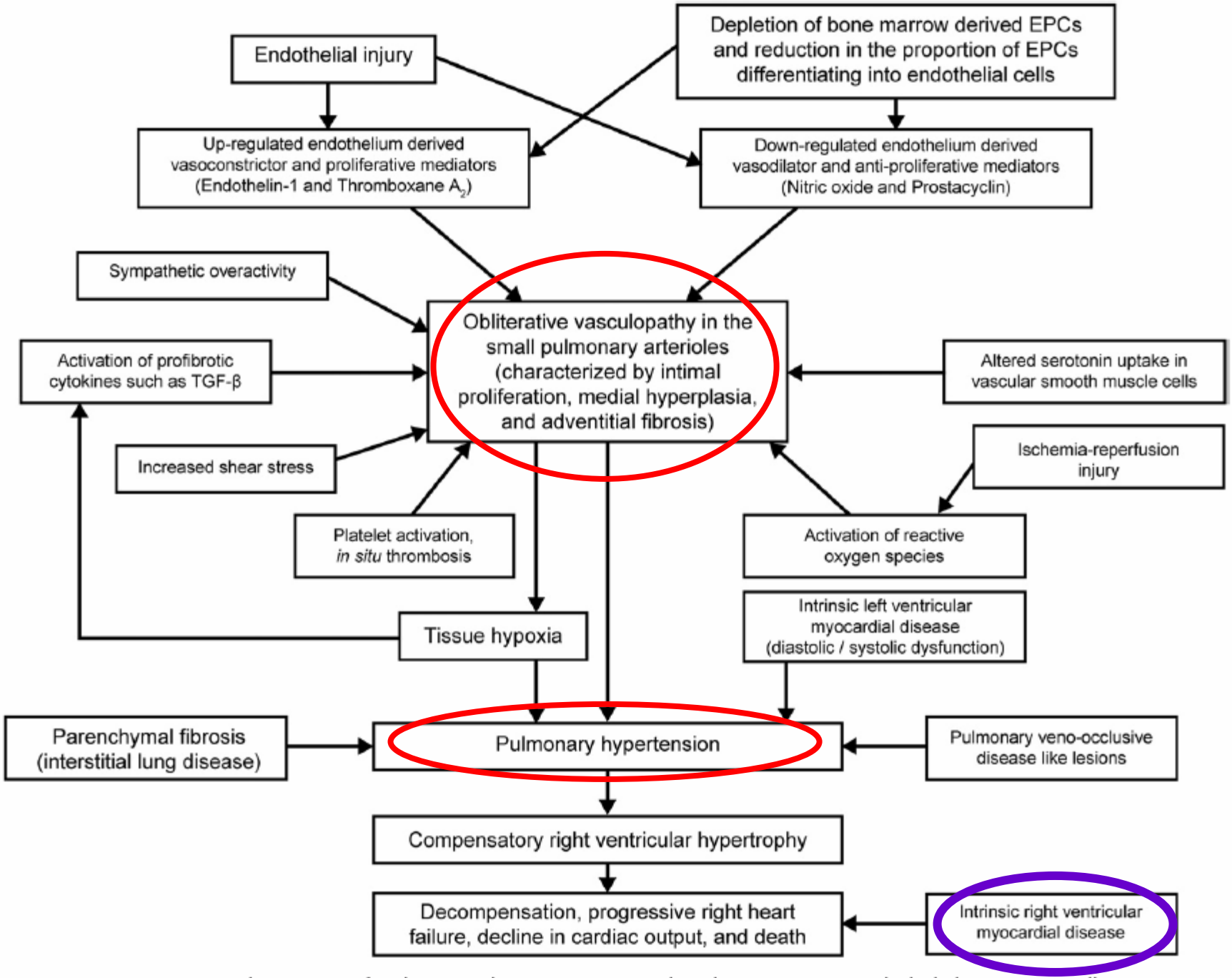
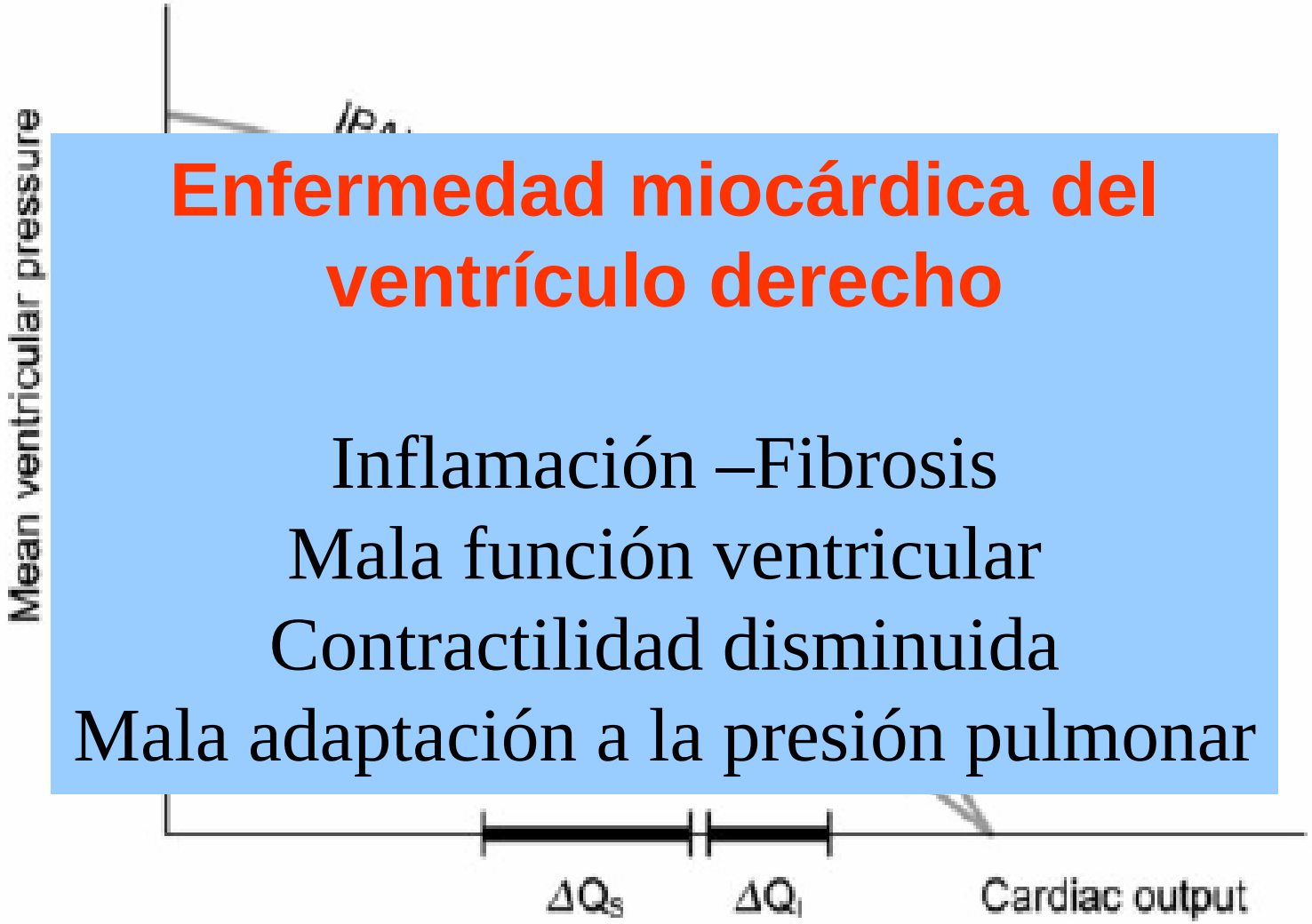


Figure 1 Pathogenesis of pulmonary hypertension in scleroderma. EPC = endothelial precursor cells.



Enfermedad miocárdica del ventrículo derecho

Inflamación –Fibrosis
Mala función ventricular
Contractilidad disminuida
Mala adaptación a la presión pulmonar

A Vonk Noordegraaf et al. *Rheumatology*, 2008

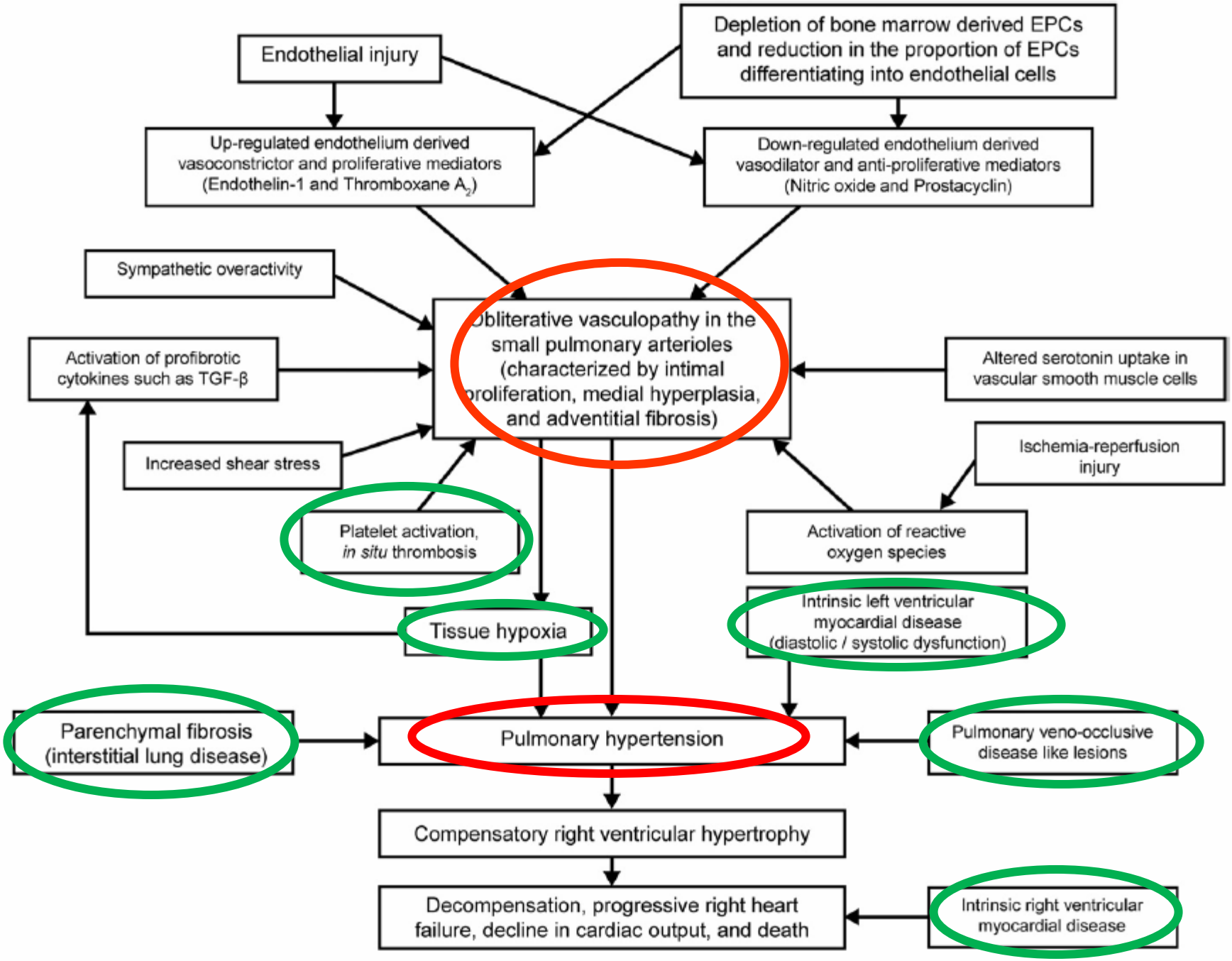


Figure 1 Pathogenesis of pulmonary hypertension in scleroderma. EPC = endothelial precursor cells.

CONCLUSIONES

Factores de riesgo

Seguimiento: controles periódicos

Diagnóstico precoz

Indicadores de gravedad

Valoración cardiológica

Esclerodermia. Hipertensión arterial pulmonar

Pulmonary hypertension:
The Bête Noire of the
Diffuse Connective
Tissue Diseases.
E. Carwile LeRoy, 1991

Pulmonary hypertension
in systemic sclerosis:
bête noire no more ?
J. Varga, 2002