7TH INTERNATIONAL MEETING ON PULMONARY RARE DISEASES AND ORPHAN DRUGS

Pulmonary hypertension in sarcoidosis

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Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

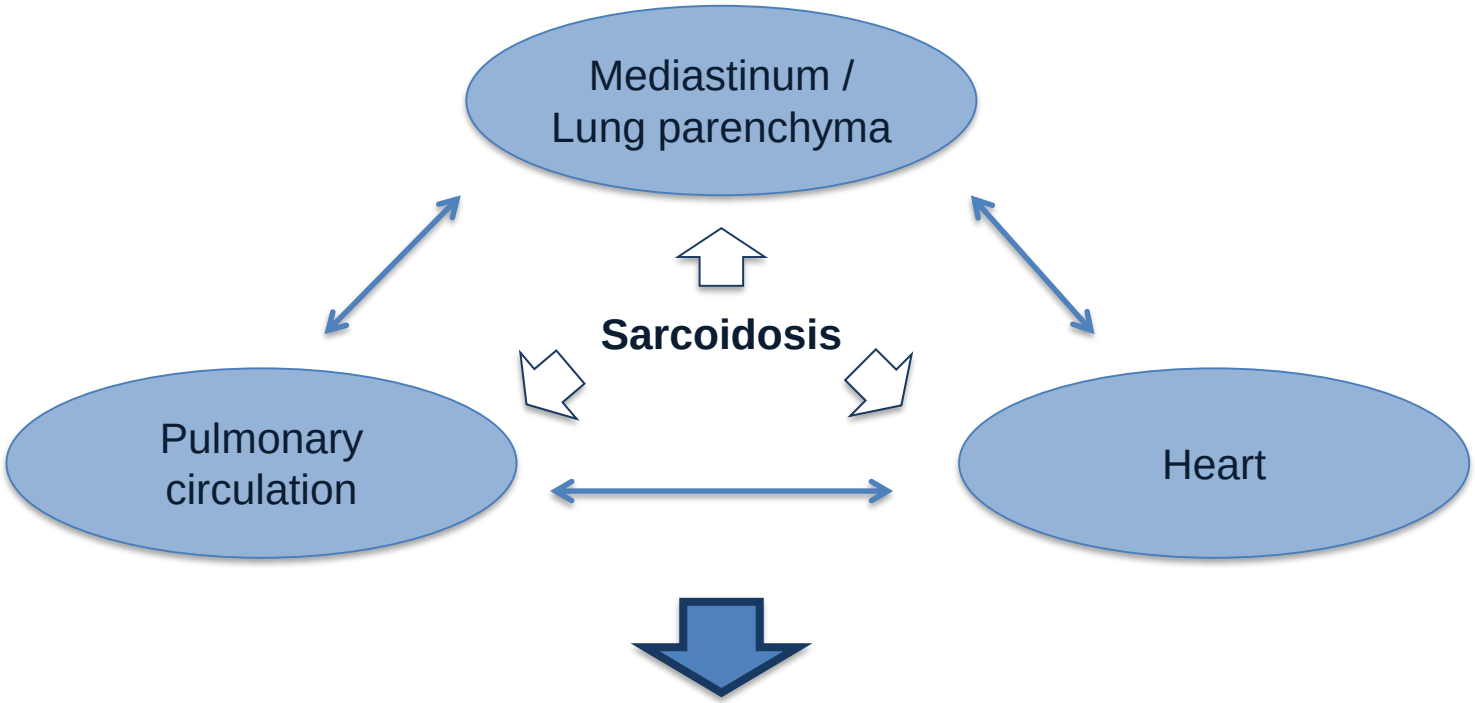
LabEx LERMIT Laboratoire d'Excellence en Recherche sur le Médicament et l'Innovation Thérapeutique

TORINO DHU Thorax Innovation

Hôpitaux universitaires Paris-Sud Antoine-Béclère Bicêtre Paul-Brousse

Pulmonary hypertension associated with sarcoidosis

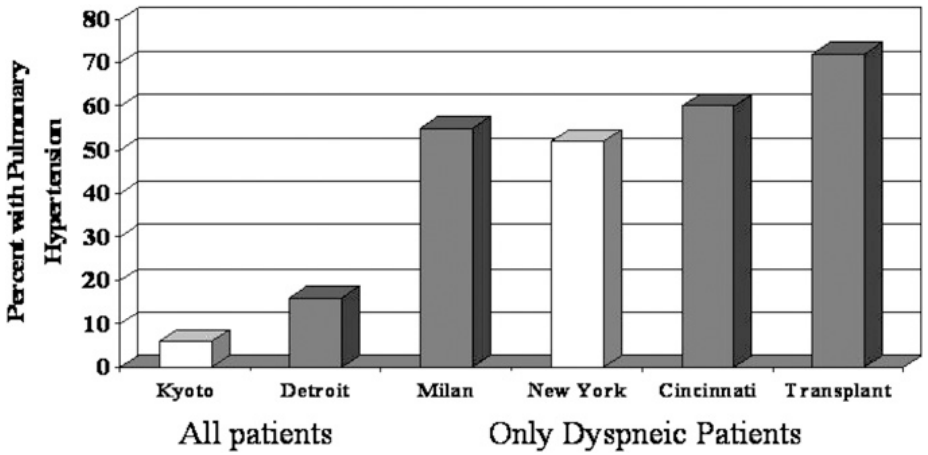
1951: First case of elevated PAP in a patient with sarcoidosis



PH associated with sarcoidosis: complex pathophysiological mechanisms

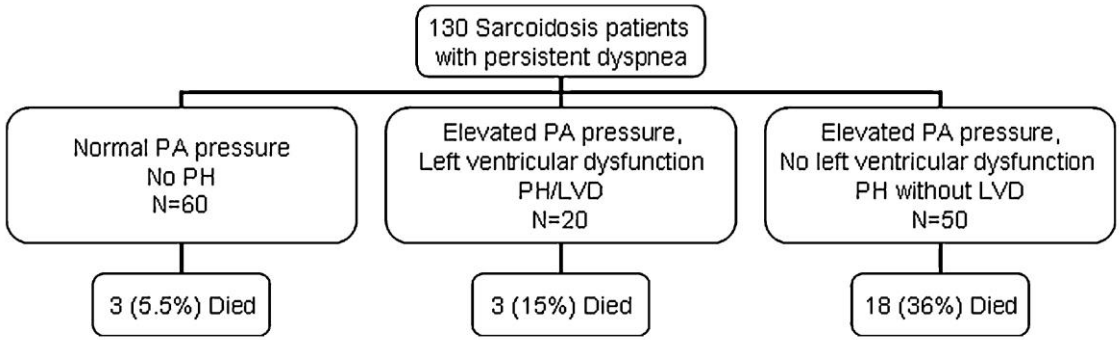
Prevalence of PH in sarcoidosis: 5 to 74%...

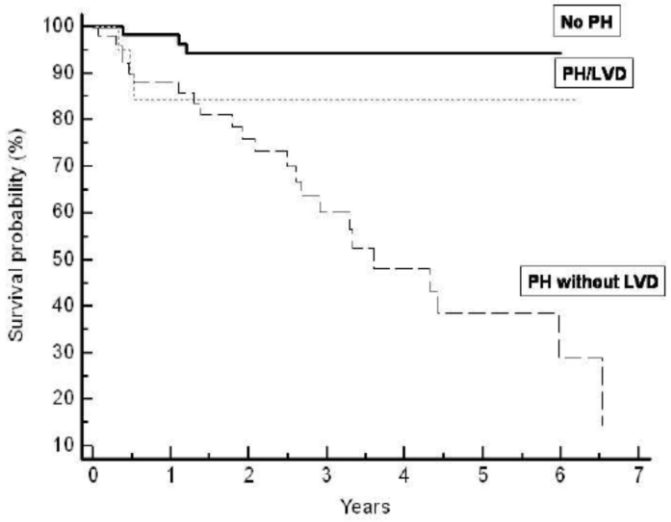
Author, *Journal*, Year	n	Patients	Definition of PH	Prevalence
Handa, *Chest* 2006	212	All patients	sPAP>40 mmHg (**TTE**)	5.7%
Bourbonnais, *ERJ* 2008	161	All patients	mPAP>25 mmHg & PAWP<15 mmHg (**RHC**)	13.7%
Sulica, *Chest* 2005	106	Patients with dyspnea	sPAP>40 mmHg (**TTE**)	51%
Shorr, *ERJ* 2005	363	Patients on LT waiting list	mPAP>25 mmHg (**RHC**)	72.5% (36% with mPAP>40 mmHg)

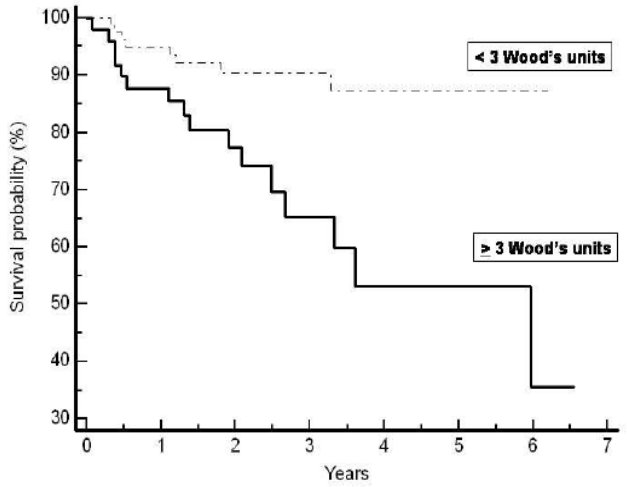


Baughman RP, *et al. Am J Respir Crit Care Med* 2011;183:573-81.

PH in sarcoidosis: Major impact on survival







- Median survival = 4.2 years if PH without left heart failure
- Increased mortality if sPAP estimated with TTE > 50 mmHg (HR=4.4 (95%CI = 1.92-22.95), p<0.005)

Baughman RP, *et al. Chest*. 2010;138:1078-85.

PH Classification

PH associated with sarcoidosis: **GROUP 5**

Multifactorial mechanisms

1. Pulmonary arterial hypertension

1.1 Idiopathic
1.
1.
1.

1'
haemangiomatosis

1'.1 Idiopathic
1'.2 Heritable
1'.2.1 EIF2AK4 mutation
1'.2.2 Other mutations
1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
1'.4.1 Connective tissue disease
1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

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
2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease

4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenoses
4.2.5 Parasites (hydatidosis)

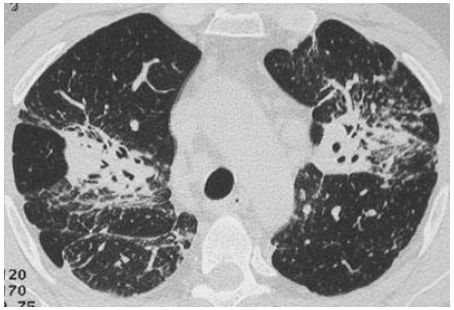
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

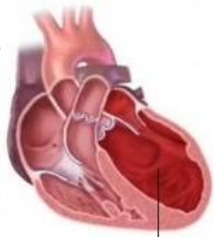
Galiè N, Humbert M, *et al. Eur Respir J* 2015 & *Eur Heart J* 2016.

PH in sarcoidosis: Multifactorial mechanisms

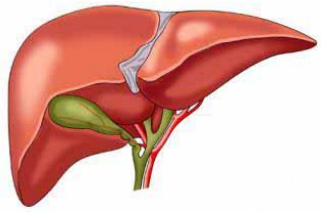
Hypoxic vasoconstriction
Pulmonary vascular rarefaction



Left heart disease

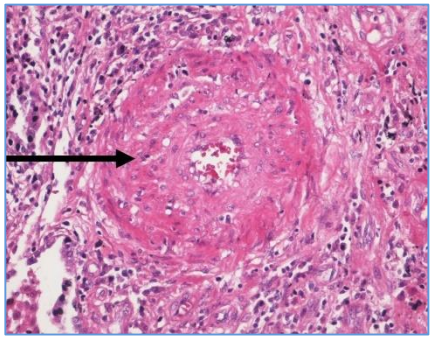


Portal hypertension

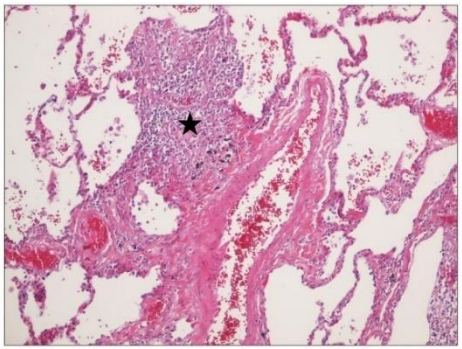


Pulmonary Hypertension

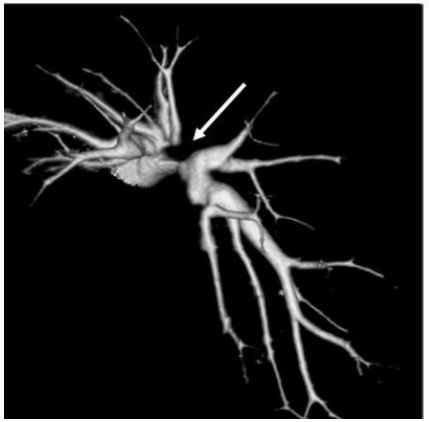
Vascular remodelling



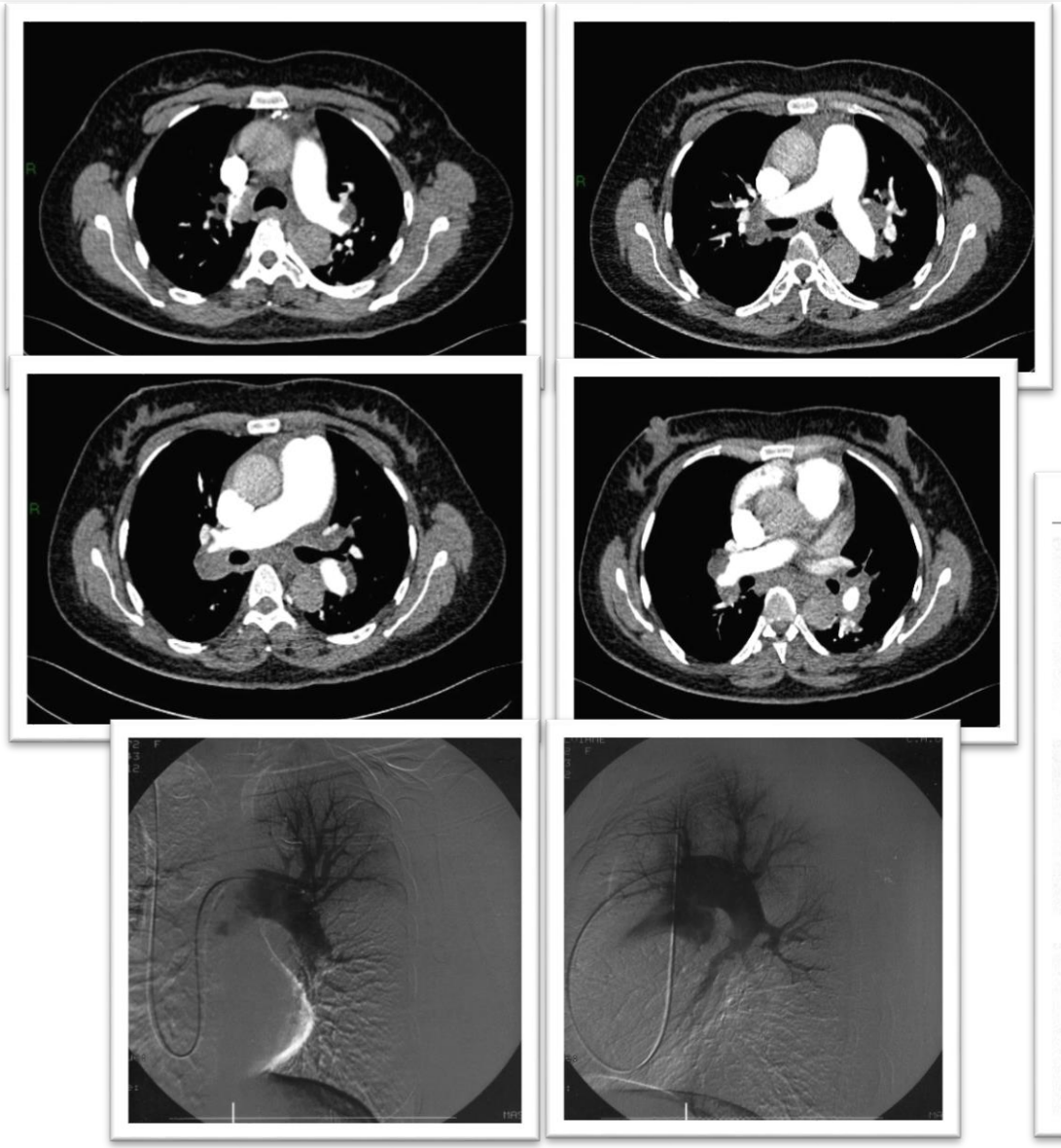
"PVOD"



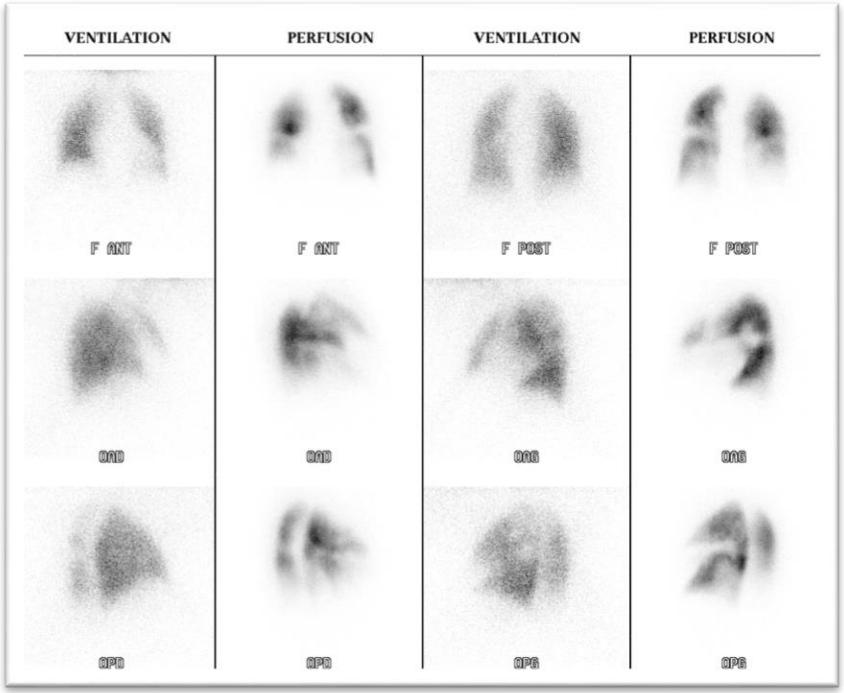
Fibrosing mediastinitis or compressive lymph nodes



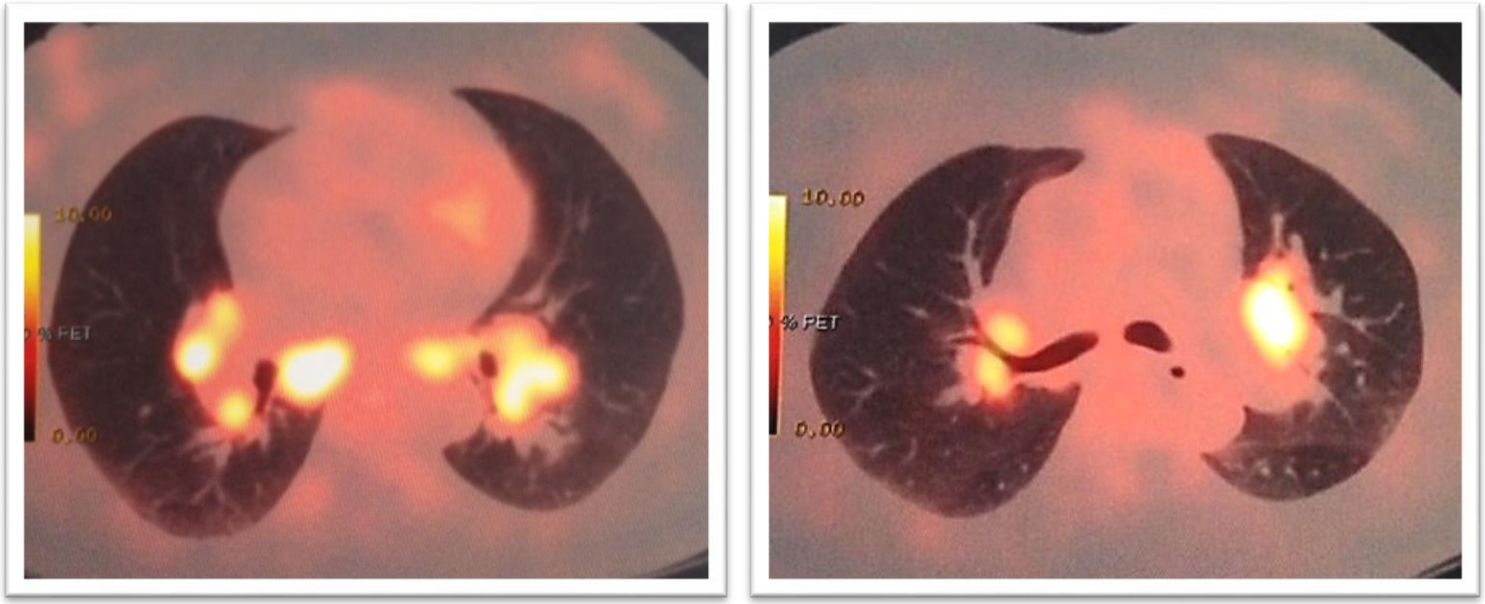
Extrinsic compression by lymph nodes



NYHA FC	III
6MWD, m	420
PAP s/d-m, mmHg	81/34-51
RAP, mmHg	16
PAWP, mmHg	12
CI, L/min/m²	2.07
PVR, dyn.s.cm^{-5}	712



Extrinsic compression by lymph nodes



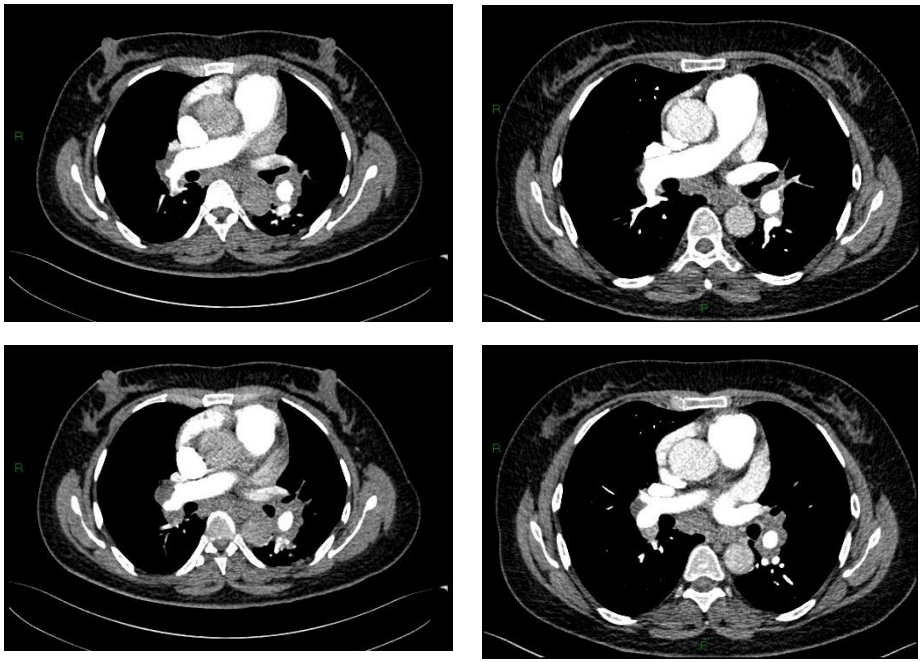
^{18}F-FDG PET-CT revealed metabolically hyperactive mediastinal lymph nodes with an important uptake of ^{18}F-FDG

→ First-line immunosuppressive therapy (corticosteroid)

→ No PAH-targeted therapy

PH due to extrinsic compression by lymph nodes: outcome on corticosteroids

	Baseline	After 1 year
NYHA FC	III	I
6MWD, *m*	420	640
PAP s/d-m, *mmHg*	81/34-51	59/22-35
RAP, *mmHg*	16	6
PAWP, *mmHg*	12	12
CI, *L/min/m²*	2.07	3.8
PVR, *dyn.s.cm^{-5}*	712	211

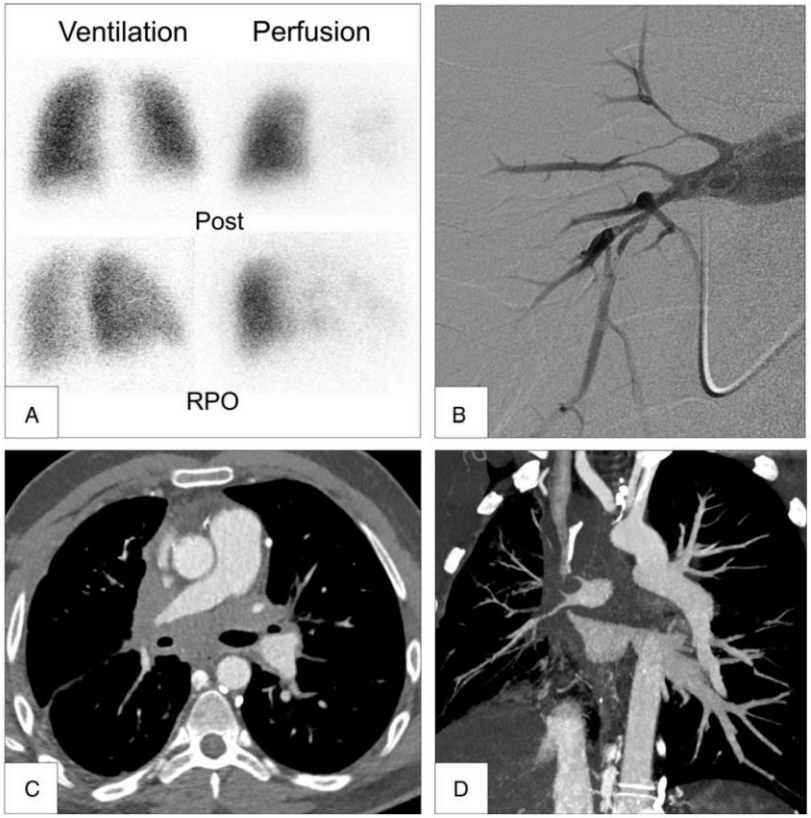


Fibrosing mediastinitis

- Proliferation of fibrous tissue in the mediastinum leading to extrinsic compression of mediastinal bronchovascular structures including pulmonary arteries and veins
- Granulomatous diseases (tuberculosis, sarcoidosis, histoplasmosis) are the main causes of FM

TABLE 1. Etiologies of Fibrosing Mediastinitis

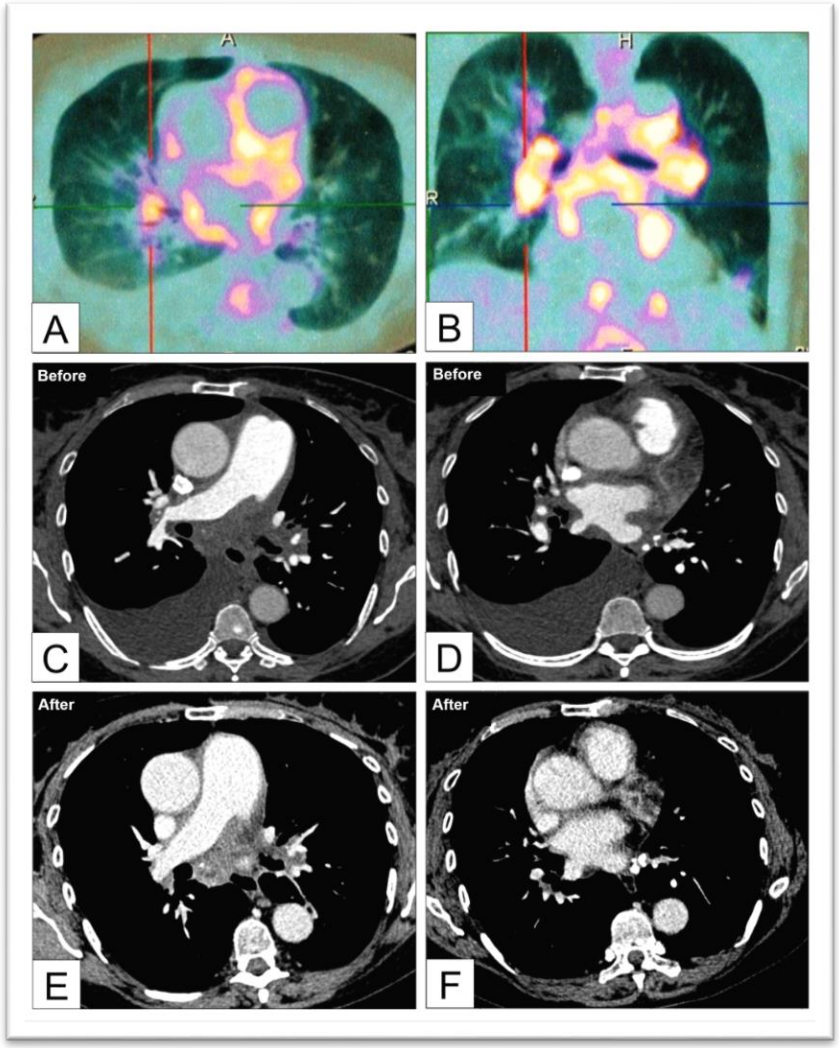
	PH Associated with Fibrosing Mediastinitis, n = 27
Sarcoidosis (stage 4)	13 (7)
Tuberculosis	9
–confirmed	3
–possible	6
Mediastinal irradiation	2
Idiopathic	3



- HRCT and pulmonary angiogram are key tools to correctly diagnose FM and rule out CTEPH

Seferian A, Montani D, *et al. Medicine* 2015.

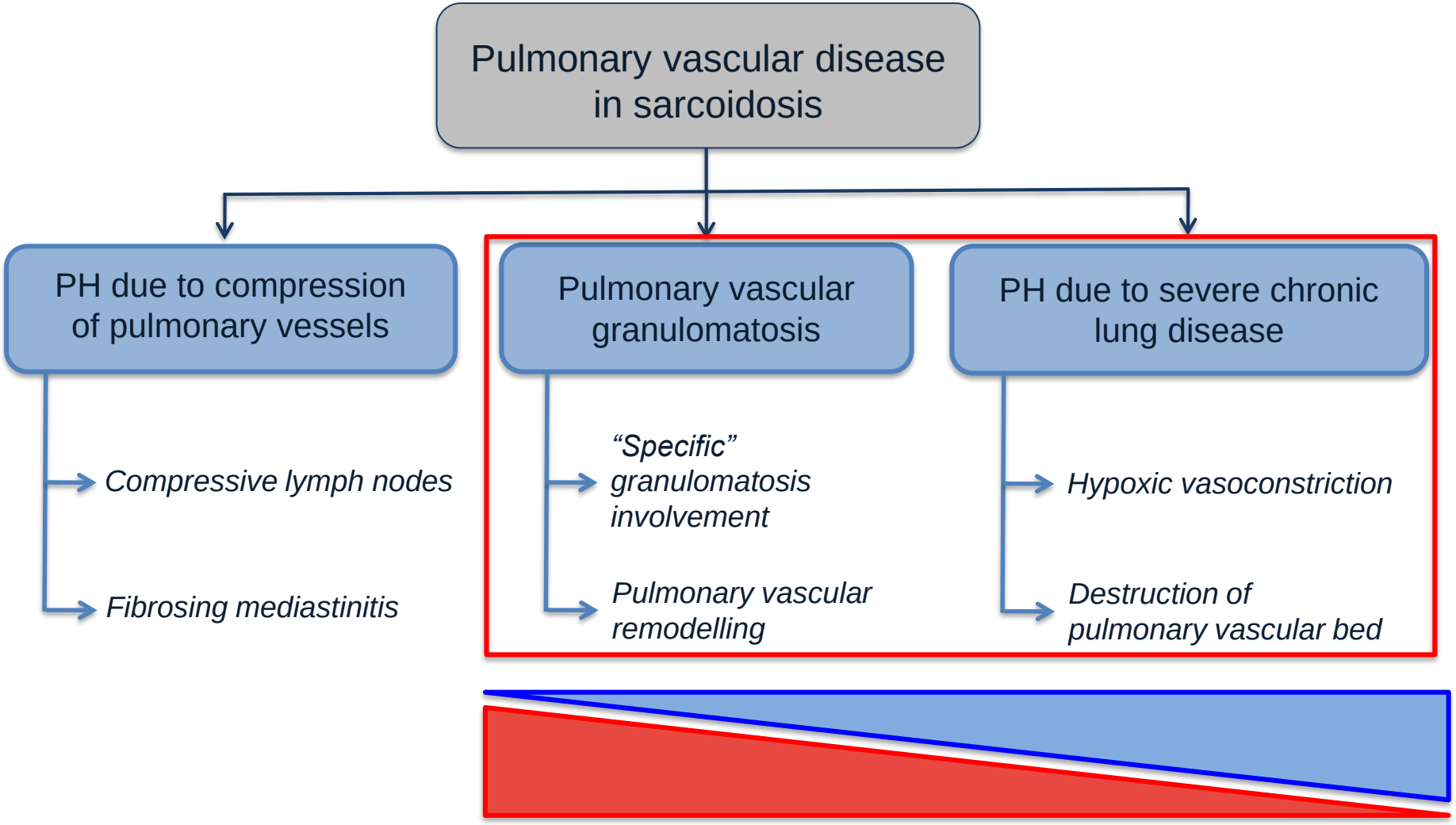
Fibrosing mediastinitis: an indication for corticosteroids?



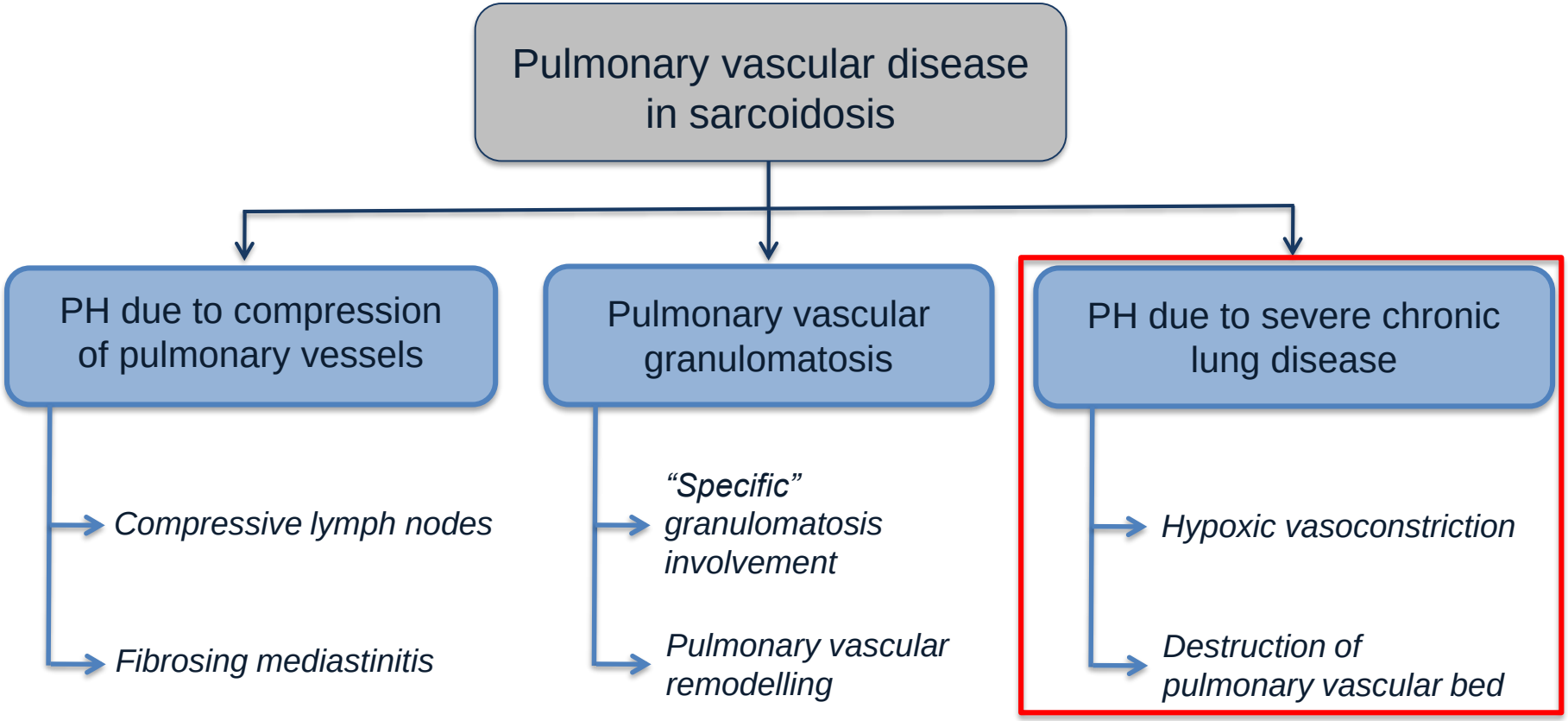
	Baseline	After 1 year on CS therapy
NYHA FC	IV	III
6MWD, *m*	190	295
RHC		
RAP, *mmHg*	4	5
mPAP, *mmHg*	46	44
PAWP, *mmHg*	6	5
CI, *L/min/m²*	3.31	3.29
PVR, *Wood U.*	7.4	8.3
PFTs		
FVC, *% of predicted*	46% th	79% th
TLC, *% of predicted*	73% th	76% th

Seferian A, Montani D, *et al. Medicine* 2015.

“Non-compressive” PH in sarcoidosis



“Non-compressive” PH in sarcoidosis



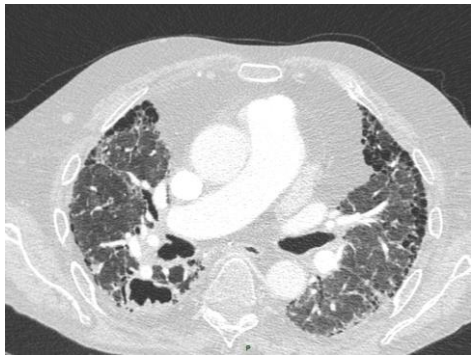
PH due to severe chronic lung disease

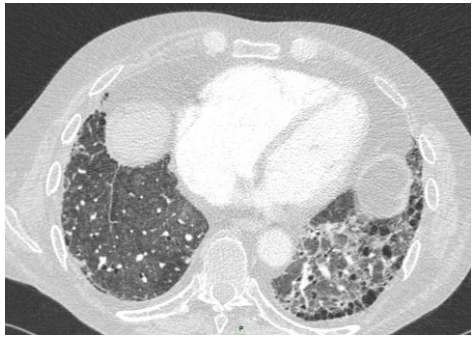
Chronic hypoxia

Rarefaction of pulmonary vessels

Mild pulmonary hypertension
Normal or elevated cardiac output
(Group 3)

mPAP<35 mmHg
AND
CI≥2.5 L/min/m^2





PFTs		RHC	
TLC, *% of predicted*	48%	RAP, *mmHg*	6
FVC, *% of predicted*	43%	mPAP, *mmHg*	32
DLCO, *% of predicted*	25%	CI, *L/min/m^2*	3,1
PaO_2 / $PaCO_2$, *mmHg*	54 / 48	PVR, *Wood U.*	5

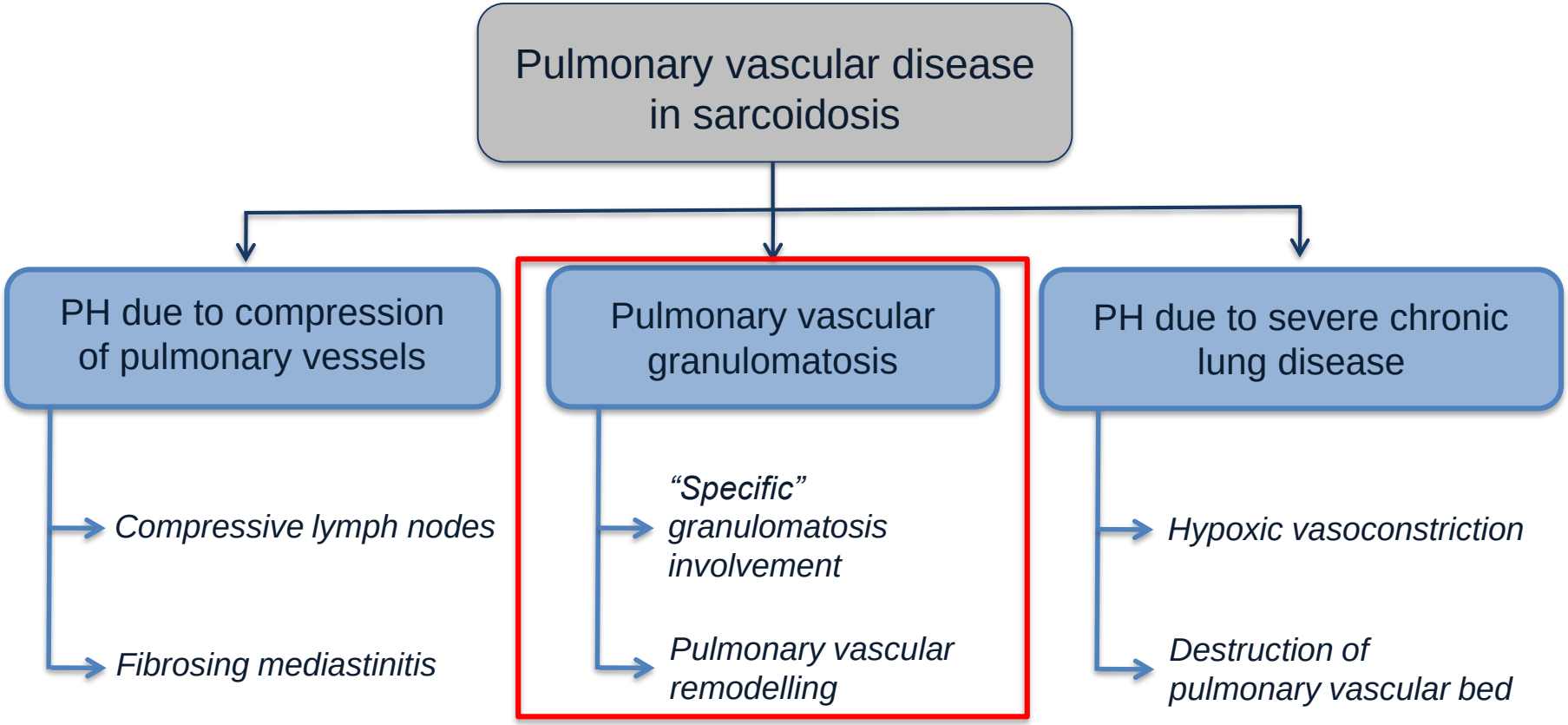
Classification of pulmonary hypertension – Group 3 (PH associated with chronic lung diseases)

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

The optimal treatment of the underlying lung disease, including long-term O_2 therapy in patients with chronic hypoxaemia, is recommended in patients with PH due to lung diseases	I	C
The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases	III	C

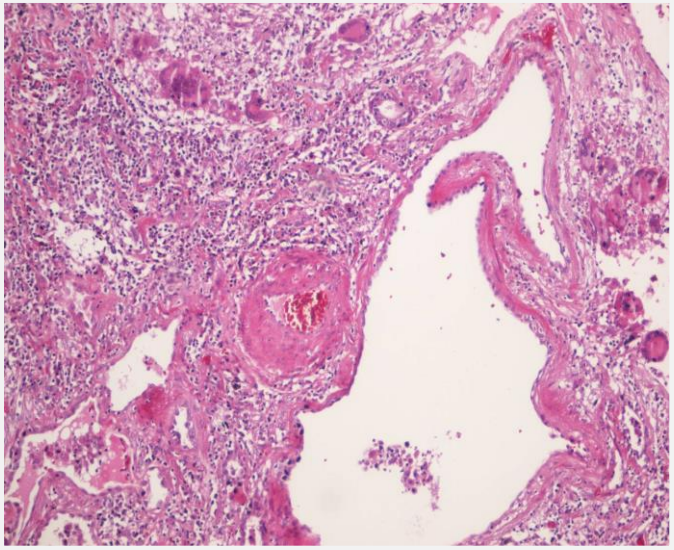
Galiè N, Humbert M, *et al.* ESC/ERS Guidelines. *Eur Heart J* 2016 *& Eur Respir J* 2015.

“Non-compressive” PH in sarcoidosis

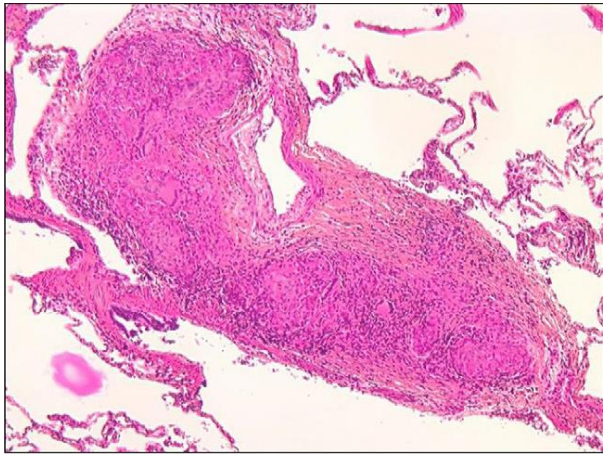


PH in sarcoidosis: Histopathology

- Pulmonary artery and vein obliteration and/or destruction due to lung fibrosis in radiologic stage IV[1,2]
- Granulomatous involvement of PA and PV ("sarcoidosic vasculopathy")
  - 69-100% of patients with invasion of PA and PV wall with granulomas[1,2]
  - Retrospective series of 22 patients with sarcoidosis-associated PH[3]:
    - 7 patients with severe PH without lung fibrosis (mPAP 52 mmHg)
    - 5 transplanted patients: veinular involvement (n=4), arterial involvement (n=2)

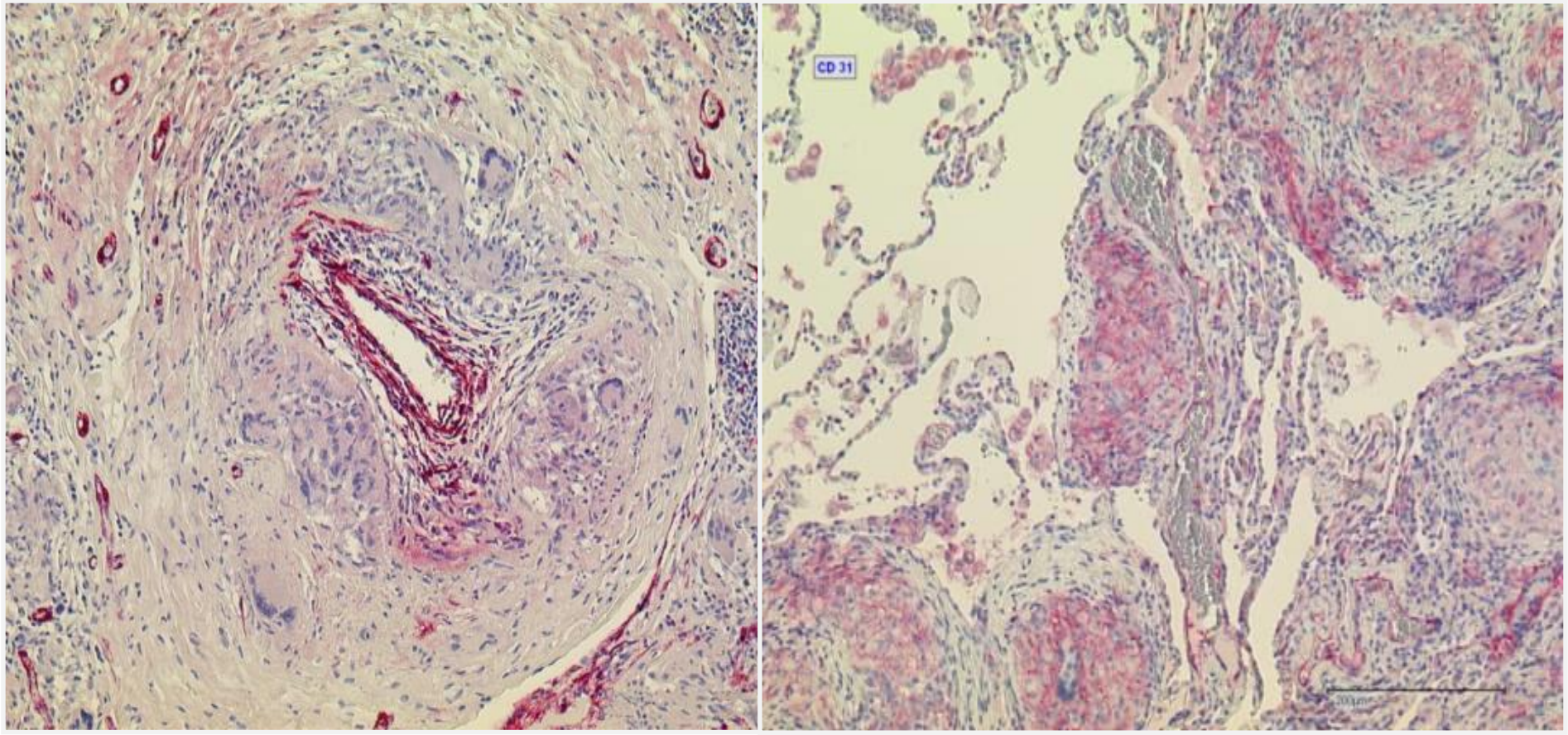


Pulmonary sarcoidosis: Arterial remodelling within fibrotic lung parenchyma



1. **Diaz-Guzman E, *et al. Clin Chest Med* 2008.**
2. **Corte TJ, *et al. Respirology* 2011.**
3. **Nunes H, *et al. Thorax* 2006.**

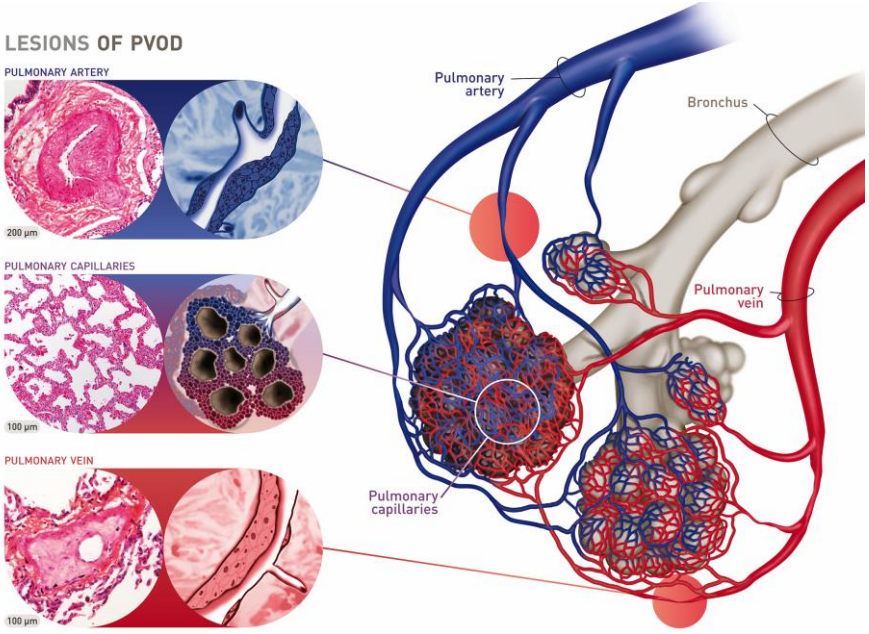
PH in sarcoidosis: “Sarcoidosic vasculopathy”

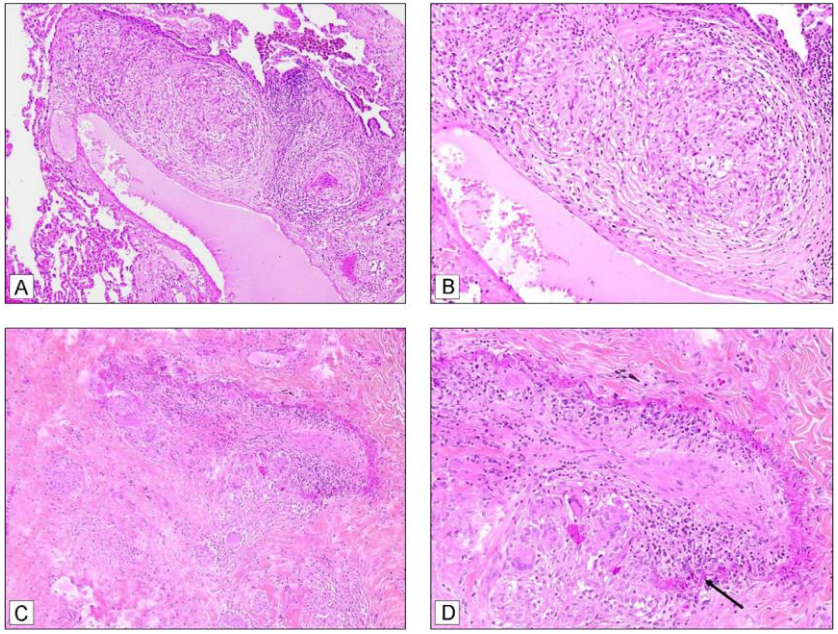


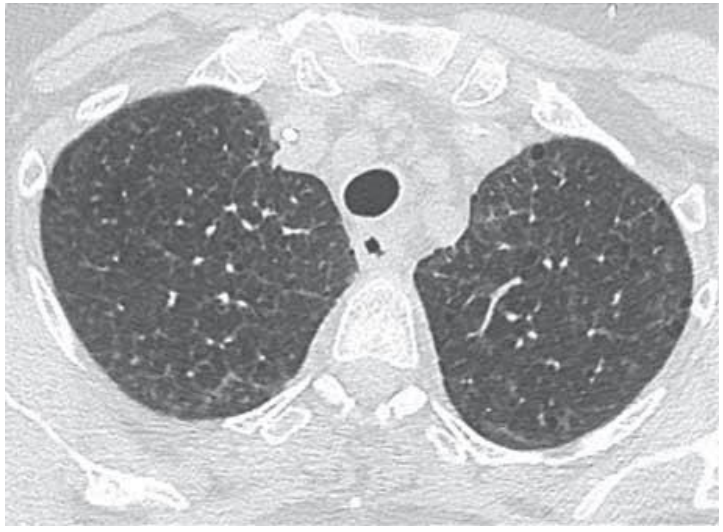
Pulmonary sarcoidosis: luminal obstruction by epitheloid granulomas with giant cells

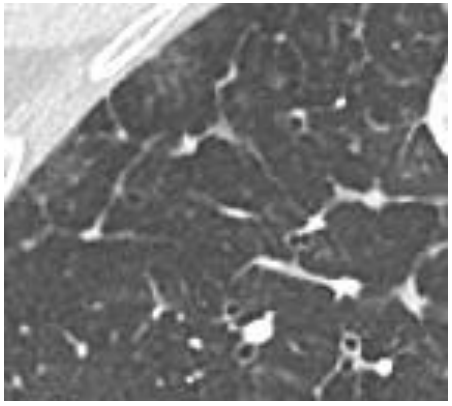
Courtesy of Dr. P. Dorfmüller, Marie-Lannelongue Hospital, Paris-Sud University, Le Plessis-Robinson, France.

PH in sarcoidosis: pulmonary vein involvement





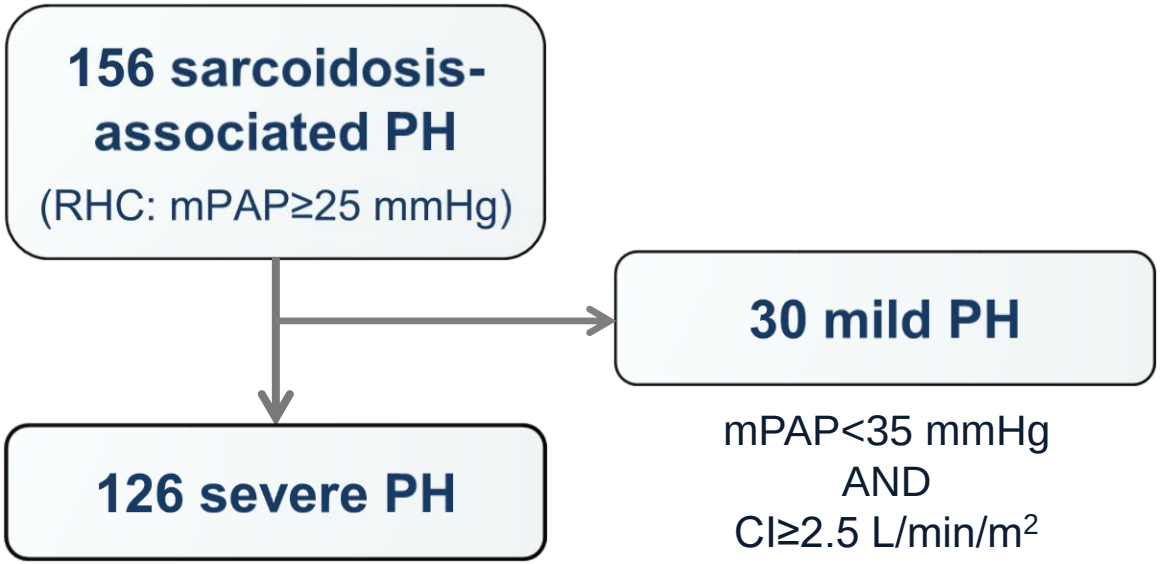




Nunes H, *et al. Presse Med.* 2012;41:e303–e316.
Montani D, *et al. Eur Respir J.* 2016;47:1518-34.

PH in sarcoidosis: Experience from the French Network of Severe PH

Retrospective
Multicentre
2004 - 2014



Boucly A, *et al. Presented at ATS 2016. Submitted.*

PH in sarcoidosis: Experience from the French Network of Severe PH

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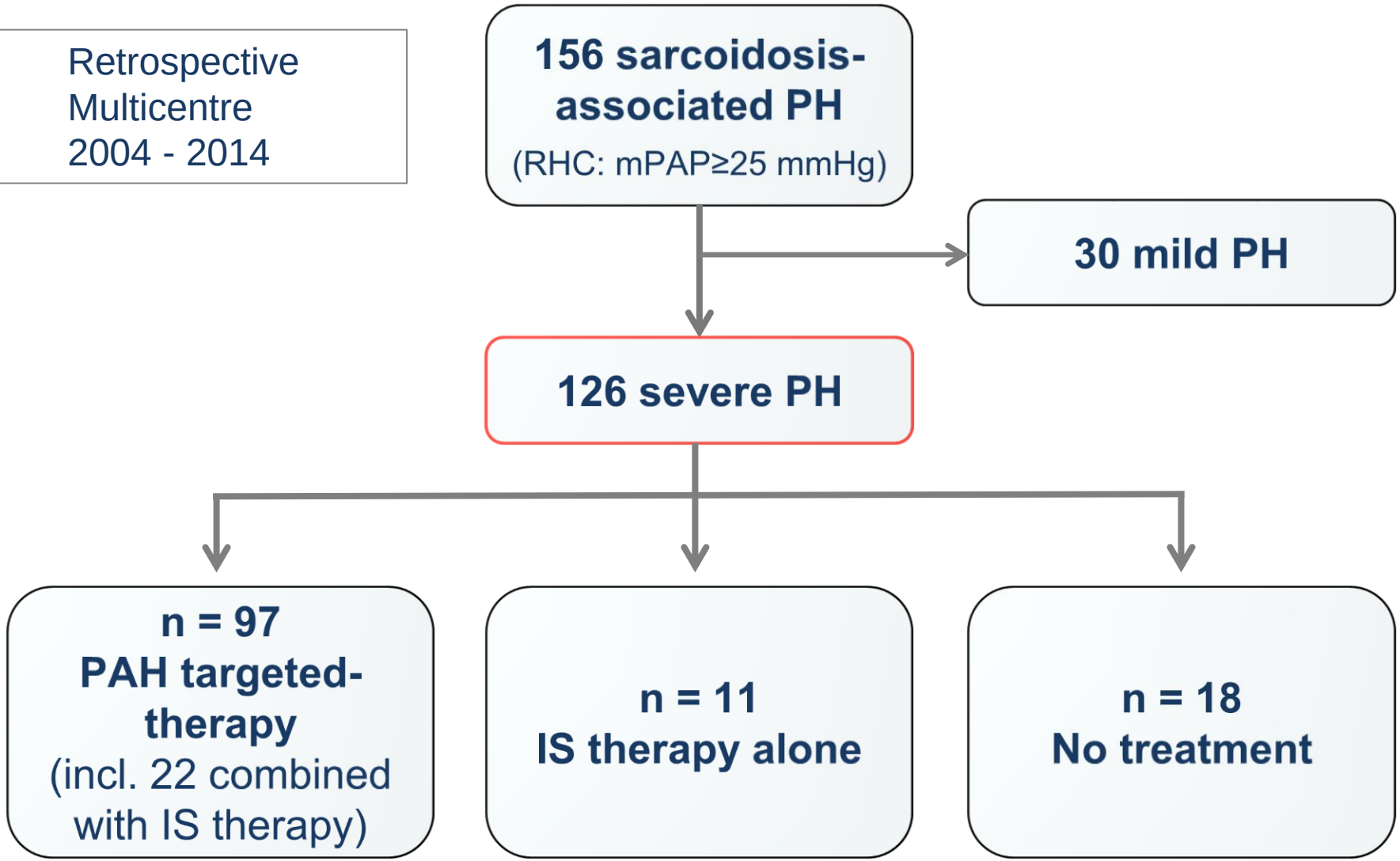


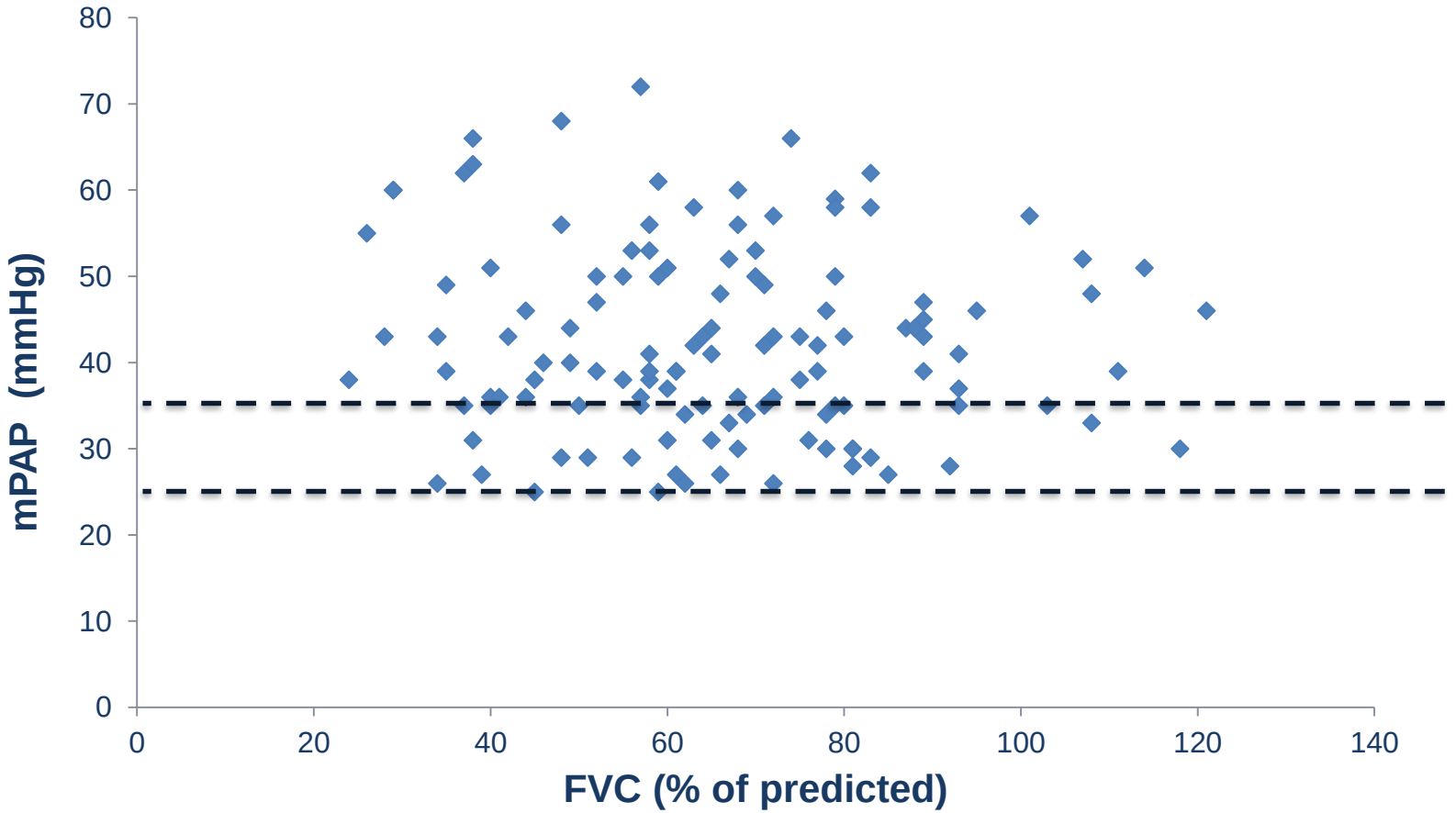
Boucly A, *et al. Presented at ATS 2016. Submitted.*

PH in sarcoidosis: Baseline characteristics

Male/ Female, *n (%)*		65 (52) / 61 (48)
Age, *years*		57.5 ±10.6
Median time between sarcoidosis and PH diagnoses, *months (IQR)*		204 (59-313)
Radiologic stage I : II : III : IV, *%*		4 : 17 : 5 : 74
NYHA FC I-II / III / IV, *%*		17 / 63 / 20
6MWD *(m)*		319 ± 143
RHC	**mPAP** *(mmHg)*	46 ± 10
	RAP *(mmHg)*	7 ± 5
	PAWP *(mmHg)*	9 ± 4
	CI *(L/min/m^2)*	2.6 ± 0.8
	PVR *(WU)*	8.8 ± 4.3
LFTs	**FVC** *(%)*	64 ± 21
	FVC < 50%, *n (%)*	30 (24)
	FEV1 *(%)*	55 ± 22
	KCO *(%)*	54 ± 23
LT oxygen therapy, *n (%)*		68 (54)

Boucly A, ***et al. Presented at ATS 2016. Submitted.***

No correlation between FVC and mPAP



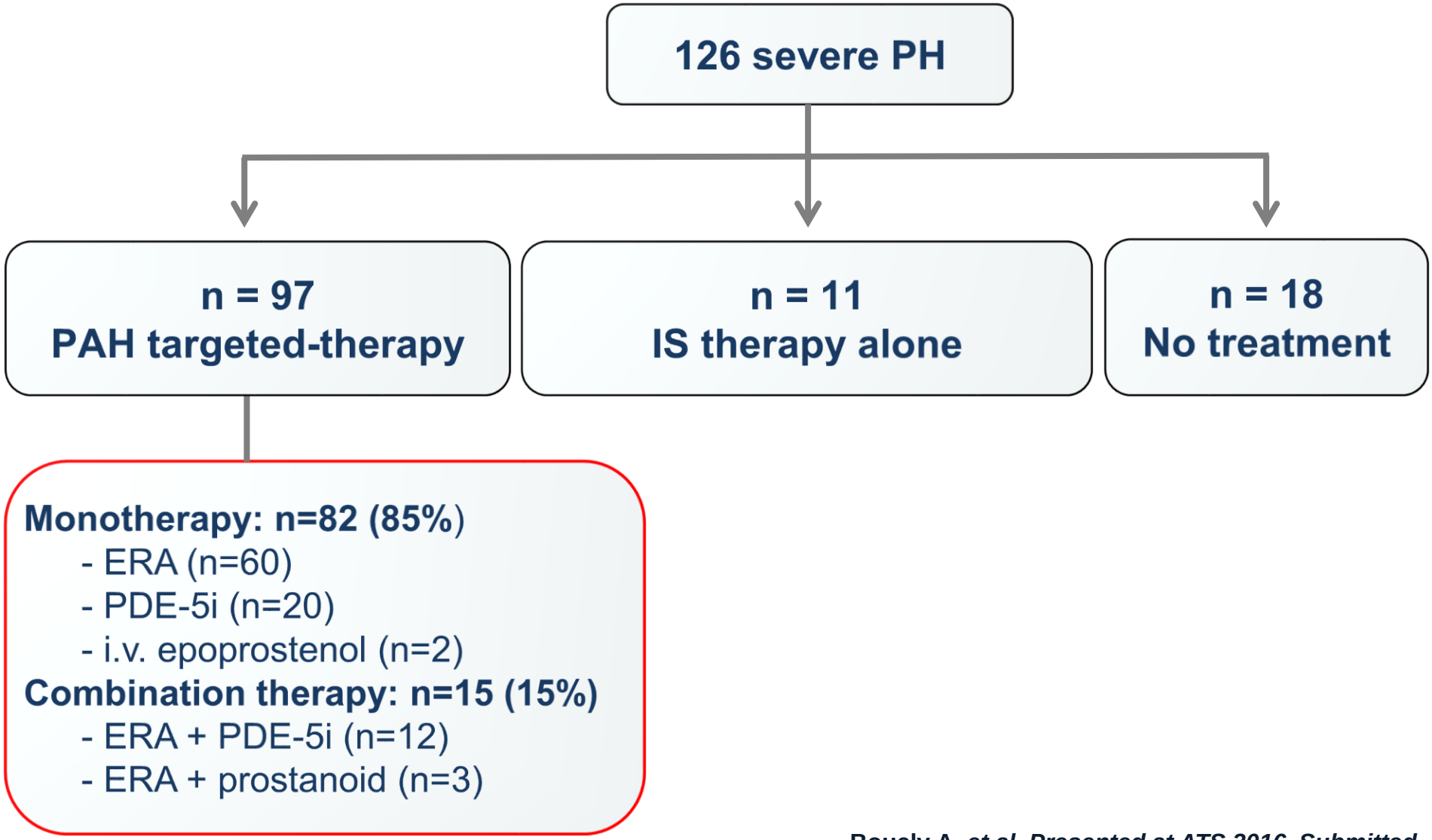
Boucly A, *et al. Presented at ATS 2016. Submitted.*

PH in sarcoidosis: PAH-targeted therapy

- Small retrospective studies
- A single RCT of bosentan vs placebo

Study	Type of study	N	Treatment	Effect
Barnett, *Chest* 2009.	Retrospective	22	Various	6MWD+, mPAP+
Keir, *Sarcoidosis Vasc Diffuse Lung Dis* 2014.	Retrospective	33	Various	6MWD+, NYHA+
Fisher, *Chest* 2006.	Retrospective	8	Epoprostenol	6MWD−, NYHA+, PVR+
Milman, *Clin Respir J* 2009.	Retrospective	13	Sildenafil	6MWD−, PVR+
Ford, Pulm Circ. 2016.	Prospective, open-label	12	Tadalafil	6MWD−, 5/12 dropped out
Judson, *Sarcoidosis Vasc Diffuse Lung Dis.* 2011.	Prospective, open-label	21	Ambrisentan	52% dropped out
Baughman, *Chest* 2014.	Prospective RCT *vs* placebo	39	Bosentan	6MWD−, RVP+

PH in sarcoidosis: PAH-targeted therapy



Boucly A, *et al. Presented at ATS 2016. Submitted.*

Short-term response to PAH-targeted therapy

Repeated assessment in 81/97 patients initiated with PAH-targeted therapy

16 patients not reassessed: 7 deaths, 2 LT, 4 no RHC, 3 lost to follow-up

n= 81	Baseline	6 months	p
NYHA FC I-II/III/IV *(n)*	11 / 52 / 18	26 / 45 / 10	0.01
6MWD *(meters)*	311 (±127)	324 (±138)	0.33
RAP *(mmHg)* **mPAP** *(mmHg)* **CI** *(L/min/m2)* **PVR** *(WU)*	7 (±4) 48 (±9) 2.6 (±0.8) 9.7 (±4.4)	6 (±4) 42 (±11) 2.9 (±0.8) 6.9 (±3.0)	0.007 <0.00001 <0.00001 <0.00001

Results as mean ± SD

Boucly A, *et al. Presented at ATS 2016. Submitted.*

PH in sarcoidosis: Immunosuppressive therapy

Corticosteroids

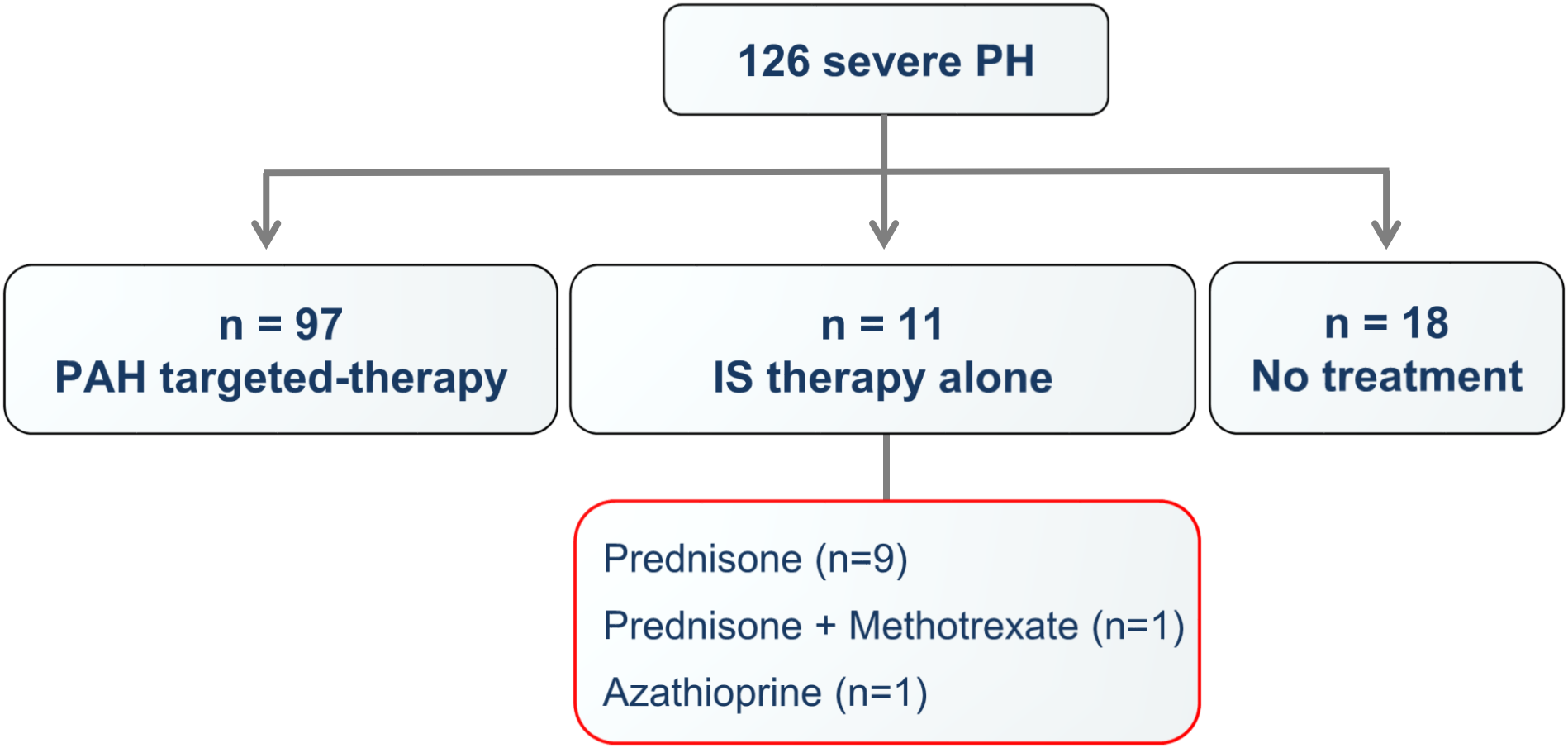
- modest effect in 2 small studies[1,2]
- 0.5-1.0 mg/kg/d
- 3 out of 10 patients improved in the series by Nunes et al.[2]

Table 3 Patients treated with corticosteroids for sarcoidosis and PH*

Sex/age	Chest radiographic stage	Associated treatment	Systolic PAP		
			Baseline	3–6 months	Last evaluation
F/55	0	Methotrexate	66	35	<30 mm Hg at 12 months
M/61	II	Oxygen, warfarin	121	125†	Dead at 11 months
F/52	II	–	60	40	30 mm Hg at 14 months
M/28	II	–	77	60†	30 mm Hg at 36 months
M/63	II	–	80	82	Dead at 18 months
M/55	IV	–	50	55	Not re-evaluated
F/62	IV	–	45	45†	50 mm Hg at 18 months†
M/57	IV	Oxygen	80	85	Transplanted at 14 months
M/47	IV	–	83	100	Transplanted at 39 months
M/42	IV	Oxygen, Cyc	56	59	91 mm Hg at 48 months†

1. Gluskowski J, *et al. Eur Respir J* 1990.
2. Nunes H, *et al. Thorax* 2006.

PH in sarcoidosis: Immunosuppressive therapy

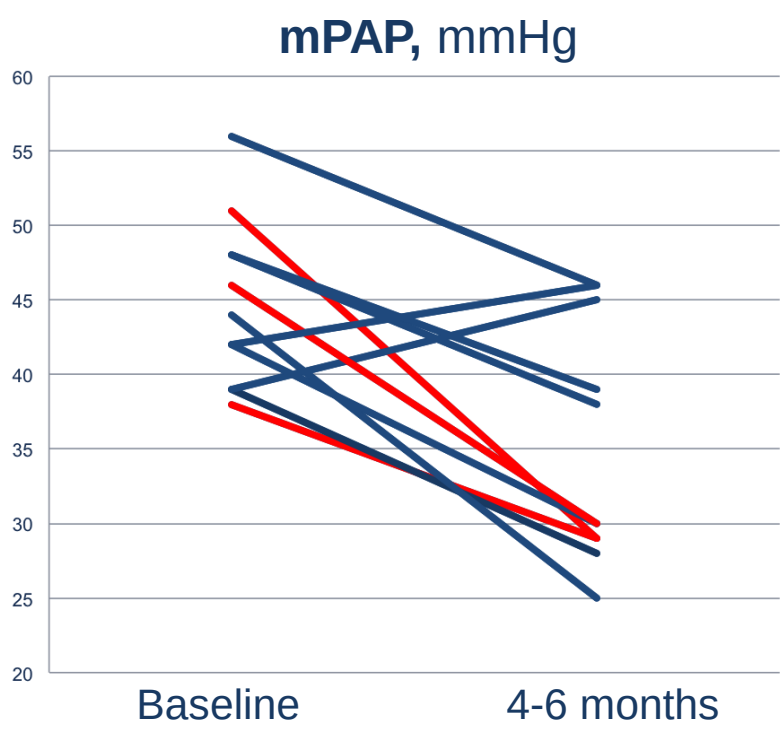


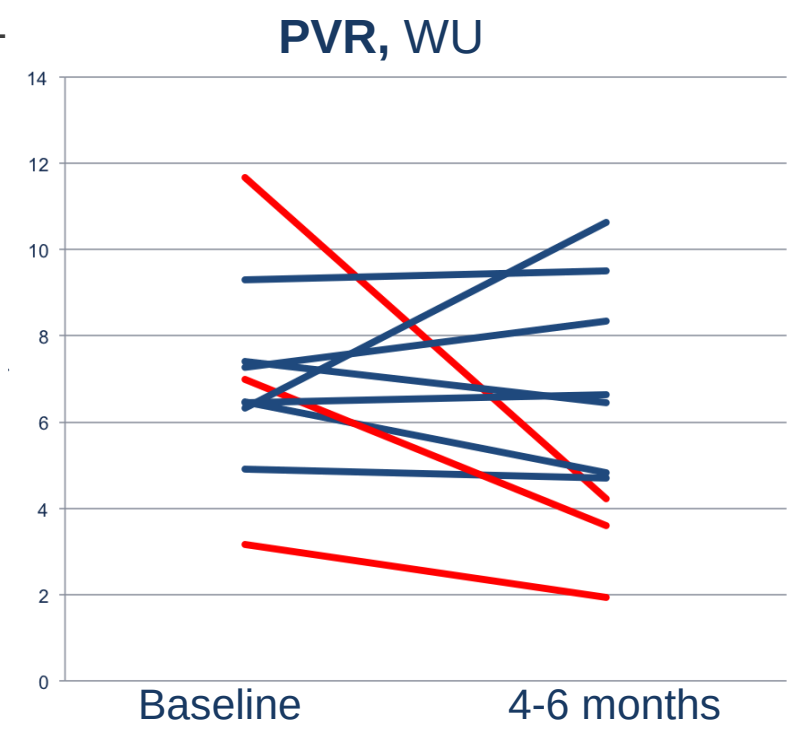
Boucly A, *et al. Presented at ATS 2016. Submitted.*

Short-term response to immunosuppressive therapy

Immunosuppressive therapy ALONE
(initiated or reinforced after PH diagnosis)

n=11





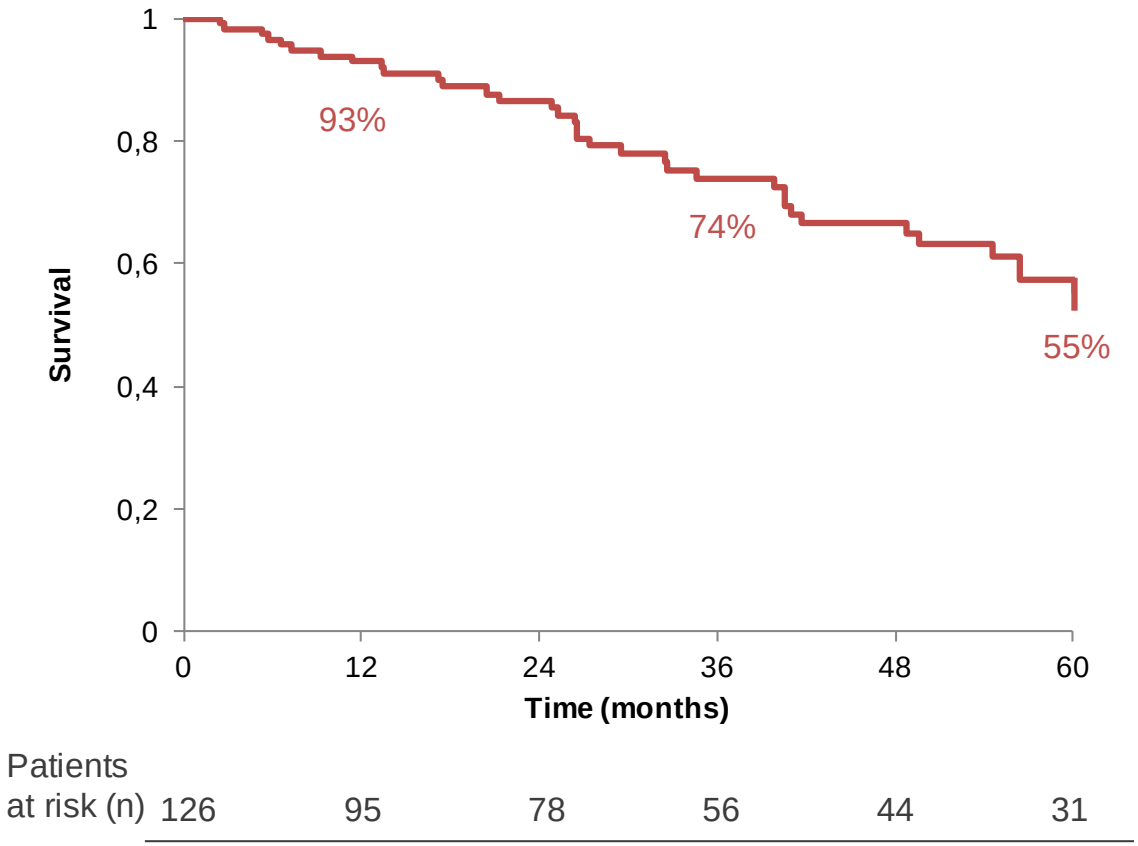
−−− Patients with an important uptake of ^{18}F-FDG at PET-CT

Boucly A, ***et al. Presented at ATS 2016. Submitted.***

PH in sarcoidosis: Outcomes

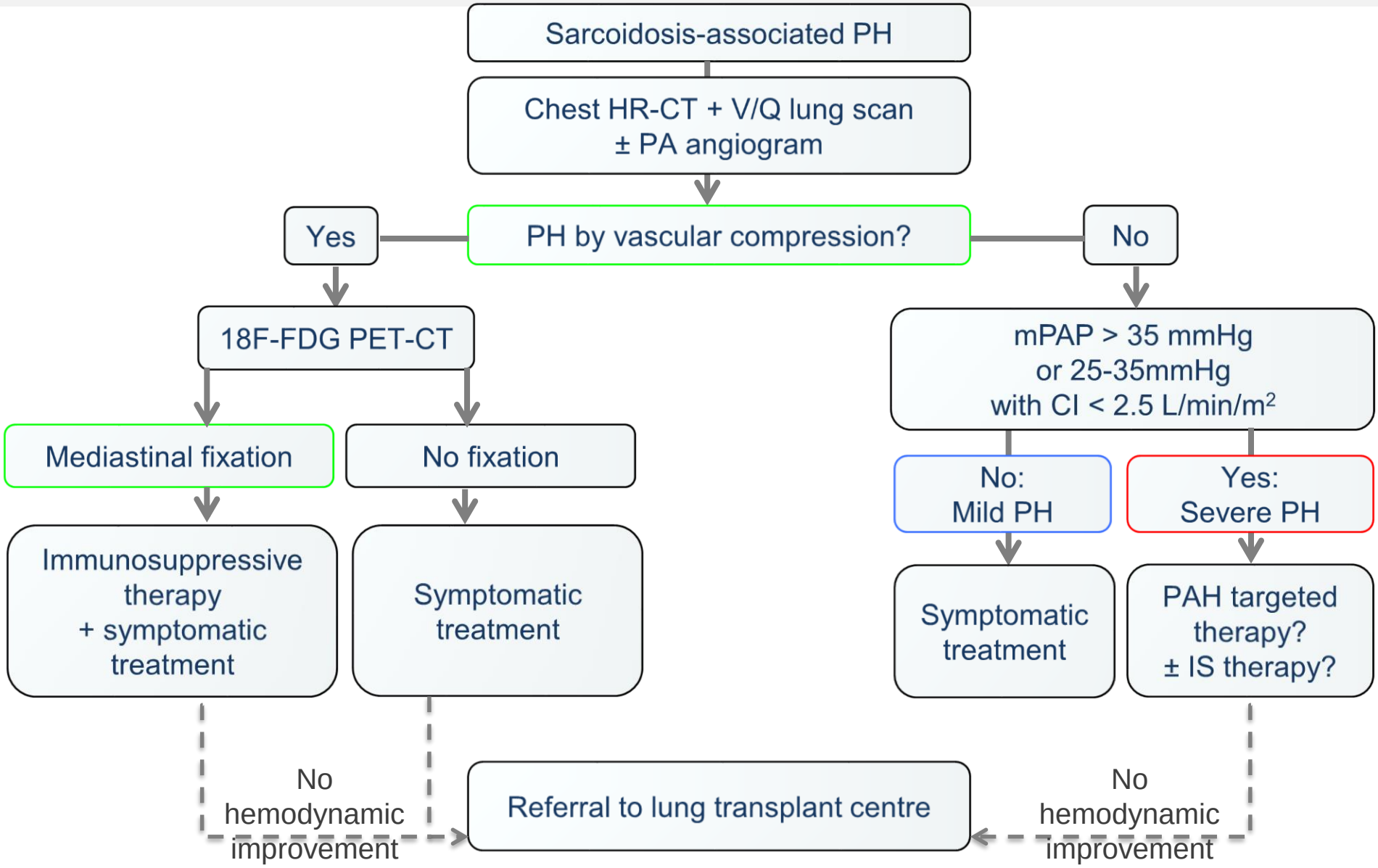
Median follow-up 28 months
(IQR: 11-56 months)

Death	n = 42 (33%)
Lung transplantation	n = 9 (7%)
Treatment escalation	n = 39 (31%)



Boucly A, *et al. Presented at ATS 2016. Submitted.*

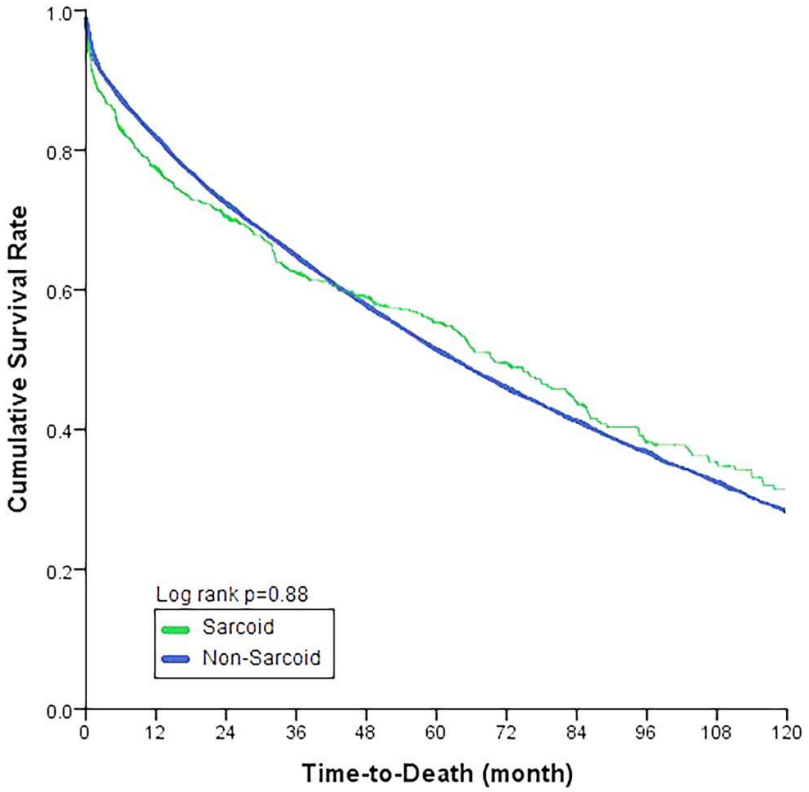
Management algorithm



Lung transplantation in sarcoidosis

20 896 lung transplants performed in the USA in 25 years
695 were transplanted for pulmonary sarcoidosis

Similar long-term outcomes compared with nonsarcoid lung recipients



Taimeh Z, *et al. Thorax* 2016;71:378–379.

PH in sarcoidosis: Take-home messages

- Prevalence of PH in sarcoidosis is not well established
- Severe PH occurs mainly in advanced sarcoidosis (radiologic stage IV)
- PH has a major impact on prognosis of patients with sarcoidosis
- Pathophysiological mechanisms are complexes and often multiple
- In sarcoidosis associated with severe PH, PAH-targeted therapy improves pulmonary haemodynamics without change in exercise capacity. Impact on survival remains unknown.
- Corticosteroids and immunosuppressive therapy are beneficial in PH due to compression of pulmonary vessels by metabolically hyperactive mediastinal lymph nodes (PET-CT). Their effects on other forms of PH are questionable
- Overall survival remains poor and lung transplantation has to be considered in eligible patients with severe PH associated with sarcoidosis.