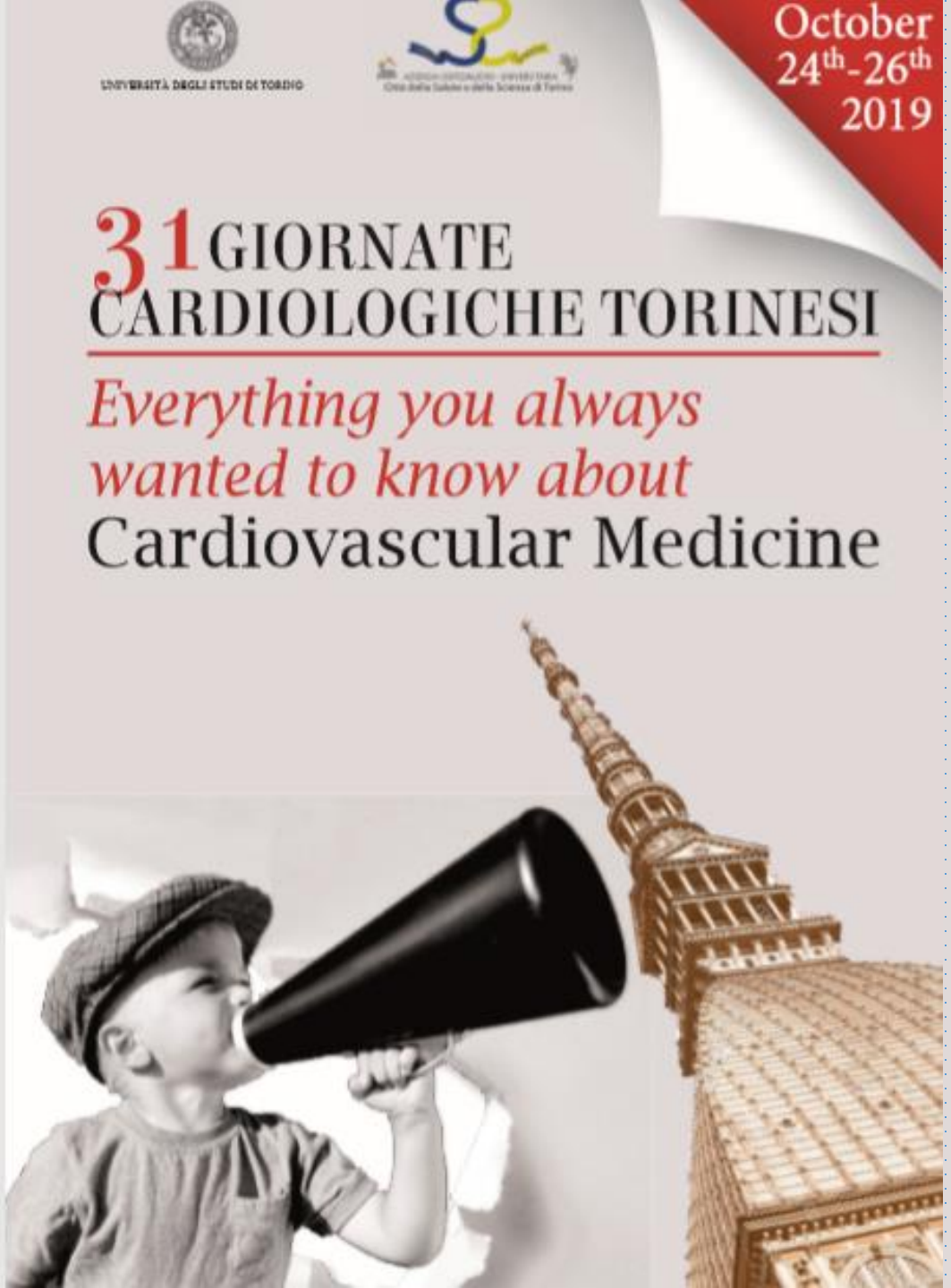


# FORUM ON PULMONARY HYPERTENSION:
## The role of radiologist in differential diagnosis

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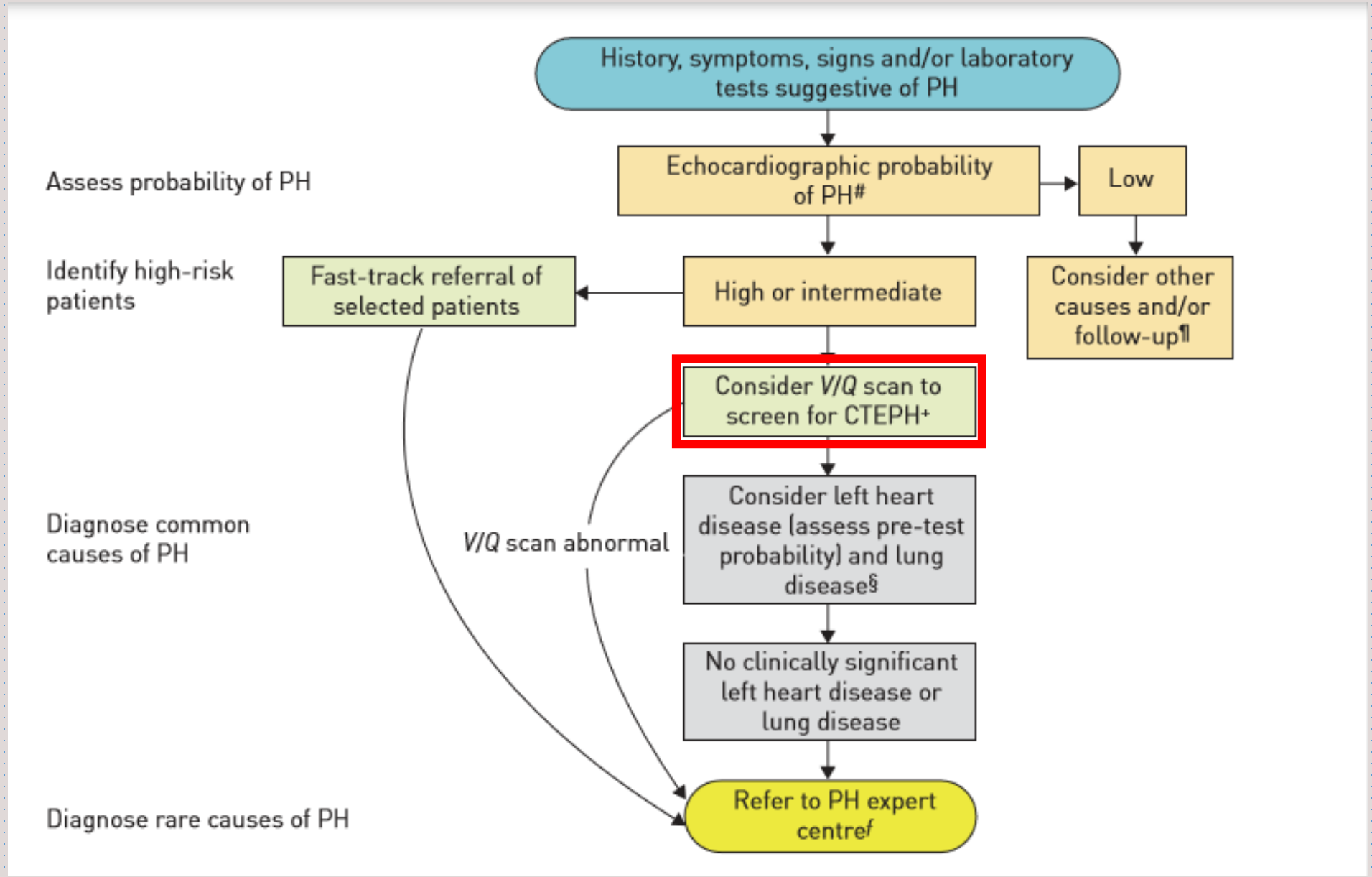
Fondazione IRCCS Policlinico San Matteo, Pavia




Eur Respir J 2019; 53: 1801904

# Chronic thromboembolic pulmonary hypertension

Nick H. Kim[1], Marion Delcroix[2], Xavier Jais[3], Michael M. Madani[4], Hiromi Matsubara[5], Eckhard Mayer[6], Takeshi Ogo[7], Victor F. Tapson[8], Hossein-Ardeschir Ghofrani[6,9,10,12] and David P. Jenkins[11,12]

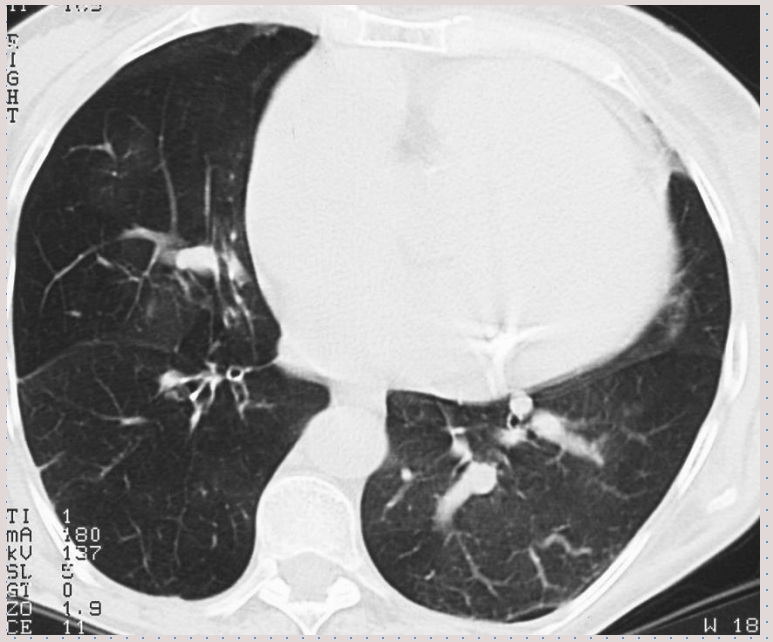
## Diagnosis of CTEPH

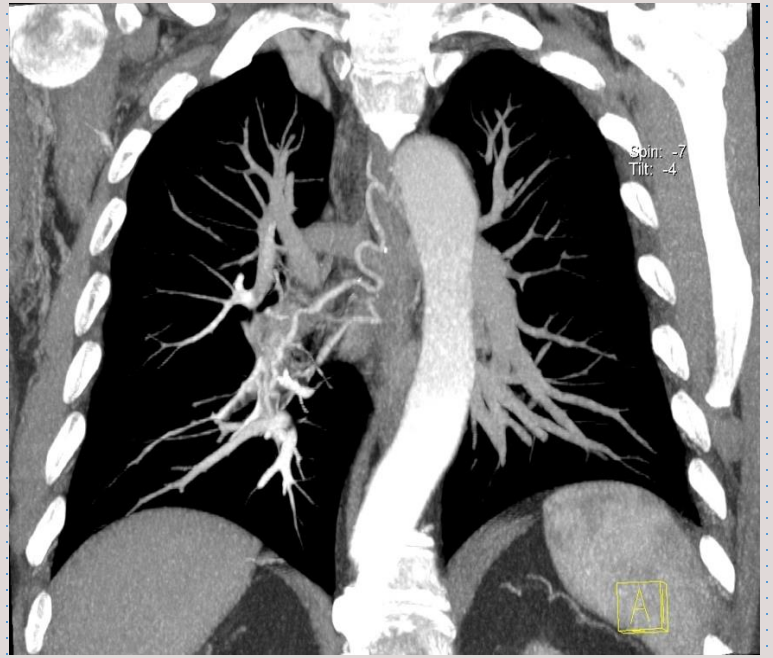
A normal *V/Q* scan effectively excludes CTEPH with a sensitivity of 90–100% and a specificity of 94–100% [39, 40]. In a study of confirmed cases of CTEPH, *V/Q* scan was found to be superior to CTPA with a sensitivity of 97.4% *versus* 51% [39]. This difference has narrowed as CT technology and interpretation have advanced. Indeed, a more recent study has shown that both *V/Q* scan and CTPA are accurate methods for the detection of CTEPH with excellent diagnostic efficacy (100% sensitivity, 93.7% specificity and 96.5% accuracy for *V/Q* scan; 96.1% sensitivity, 95.2% specificity and 95.6% accuracy for CTPA) [40]. However encouraging, *V/Q* scan remains the preferred initial imaging test for CTEPH screening [5, 29].

Digital subtraction angiography (DSA) had been considered the gold standard for characterising vessel morphology in CTEPH, but is being challenged by advances in non-invasive modalities. CTPA is currently widely used for assessment of operability. CTPA in more recent reports has a high sensitivity and specificity in detecting chronic thromboembolic lesions at the main/lobar (89–100% and 95–100%, respectively) and segmental (84–100% and 92–99%, respectively) levels [43–45]. CTPA can also be

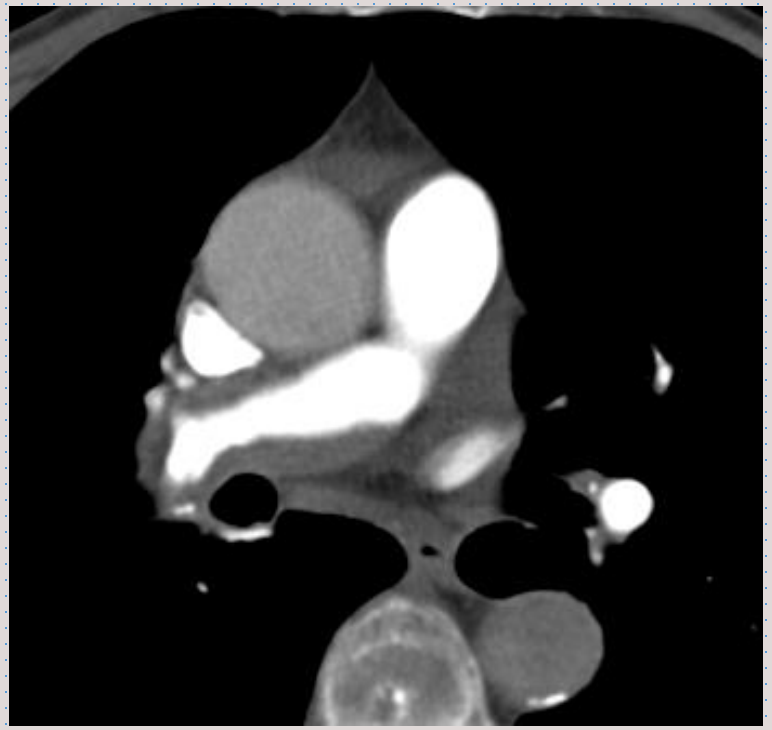
# Characterisation of CTEPH

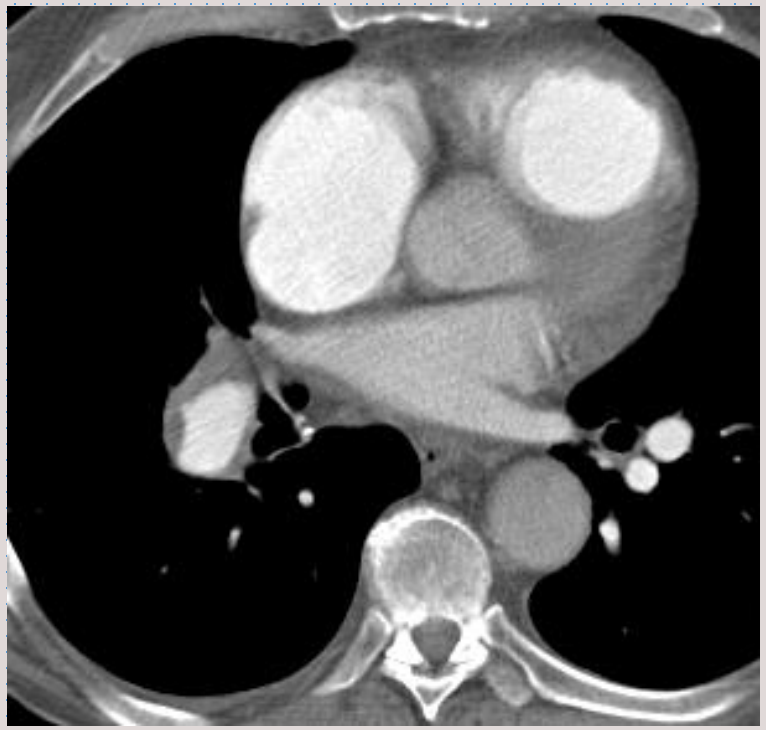
- Pulmonary Artery Findings:
  - Occlusions, mural thrombus or eccentric emboli in the pulmonary arteries
- Pulmonary Parenchymal Findings:
  - Mosaic Attenuation
  - Subpleural Peripheral Opacities:  manifestations of pulmonary infarction or subpleural scarring from healed infarction
  - Vascular asymmetries
- Mediastinal Findings:
  - Hypertrophied Bronchial Arteries
  - No bronchial systemic collaterals—commonly the intercostal, inferior phrenic, and internal mammary arteries

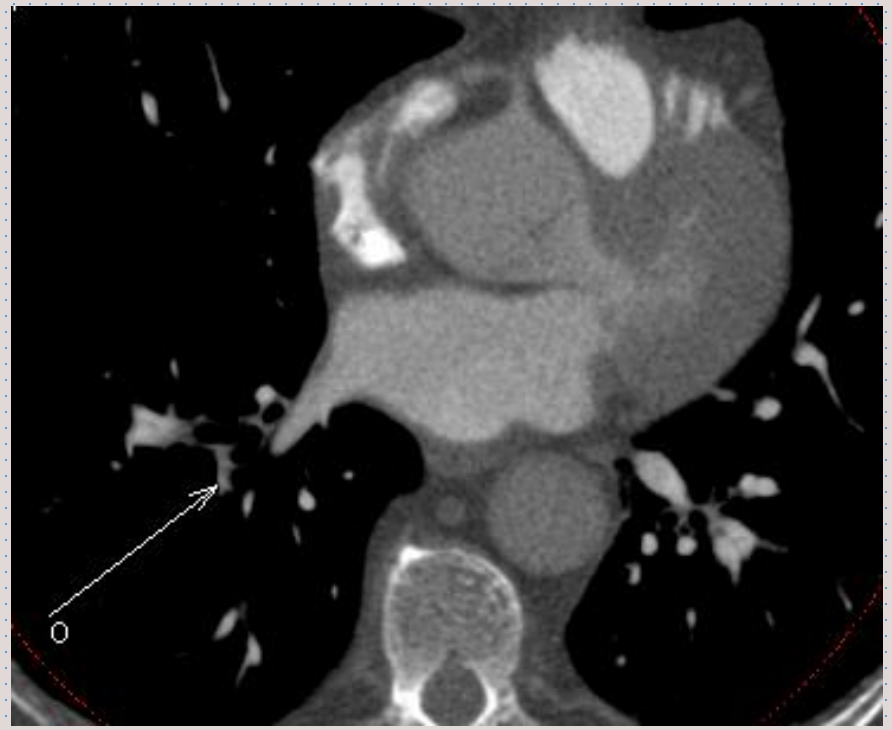


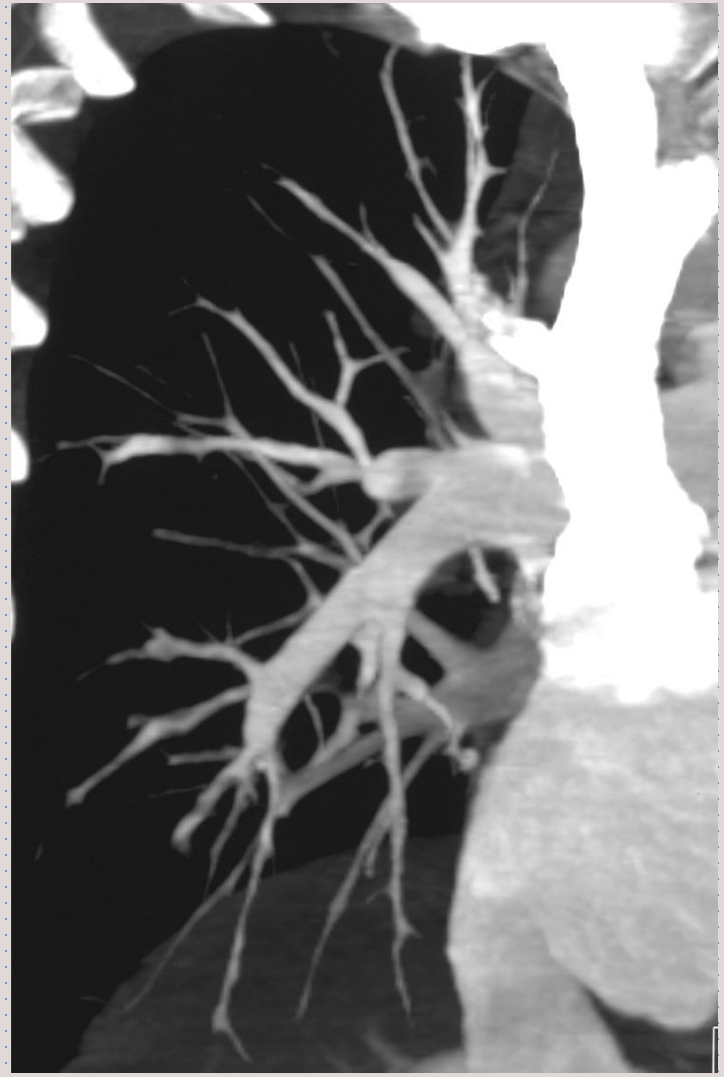
# Characterisation of CTEPH: Pulmonary Artery Findings

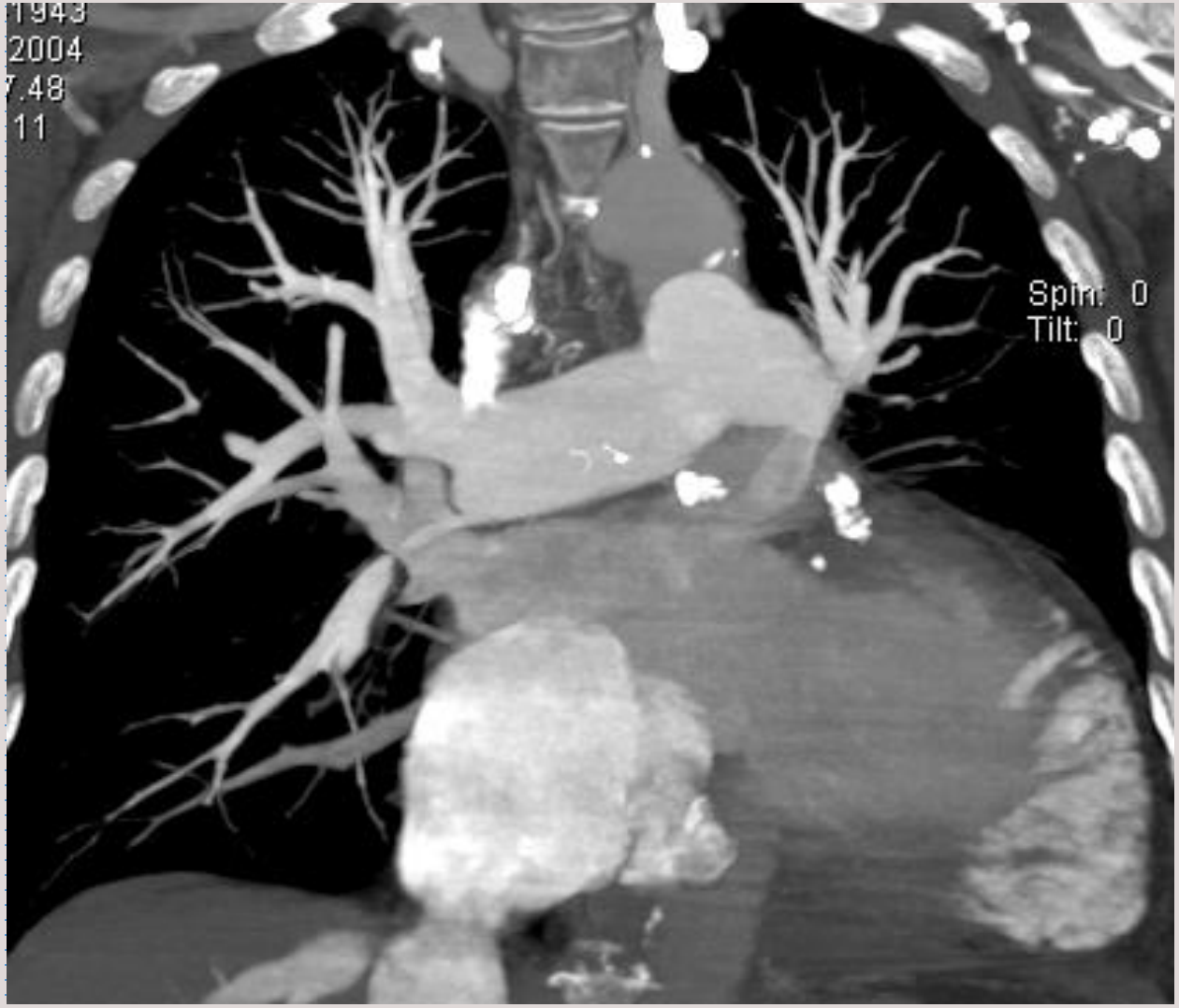




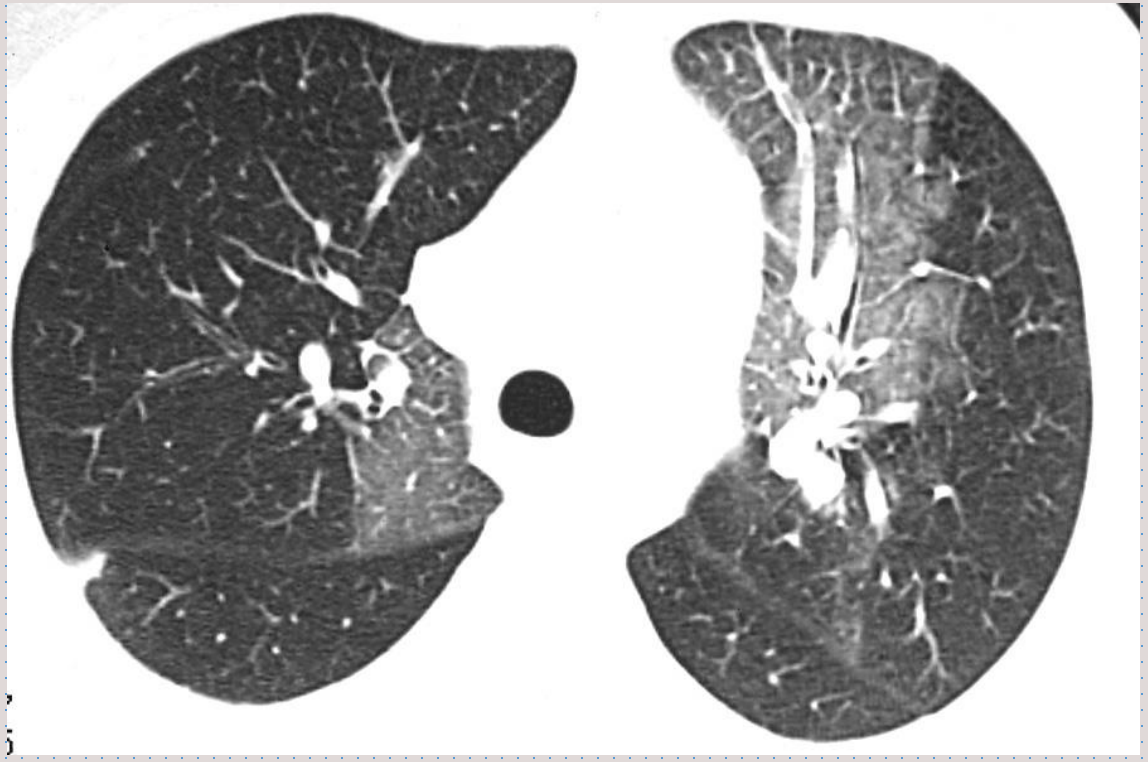


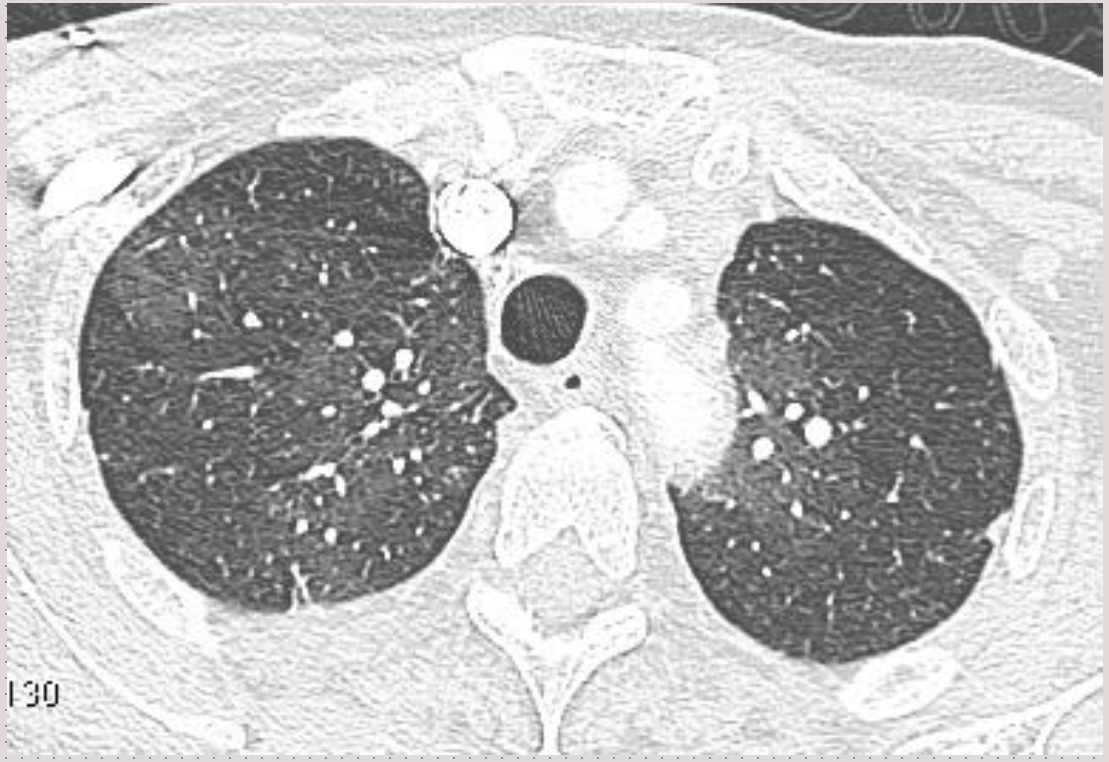
# Characterisation of CTEPH: Pulmonary Artery Findings





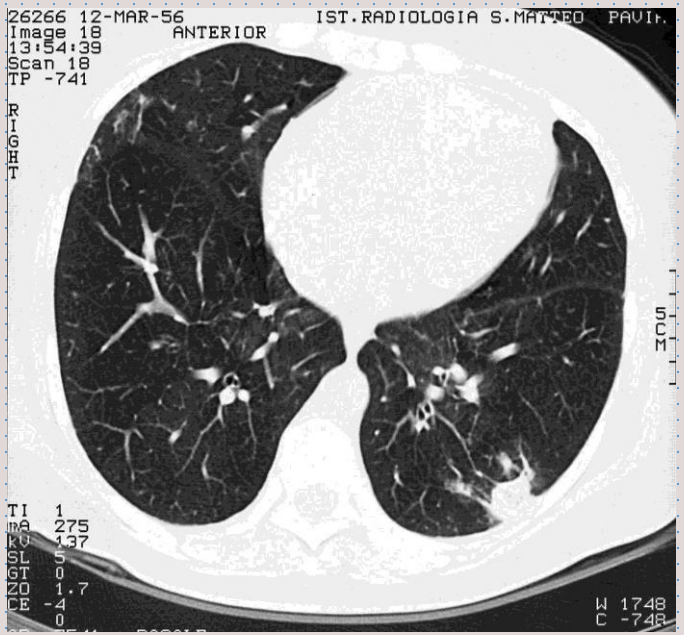
# Characterisation of CTEPH: Pulmonary Parenchymal Findings

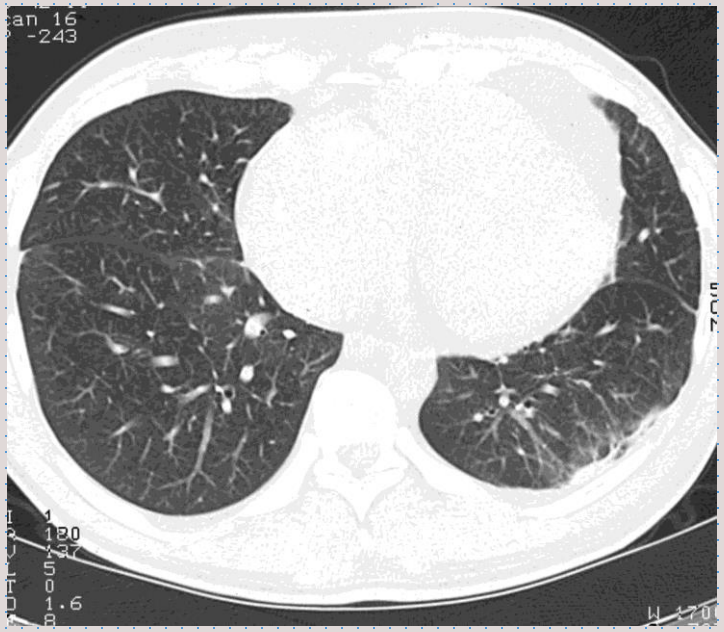


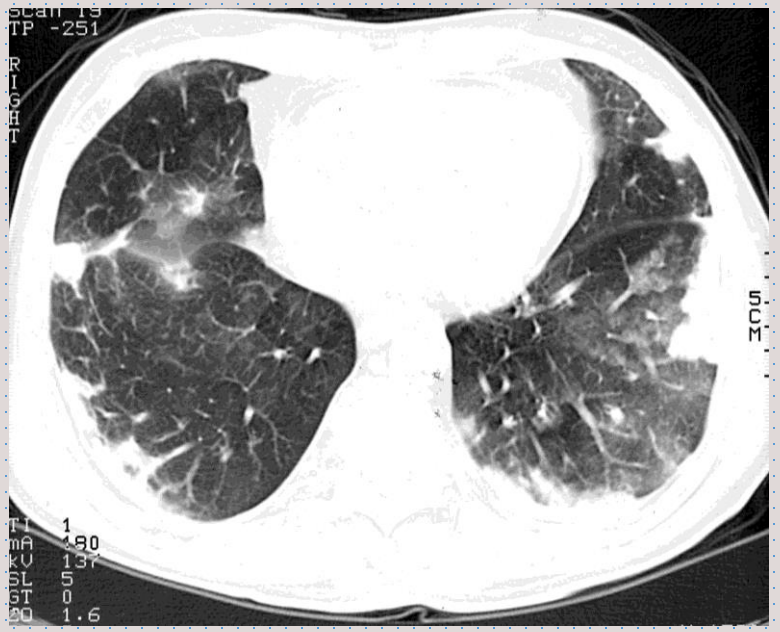


Mosaic Attenuation

# Characterisation of CTEPH: Pulmonary Parenchymal Findings

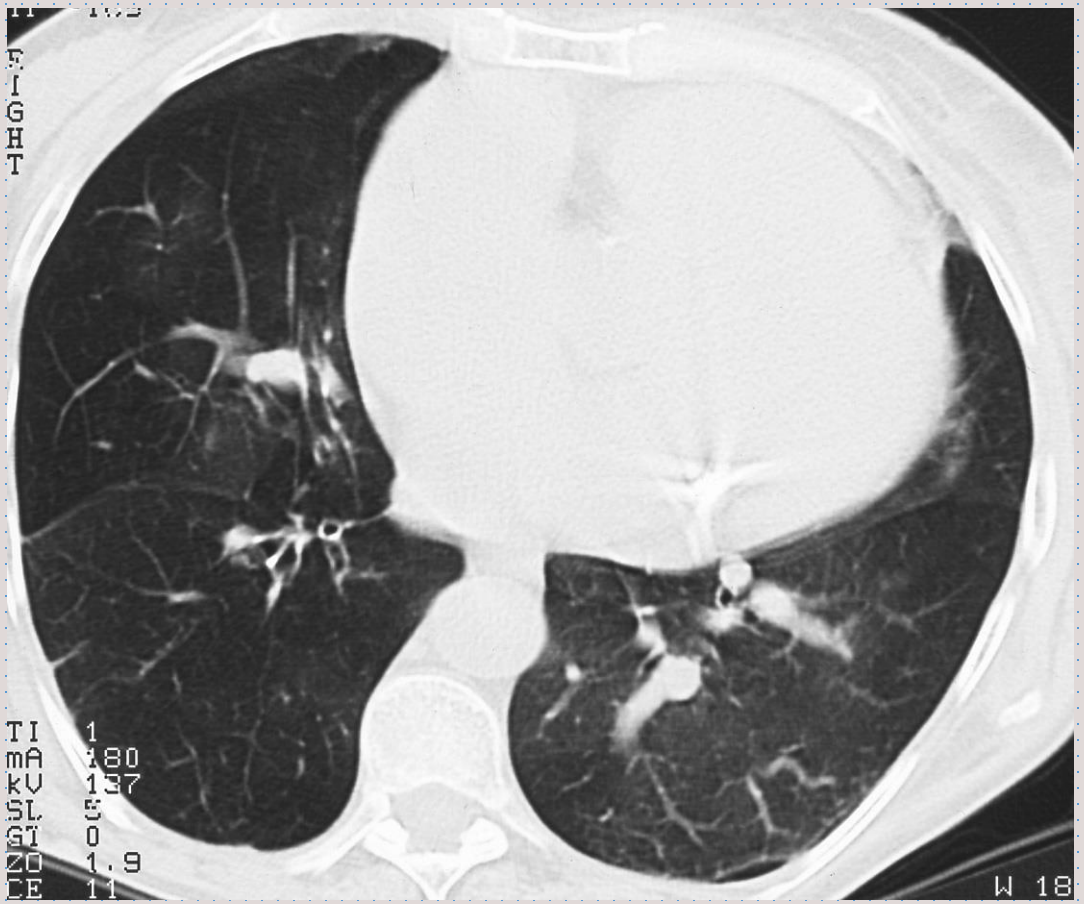


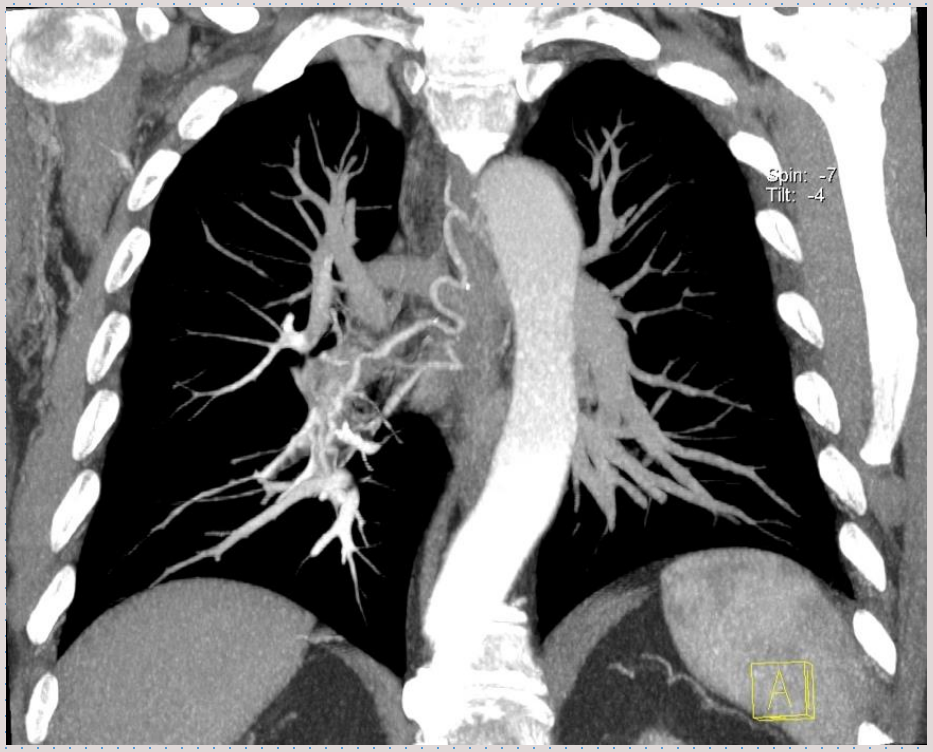

Subpleural Peripheral Opacities

# Characterisation of CTEPH: Pulmonary Parenchymal Findings

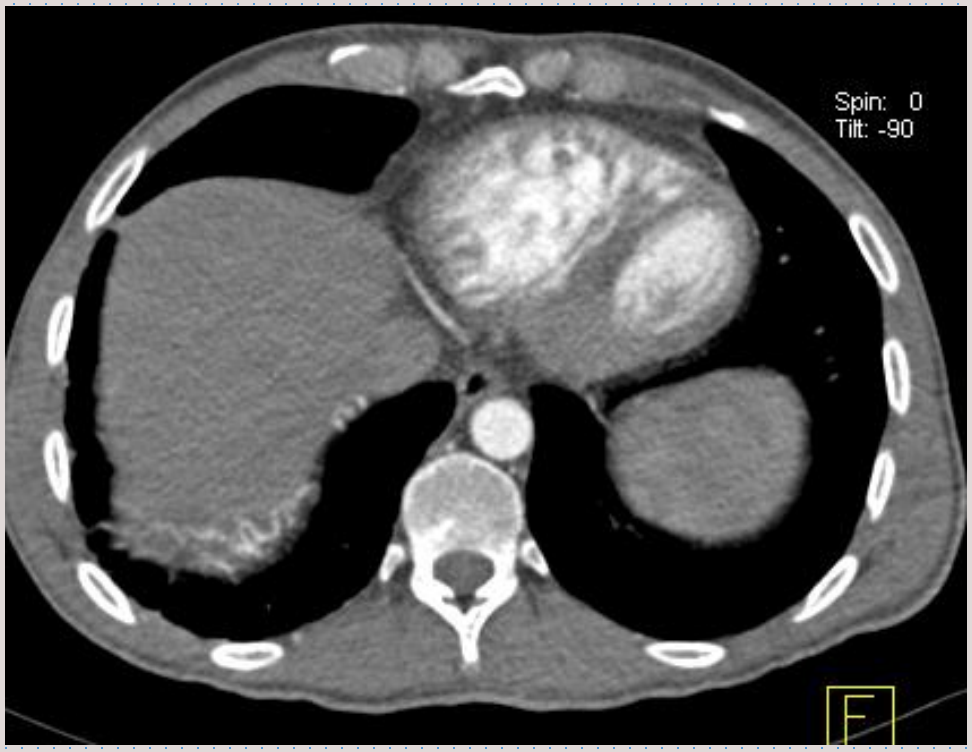



Vascular Asymmetries

# Characterisation of CTEPH: Mediastinal Findings

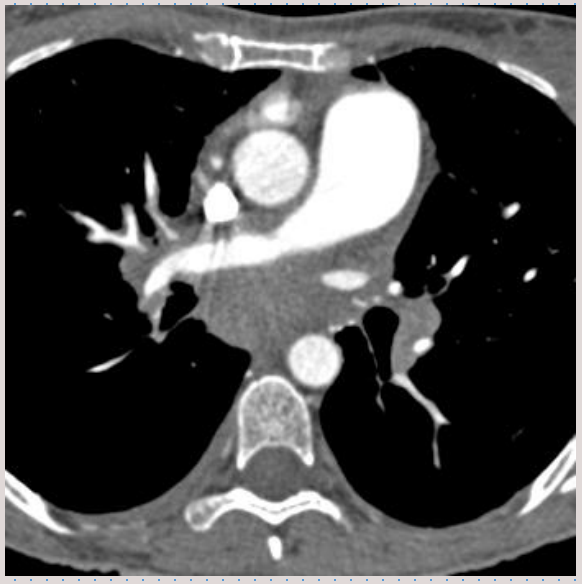


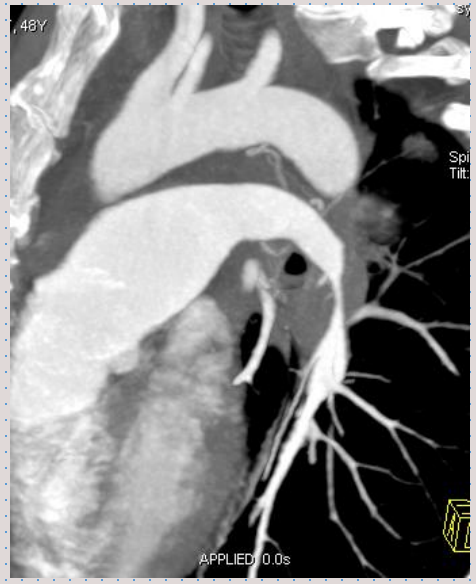

Hypertrophied Bronchial Arteries



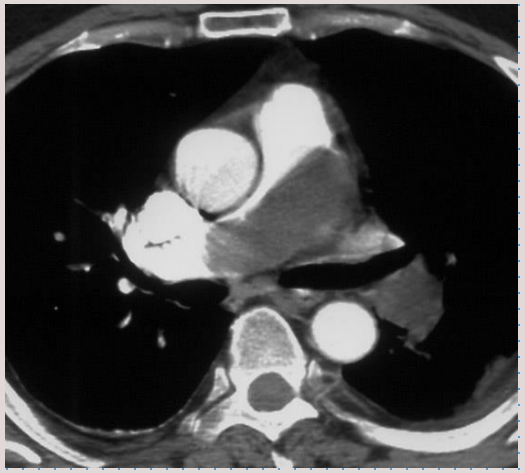

No Bronchial Systemic Collaterals

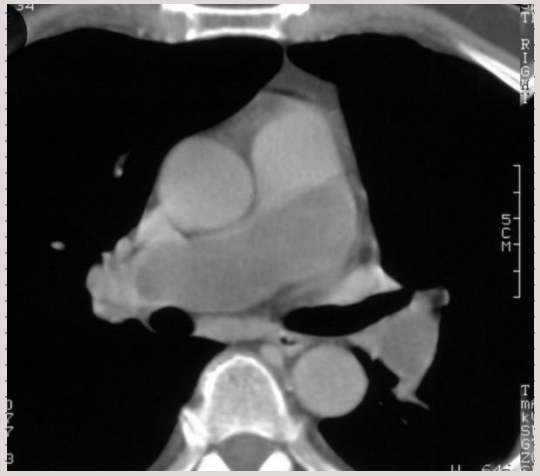
# Other Pulmonary Artery Obstructions



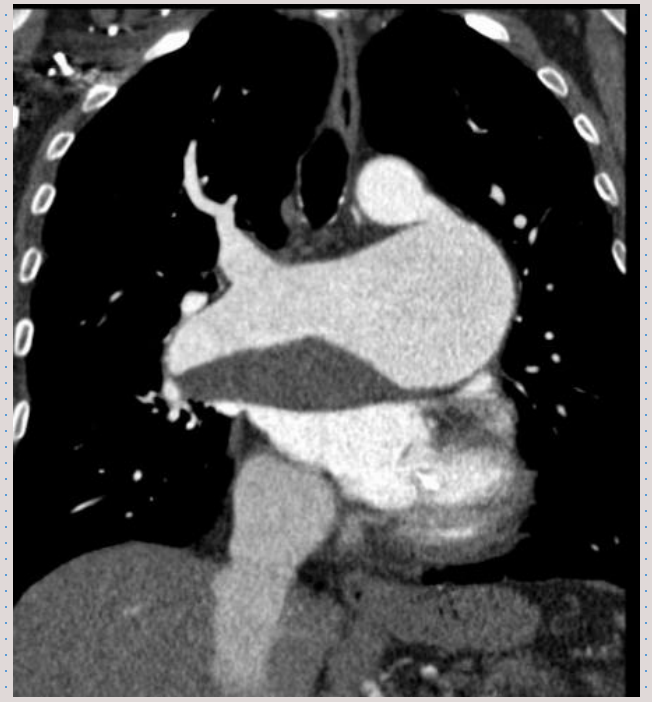


SARCOIDOSIS: Fibrosing Mediastinitis

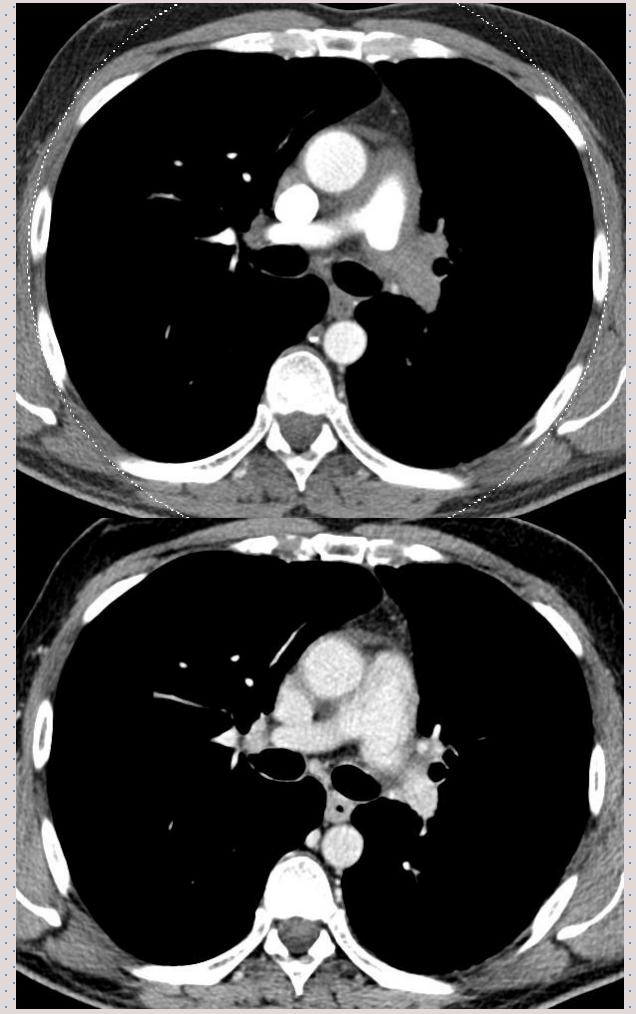




Pulmonary Artery Angiosarcoma

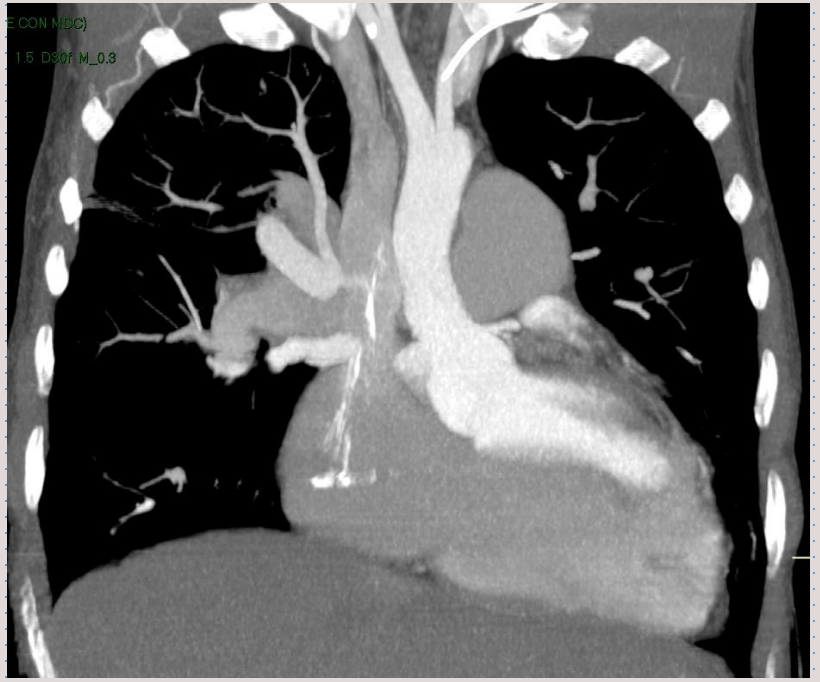


In Situ Thrombus

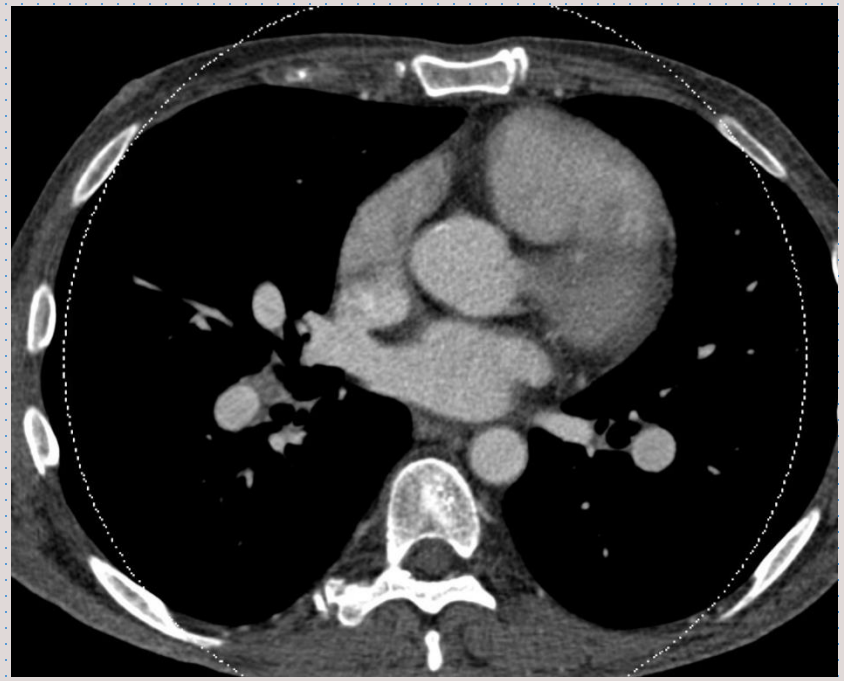


Vasculitis

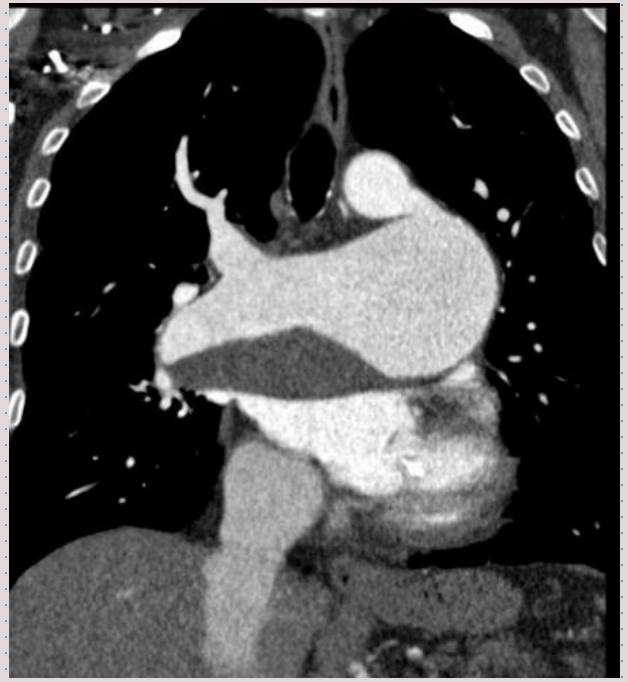
# Group 1: Congenital Heart Diseases



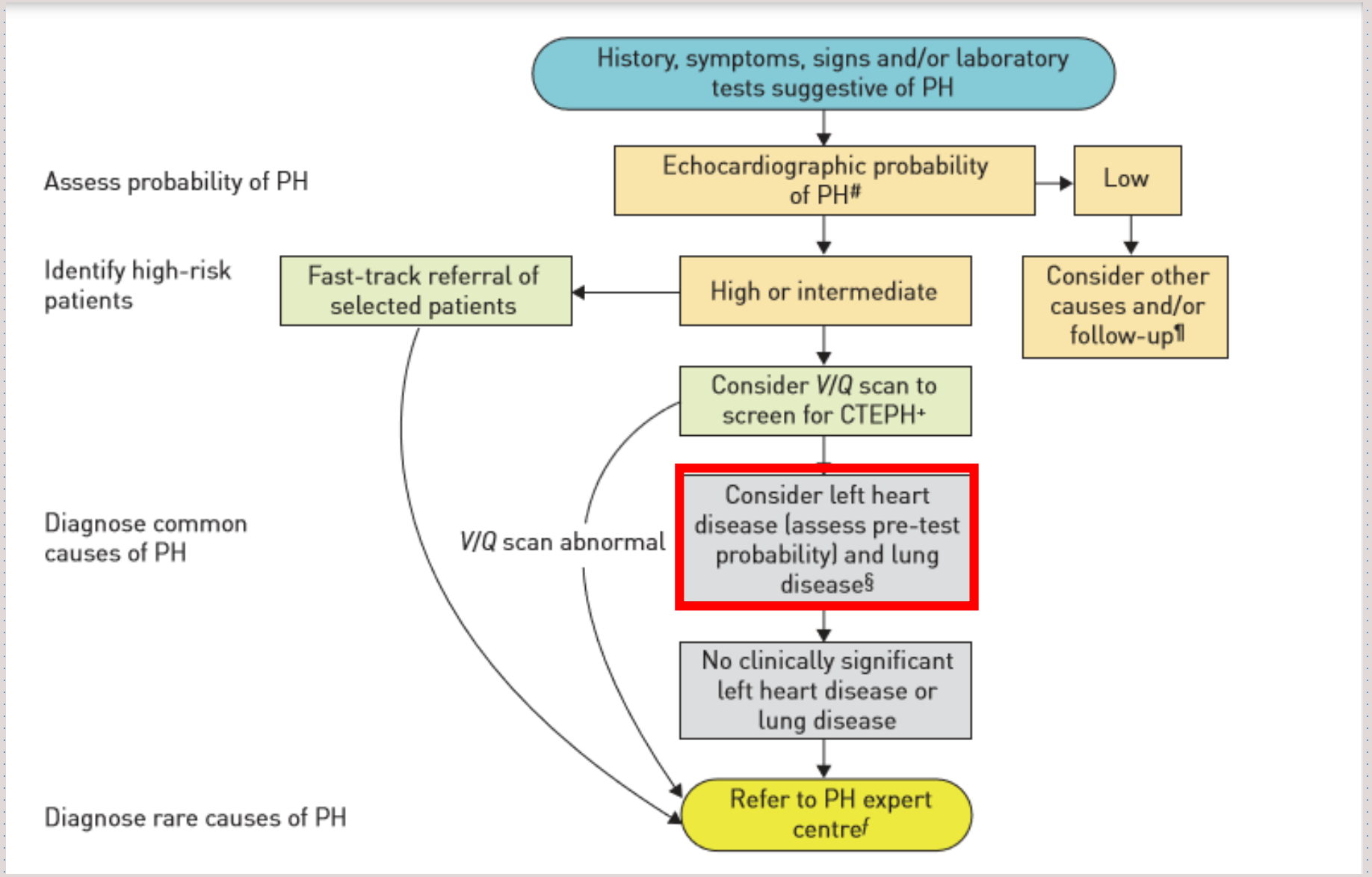
ABNORMAL VENOUS RETURNS



INTRACARDIAC SHUNT



PATENT DUCTUS ARTERIOSUS




Eur Respir J 2019; 53: 1801904

# TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

**1 PAH**
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

**2 PH due to left heart disease**
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

**3 PH due to lung diseases and/or hypoxia**
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

**4 PH due to pulmonary artery obstructions (table 6)**
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

**5 PH with unclear and/or multifactorial mechanisms (table 7)**
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

Eur Respir J 2019; 53: 1801913

**3 PH due to lung diseases and/or hypoxia**

- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

TABLE 1 Haemodynamic definitions of pulmonary hypertension (PH)

| Definitions | Characteristics | Clinical groups[#] |
|---|---|---|
| **Pre-capillary PH** | mPAP >20 mmHg<br>PAWP ⩽15 mmHg<br>PVR ⩾3 WU | 1, 3, 4 and 5 |

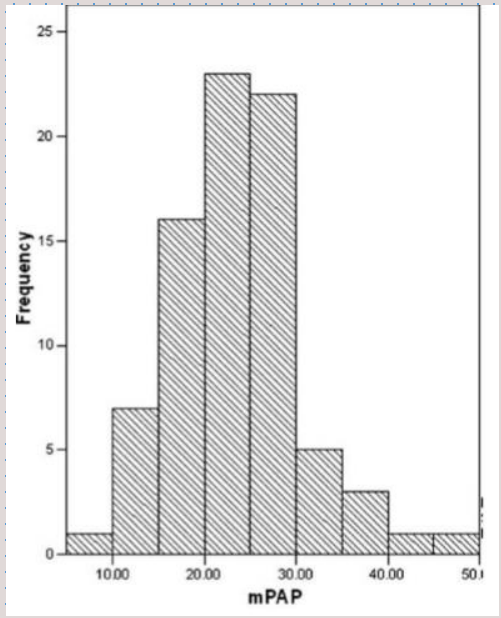
Eur Respir J 2019; 53: 1801913

# PULMONARY HYPERTENSION due to lung disease and/or hypoxia

1) CLD *without* PH (mPAP <21 mmHg, or mPAP 21–24 mmHg with pulmonary vascular resistance (PVR) <3 Wood Units (WU)).
2) CLD *with* PH (mPAP 21–24 mmHg with PVR ⩾3 WU, or mPAP 25–34 mmHg) (CLD-PH).
3) CLD *with severe* PH (mPAP ⩾35 mmHg, or mPAP ⩾25 mmHg with low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$)) (CLD-severe PH).

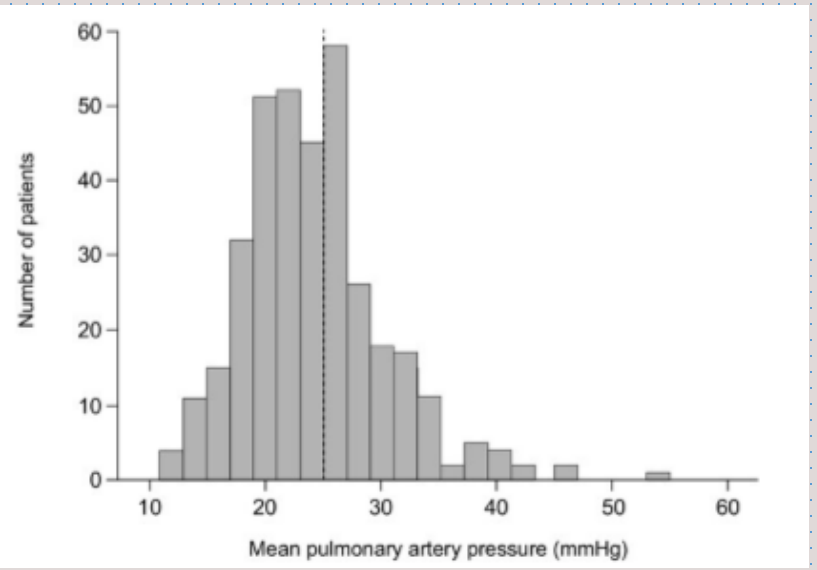
Eur Respir J 2019; 53: 1801914

## IPF with PH



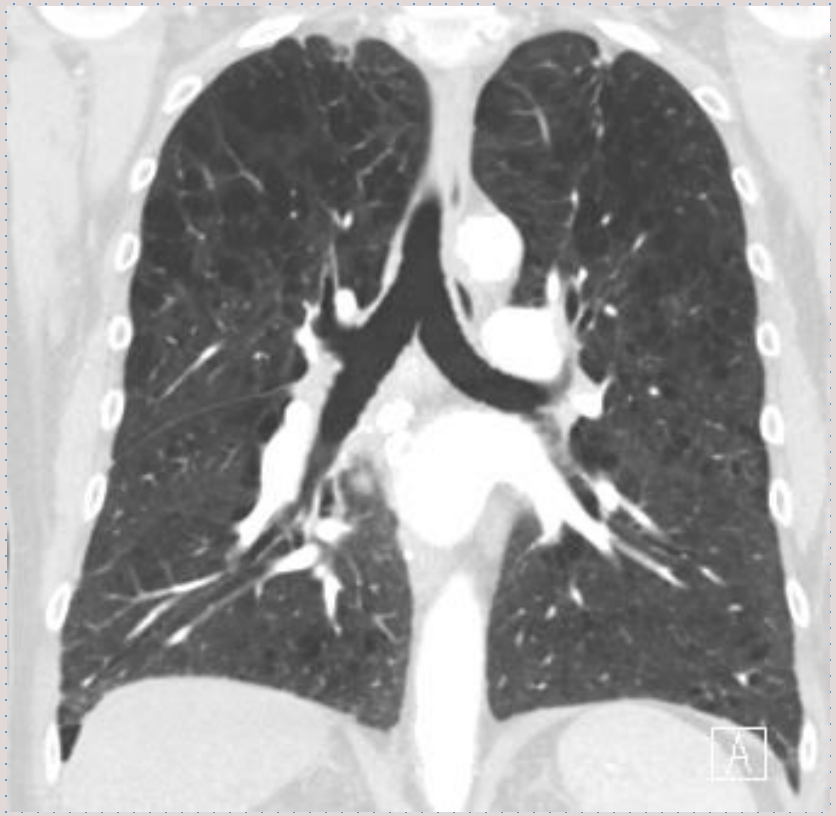

CHEST / 129/3/MARCH, 2006

## COPD with PH

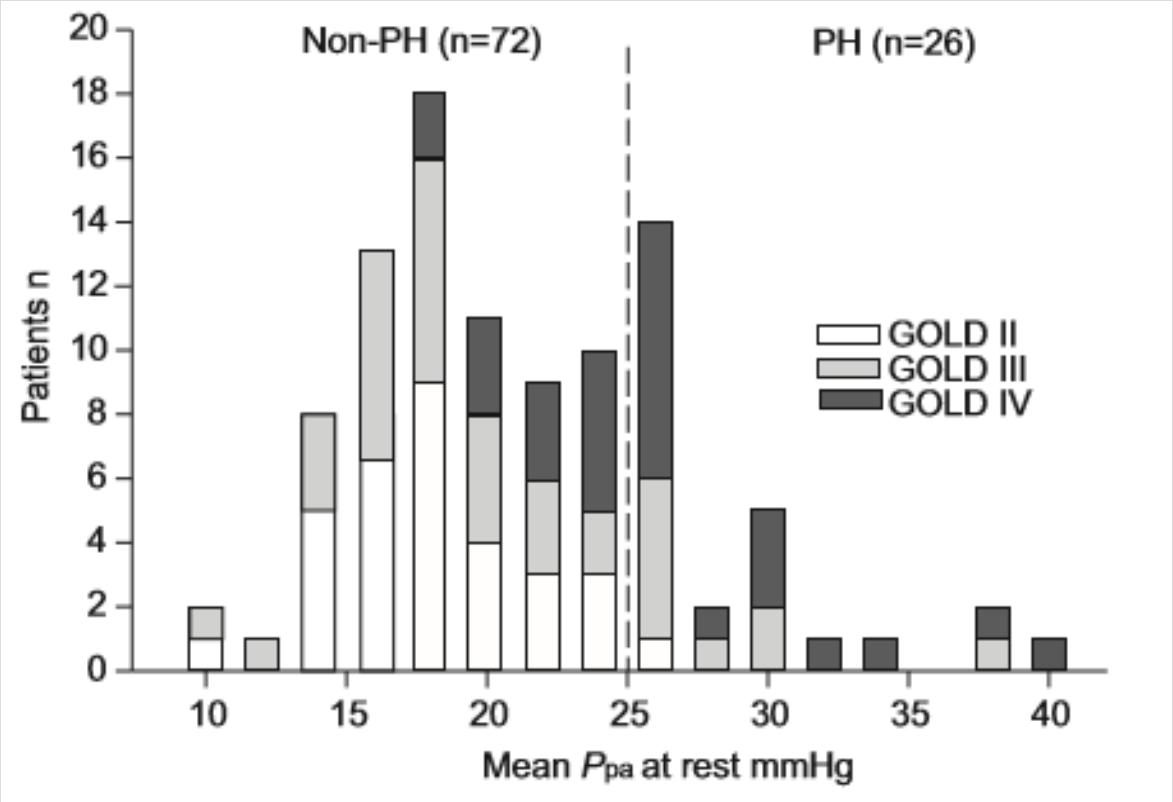



J Heart Lung Transplant 2012;31:373-80

# PH-COPD

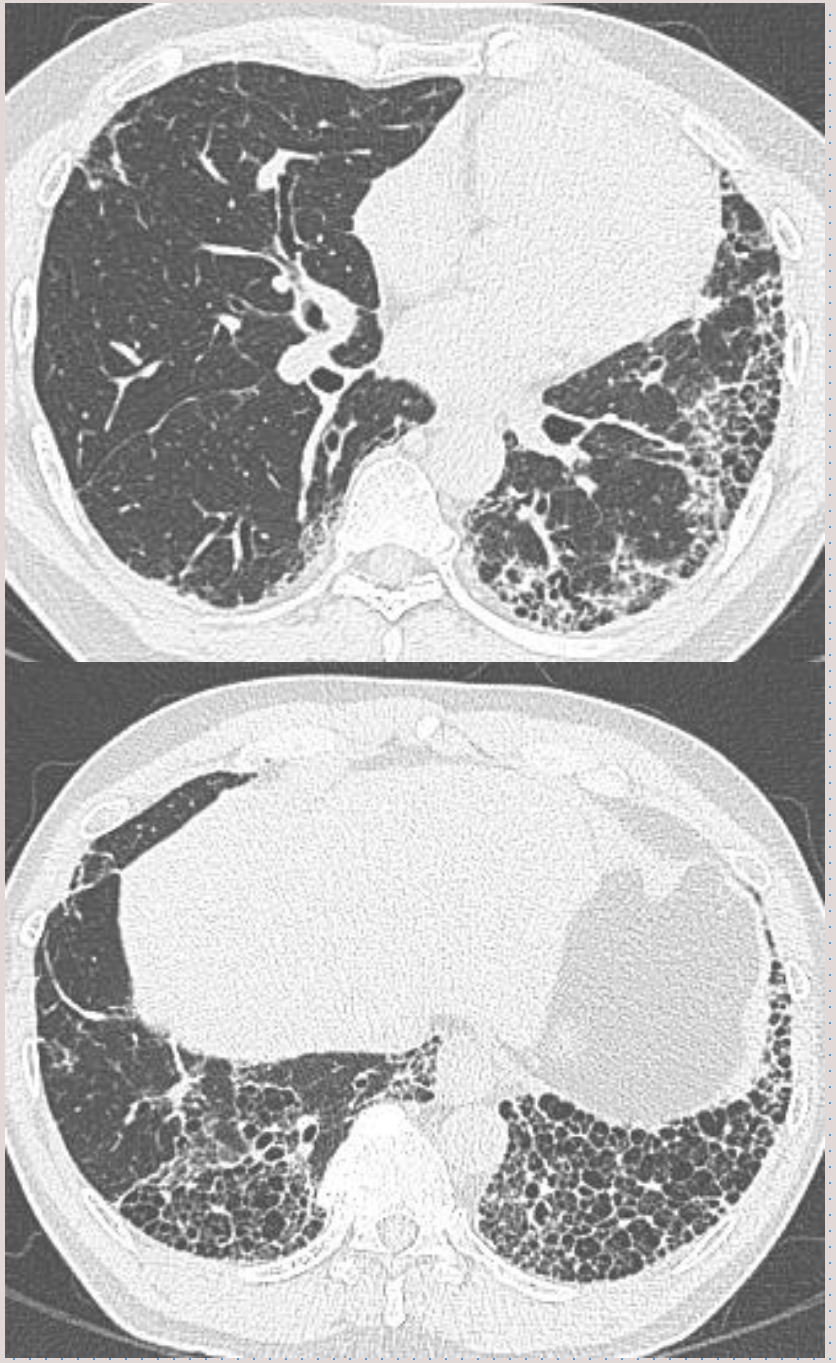


Emphysema




- GOLD II 5%
- GOLD III 27%
- GOLD IV 53%

Eur Respir J 2013; 41: 1031–1041



# PH-IPF

- Prevalence oh PH varies greatly according to the severity of  the disease:  lower prevalence in relatively early stages of IPF 8,1-14%, common in advanced  IPF, more than 60% in end stage IPF
- MPAP did not correlate with CT-based measurements of lung fibrosis

Chest. 2007 September ; 132(3): 773–779.

Eur Respir J 2007; 30: 715–721

JACC Vol. 62, No. 25, Suppl D, 2013 December 24, 201

# PH-COPD

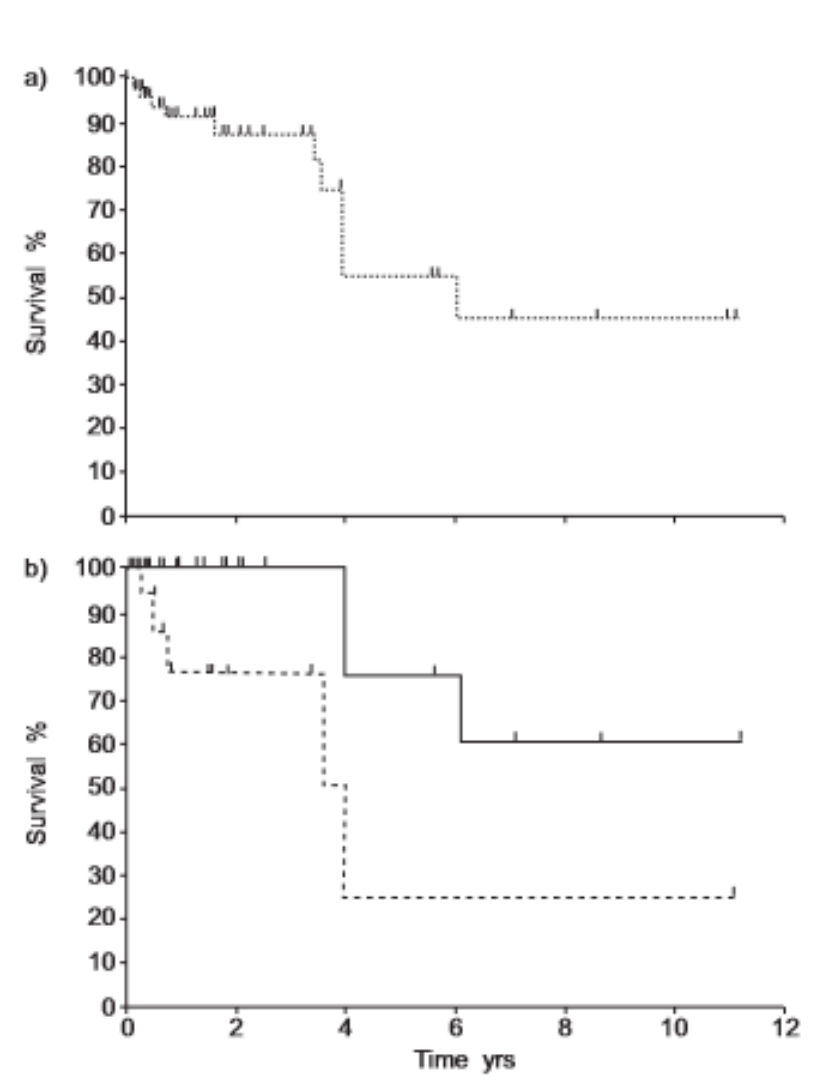
**TABLE 1** Baseline characteristics

| | COPD mean PAP 25–39 mmHg | COPD mean PAP ⩾40 mmHg | p-value |
|---|---|---|---|
| **CT scan** | | | |
| Total emphysema score | 5 ( 1–15) | 9.5 (2–18) | 0.191# |
| Total upper zone emphysema | 3.5 (0–6) | 5.5 (1–7) | 0.214# |
| Total lower zone emphysema | 0 (0–3) | 0.5 (0–4) | 0.178# |
| Total fibrosis score | 0 (0–2) | 0 (0–2.5) | 0.509# |
| Total upper zone fibrosis | 0 (0–0) | 0 (0–0) | 0.790# |
| Total lower zone fibrosis | 0 (0–1.5) | 0 (0–2) | 0.330# |
| **Pulmonary artery/aorta** | 1.0±0.1 | 1.0±0.1 | 0.202 |
| **Right ventricle/left ventricle** | 1.1±0.4 | 1.3±0.4 | 0.031 |

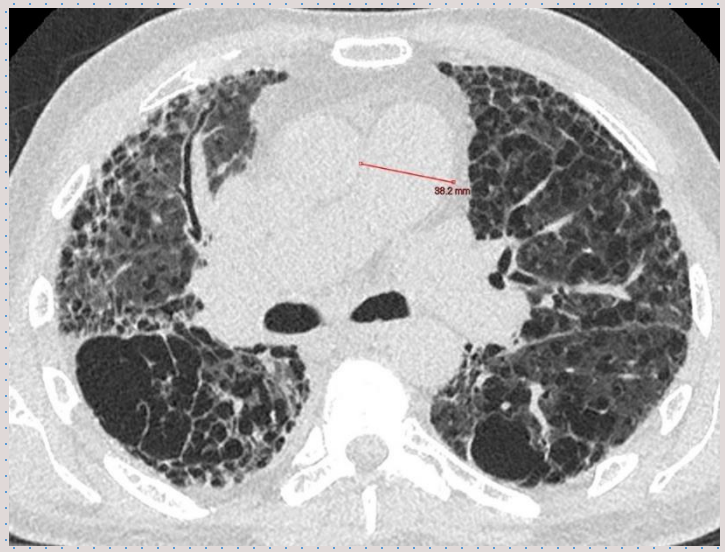
- Difference in overall HRCT scores for emphysema or fibrosis between those with mild–moderate versus severe PH-COPD did not reach statistical significance

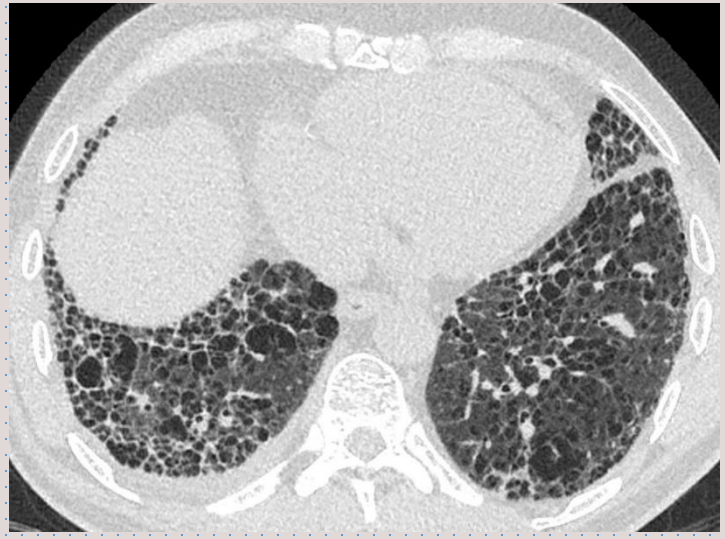
Eur Respir J 2013; 41: 1292–1301

# CPFE end PH




- Pulmonary Hypertension is frequent in patients with CPFE syndrome: prevalence of 47% at diagnosis, and 55% during follow-up
- mean PAP was >35 mmHg with a mean PAP of 45± 6 mmHg
- Patients with pulmonary hypertension and CPFE had a dismal prognosis, with a 60% probability of survival at 1 yr from the diagnosis of pulmonary hypertension



Eur Respir J 2005; 26: 586–593

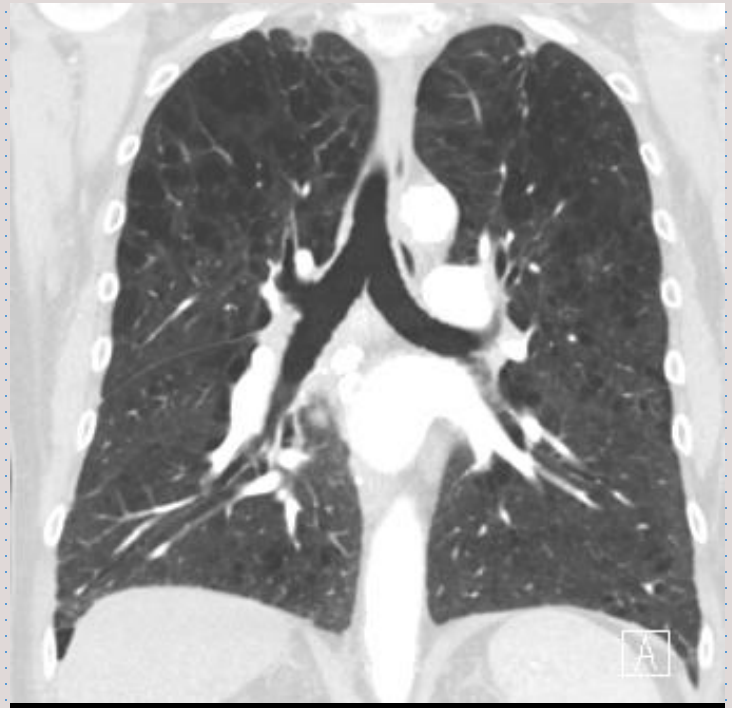
Eur Respir J 2010; 35: 105–11

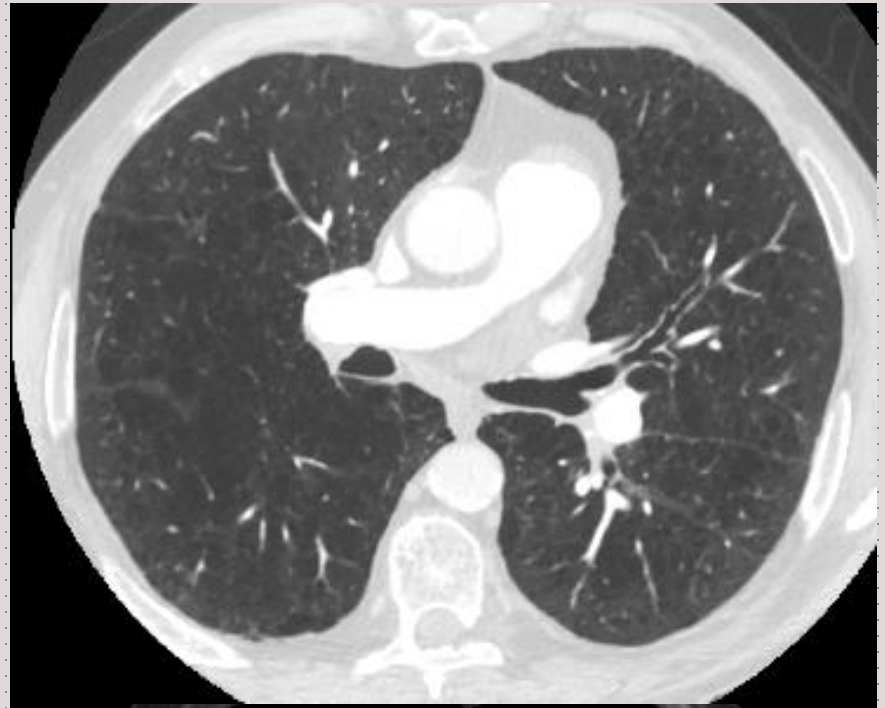
TABLE 1 Criteria favouring group 1 *versus* group 3 pulmonary hypertension (PH)#

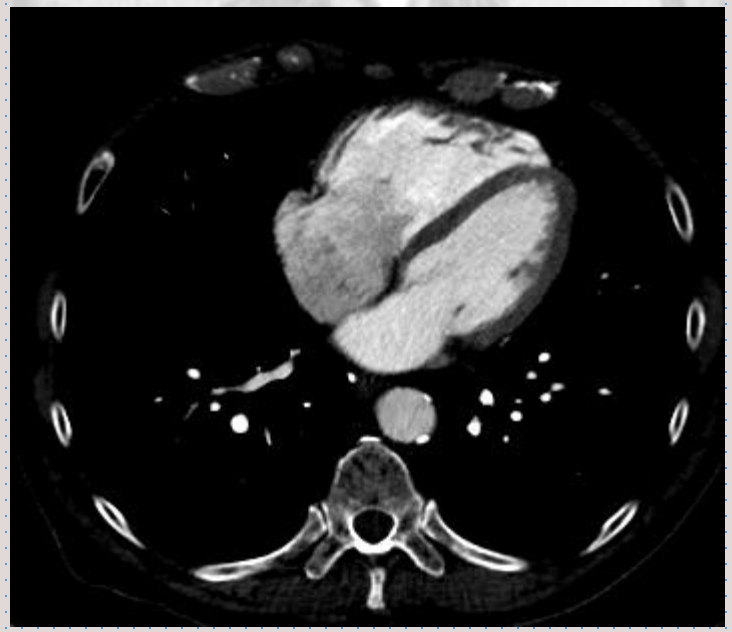
| Criteria favouring group 1 (PAH) | Testing | Criteria favouring group 3 (PH due to lung disease) |
|---|---|---|
| **Extent of lung disease** | | |
| Normal or mildly impaired:<br>• $FEV_1$ >60% pred (COPD)<br>• FVC >70% pred (IPF)<br>• Low diffusion capacity in relation to obstructive/restrictive changes | Pulmonary function testing | Moderate to very severely impaired:<br>• $FEV_1$ <60% pred (COPD)<br>• FVC <70% pred (IPF)<br>• Diffusion capacity "corresponds" to obstructive/restrictive changes |
| Absence of or only modest airway or parenchymal abnormalities | High-resolution CT scan¶ | Characteristic airway and/or parenchymal abnormalities |
| **Haemodynamic profile** | | |
| Moderate-to-severe PH | Right heart catheterisation<br>Echocardiogram | Mild-to-moderate PH |
| **Ancillary testing** | | |
| Present | Further PAH risk factors (*e.g.* HIV, connective tissue disease, *BMPR2* mutations, *etc.*) | Absent |
| Features of exhausted circulatory reserve:<br>• Preserved breathing reserve<br>• Reduced oxygen pulse<br>• Low $CO/\dot{V}O_2$ slope<br>• Mixed venous oxygen saturation at lower limit<br>• No change or decrease in $P_{ET}CO_2$ during exercise | Cardiopulmonary exercise test+<br>($P_{ET}CO_2$ particularly relevant in COPD) | Features of exhausted ventilatory reserve:<br>• Reduced breathing reserve<br>• Normal oxygen pulse<br>• Normal $CO/\dot{V}O_2$ slope<br>• Mixed venous oxygen saturation above lower limit<br>• Increase in $P_{ET}CO_2$ during exercise |
| Predominant haemodynamic profile | | Predominant obstructive/restrictive profile |

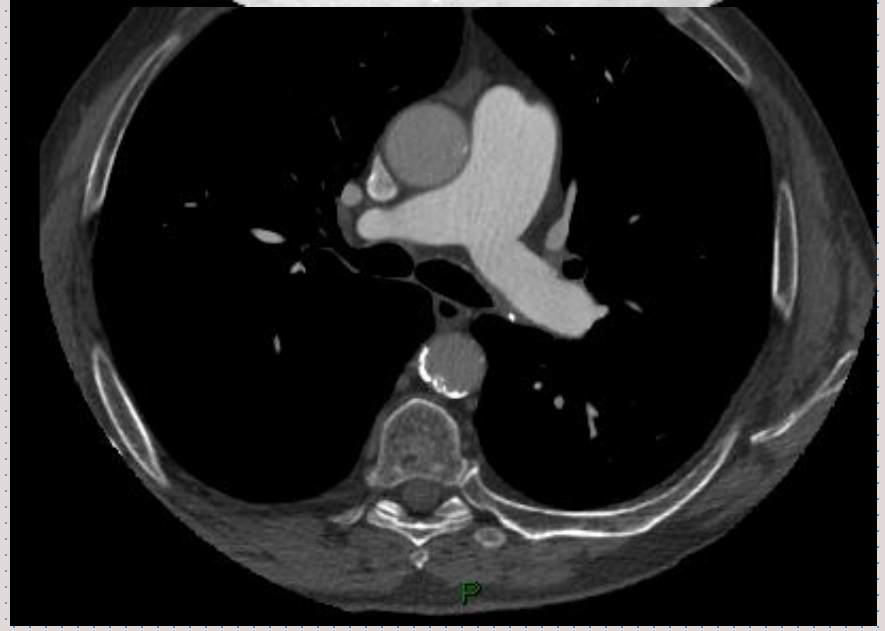
- Lung diseases (especially COPD) are common conditions and PAH developing in such patients may not be attributable to these diseases, but may be coincidental
- The spectrum of severity of both the pulmonary vascular and parenchymal lung disease is likely a continuum, which often makes the distinction between group 1 and group 3 PH very difficult

Eur Respir J 2019; 53: 1801914

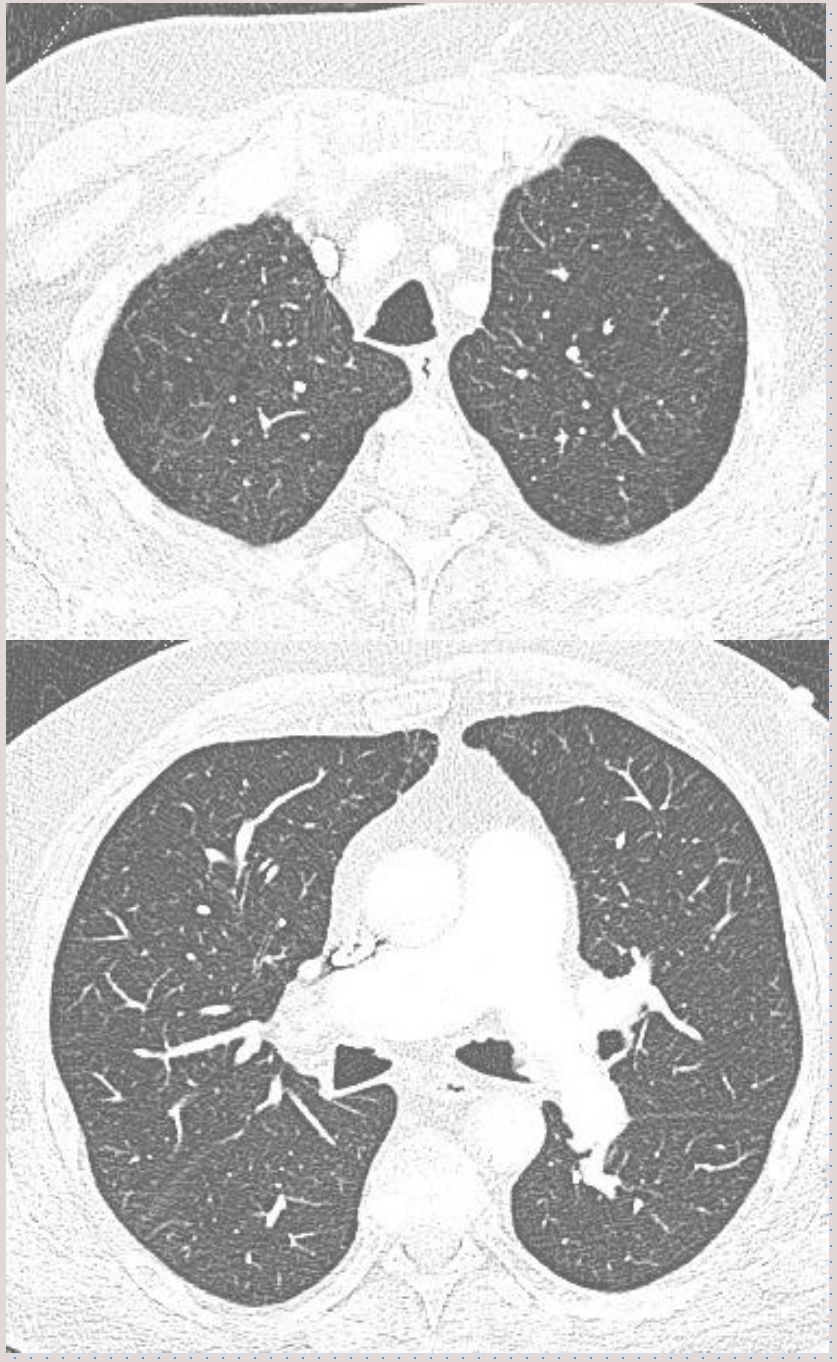


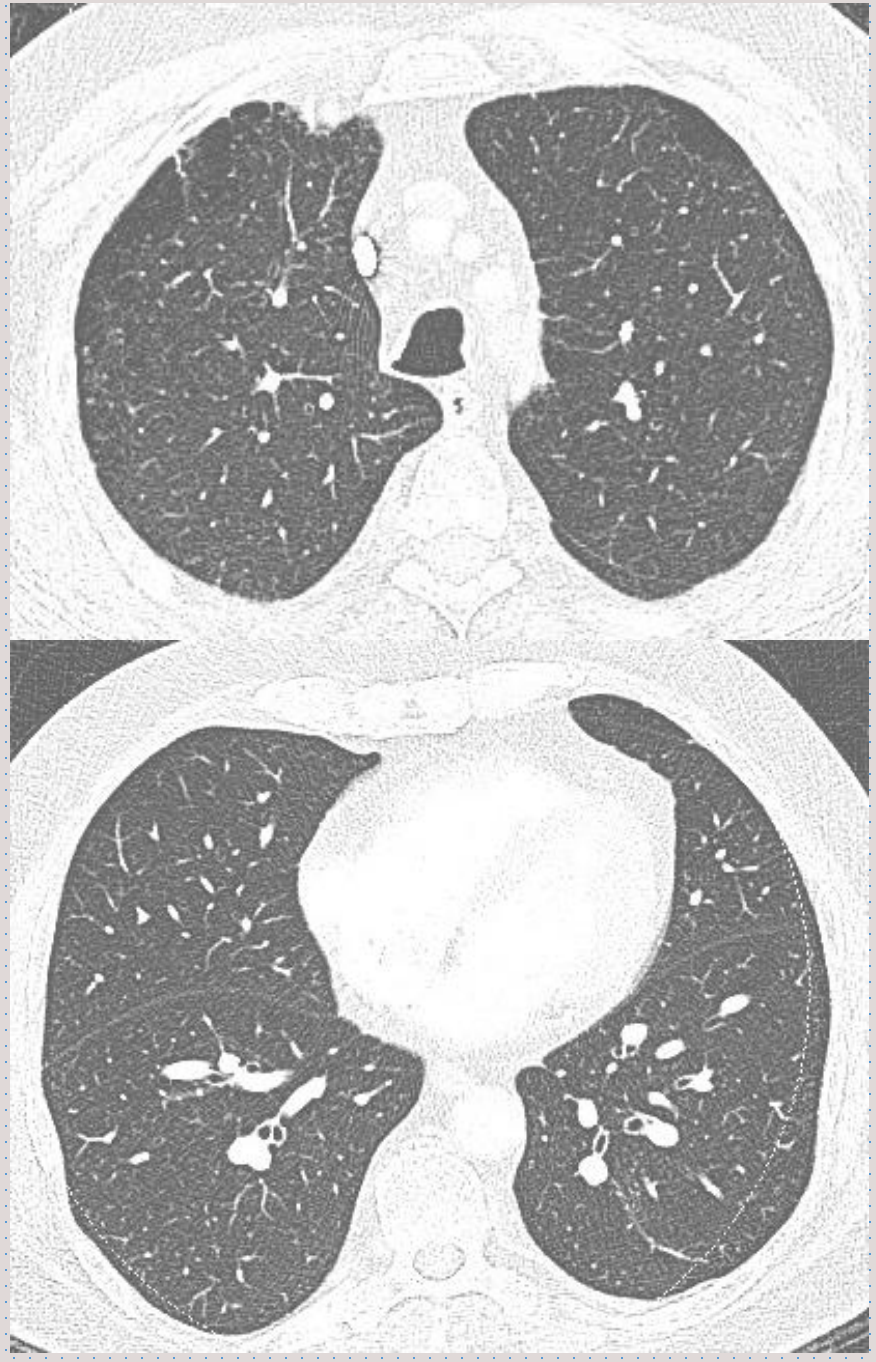








- 3 PH
- COPD
- Mild Pulmonary Hypertension

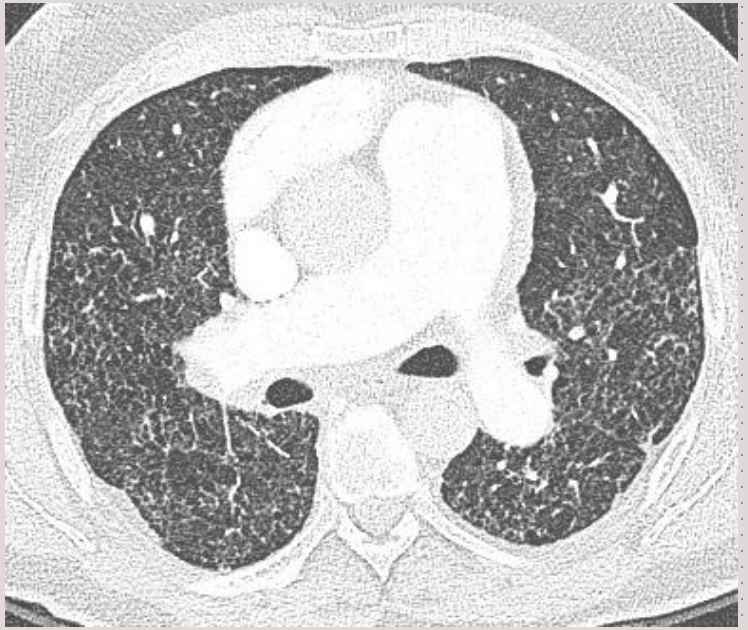


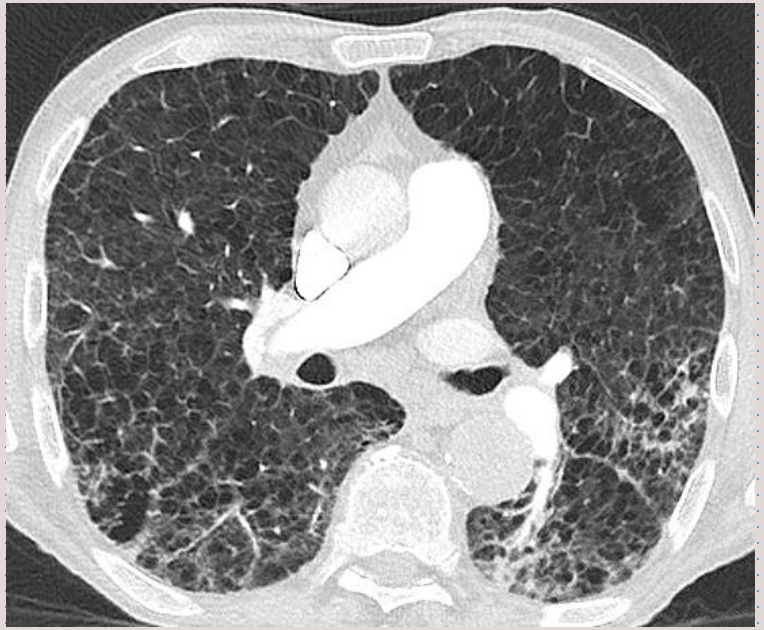


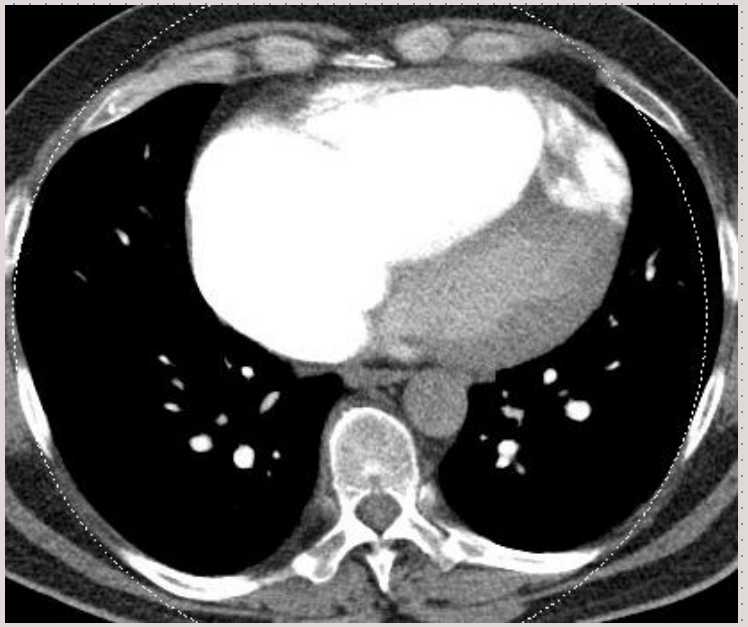
- Hischemic Heart disease
- Chronic Renal Failur
- RHC: pre-capillary PH; mean PAP 34 mmHg and preserved CI
- PFT: marked reduction of DLCO and finding of mixed ventilatory deficit of moderate-severe degree

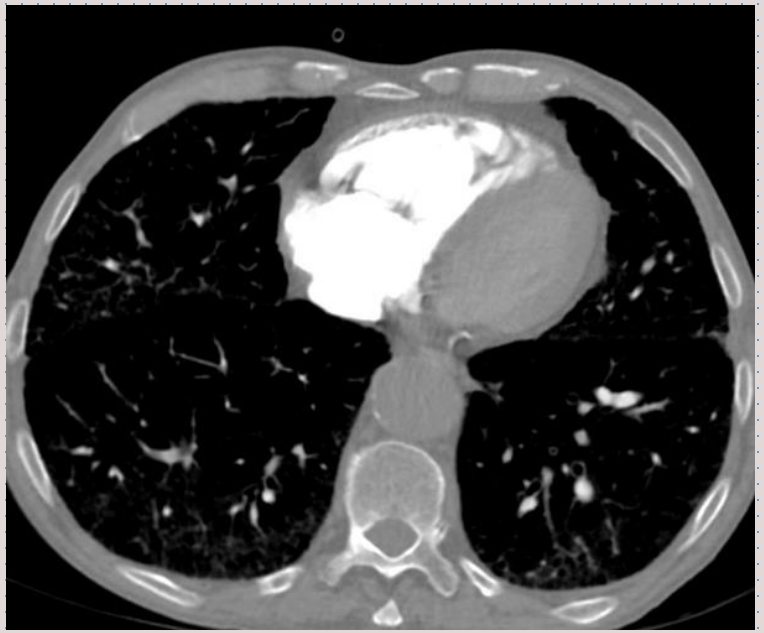
AM J RESPIR CRIT CARE MED 2000;161:216–223.

Radiol Med. 2014 Jan;119(1):41-53









Histiocytosis X

COPD

# Pulmonary hypertension in chronic lung disease and hypoxia

## Specific aspects of PH in systemic sclerosis

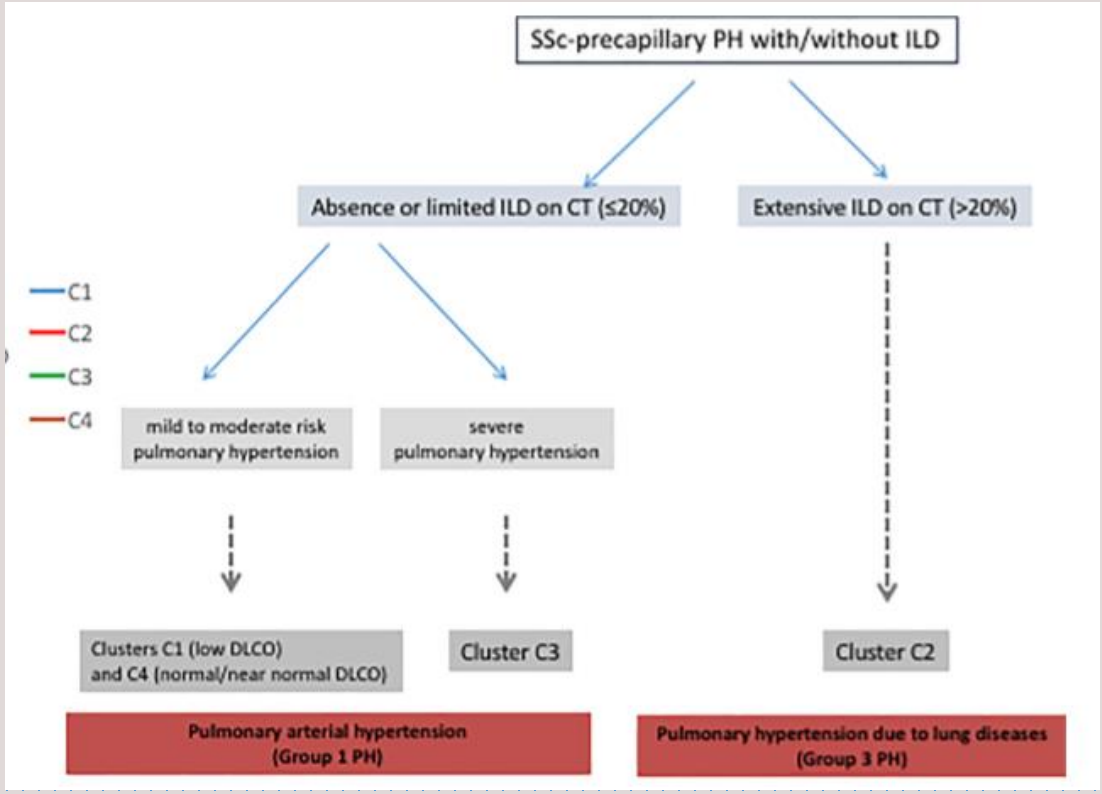
PH in patients with systemic sclerosis (SSc) can be multifactorial. These patients are at high risk of developing isolated PAH, but they may also develop significant parenchymal lung disease and/or a component of left heart disease. There is often difficulty in discriminating group 1 PAH from group 3 PH in SSc patients, since quite commonly these patients have evidence of parenchymal lung disease on high-resolution CT, which may or may not be accompanied by restrictive physiology. SSc patients with combined pulmonary fibrosis and PH have a particularly high mortality risk [72]. Both PH severity and the extent of pulmonary fibrosis can vary widely. Patients with pre-capillary PH and mild fibrosis are usually classified as having PAH, and have been included in most of the RCTs of PAH medications. However, assessment of the degree of fibrosis was usually based on pulmonary function testing and not scrutiny of the extent of fibrosis on high-resolution CT. Patients with preserved lung volumes can be safely treated with PAH drugs, but there is no evidence for treatment of PH-SSc with more advanced ILD.

Eur Respir J 2019; 53: 1801914

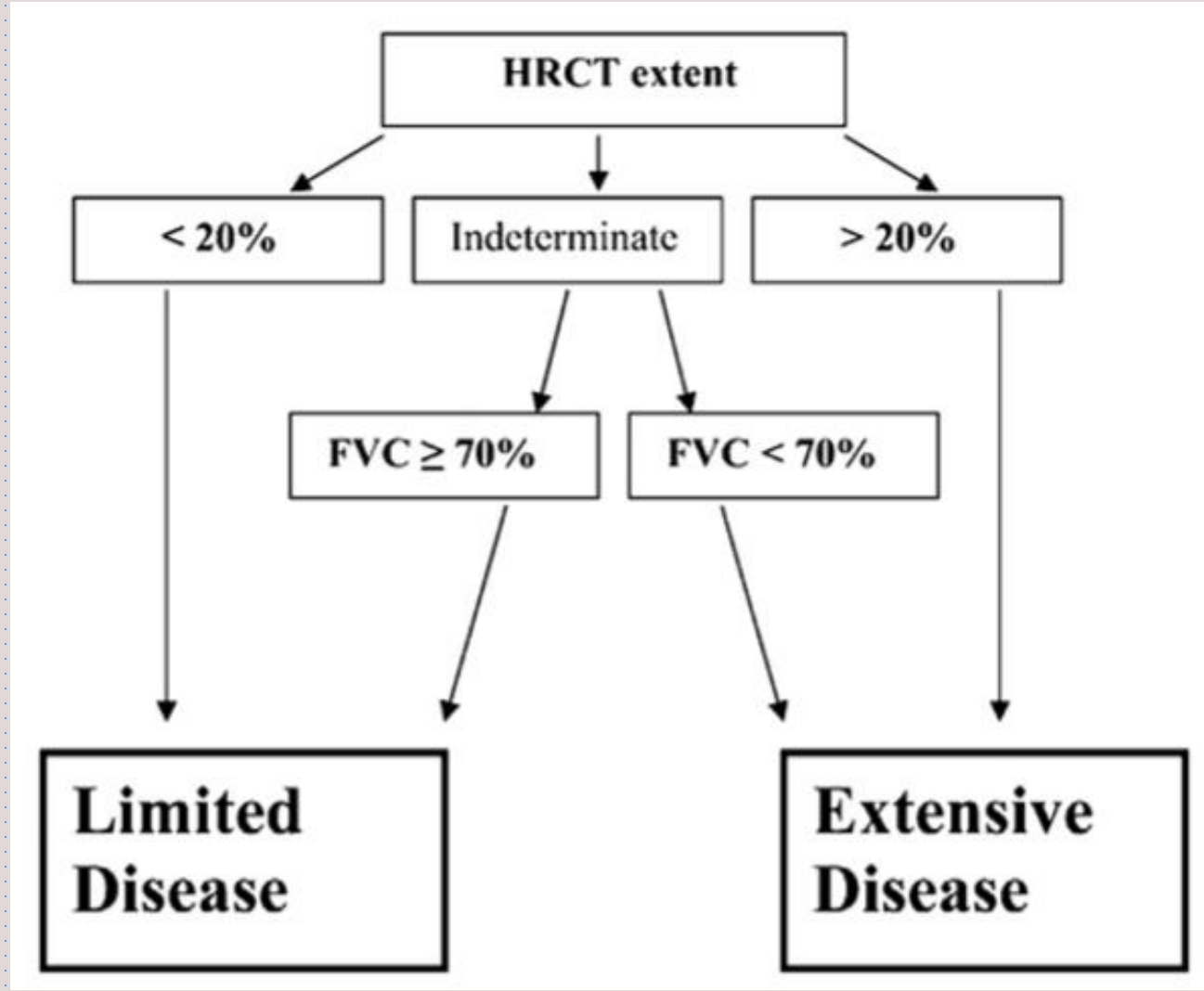
RESEARCH ARTICLE

# Clinical phenotypes and survival of pre-capillary pulmonary hypertension in systemic sclerosis

David Launay[1,2,3,4], David Montani[5,6,7], Paul M. Hassoun[8], Vincent Cottin[9], Jérôme Le Pavec[5,7,10], Pierre Clerson[11], Olivier Sitbon[5,6,7], Xavier Jaïs[5,6,7], Laurent Savale[5,6,7], Jason Weatherald[5,6,7,12], Vincent Sobanski[1,2,3,4], Stephen C. Mathai[8], Majid Shafiq[8], Jean-François Cordier[9], Eric Hachulla[1,2,3,4], Gérald Simonneau[5,6,7], Marc Humbert[5,6,7]*




PLoS ONE 13(5):e0197112.https://doi.org/10.1371/journal.pone.0197112

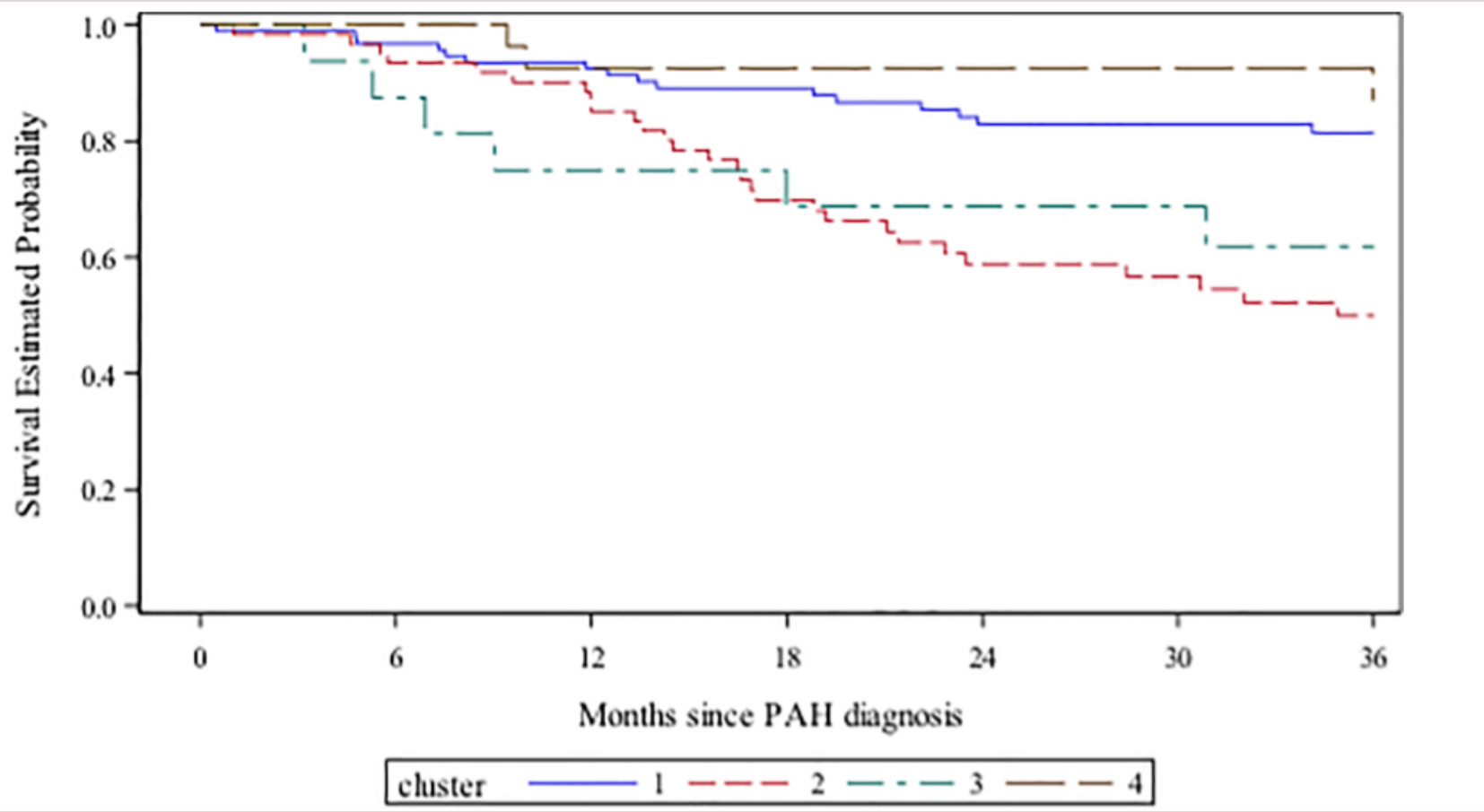



Am J Respir Crit Care Med. 2008; 177(11):1248–54

RESEARCH ARTICLE

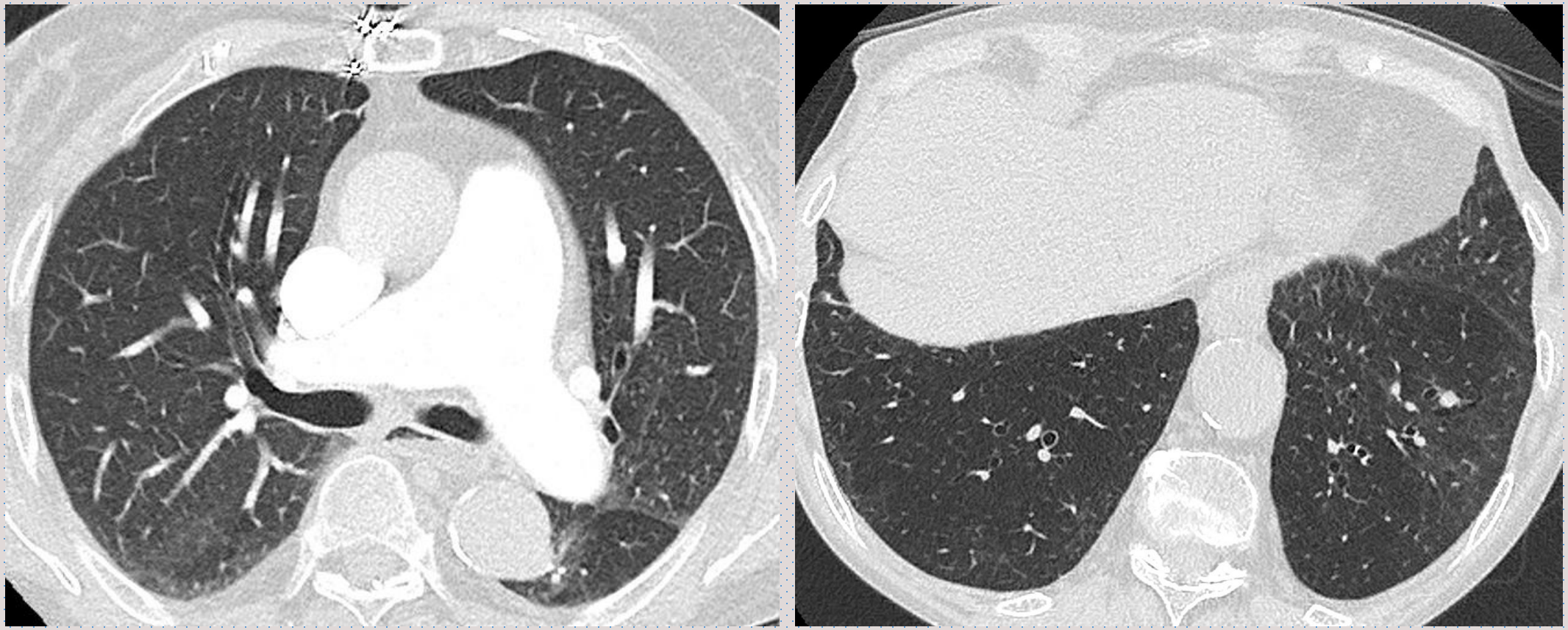
# Clinical phenotypes and survival of pre-capillary pulmonary hypertension in systemic sclerosis

David Launay[1,2,3,4], David Montani[5,6,7], Paul M. Hassoun[8], Vincent Cottin[9], Jérôme Le Pavec[5,7,10], Pierre Clerson[11], Olivier Sitbon[5,6,7], Xavier Jaïs[5,6,7], Laurent Savale[5,6,7], Jason Weatherald[5,6,7,12], Vincent Sobanski[1,2,3,4], Stephen C. Mathai[8], Majid Shafiq[8], Jean-François Cordier[9], Eric Hachulla[1,2,3,4], Gérald Simonneau[5,6,7], Marc Humbert[5,6,7]*



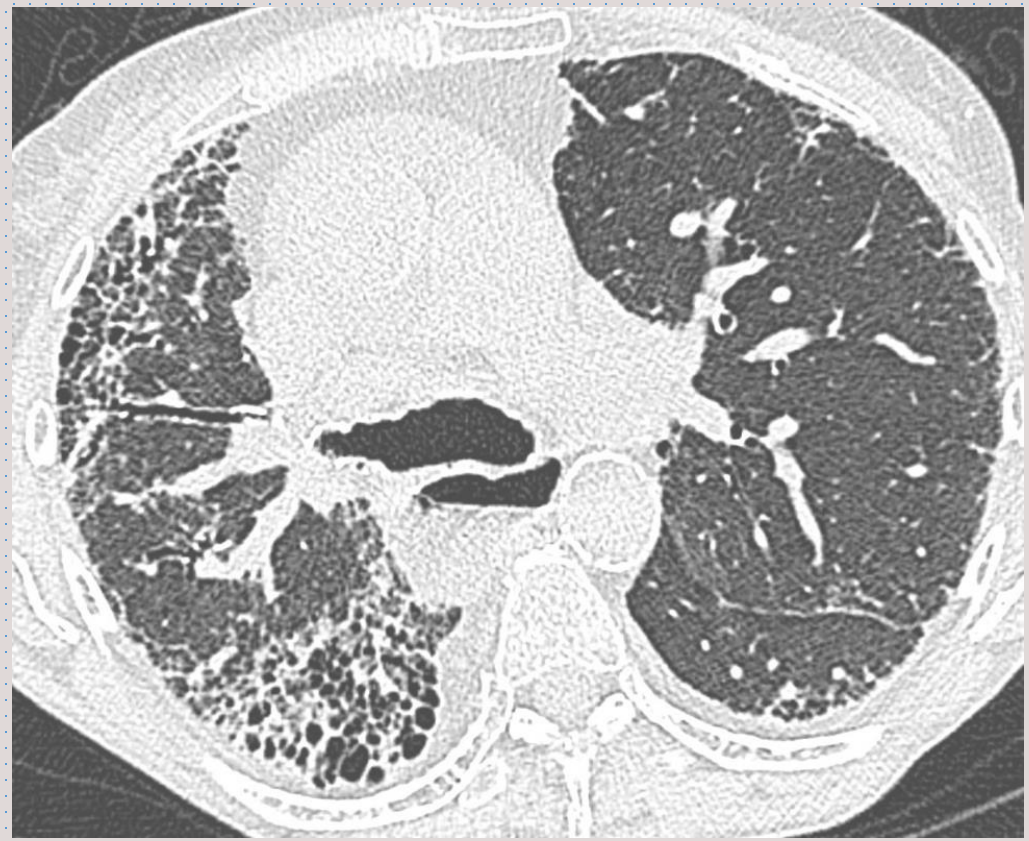

- C2 had pre-capillary PH due to extensive ILD and worse 3-year survival compared to C1 (p=0,0004)
- The presence of an extensive ILD, whatever the hemodynamics, is associated with a very severe outcome
- The presence of a limited ILD (often seen as a potent cofounder the classification of PH in tne context of SSc) has to be considered in the same group of patients with no ILD, where the severity of hemodynamics drives the prognosis

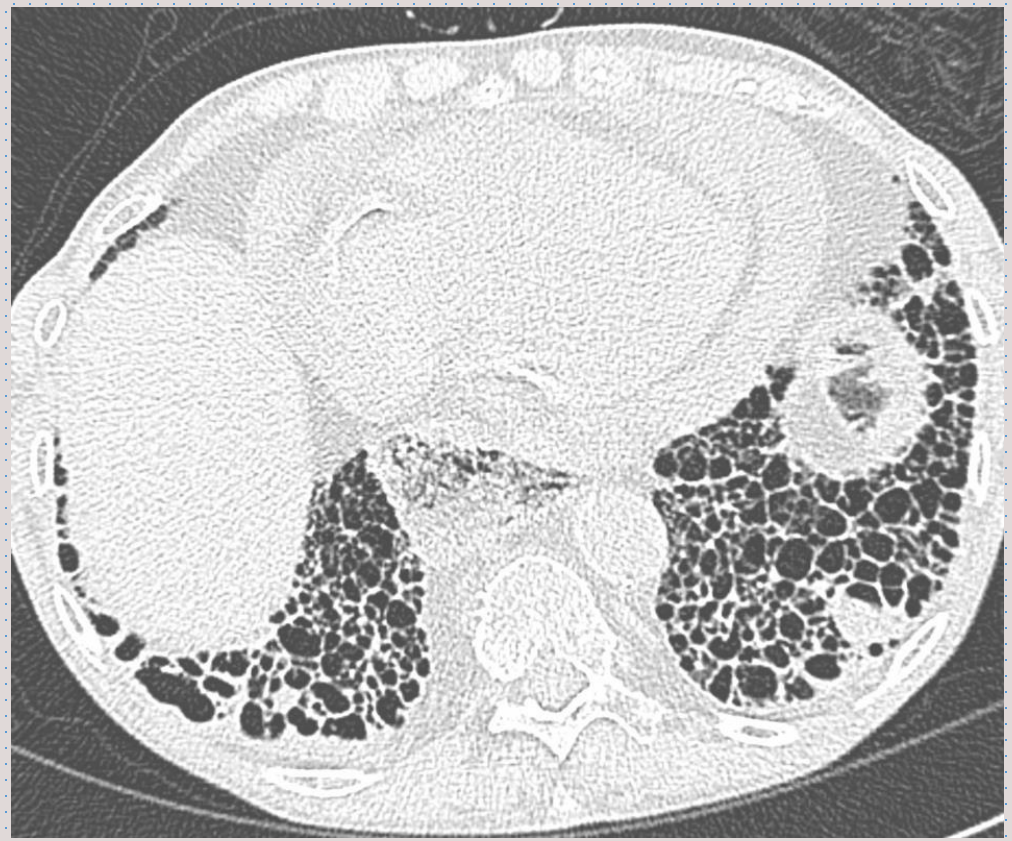
PLoS ONE 13(5):e0197112.https://doi.org/10.1371/journal.pone.0197112



Limited ILD in SSc-PAH

GROUP 1





Extensive ILD in SSc-PH

GROUP 3

**1 PAH**

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH [table 3]
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers [table 4]
- 1.6 PAH with overt features of venous/capillaries [PVOD/PCH] involvement [table 5]
- 1.7 Persistent PH of the newborn syndrome

TABLE 1 Haemodynamic definitions of pulmonary hypertension (PH)

| Definitions | Characteristics | Clinical groups[#] |
|---|---|---|
| **Pre-capillary PH** | mPAP >20 mmHg<br>PAWP ⩽15 mmHg<br>PVR ⩾3 WU | 1, 3, 4 and 5 |

- PAH and PVOD share similar clinical and hemodynamic presentations
- Both entities should be distinguished because of the worse PVOD prognosis and the possible occurrence of life threatening pulmonary edema after PAH-specific therapy initiations in PVOD-patients
- PVOD is referred to group 1 PAH because of evidence suggesting a continuum between arterial, capillary and vein involvement in PAH

# Haemodynamic definitions and updated clinical classification of pulmonary hypertension

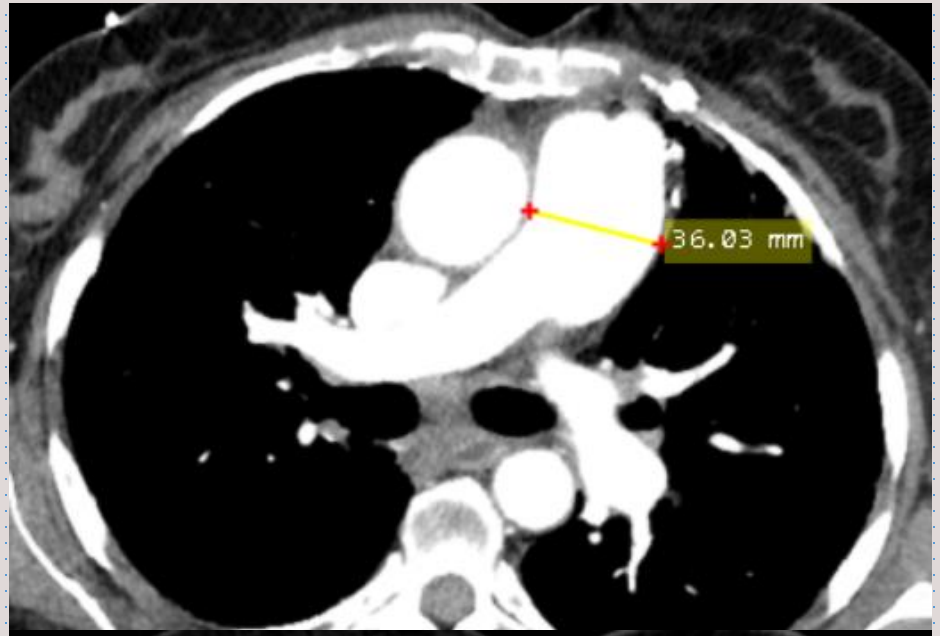
PVOD

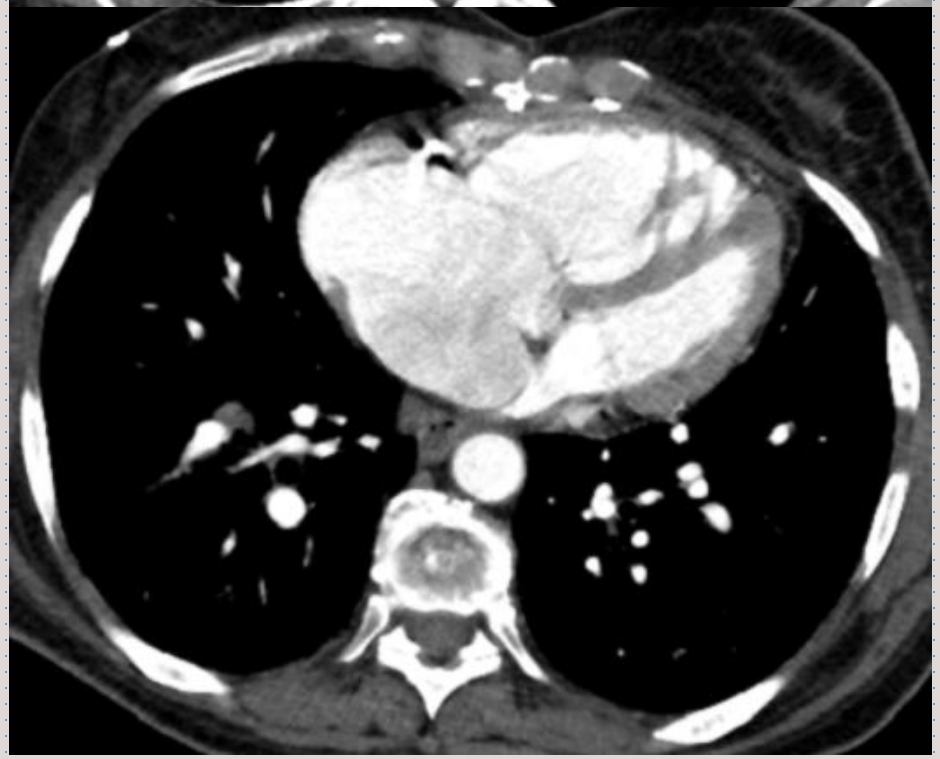
TABLE 5 Signs evocative of venous and capillary (pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis) involvement

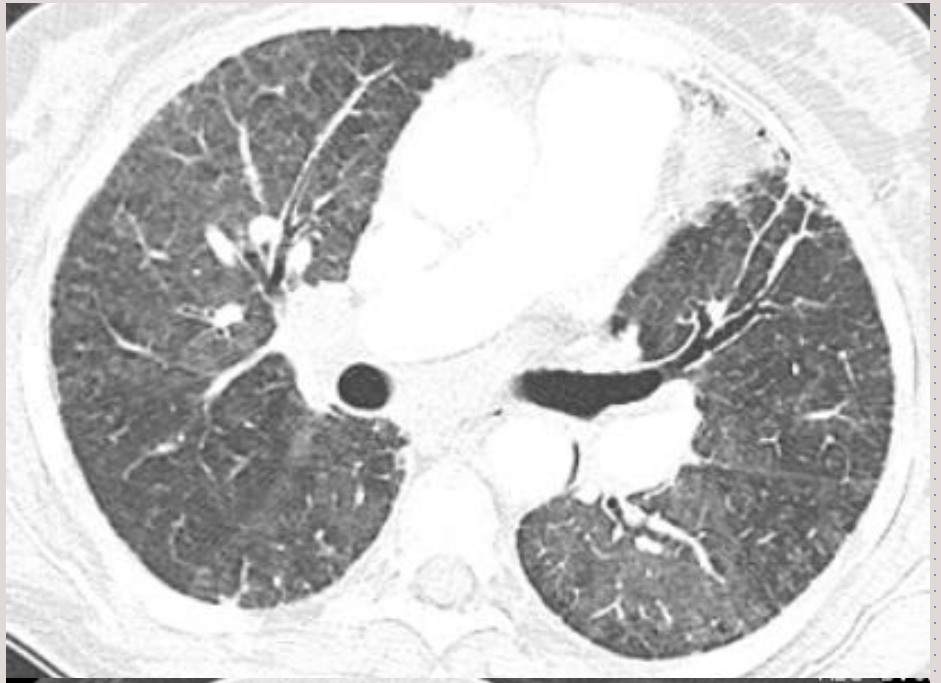
| | |
|---|---|
| **Pulmonary function tests** | Decreased *D*LCO (frequently <50%)<br>Severe hypoxaemia |
| **Chest HRCT** | Septal lines<br>Centrilobular ground-glass opacities/nodules<br>Mediastinal lymph node enlargement |
| **Response to PAH therapy** | Possible pulmonary oedema |
| **Genetic background** | Biallelic *EIF2AK4* mutations |
| **Occupational exposure** | Organic solvent (trichloroethylene) |

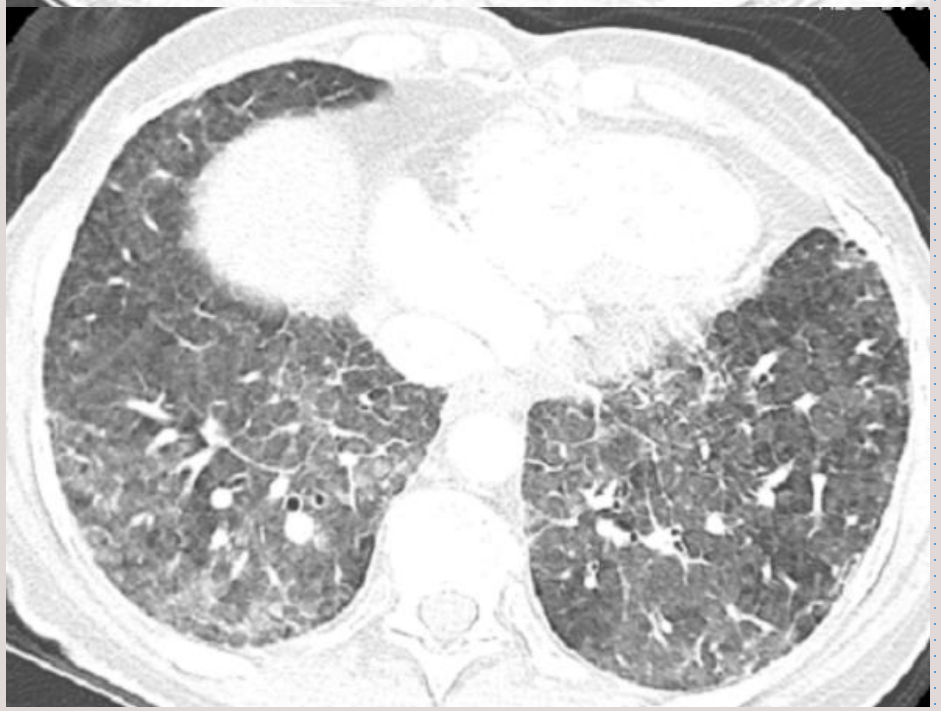
*D*LCO: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; PAH: pulmonary arterial hypertension.

Eur Respir J 2019; 53: 1801913







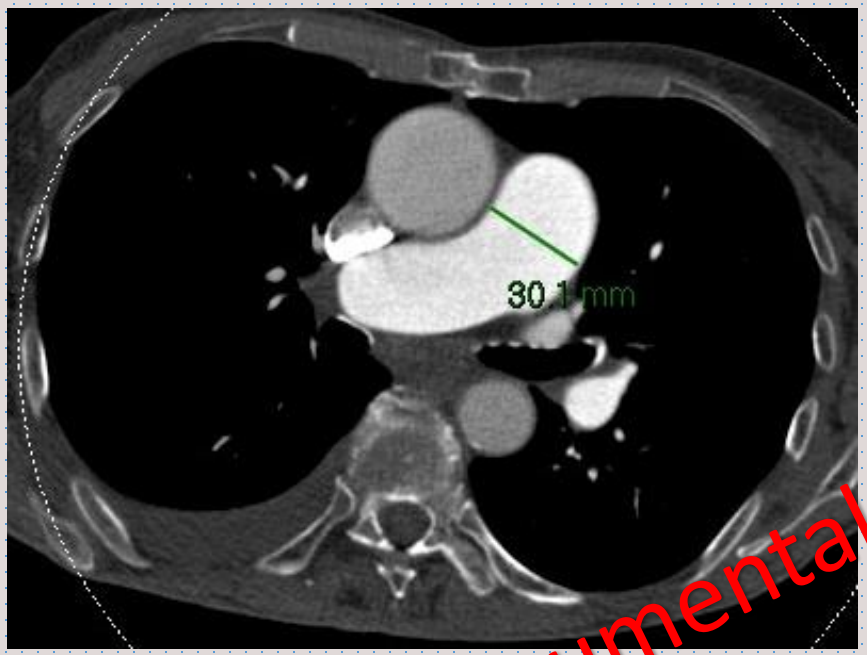
# PVOD:

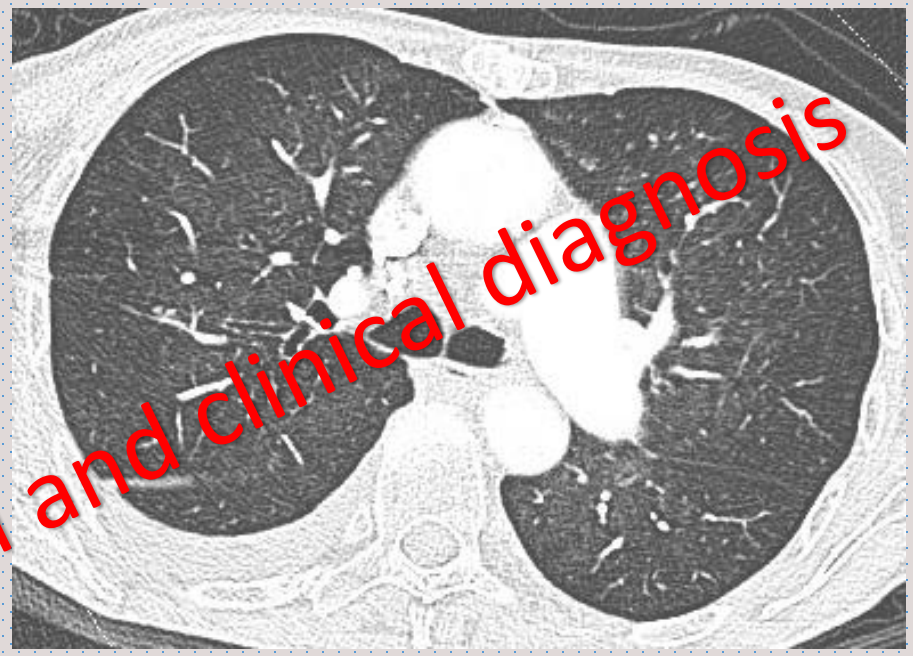
## SSc

- Septal lines
- Centrilobular ground glass opacities/ nodules
- Mediastinal linph node enlargement
- **Specificity** 100%

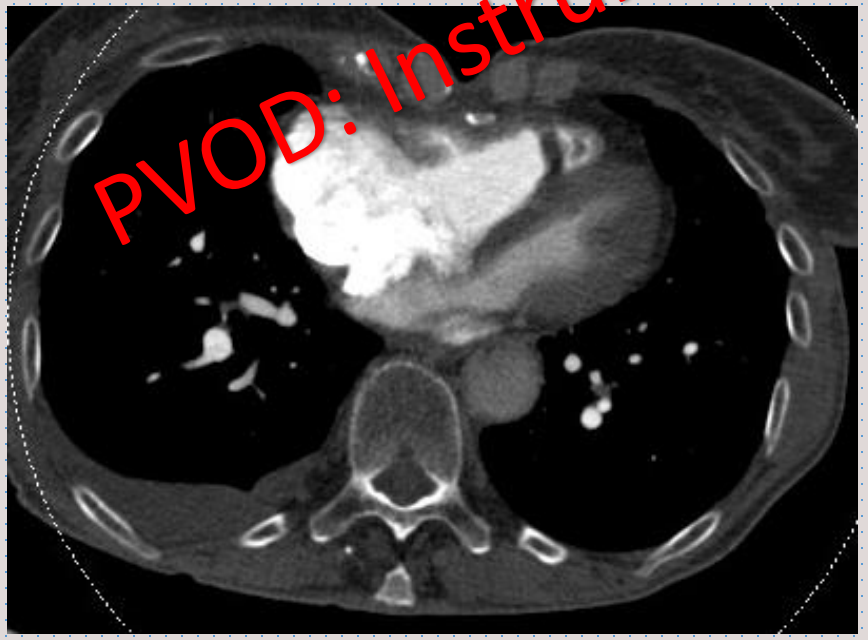
  **Sensibility** 66%

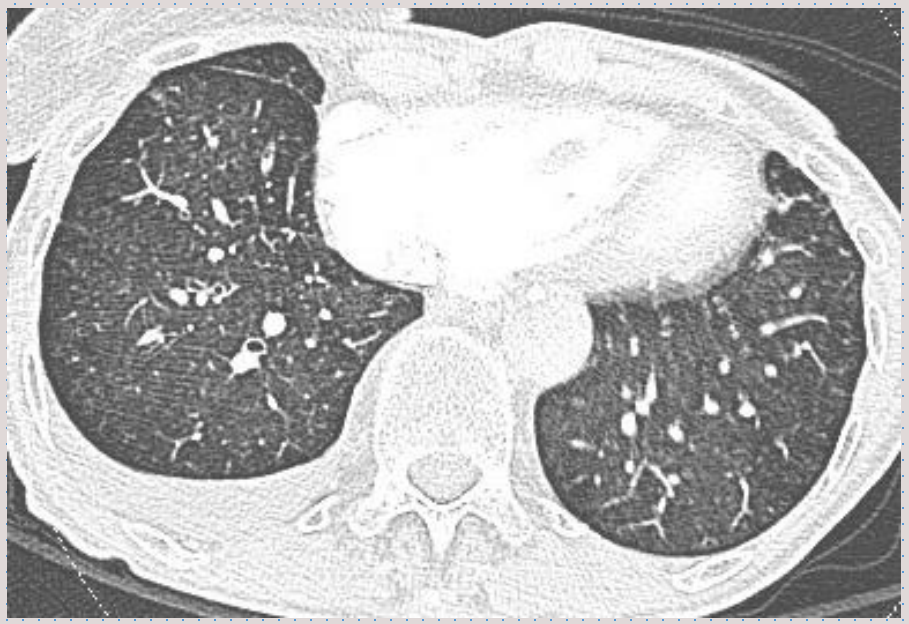
Frazier AA - RadioGraphics 2007; 27:867–882



PVOD: Instrumental and clinical diagnosis





- **SSc**
- Respiratory failure in O2 therapy
- **PFT:** marked reduction of DLCO and finding of mild obstructive disventilatory syndrome
- RHC: **pre-capillary PH with low IC** and high PVR: (PAPm 45 mmHg**, wedge 7 mmhg,** PVR 16 mmHG, IC 1,62 ml/min/mq)
- BAL: intermediate positivity to hemosiderin

RHEUMATOLOGY

Rheumatology 2017;56:2197–2203
doi:10.1093/rheumatology/kex351
Advance Access publication 26 September 2017

Original article

# Prognostic significance of computed tomography criteria for pulmonary veno-occlusive disease in systemic sclerosis-pulmonary arterial hypertension

**Michelle J. Connolly[1], Sharif Abdullah[2], Deborah A. Ridout[3], Benjamin E. Schreiber[1], Jamanda A. Haddock[2] and J. Gerry Coghlan[1]**

## Abstract

**Objectives.** SSc-pulmonary arterial hypertension (SSc-PAH) is associated with worse response to therapy and survival when compared with idiopathic PAH. It is suggested that the vasculopathy in SSc may involve postcapillary pulmonary venules resulting in pulmonary veno-occlusive disease (PVOD). This may underlie the lower gas transfer and worse outcome on therapy. We sought to test whether CT signs of PVOD (CTS-PVOD) were frequent in SSc-PAH and whether they were associated with pulmonary oedema on therapy and worse survival.

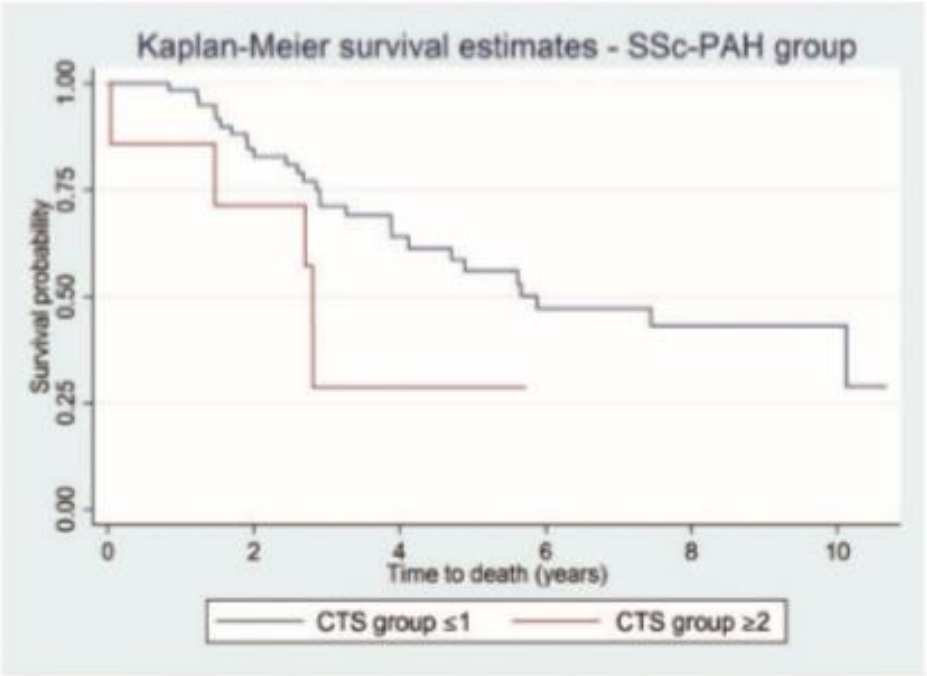
**Methods.** CT thorax of 66 SSc patients with precapillary pulmonary hypertension (PH) were blindly scored by two radiologists for CTS-PVOD ($\leqslant 1$ or $\geqslant 2$). Case note and radiograph review determined the presence of pulmonary oedema on therapy.

**Results.** Fifty-nine patients (89%) had $\leqslant 1$ CTS-PVOD and only 7 (11%) had $\geqslant 2$ CTS-PVOD. Pulmonary oedema on therapy was relatively common in those with $\geqslant 2$ CTS-PVOD. On univariate analysis $\geqslant 2$ CTS-PVOD were associated with a trend towards worse survival.

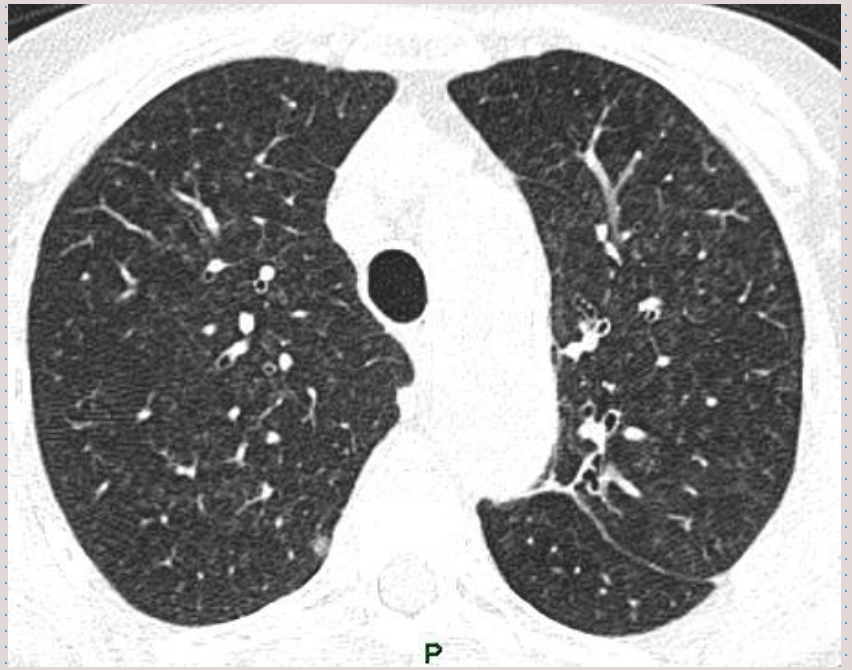
**Conclusion.** CTS-PVOD were less frequent in this SSc-PAH cohort than in previous reports but the presence of at least two of these signs is associated with pulmonary oedema on therapy and a trend towards worse survival on univariate analysis.

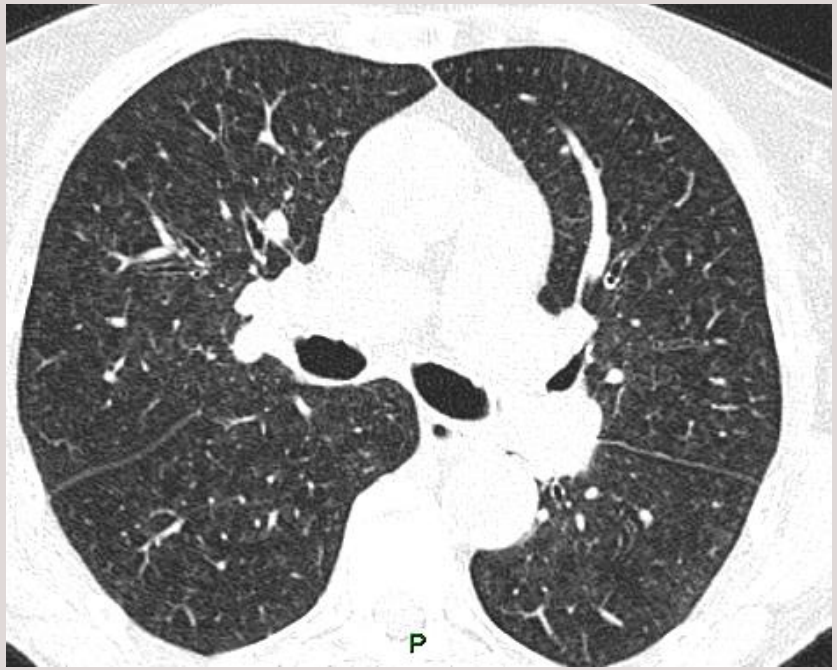
**Key words:** systemic sclerosis, pulmonary arterial hypertension, computed tomography, systemic sclerosis-pulmonary arterial hypertension, pulmonary veno-occlusive disease

**Fig. 1** Effect of number of CT features of pulmonary veno-occlusive disease on survival

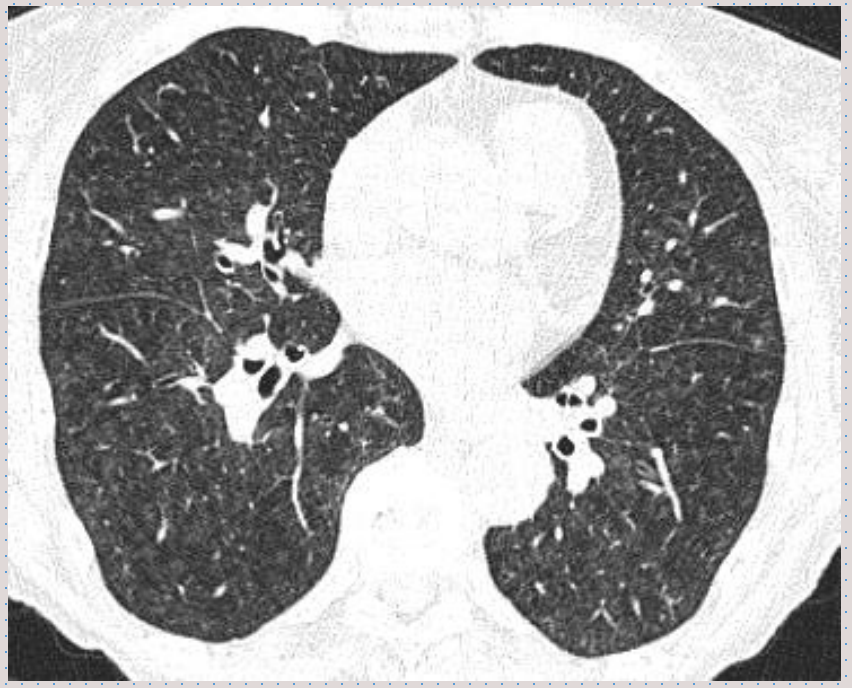


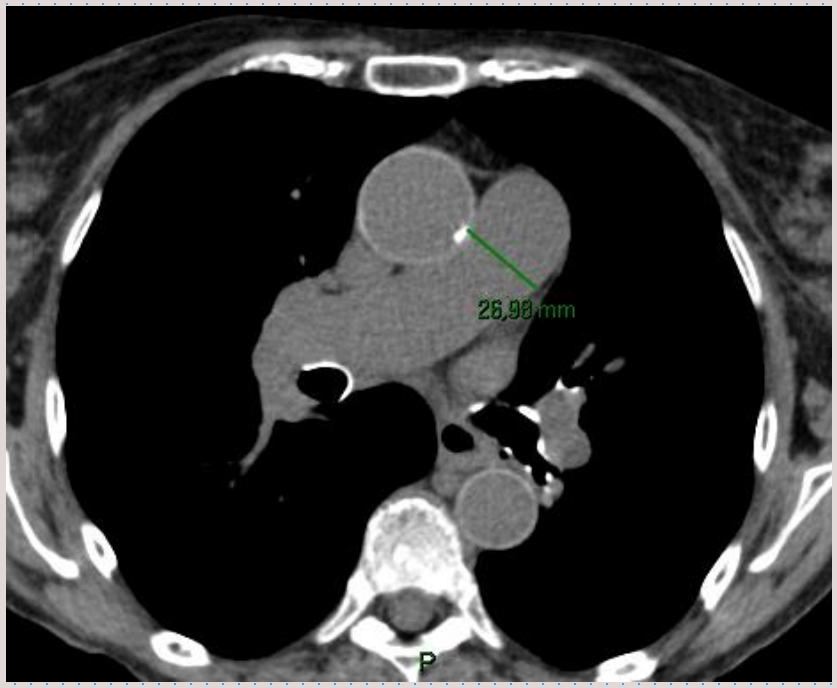

CTS, CT signs; PAH: pulmonary arterial hypertension.




SSc-PAH

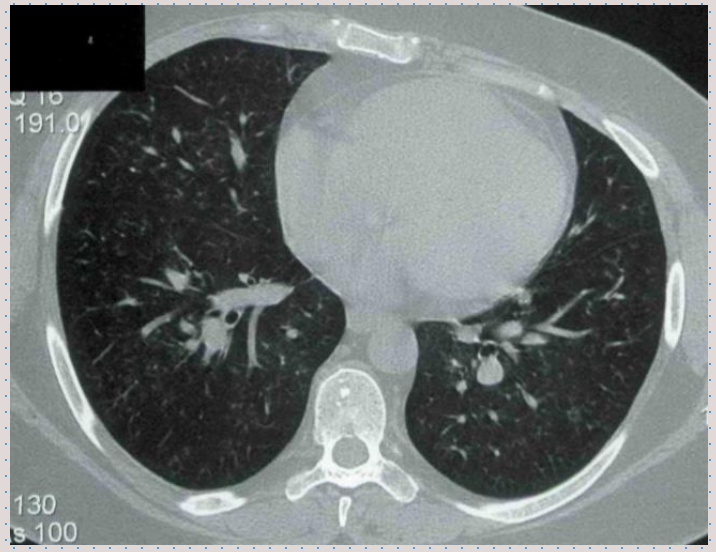


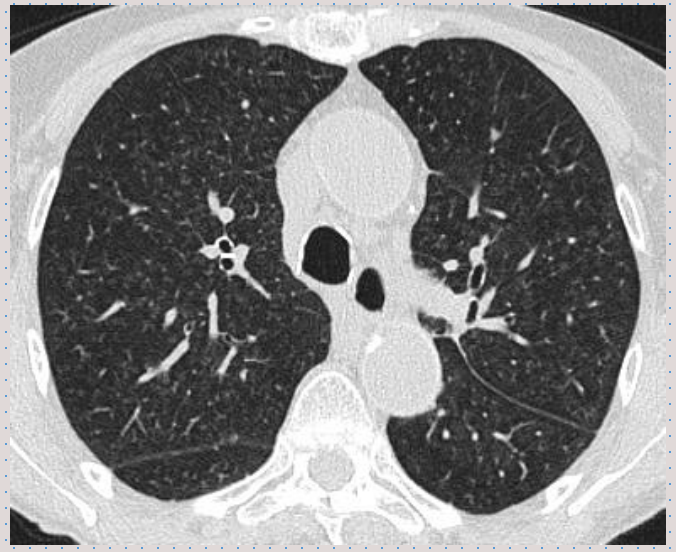


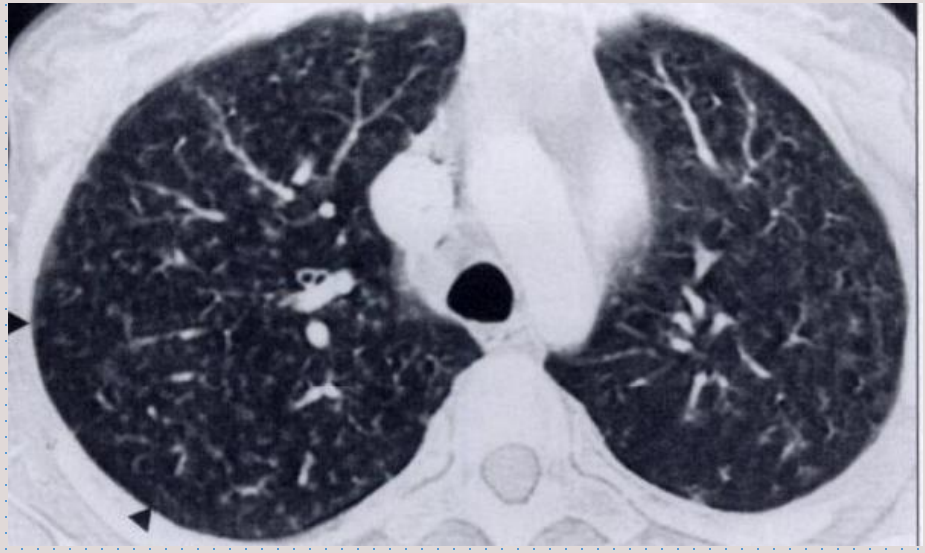
Drug Induced PAH

SSc-PAH

IPAH





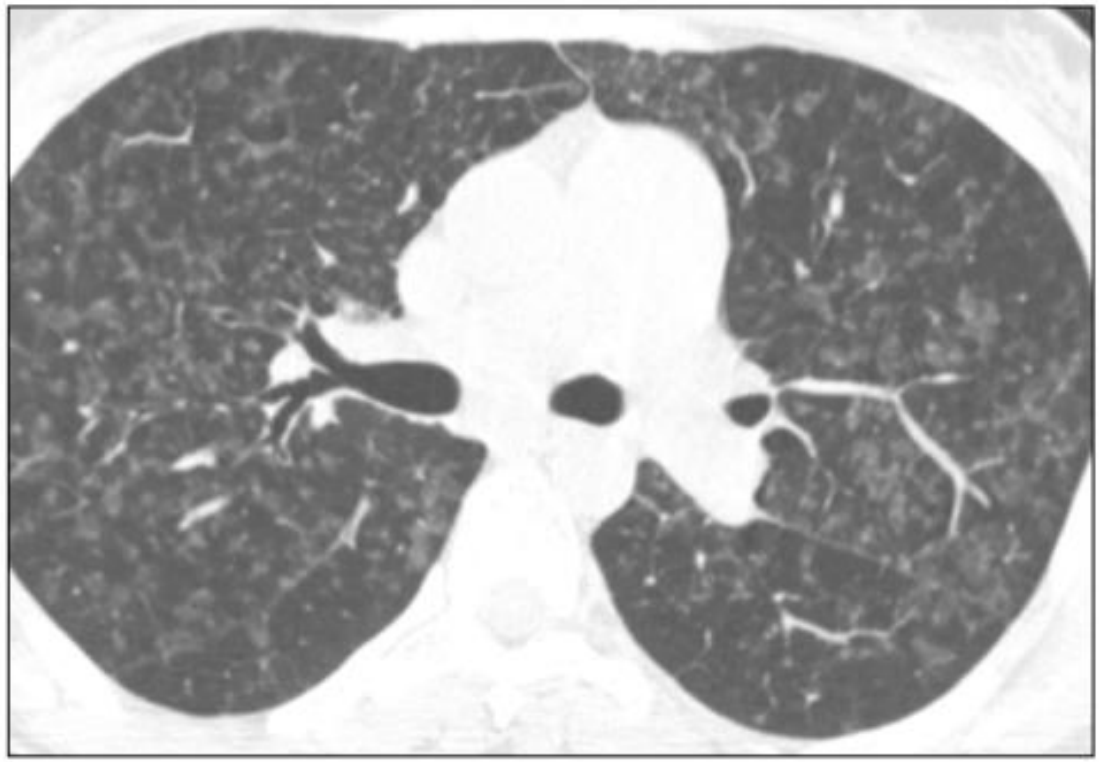


Crit Rev Comput Tomogr. 2004)

*AJR 1999:172:1317-1319*

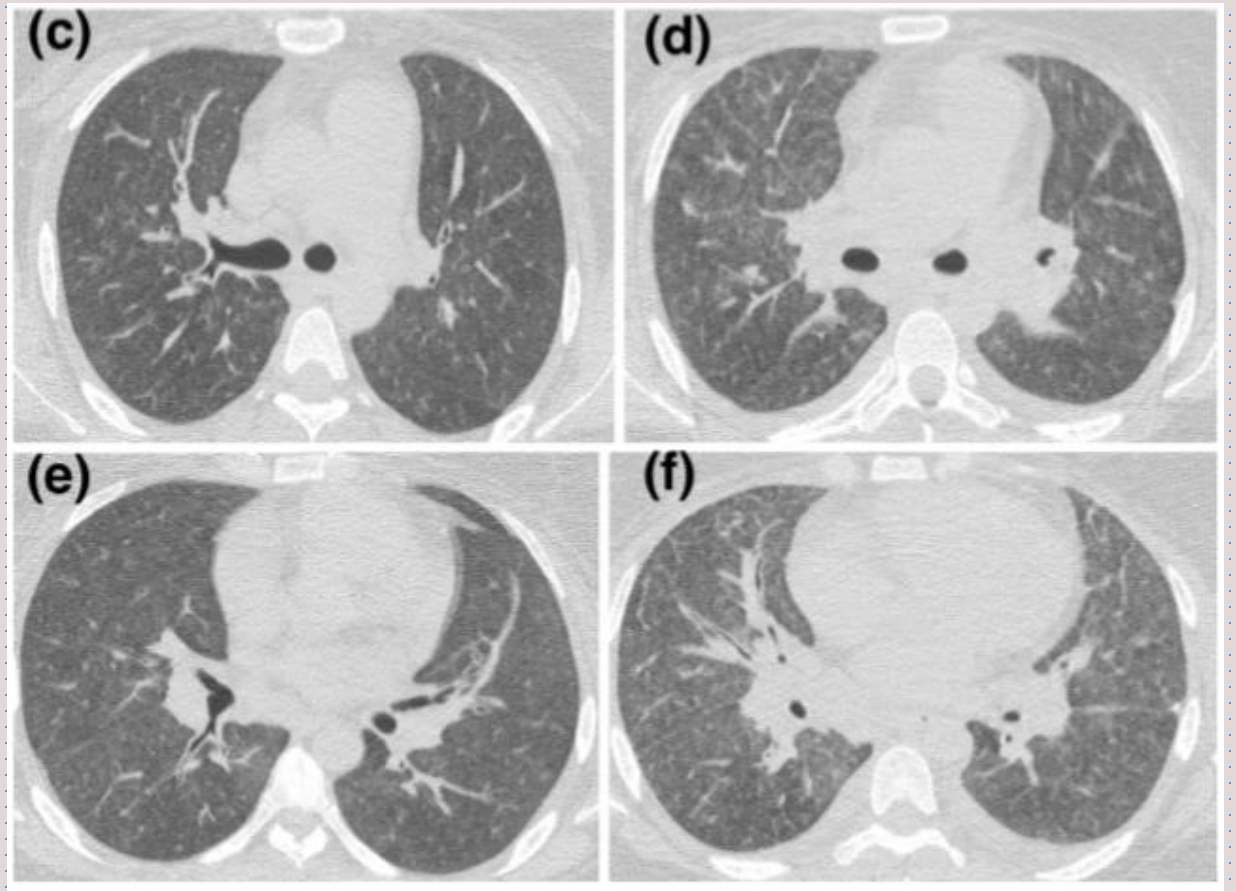
Circulation November 1, 2005)

CT of Pulmonary Venoocclusive Disease

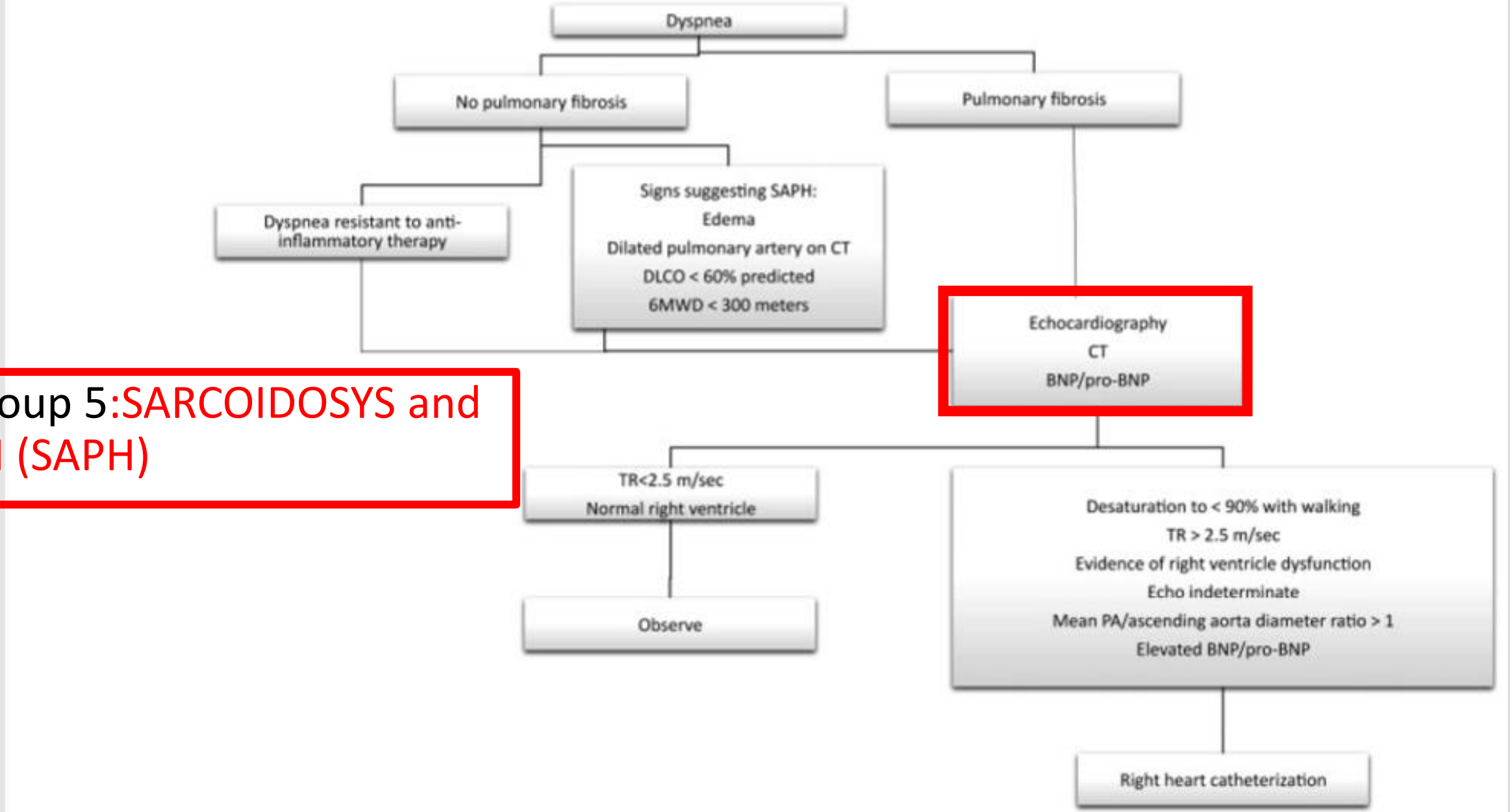


AJR:183, July 2004

Pulmonary Veno-occlusive Disease: A Surgical Lung Biopsy-proven and Autopsied Case Radiologically Mimicking Hypersensitivity Pneumonitis at the Time of a Transbronchial Lung Biopsy




Intern Med 58: 955-964, 2019




Group 5:SARCOIDOSYS and PH (SAPH)

Seminars in Respiratory and Critical Care Medicine Vol. 38 No. 4/2017

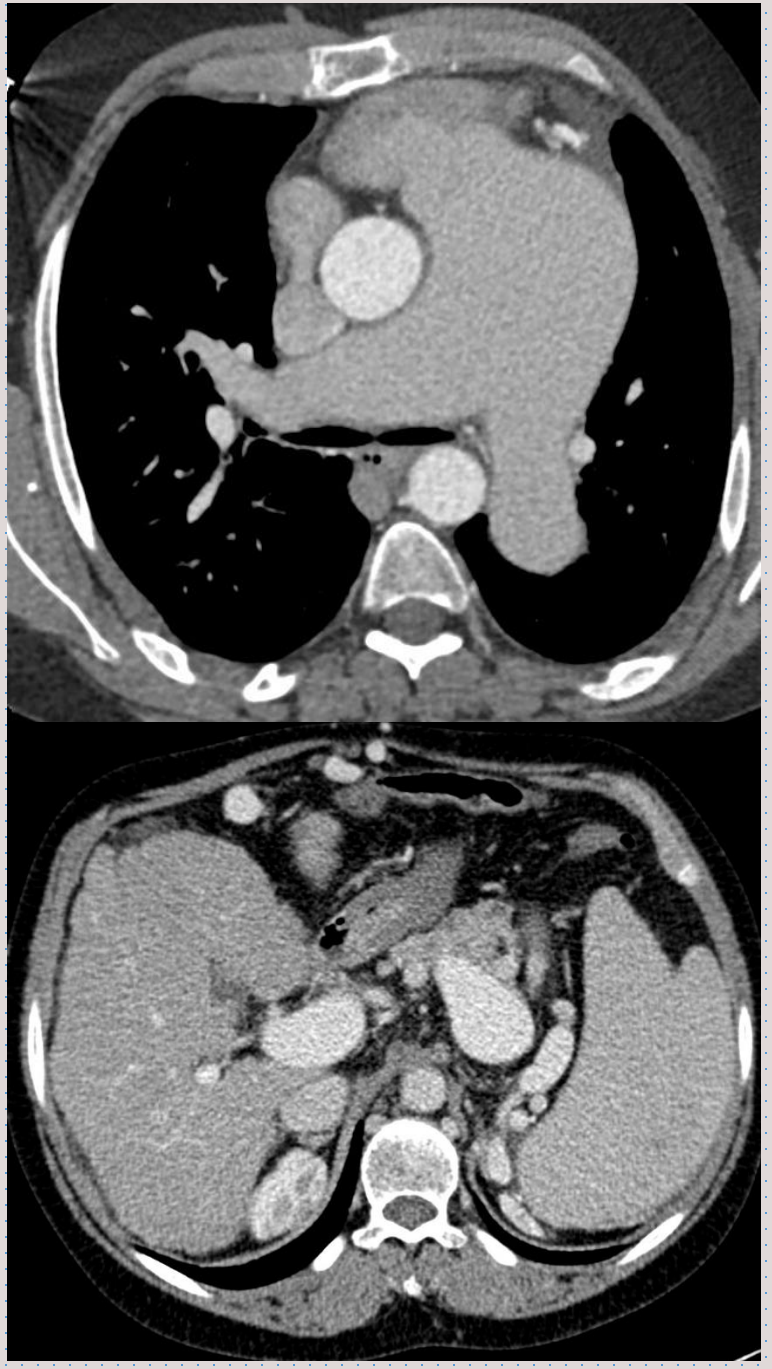
# PoPH: Portal Hypertension

- mPAP ≥ 25 mmHg
- PAWP ≤ 15 mmHg
- PVR > 240 dyne o > 3 Wood units

In presence of portal hypertension confirmed by HPVG > 5 mmHg

Or suggested by the presence of:

- Splenomegaly
- Oesophageal varices
- Thrombocytopenia
- Clinical signs of portosystemic shunt



# Group 5: Tumoral pulmonary hypertension

Eur Respir Rev 2019; 28: 180065 Laura C. Price[1], Michael J. Seckl[2], Peter Dorfmüller[3,4] and S. John Wort[1]

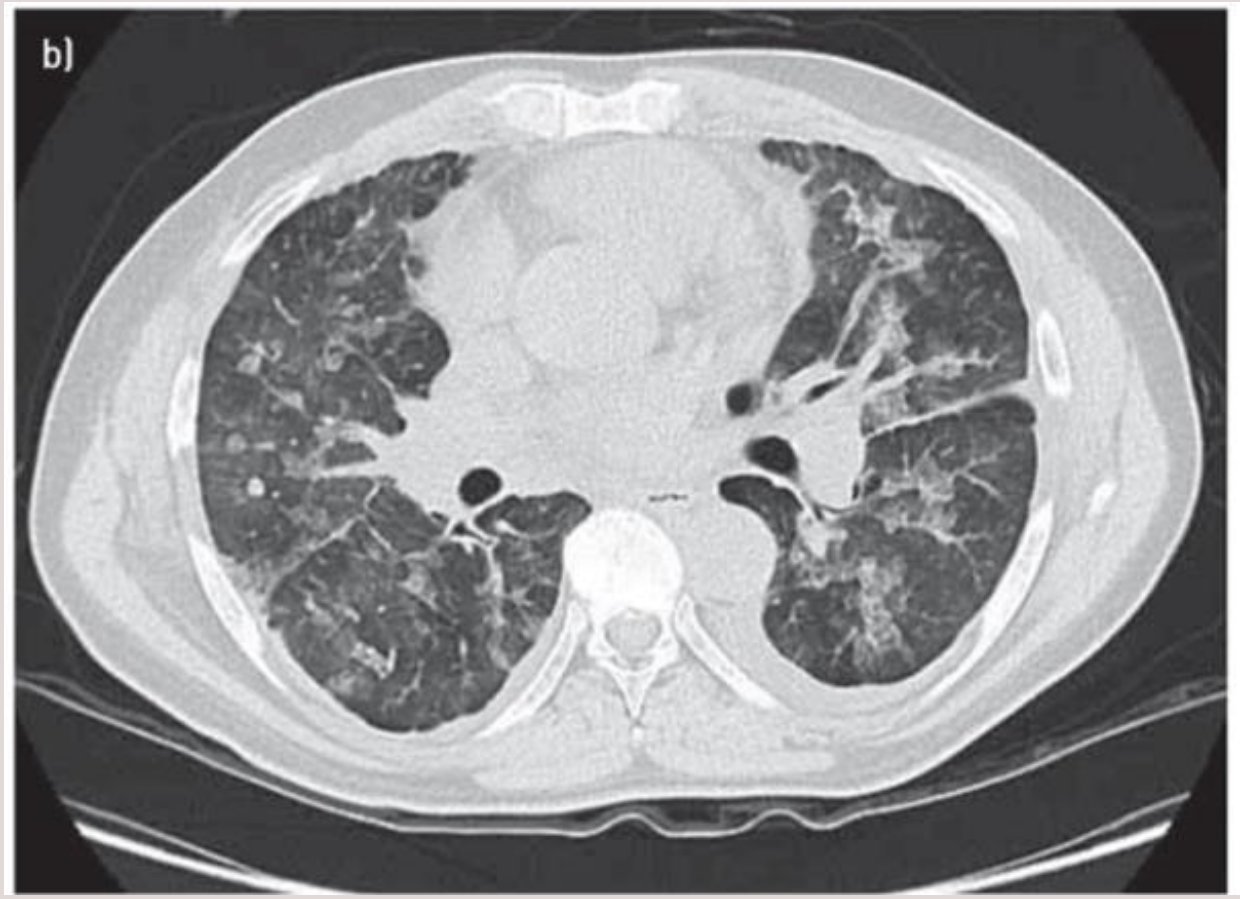
Tumoral pulmonary hypertension (PH) comprises a variety of subtypes in patients with a current or previous malignancy:

- Pulmonary tumour **"microvascular disease"** includes:
  - pulmonary tumour microembolism (PTE)
  - pulmonary tumour thrombotic microangiopathy (PTTM).
- The complications of cancer treatments including: **chemotherapy and radiotherapy** as contributors to PH are increasingly recognised, including cancer treatment-related pulmonary veno-occlusive disease (PVOD)

**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 thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

European Heart Journal (2016) 37, 67–119
doi:10.1093/eurheartj/ehv31



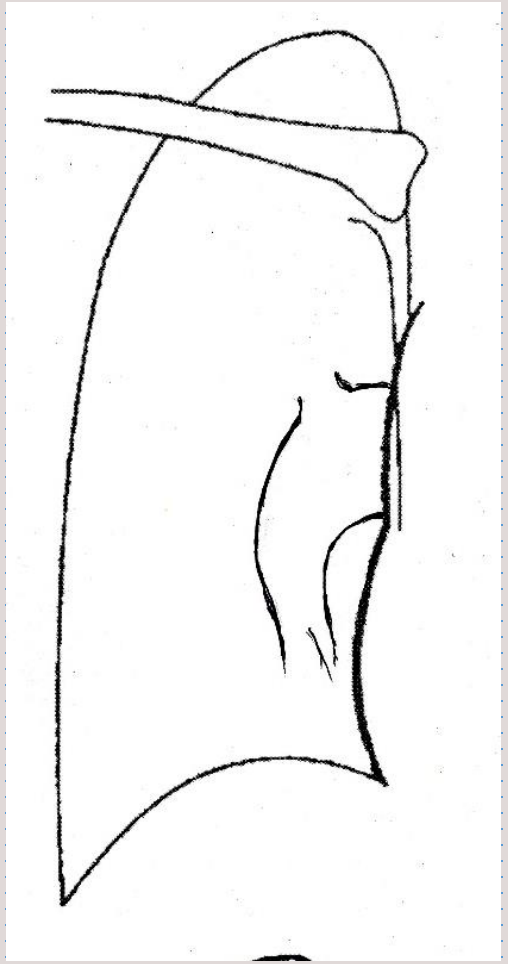

Eur Respir Rev 2019; 28: 180065

**PTTM and HRCT**: CT signs of PH and parenchymal abnormalities:

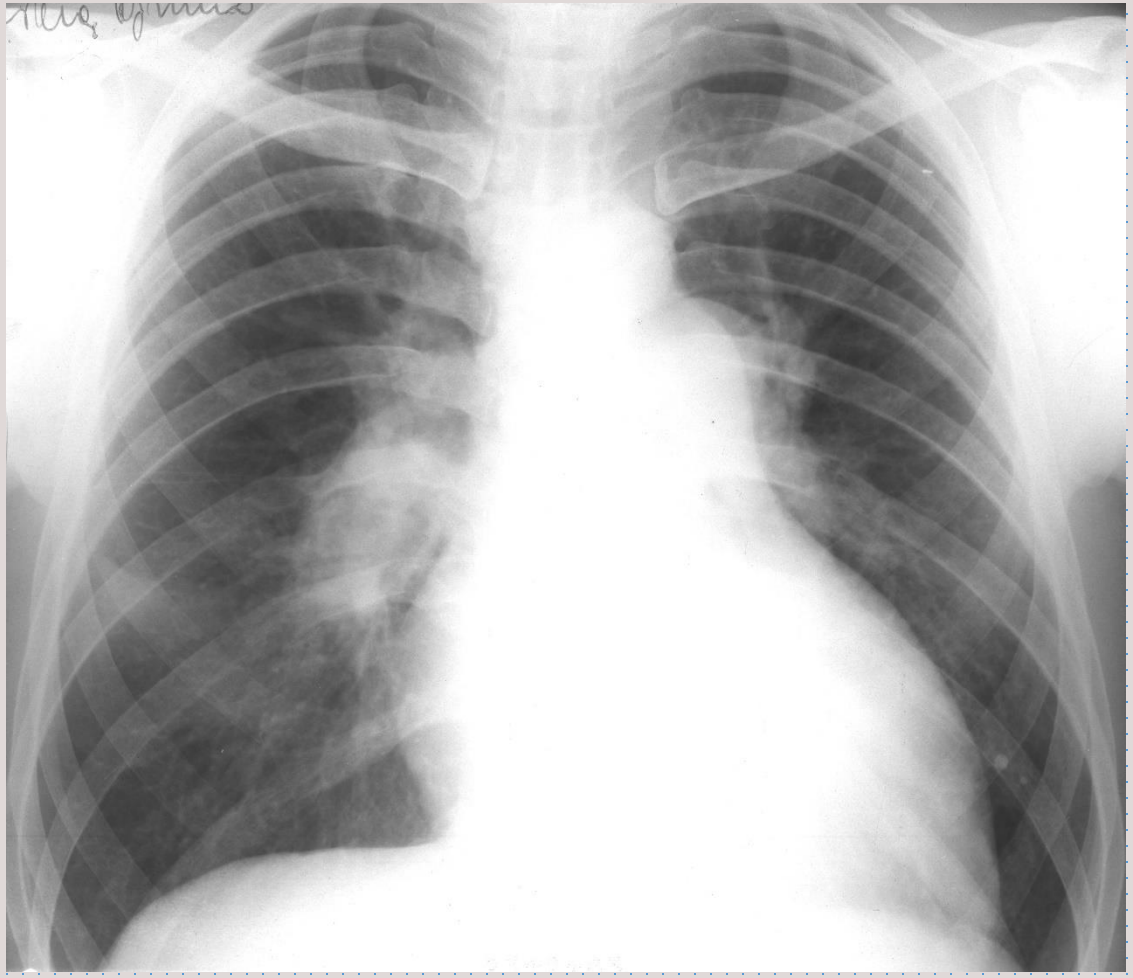
- **Centrilobular nodularity** (The nodularity is usually of an ultrafine granular appearance and is likely to represent the peripheral pulmonary arterial lesions-vascular tree in bud)
- **Ground-glass opacities** (often patchy or wedged shaped)
- **Interlobular septal thickening** (smooth and peripheral in distribution)
- Usually without pleural effusions
- Distinguishing PTTM from lymphangitis carcinomatosis may be difficult and of course these conditions may coexist, but **lymphangitic carcinomatosis does not usually cause significant PH in isolation**


GRAZIE PER L'ATTENZIONE
RADIOLOGIA

# CHEST XR: Chest radiographs are abnormal in 90% of patients with idiopathic pulmonary arterial hypertension (PAH) at the time of diagnosis

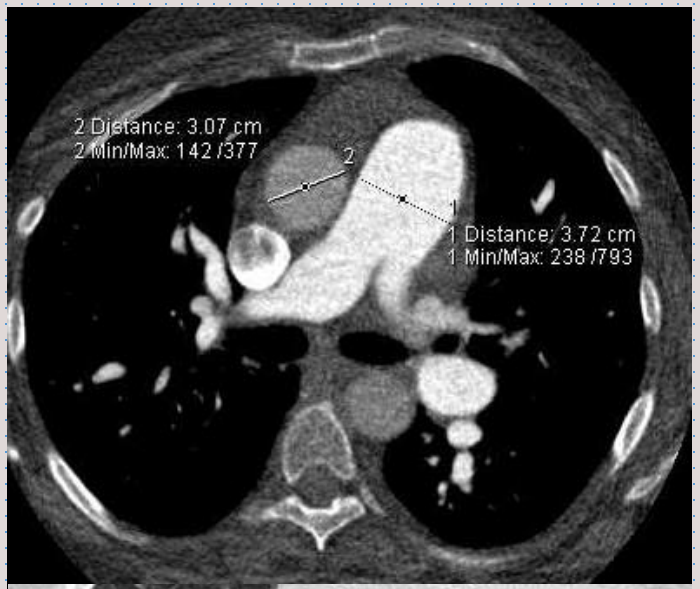


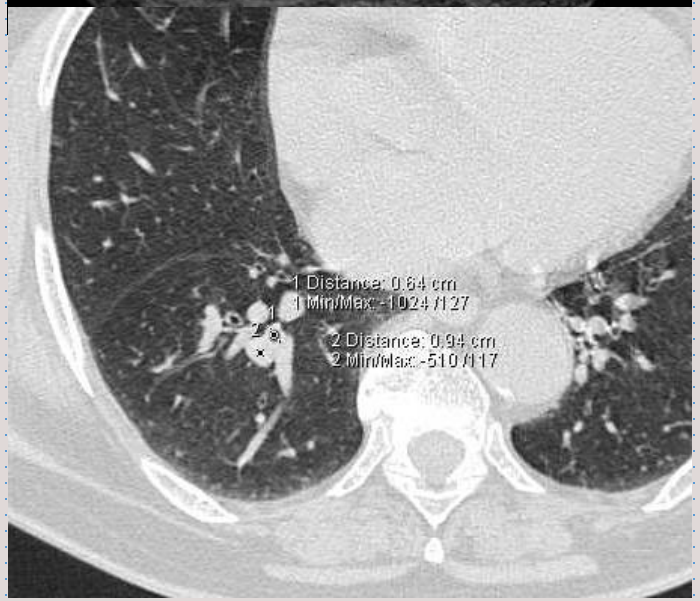
- central pulmonary arteries are classically enlarged
- rapid tapering of peripheral pulmonary vasculature (pruning)
- right-sided cardiac enlargement

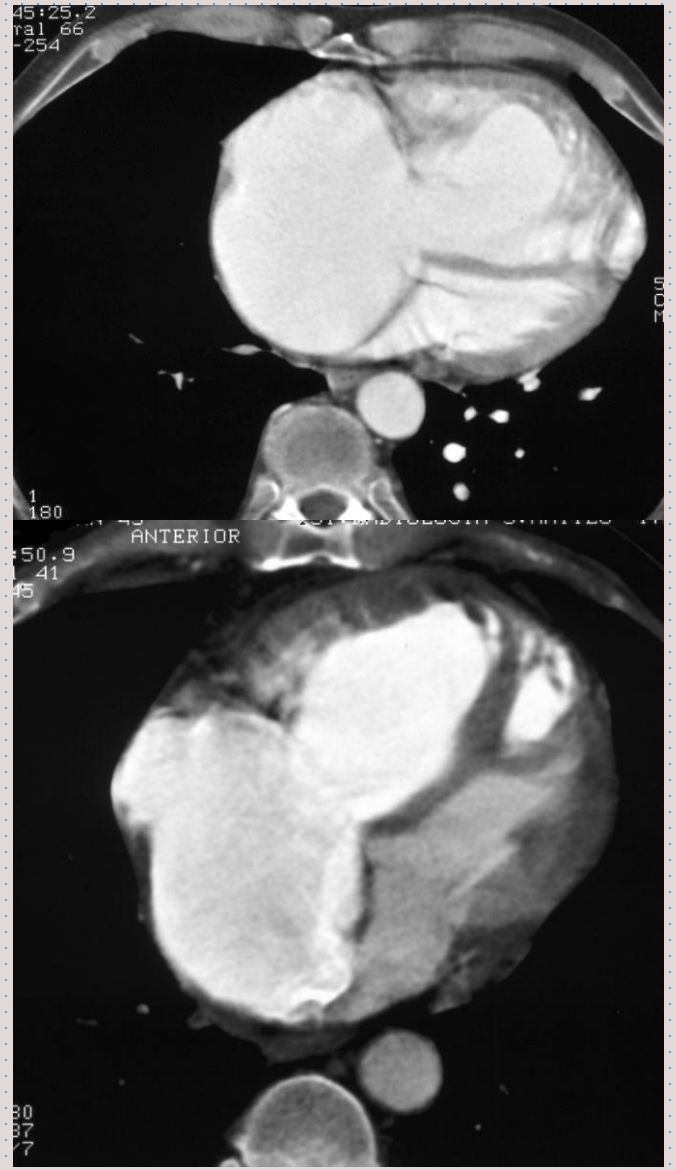


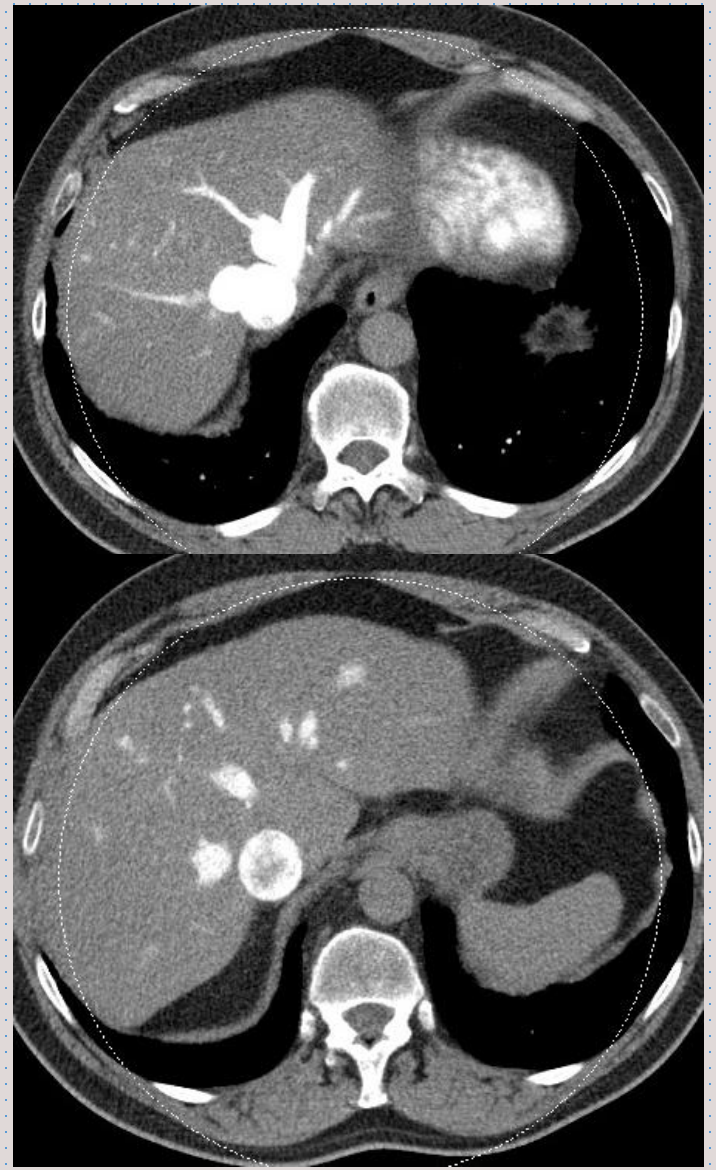
RadioGraphics 2018; 38:357–373

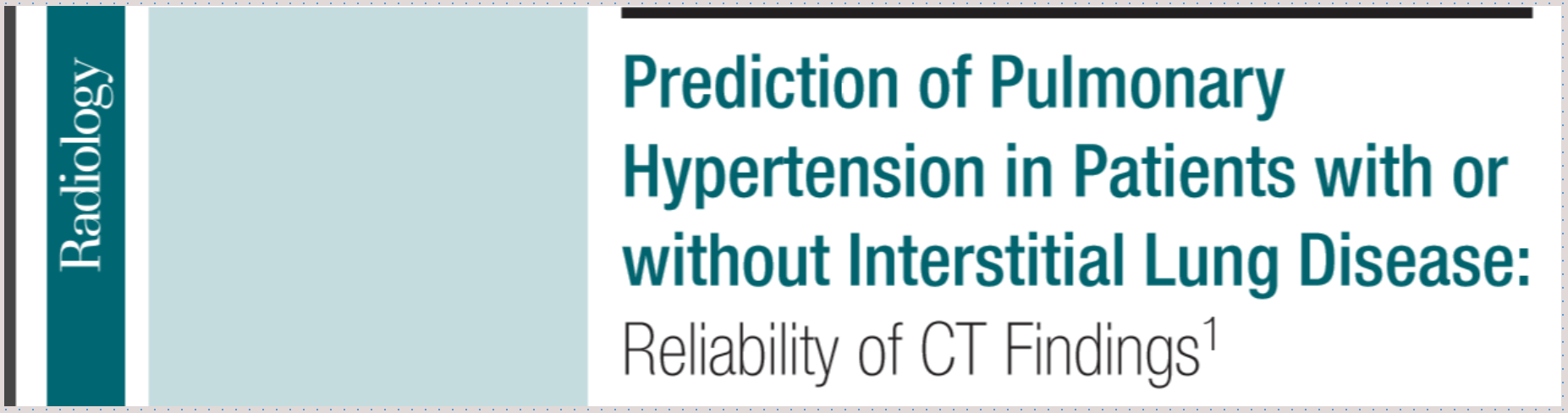
# Ct Features Of Pulmonary Hypertension






PAD, PAD/AAD ratio, RPAD, and LPAD measurements based on CT data are of limited utility for the prediction of PH in patients with ILD compared with those without ILD

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*Chest*. 2007 September ; 132(3): 773–779.

**High-Resolution Chest Computed Tomography Findings Do Not Predict The Presence of Pulmonary Hypertension in Advanced Idiopathic Pulmonary Fibrosis**

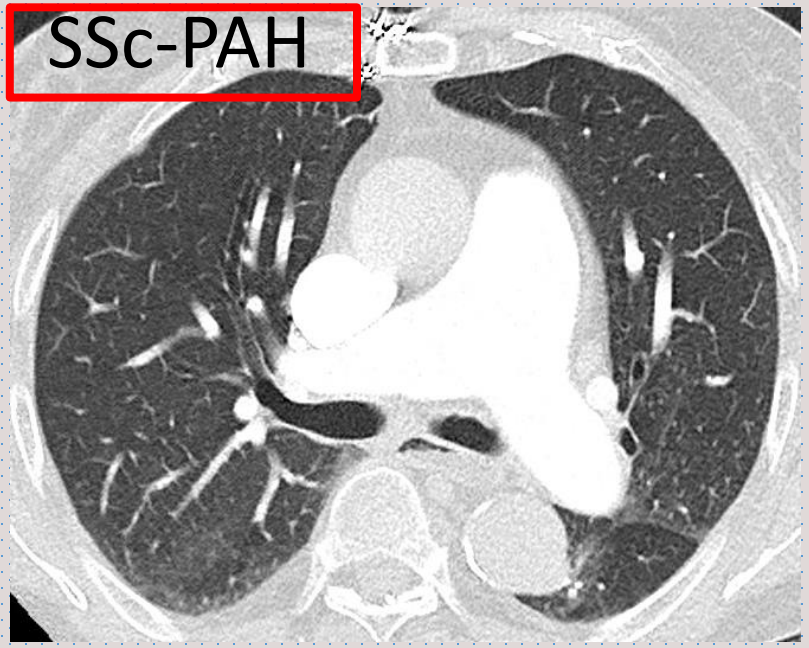
CT-derived measures of parenchymal disease and MPAD **cannot be used to screen for PH in advanced IPF patients**

Monitoring of pathological conditions that can frequently complicate with the development of Pulmonary Hypertension

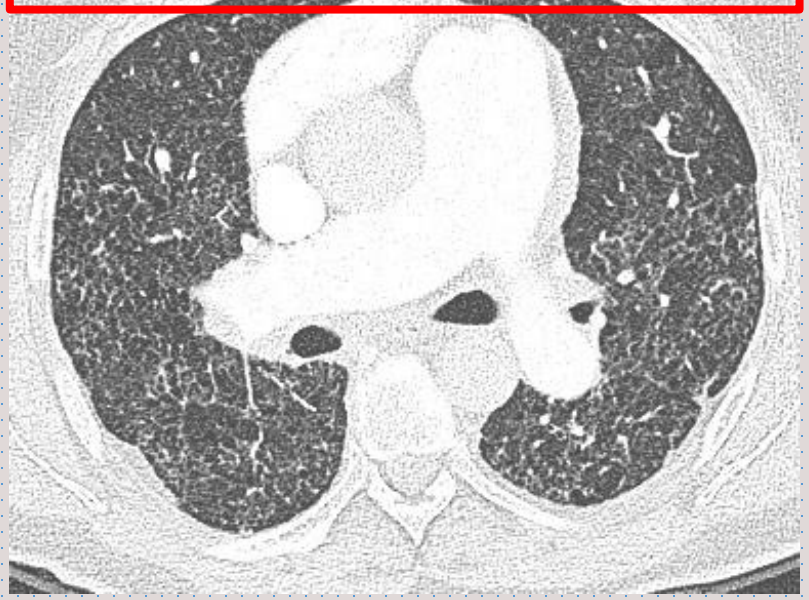
Characteristic morphologic features of Chronic Pulmonary Hypertension

Initial diagnostic workup of patients with Pulmonary Hypertension of unclear cause

SSc-PAH



Pulmonary Histiocytosis



# TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

**1 PAH**
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

**2 PH due to left heart disease**
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

**3 PH due to lung diseases and/or hypoxia**
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

**4 PH due to pulmonary artery obstructions (table 6)**
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

**5 PH with unclear and/or multifactorial mechanisms (table 7)**
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

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