Pulmonary veno-occlusive disease

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CLASSIFICATION OF PH

ESC/ERS GUIDELINES 2015

EUROPEAN SOCIETY OF CARDIOLOGY

EUROPEAN RESPIRATORY SOCIETY

1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
1.2.1 BM
1.2.2 O
1.3 Drugs
1.4 Assoc
1.4.1 C
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1.4.3 Po
1.4.4 C
1.4.5 Sc

1'. Pulmona
haemangion

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- 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
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1''. Persistent pulmonary hypertension of the newborn

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2.1 Left ventricular systolic dysfunction
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2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
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3. Pulmonary hypertension due to lung diseases and/or hypoxia

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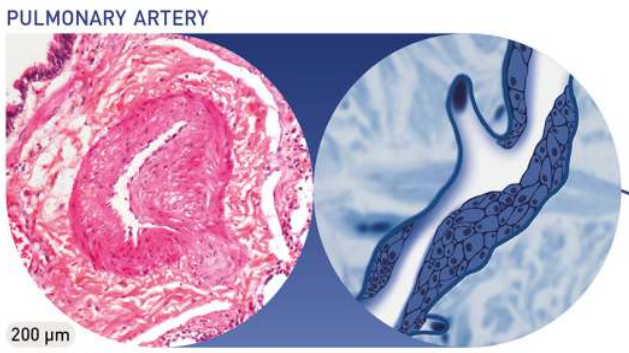
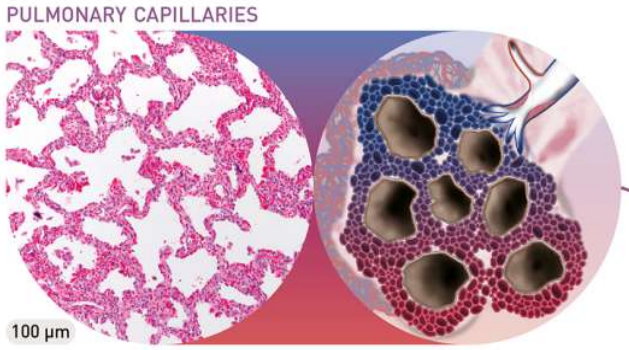
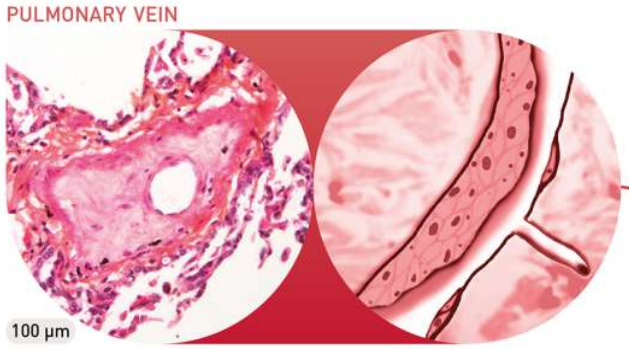
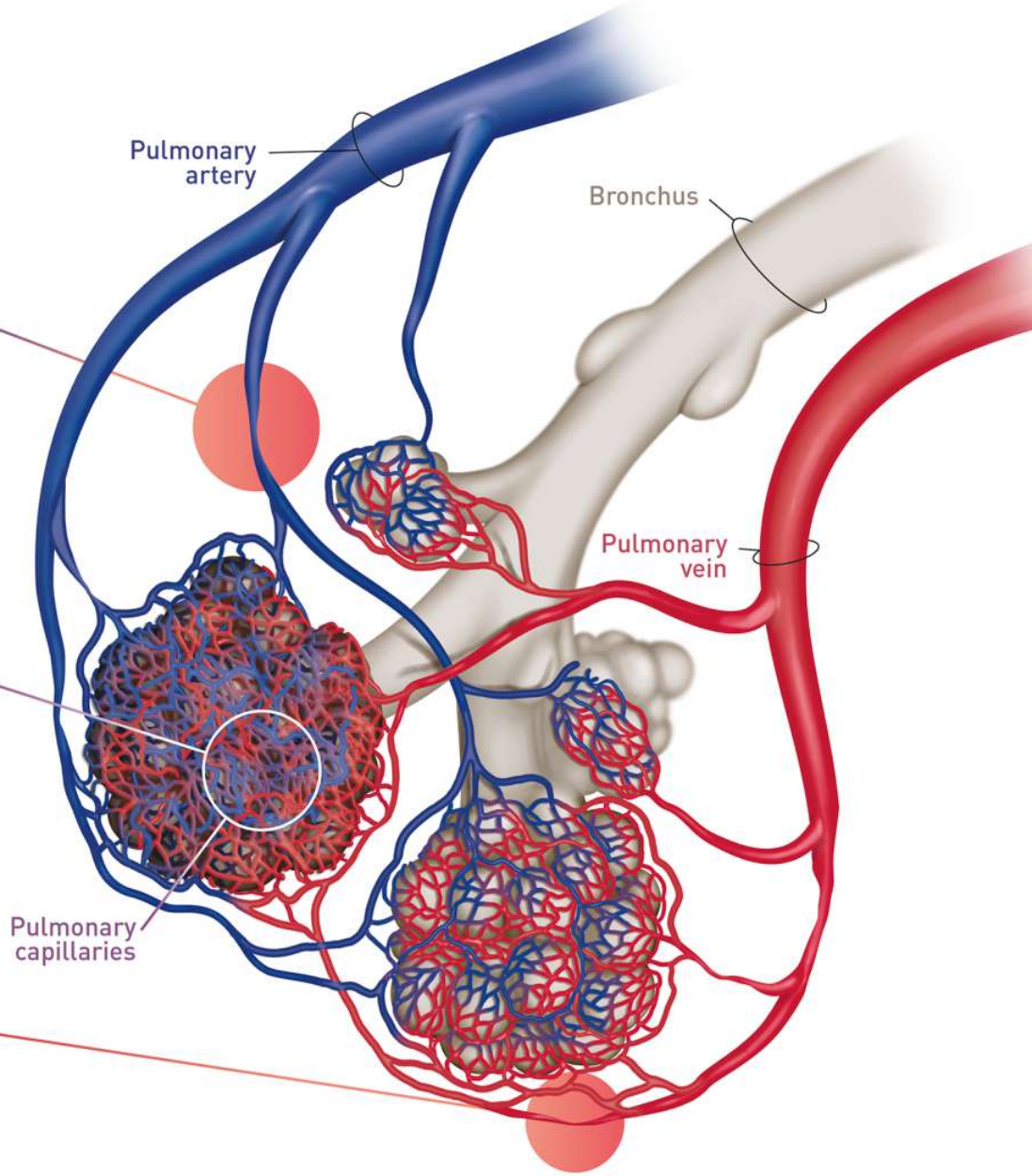
Eur Heart J 2015, Eur Respir J, 2015

Pathologic assesment









Montani D *et al. Eur Respir J* 2016

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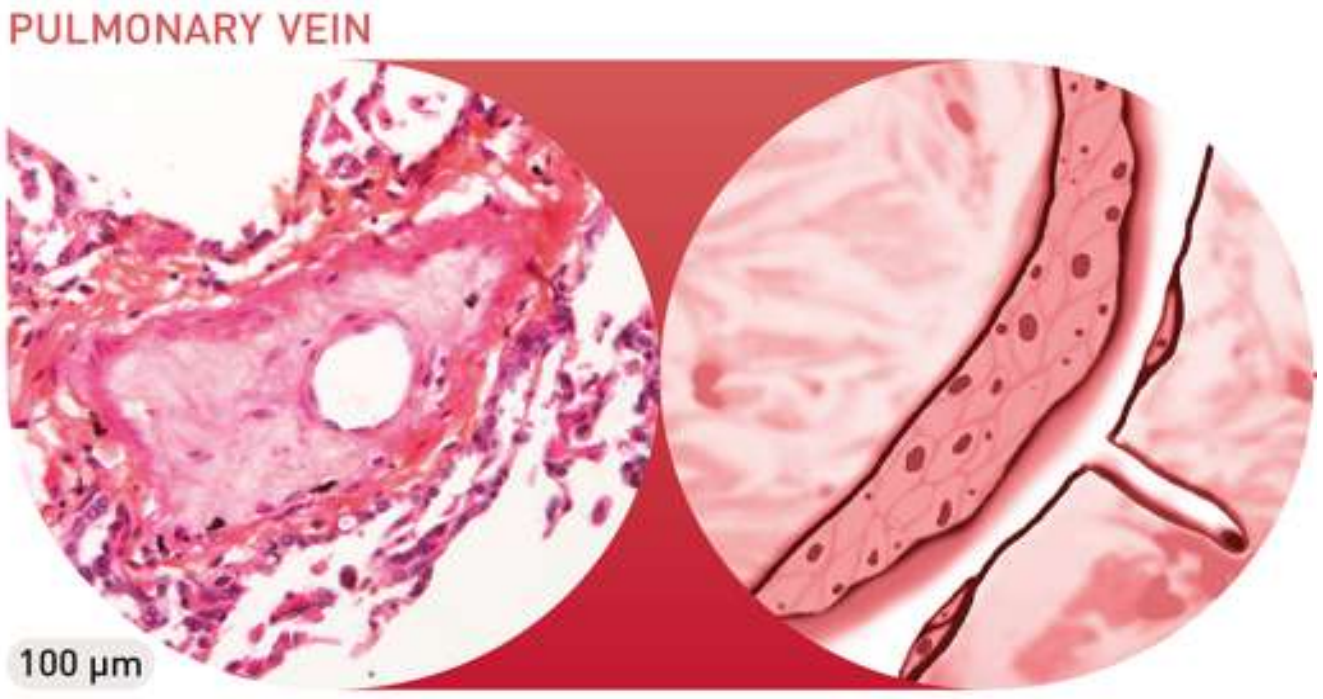

Occlusive intimal fibrosis of septal veins and small veins

Montani D *et al. Eur Respir J* 2016

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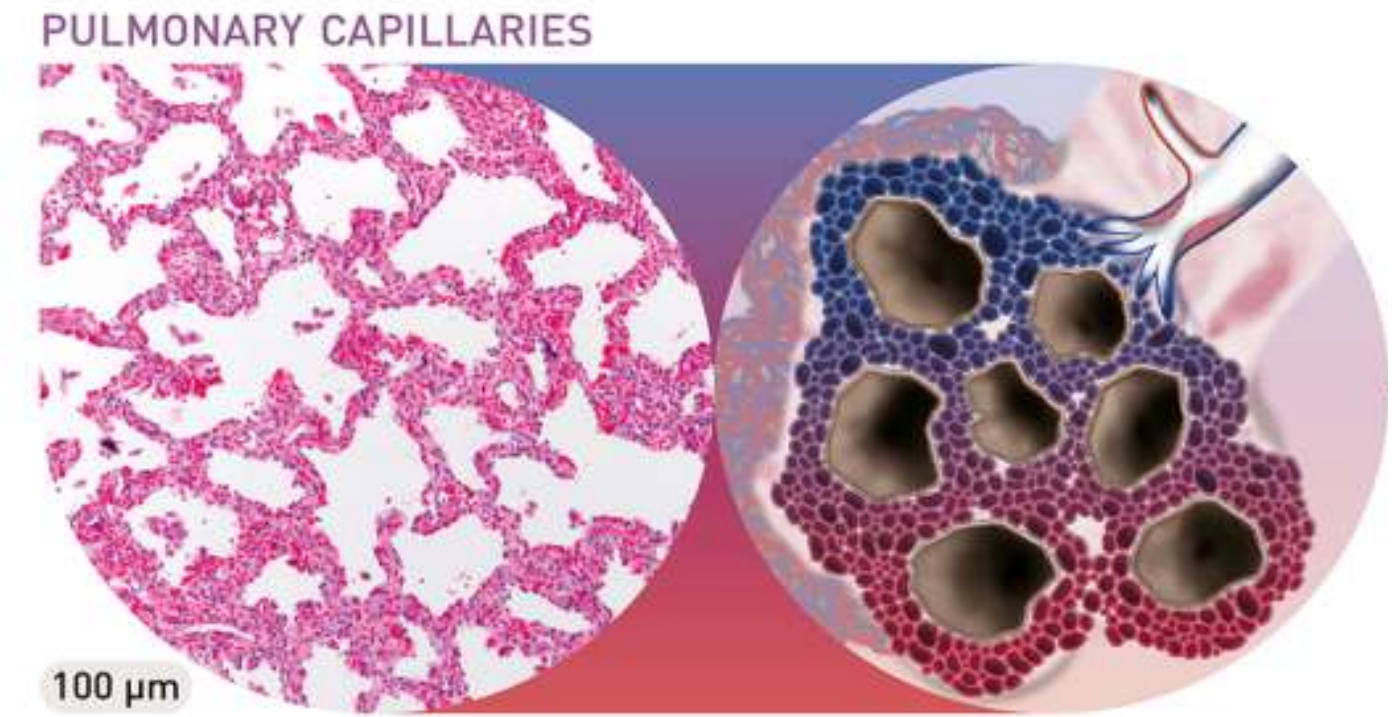

Patchy capillary proliferation

Montani D *et al. Eur Respir J* 2016

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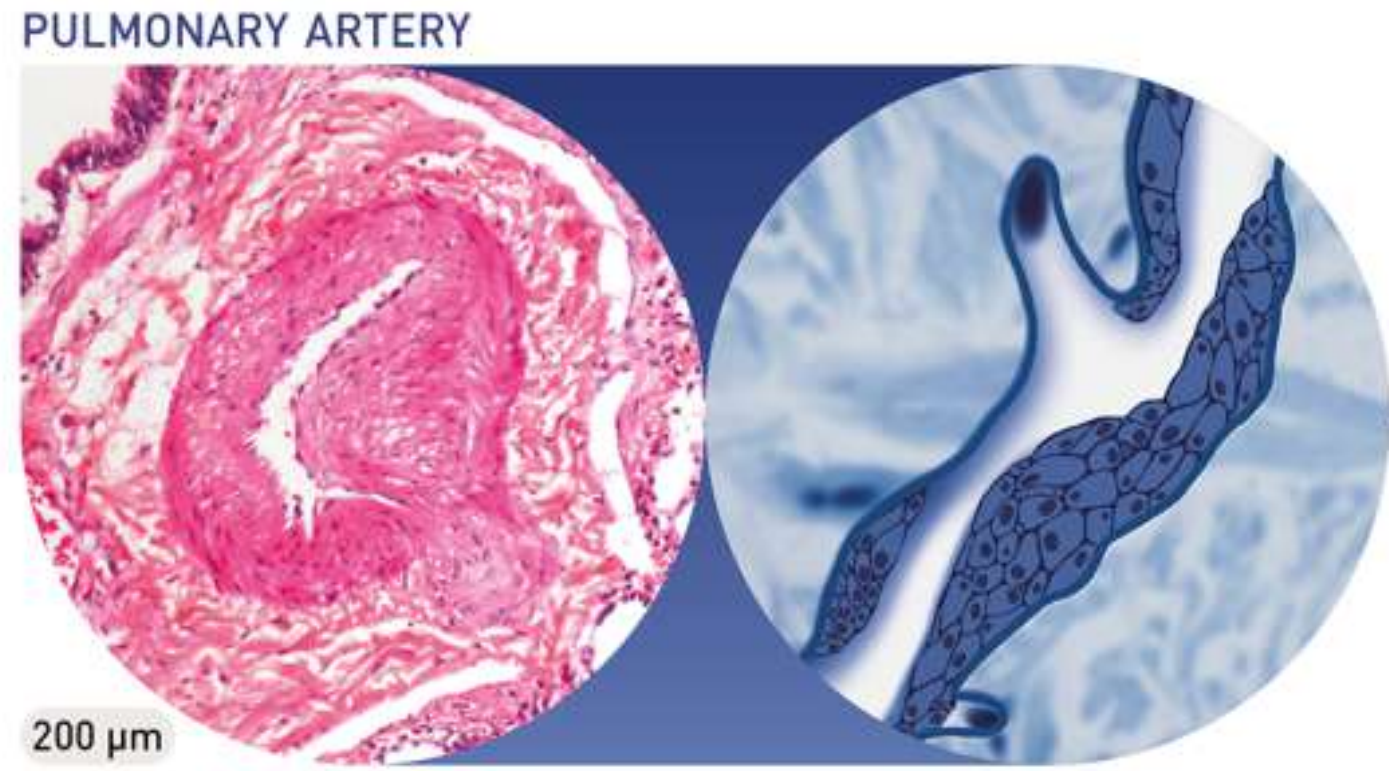

Arterial remodeling without any plexiform lesions

Montani D *et al. Eur Respir J* 2016

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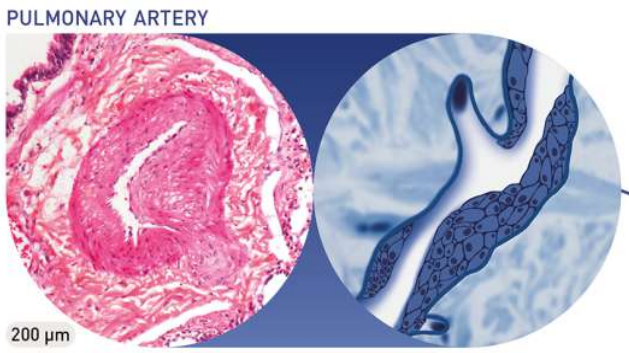
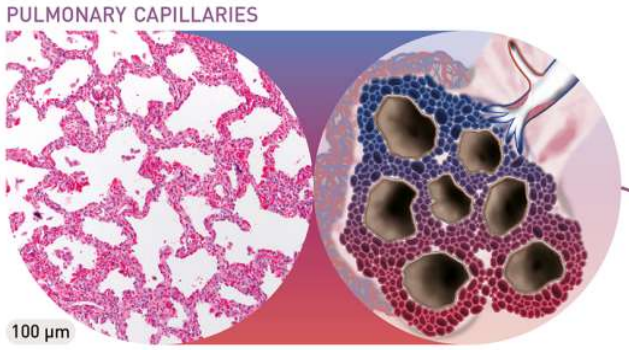
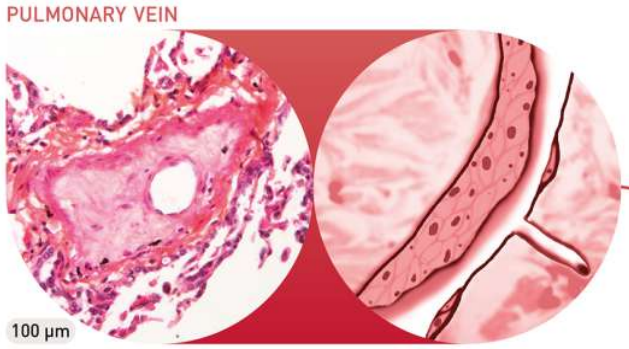
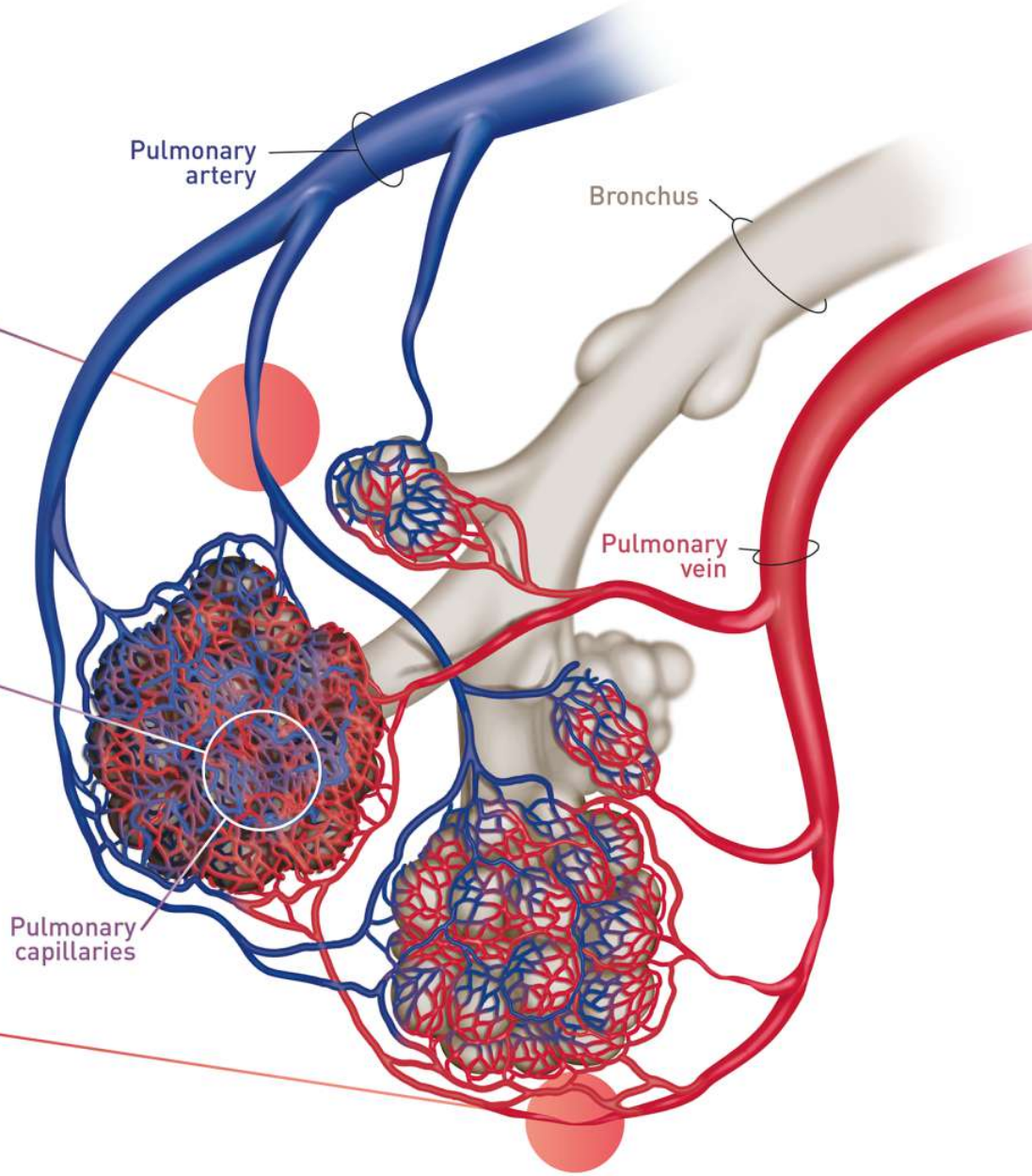


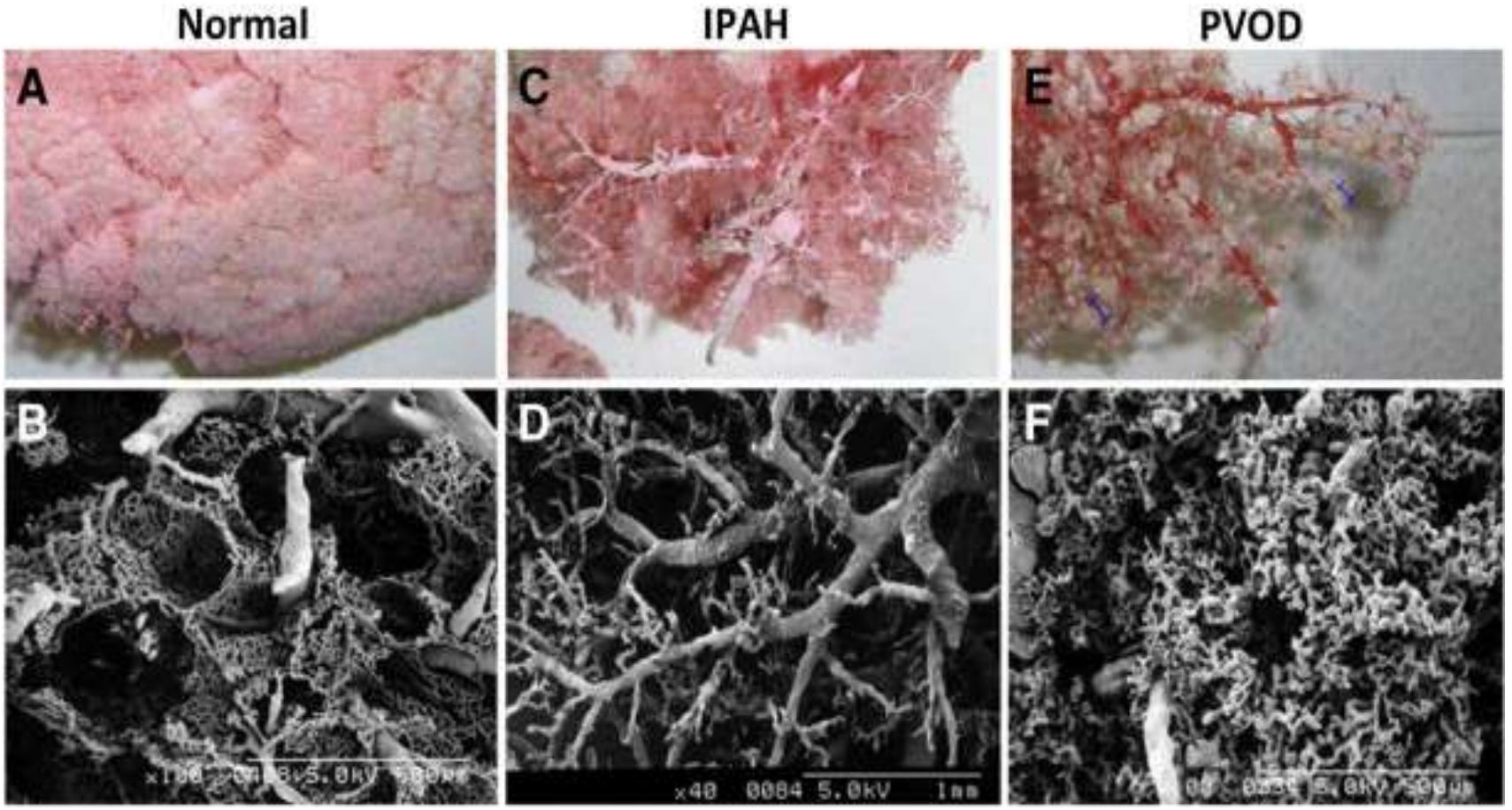




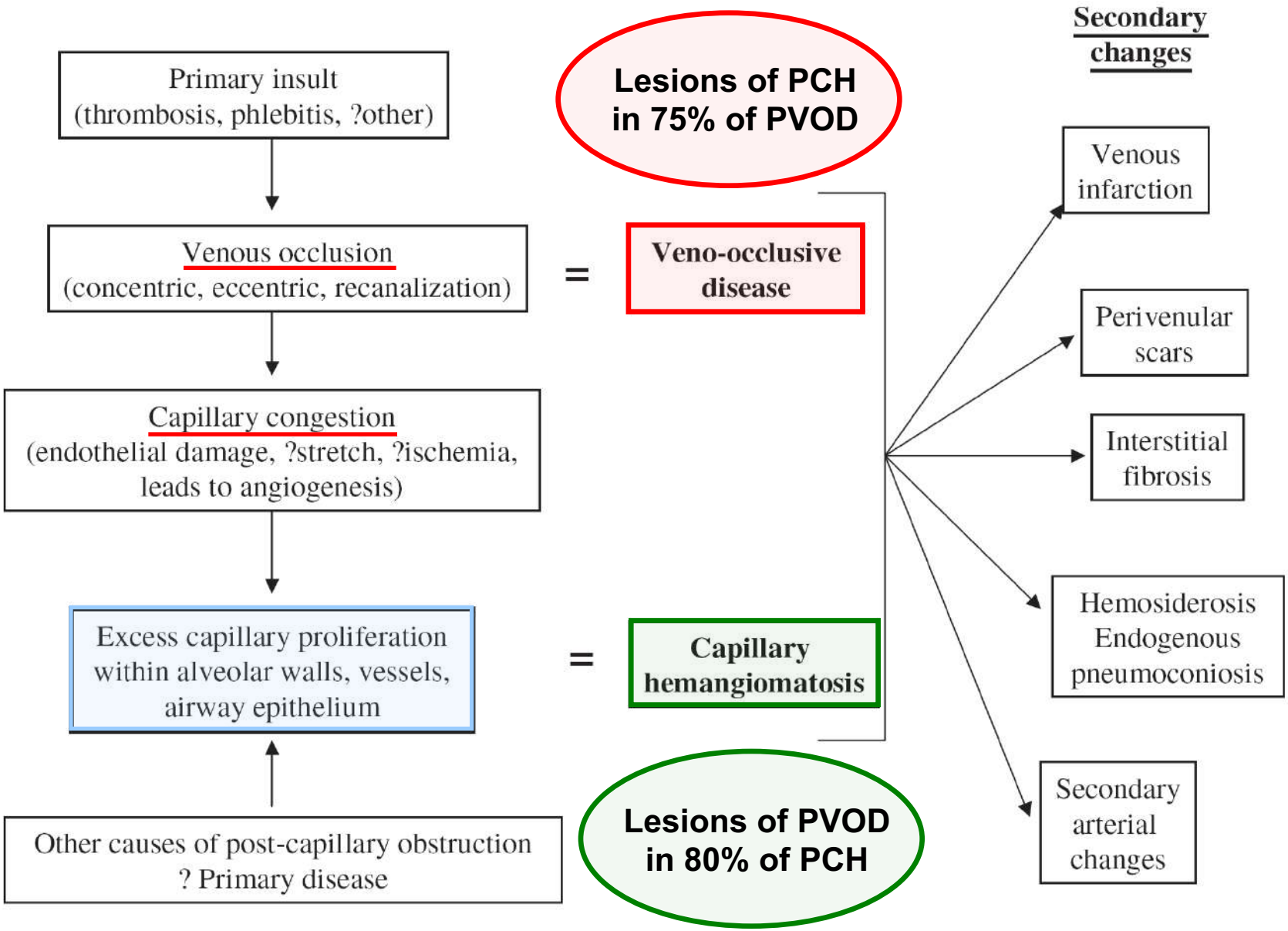


Montani D *et al. Eur Respir J* 2016

Electron Microscopy



PVOD and PCH: distinct entities ?



Lantuejoul, Am J Surg Pathol 2006

Epidemiology

EPIDEMIOLOGY

- Rare disease :
  - 5 to 10% of cases initially diagnosed as idiopathic PAH
  - Estimated incidence = 0.1 to 0.2 /million
- Underestimated incidence:
  - Histological proof rarely available
  - Difficult-to-diagnose subgoup of PAH
  - Venous involvement in PAH with associated conditions
- No female predominance : sex ratio 1/1 (≠ iPAH)
- Very wide range for age at diagnosis
  - From the first weeks of life to the 7th decade

Mandel J *et al*. Am J Respir Crit Care Med 2009
Montani D *et al*. Eur Respir J 2009

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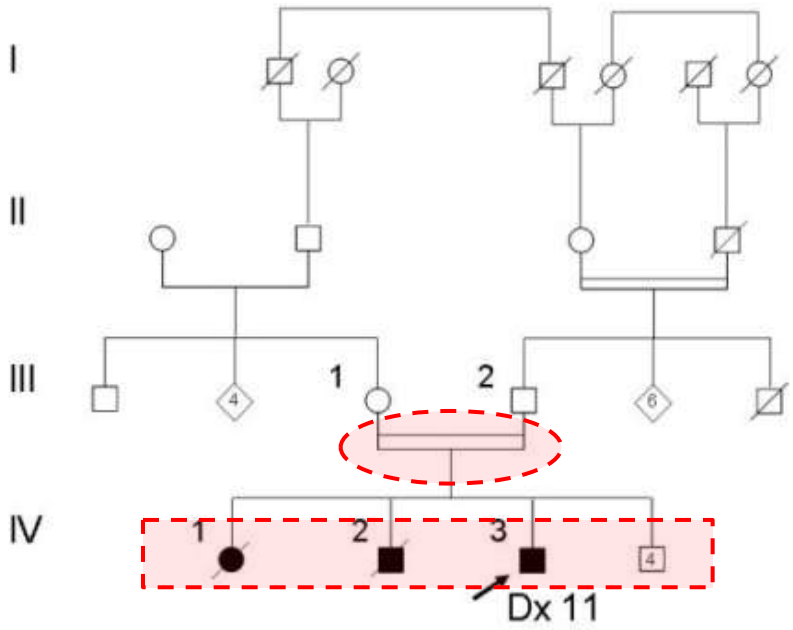
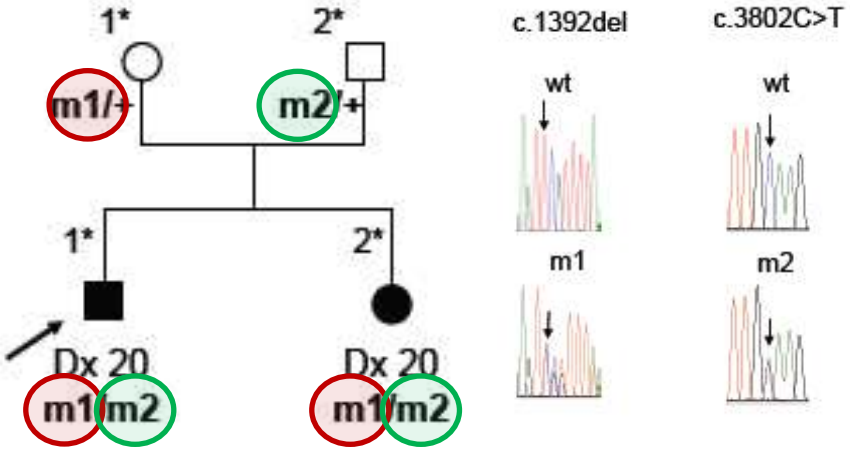
Eur Heart J 2015, Eur Respir J, 2015

PVOD or PCH family





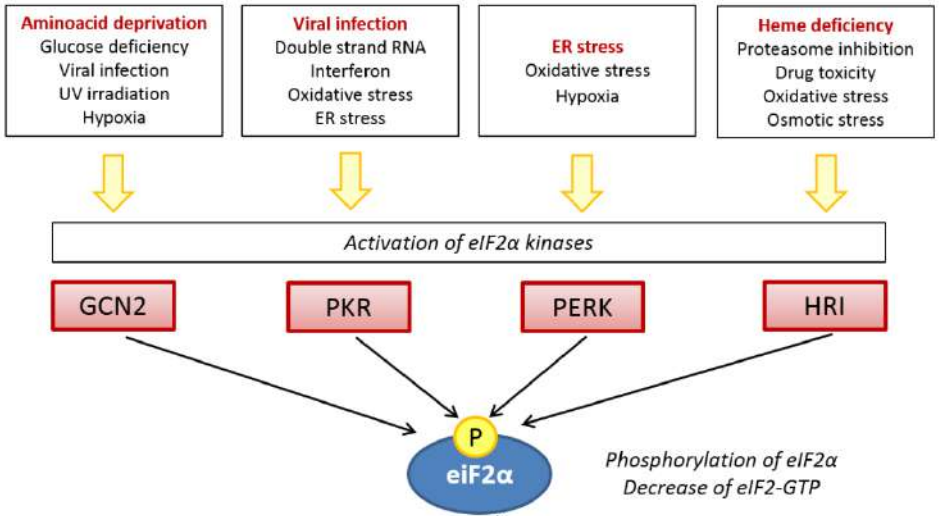
Autosomal recessive transmission

All heritable PVOD patients and 10-15% of sporadic form of PVOD had biallelic mutations in ***EIF2AK4* gene** (chr 15)

Eyries et al, *Nature Genetics* 2014

Role of GCN2

- *EIF2AK4* gene codes for **GCN2** (general control nonderepressible 2)
- GCN2 is a **serine-threonine kinase** that can induce changes in gene expression in response to aminoacid deprivation
- GCN2 belongs to a family of 4 kinases which phosphorylate eIF2α



Montani, *Eur Respir J* 2016

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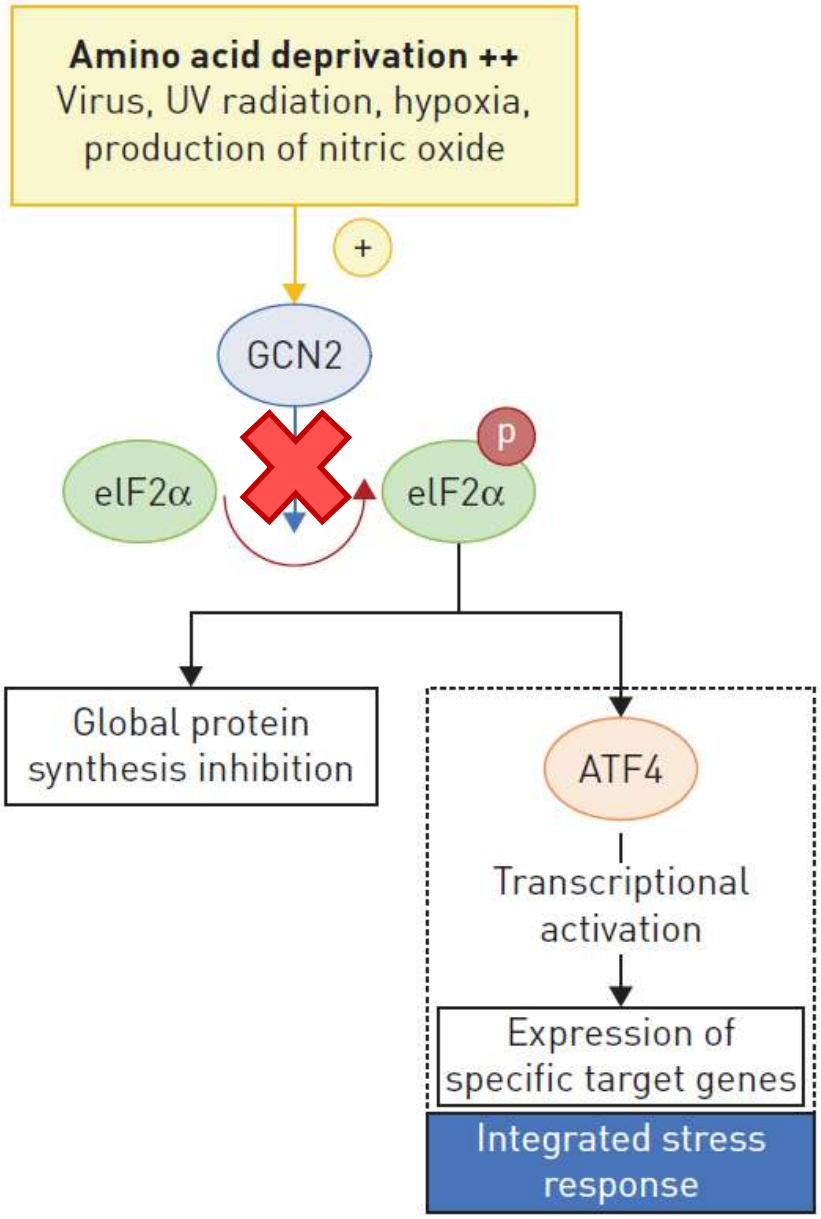
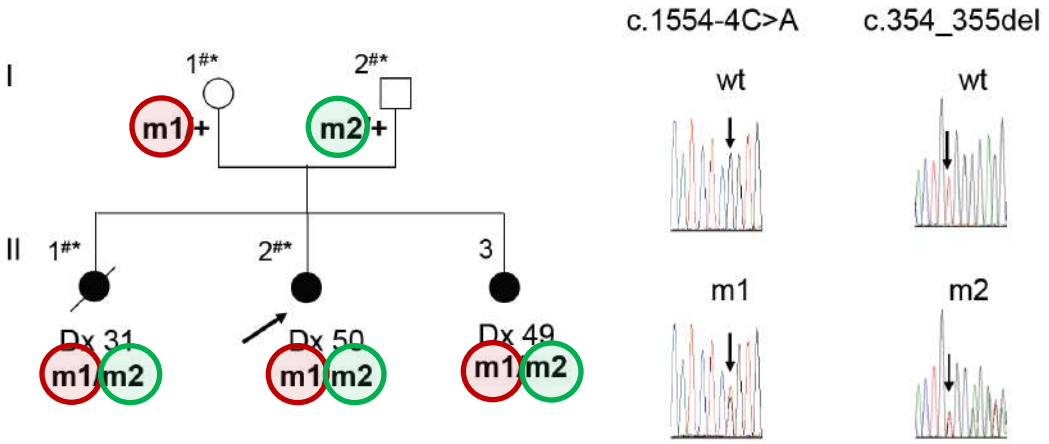
- eIF2α induce or inhibit the transcription of several target genes mediating **Integrated Stress Response (ISR)**

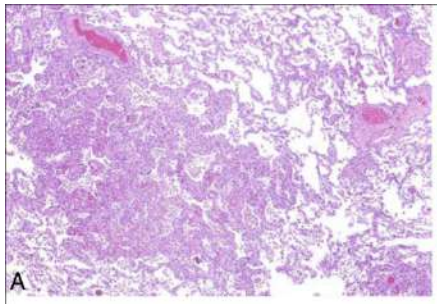


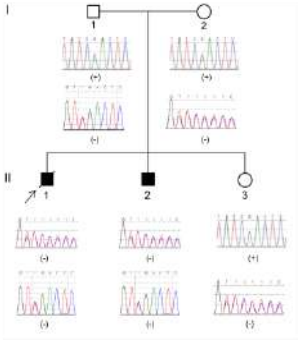
Montani, *Eur Respir J* 2016

- One family was diagnosed as having **pulmonary capillary hemangiomatosis**
  - Biallelic *EIF2AK4* mutations was found.



- Presence *EIF2AK4* mutations was confirmed in another series of PCH :
  - 1 PCH family
  - 2/10 sporadic PCH





Eyries et al, *Nature Genetics* 2014; Best et al, *Chest* 2014

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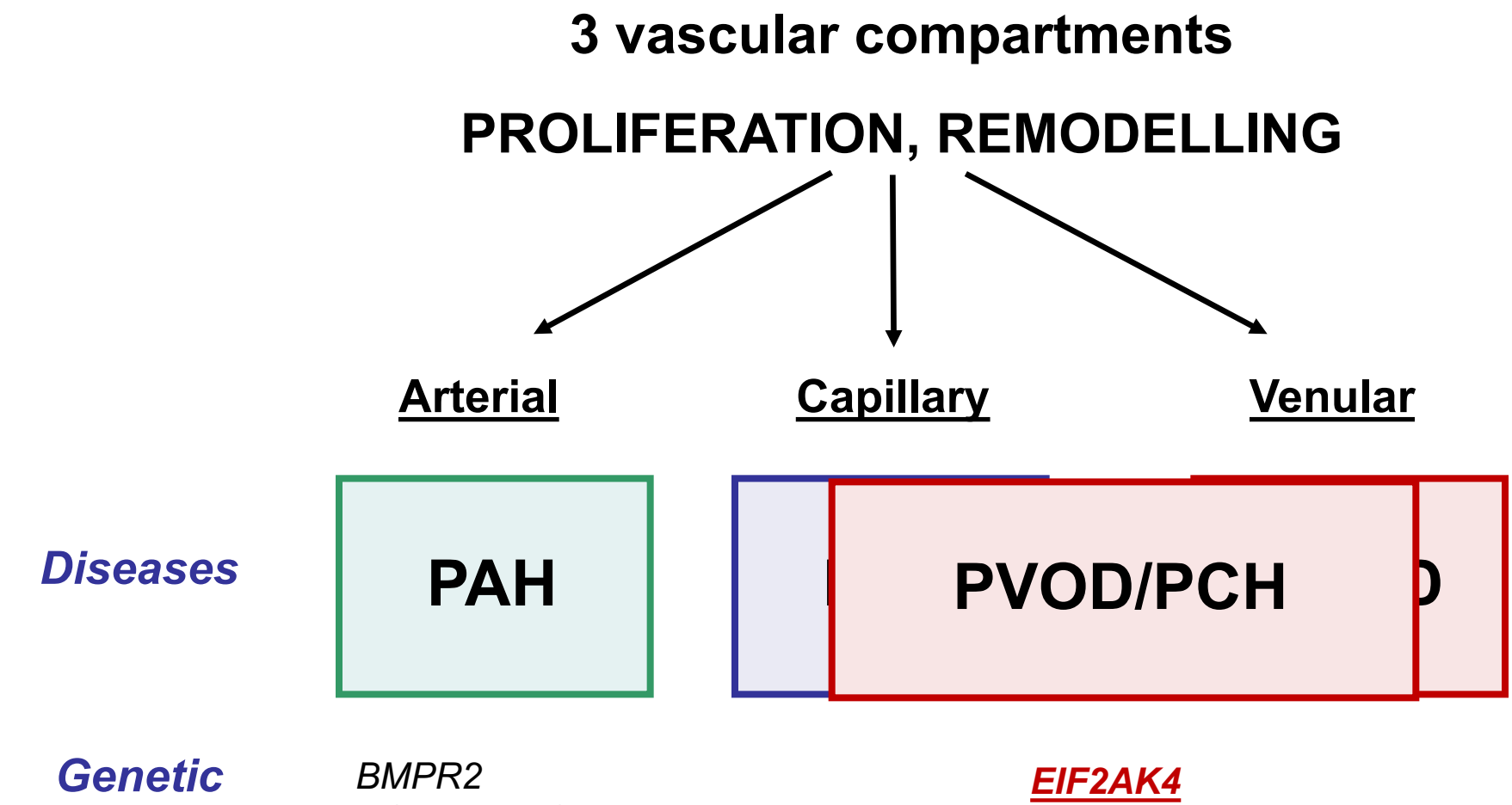

PVOD and PCH:
2 presentations of the same disease

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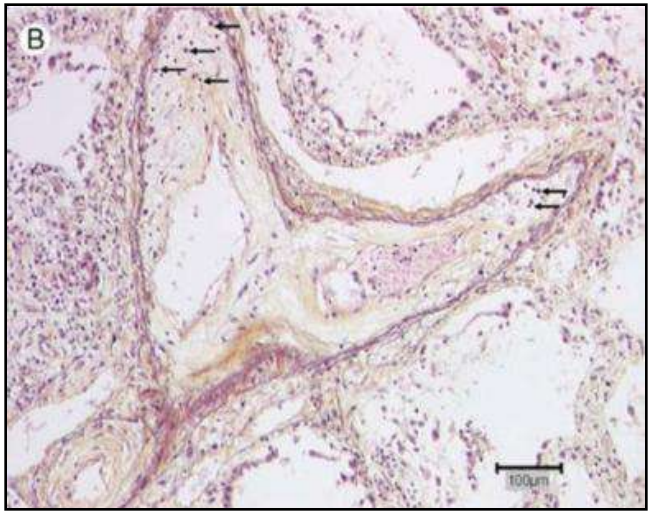
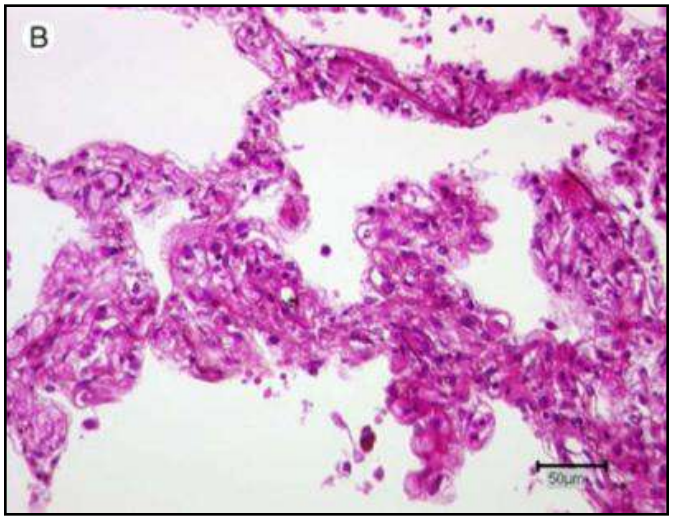
Eur Heart J 2015, Eur Respir J, 2015

« PVOD » with ASSOCIATED CONDITIONS

- Venous and capillary involvement are frequent in PAH associated with CTD:
  - **Systemic sclerosis ++**
  - Lupus
  - Mixed connective tissue disease



Venous involvement: 75%



Capillary proliferation: 63%

Dorfmüller *et al. Hum Pathol.* 2007.

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PVOD in SCLERODERMA

	SSc patients with precapillary PH with ≥2 signs of PVOD on HRCT (n = 16)	SSc patients with precapillary PH with ≤1 sign of PVOD on HRCT (n = 10)	*P*
NYHA functional class, no. (%)			0.013
II	0 (0)	4 (40)	
III	13 (81.3)	6 (60)	
IV	3 (18.7)	0 (0)	
Six-minute walk test, meters	294 ± 85	381 ± 70	0.013
Arterial blood gases, mm Hg			
Pa_{O_2}	62 ± 12	76 ± 16	0.016
Pa_{CO_2}	31 ± 4	32 ± 4	0.373
Pulmonary function testing, % predicted			
FEV_1	87 ± 23	95 ± 19	0.359
TLC	91 ± 19	98 ± 15	0.331
DLCO	34 ± 9	44 ± 11	0.019
Hemodynamic parameters			
Mean PAP, mm Hg	48 ± 10	37 ± 11	0.014
Right atrial pressure, mm Hg	7 ± 5	5 ± 4	0.372
PCWP, mm Hg	7 ± 3	8 ± 4	0.559
CI, liters/minute/m^2	2.8 ± 0.8	3.1 ± 0.7	0.256
CO, liters/minute	4.6 ± 1.3	5.5 ± 1.6	0.138
PVR, Wood Units	9.8 ± 4.2	5.9 ± 4.2	0.020
Sv_{O_2}, %	60 ± 11	66 ± 6	0.129
Pulmonary edema with PAH-specific therapy, no. (%)	8 (50)	0 (0)	<0.05

Gunther et al, *Arthr & Rheum* 2012

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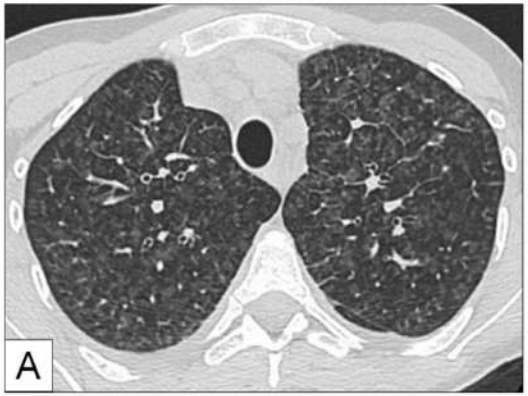
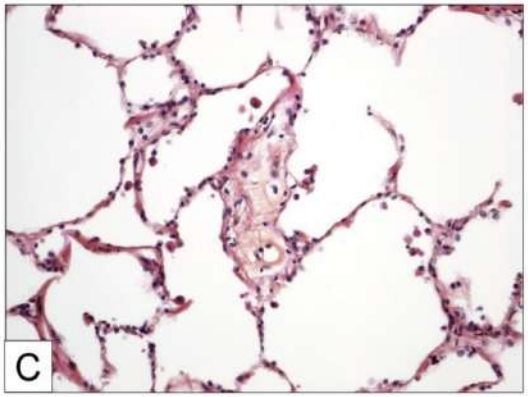
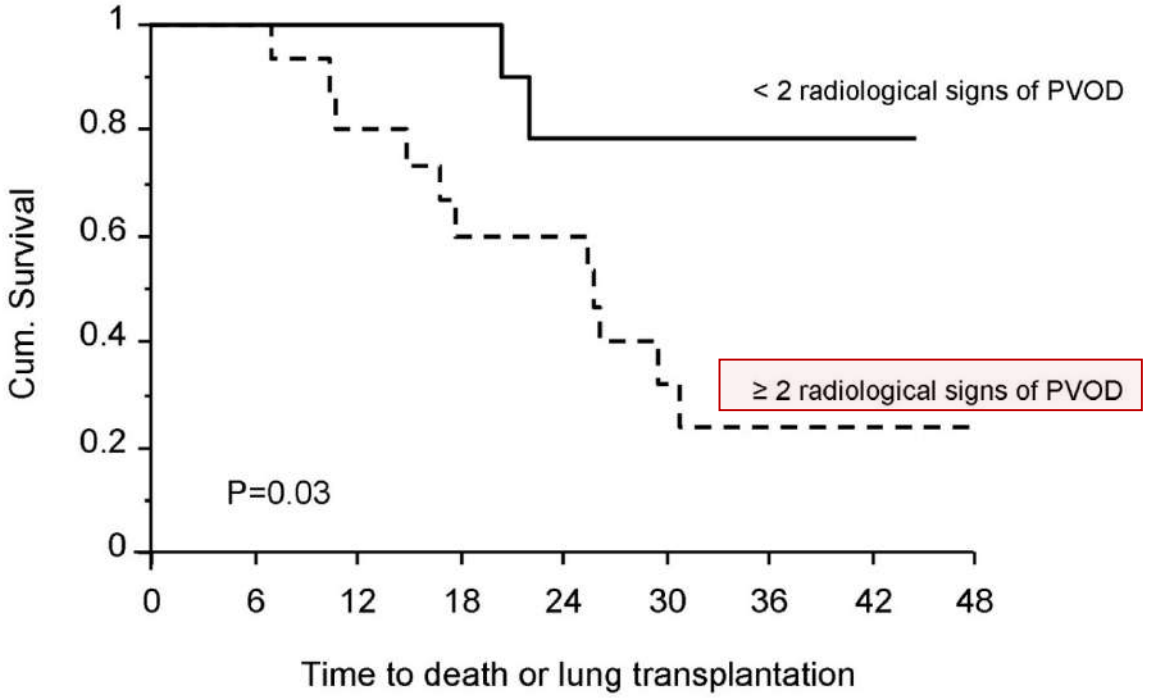
PVOD in SCLERODERMA

Computed Tomography Findings of Pulmonary Venoocclusive Disease in Scleroderma Patients Presenting With Precapillary Pulmonary Hypertension







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Eur Heart J 2015, Eur Respir J, 2015

Occupational exposure to organic solvents: a risk factor for pulmonary veno-occlusive disease

QUESTIONNAIRE D'EVALUATION DES NUISANCES CHIMIQUES

Critères d'inclusion : Age > 18 ans

1) **MVO confirmée :**
   - Preuve histologique
   - Œdème pulmonaire sous traitement spécifique de l'HTAP

2) **MVO hautement probable**
   2 critères parmi :
   - 2 anomalies radiologiques *(lignes septales, adénopathies médiastinales et opacité en verre dépoli centrolobulaire)*
   - DLCO/VA <55% ou PaO2 au repos < 65 mmHg
   - Hémorragie intra-alvéolaire (*Golde >80, sidéro >30%*)

3) **Groupe contrôle : HTAP idiopathique, familiale ou associée à la prise d'anorexigènes**

Critères d'exclusion :

1) **Conditions associées à l'HTAP** : connectivites, cardiopathies congénitales, hypertension portale, infection HIV.

2) **Hypertensions pulmonaires secondaires** : maladies respiratoires chroniques, cœur pulmonaire post-embolique.

100 PH patients :

- iPAH : n=65

- PVOD : n=35
(highly probable or confirmed)

Travail réalisé en collaboration avec l'équipe de Pathologies Professionnelles de Garches

Montani et al, *Eur Respir J* 2015

Tobacco exposure:

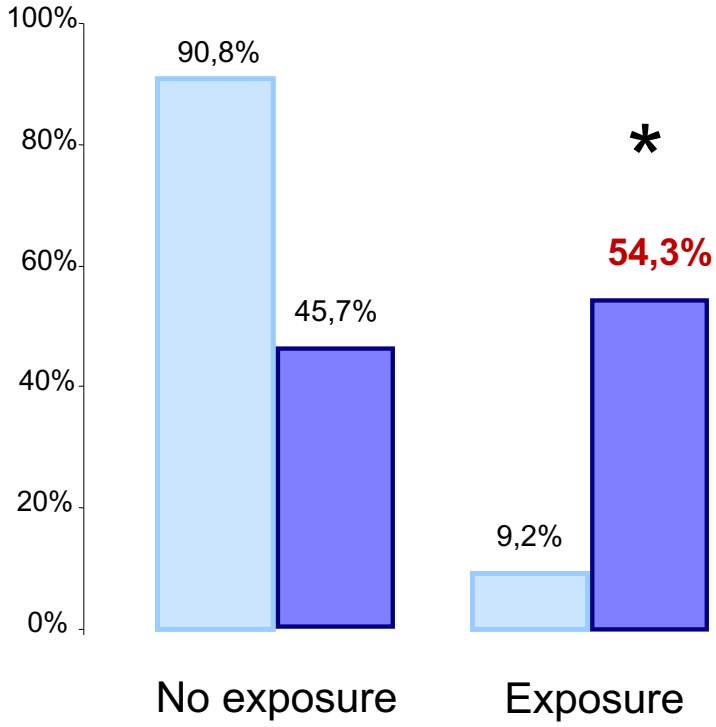
	PAH n = 65	PVOD n = 35	Odd Ratio	*p value*
Tobacco exposure				
Former or active smocking (> 5 p.y)	22 (33.8 %)	27 (77.1 %)	6.6 [2.57 – 16.92]	*< 0.001*
Length of exposure, yrs	9.6 ± 14.2	26.6 ± 16.7		*< 0.0001*
Pack / year (mean +/- STD)	8.2 ± 14.4	32.5 ± 25.6		*< 0.0001*

Montani et al, *Eur Respir J* 2015

EUROPEAN RESPIRATORY *journal*
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

Occupational exposure to organic solvents: a risk factor for pulmonary veno-occlusive disease

iPAH (n=65)
PVOD (n=35)



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RISK FACTORS FOR PVOD

Trichloroethylene exposure: Max between 1940-1970 (USA – Europe)

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Increase in ASIA +++

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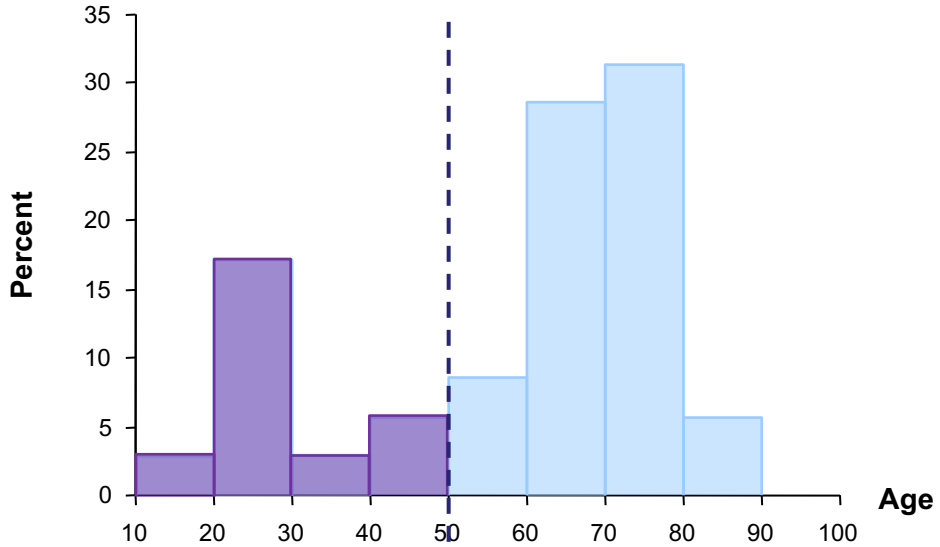
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

Occupational exposure to organic solvents: a risk factor for pulmonary veno-occlusive disease



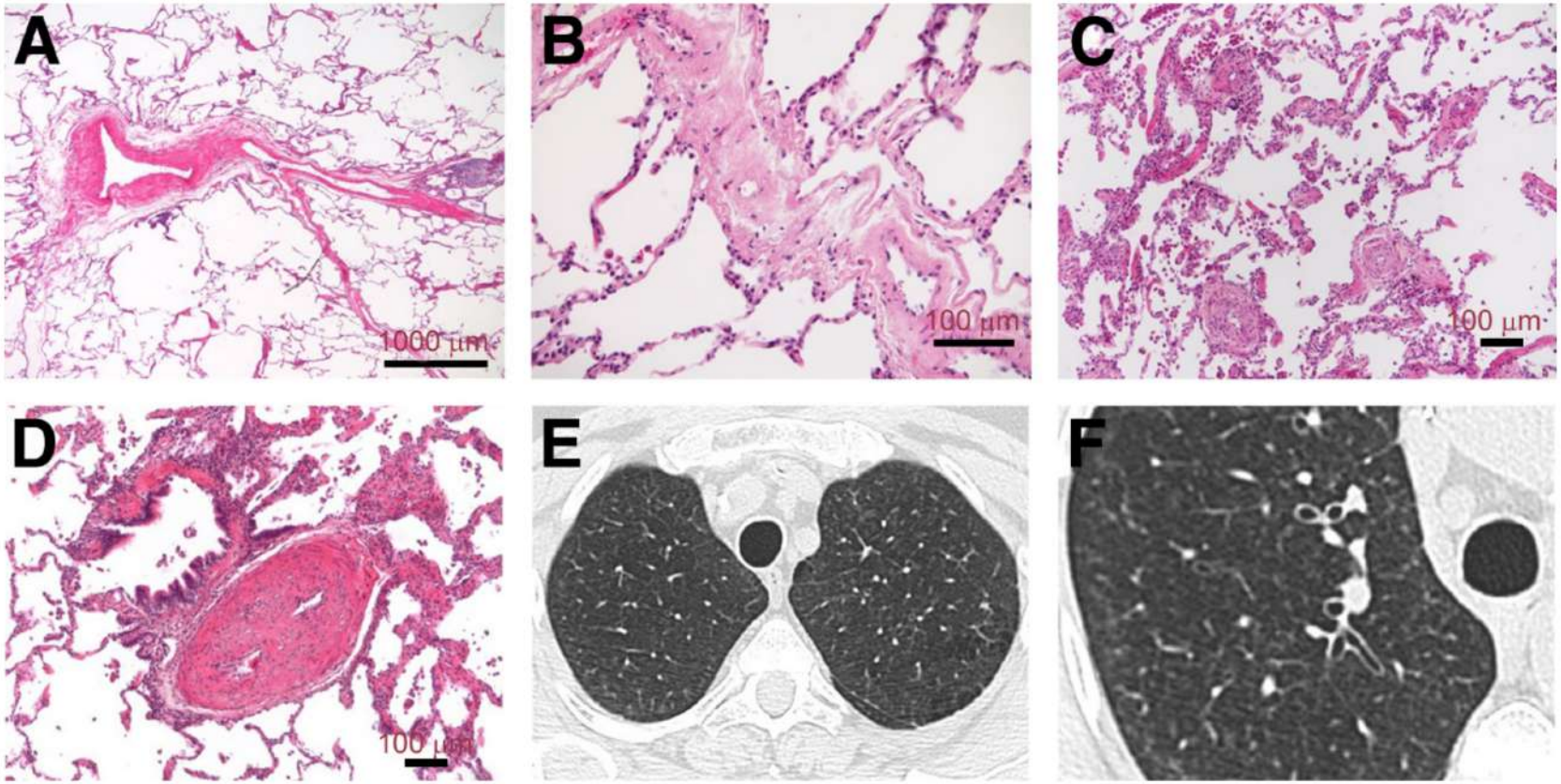
Sex ratio : 1
EIF2AK4 mutations >30%
Solvent exposure <10%

Sex ratio M/F: 3
EIF2AK4 mutations 0%
Solvent exposure >70%

Montani et al, *Eur Respir J* 2015

Chemotherapy-Induced Pulmonary Hypertension
Role of Alkylating Agents

Literature analysis (1960-2014) + experience of the French PH network



Ranchoux, *Am J Pathol* 2015

Chemotherapy-Induced Pulmonary Hypertension
Role of Alkylating Agents

Ranchoux, *Am J Pathol* 2015

Literature analysis (1960-2014) + experience of the French PH network

Chemotherapeutic group	Molecules	Chemotherapy-induced PVOD patients, No. (%)
Alkylating or alkylating-like agents, $n = 31$ (83.8%)	Cyclophosphamide	16 (43.2)
	Mitomycin	9 (24.3)
	Cisplatin	8 (21.6)
	Carmustine	5 (13.5)
	Procarbazine	4 (10.8)
	Ifosfamide	2 (5.4)
	Melphalan	2 (5.4)
	Busulfan	2 (5.4)
	Mustine	1 (2.7)
	Dacarbazine	1 (2.7)
Antimetabolites, $n = 15$ (40.5%)	Cytarabine	9 (24.3)
	Methotrexate	6 (16.2)
	Fluorouracil	3 (8.1)
	Mercaptopurine	2 (5.4)
	Fludarabine	2 (5.4)
	Hydroxyurea	1 (2.7)
Plant alkaloid and naturally occurring molecules, $n = 17$ (45.9%)	Vincristine	14 (37.8)
	Etoposide	7 (18.9)
	Docetaxel	3 (8.1)
	Teniposide	1 (2.7)
Cytotoxic antibiotic and related molecules, $n = 16$ (43.2%)	Doxorubicin	10 (27)
	Daunorubicin	4 (10.8)
	Bleomycin	3 (8.1)
	Epirubicin	1 (2.7)
	Idarubicin	1 (2.7)
	Mitoxantrone	1 (2.7)
	Dactinomycin	1 (2.7)
Others, $n = 9$ (21.6%)	Cyclosporine	4 (10.8)
	Asparaginase	3 (8.1)
	Mycophenolate mofetil	2 (5.4)
	Anagrelide	1 (2.7)
	Interferon	1 (2.7)
	Anti-thymocyte globin	1 (2.7)
	Monoclonal antibody	1 (2.7)

regimen associating several chemotherapy drugs

Chemotherapy-Induced Pulmonary Hypertension

Role of Alkylating Agents

Benoît Ranchoux,[*†] Sven Günther,[*†‡] Rozenn Quarck,[§] Marie-Camille Chaumais,[*†¶] Peter Dorfmüller,[*†‖] Fabrice Antigny,[*†] Sébastien J. Dumas,[*†] Nicolas Raymond,[*†‖] Edmund Lau,[*†‡] Laurent Savale,[*†‡] Xavier Jaïs,[*†‡] Olivier Sitbon,[*†‡] Gérald Simonneau,[*†‡] Kurt Stenmark,[**] Sylvia Cohen-Kaminsky,[*†] Marc Humbert,[*†‡] David Montani,[*†‡] and Frédéric Perros[*†]

Literature analysis (1960-2014) + experience of the French PH network

Chemotherapeutical group	Molecules	Chemotherapy-induced PVOD patients (n, %)
Alkylating or alkylating-like agents (>80%)	31 (83.8%)	
	cyclophosphamide	16 (43.2%)
	mitomycin	9 (24.3%)
	cisplatin	8 (21.6%)
	carmustine	5 (13.5%)
	xarmustine	4 (10.8%)
	procarbazine	4 (10.8%)
	ifosphamide	2 (5.4%)
	melphalan	2 (5.4%)
	busulfan	2 (5.4%)
	mustragen	1 (2.7%)
	dacarbazine	1 (2.7%)

⇒ Cyclophosphamide and Mitomycin : 2 animal models of PVOD

Ranchoux, *Am J Pathol* 2015

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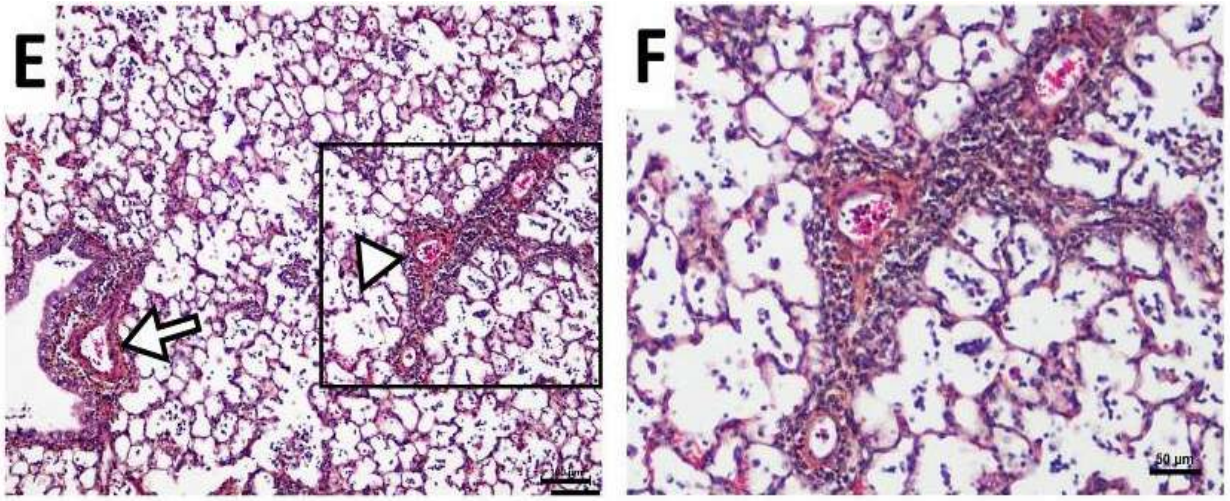
Mitomycin associated PVOD

MMC-rats

venular remodeling

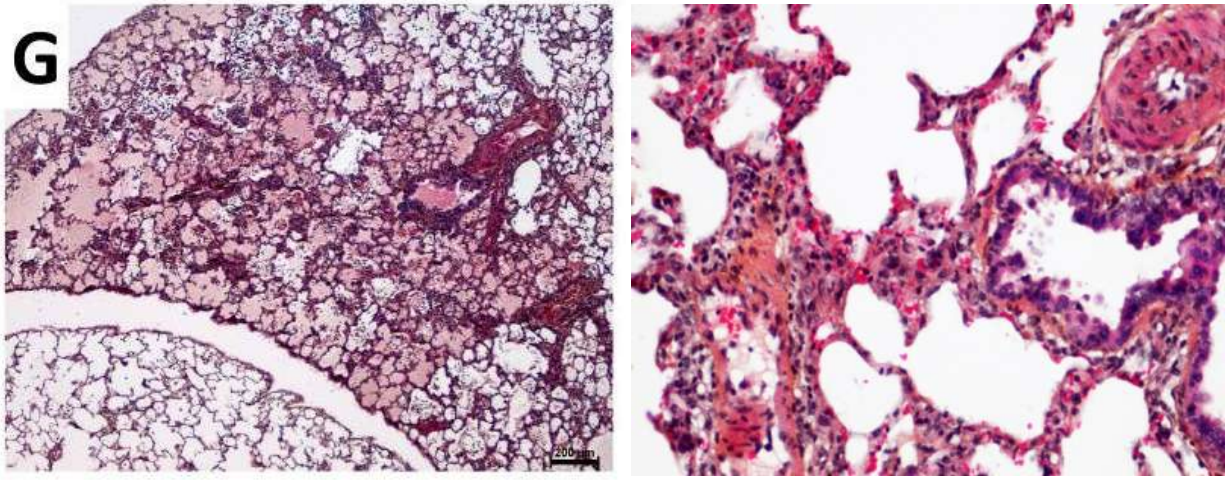
inflammation



MMC-rats

capillary proliferation

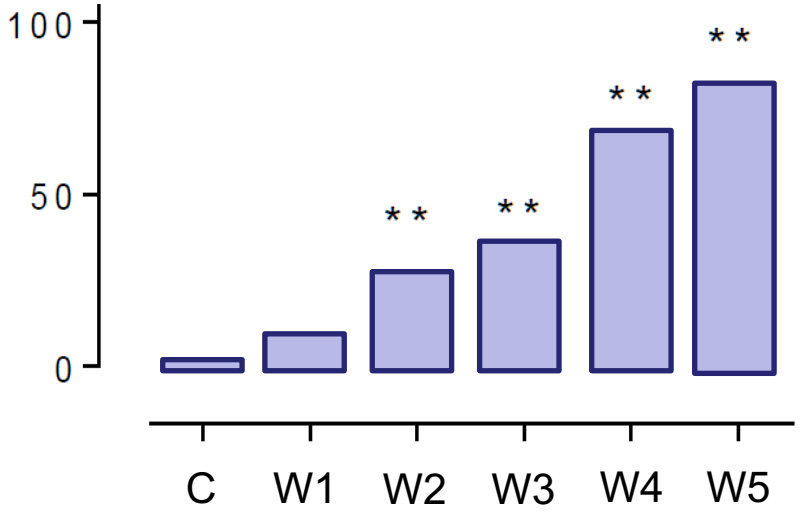
pulmonary edeam



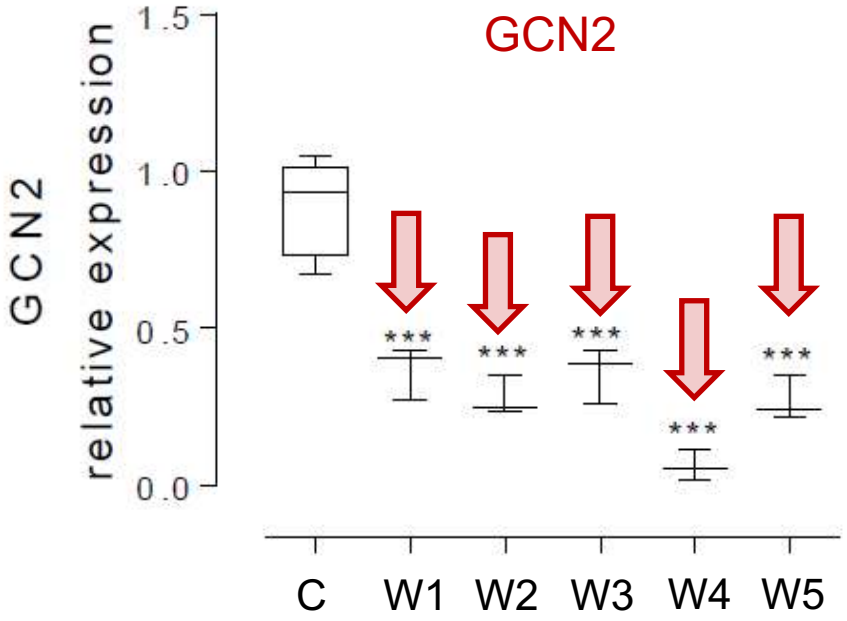
Perros, *Circulation* 2015

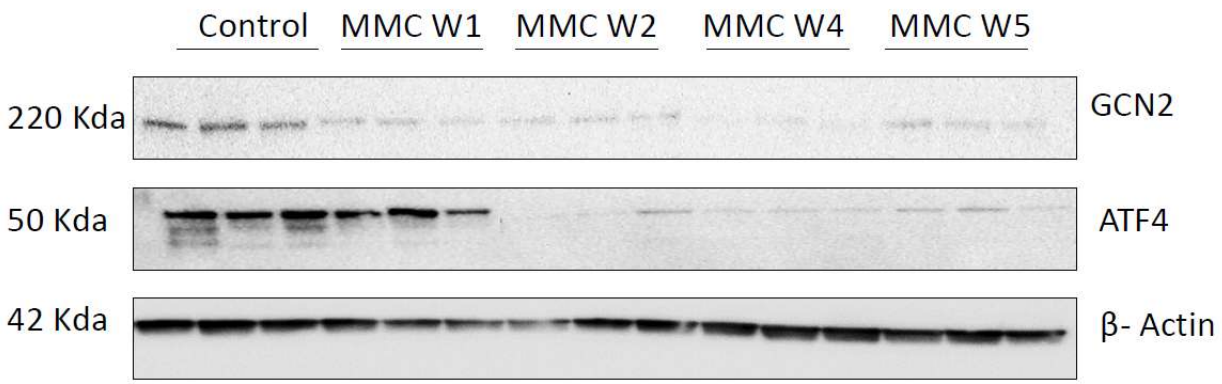
Mitomycin induced PVOD

% of remodeled microvessels



GCN2





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Risk factors for PVOD

EIF2AK4 mutations

Connective tissue diseases

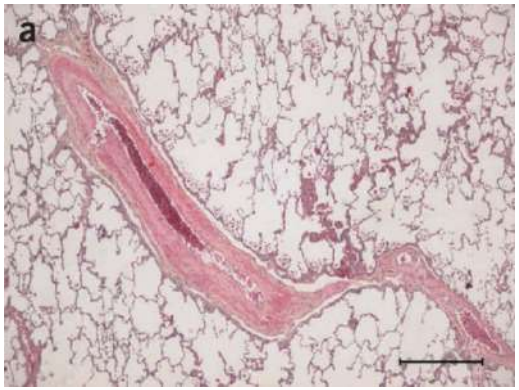
Chemotherapy *Alkylating agents*

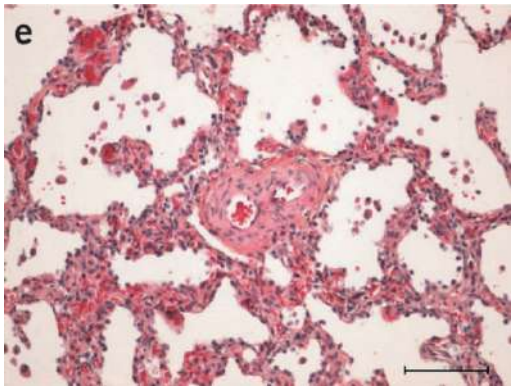
Solvent exposure

Oxydative stress ? ?

PVOD/PCH

Veinular remodelling





Capillary proliferation

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Relation Genotype - Phenotype

		Heritable PVOD (n=27)	Sporadic PVOD (n=67)	P-Value
Age at diagnosis, years (median; min-max)		26 (0-50·3)	60 (6·7-81·4)	<0·0001
Gender, female/male (ratio)		14/13 (1·1)	19/48 (0·4)	0·031
NYHA functional class,	II	4 (15·4)	3 (4·5)	0·20
	III	17 (65·4)	50 (74·6)	
	IV	5 (19·2)	14 (20·9)	
Six-minute walk distance, % pred		49·3 (22·6)	44·1 (27·5)	0·42
mPAP, mmHg		49 (14)	46 (11)	0·29
CO, L/min		4·37 (1·47)	4·51 (1·50)	0·69
PVR, WU		11·4 (6·7)	9·4 (4·4)	0·10
DLCO, % pred		30 (7)	31 (10)	0·65
Exposure to organic solvents, n (%)		0	28 (42)	<0·0001
Previous Chemotherapy, n (%)		0	7 (10)	0·081

Montani D *et al*. Lancet Respir Med (Epub)

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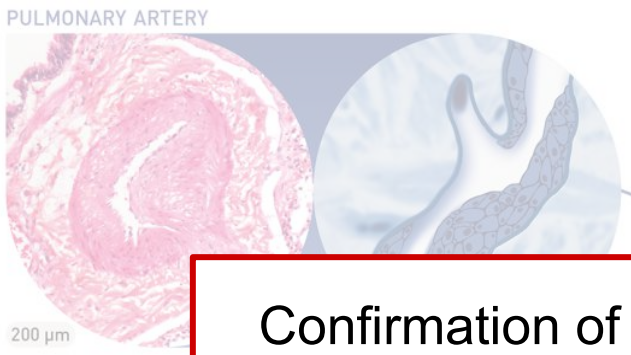
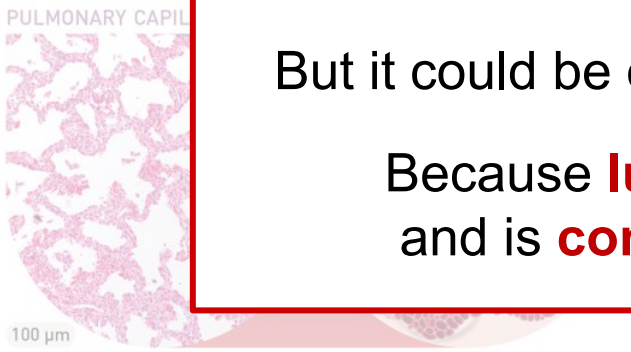
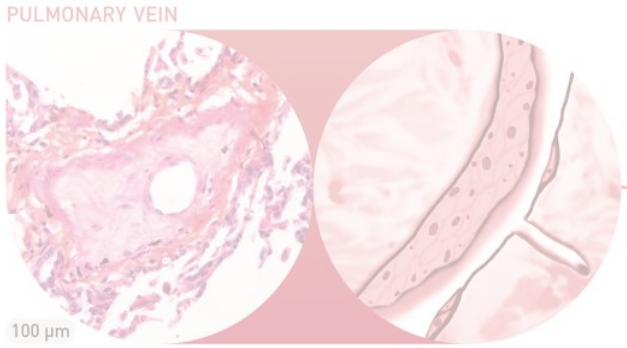
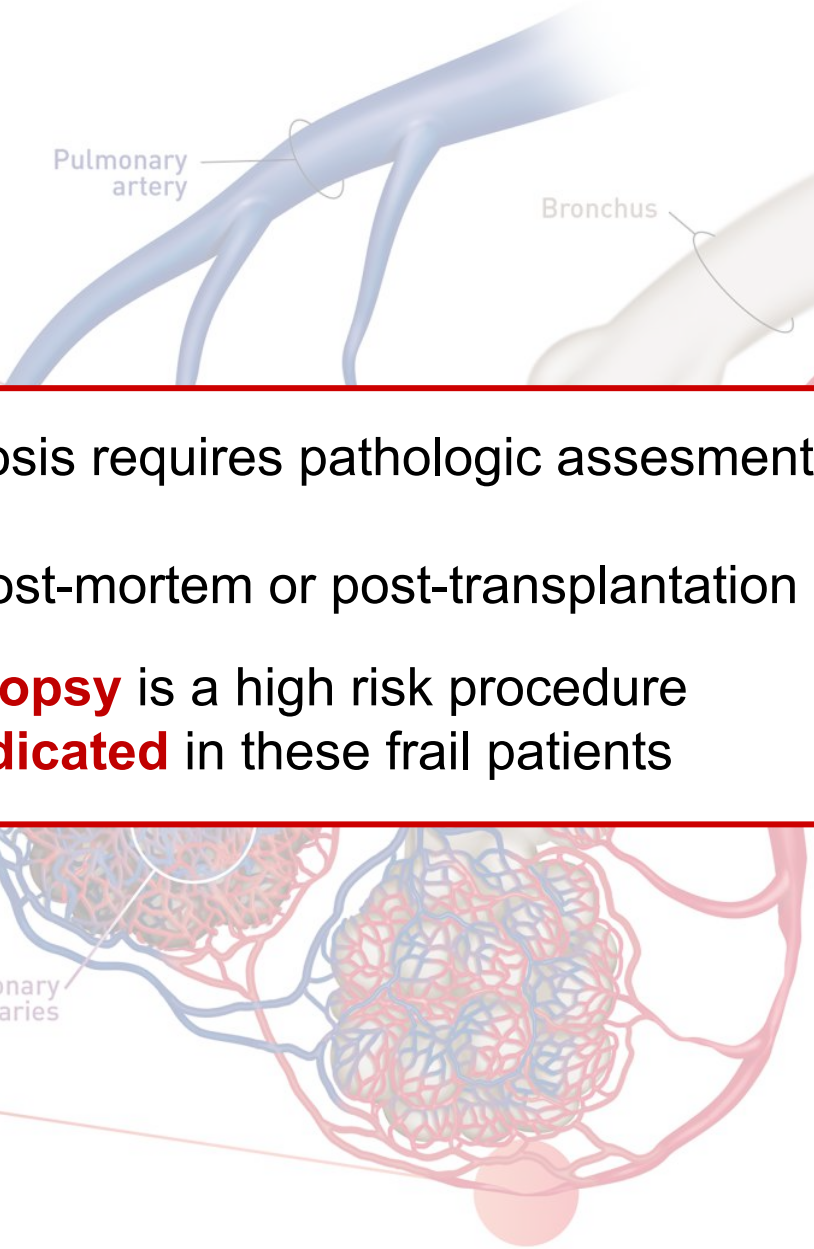
DIAGNOSIS
Non-invasive approach

Pathologic assesment









Confirmation of diagnosis requires pathologic assesment

But it could be only post-mortem or post-transplantation

Because **lung biopsy** is a high risk procedure
and is **contraindicated** in these frail patients

24 PVOD vs 24 iPAH with histological confirmation

Characteristic	PVOD (n = 24)	PAH (n = 24)	p Value
Sex			
Male	12	4	0.02
Female	12	20	
Age at diagnosis†, yr	40.1 ± 19.5	36.7 ± 13.3	0.49
Time to diagnosis†, mo	12.7 ± 11.7	15.0 ± 17.9	0.59
NYHA class at diagnosis			NS
Class II	2 (8.3%)	4 (16.7%)	
Class III	12 (50%)	15 (62.5%)	
Class IV	10 (41.7%)	5 (20.8%)	
Hemoptysis	1 (4.2%)	2 (8.3%)	NS
Raynaud phenomenon	2 (8.3%)	4 (16.7%)	NS
Syncope/near syncope	11 (45.8%)	11 (45.8%)	NS
Right heart failure	13 (54.2%)	14 (58.3%)	NS
Clubbing	4 (16.7%)	2 (8.3%)	NS

Montani D, *et al*. *Medicine* 2008.

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No difference between PVOD and iPAH

	PVOD (n = 24)	PAH (n = 24)	p Value
mPAP (mm Hg)	58.3 ± 12.4	62.9 ± 15.3	0.29
PCWP (mm Hg)	7.3 ± 3.1	7.8 ± 3.2	0.63
CI (L/min/m^2)	2.3 ± 0.8	2.1 ± 0.6	0.28
Systolic index (mL/min/m^2)	25.7 ± 10	24.3 ± 7.2	0.61
TPRi (U/m^2)	29.2 ± 13.5	31.9 ± 11.2	0.44
PVRi (U/m^2)	24.6 ± 12.6	25.7 ± 7.7	0.75
SvO2 (%)	59.7 ± 8.9	59.9 ± 10.7	0.94
Acute NO responders	1 (4.2%)	0	NS

Montani D. *Medicine* 2008.

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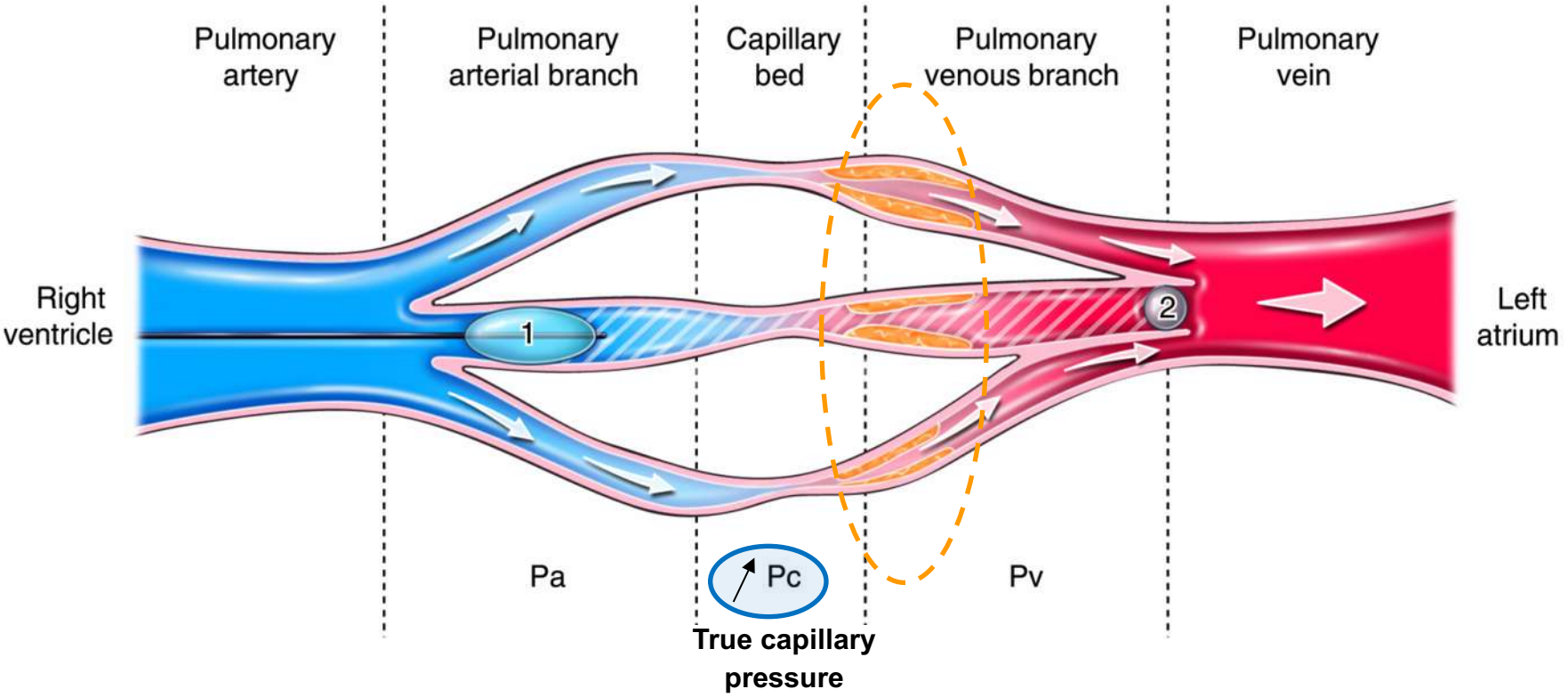
Why PCWP is normal in PVOD?



True capillary pressure is increased but PCWP is normal because it is a reflection of the pressure in the large veins that are not affected by obstruction

Montani D *et al. Eur Respir J* 2009

PFTs and DLCO

Histologically confirmed PVOD & PAH

Result	PVOD (n = 24)	PAH (n = 24)	p Value
PaO2 (mm Hg)	61.3 ± 17.3	75.4 ± 13.8	0.0085
PaCO2 (mm Hg)	30.6 ± 5.9	30 ± 3.5	0.71
FEV1 (% pred)	84.8 ± 14.7	90.2 ± 14.3	0.24
VC (% pred)	86.5 ± 17.6	93.8 ± 14.5	0.16
FEV1/VC (% pred)	80.7 ± 10.4	82 ± 6.4	0.63
TLC (% pred)	94.8 ± 18.0	98.1 ± 11.7	0.50
DLCO (% pred)	51.9 ± 19.3	70.5 ± 15.2	0.005
DLCO/VA (% pred)	41.8 ± 23.9	63.2 ± 13.6	0.002
Six-minute walk test			
Distance, m	273.7 ± 137.2	283.3 ± 127.8	0.81
Nadir SpO2, %	80.3 ± 8.9	87.2 ± 7.1	0.015

FEV1, forced expiratory volume in 1 second; PFT, pulmonary function test; VA, alveolar volume; VC, vital capacity; TLC, total lung capacity.

Montani D *et al. Medicine (Baltimore)* 2008

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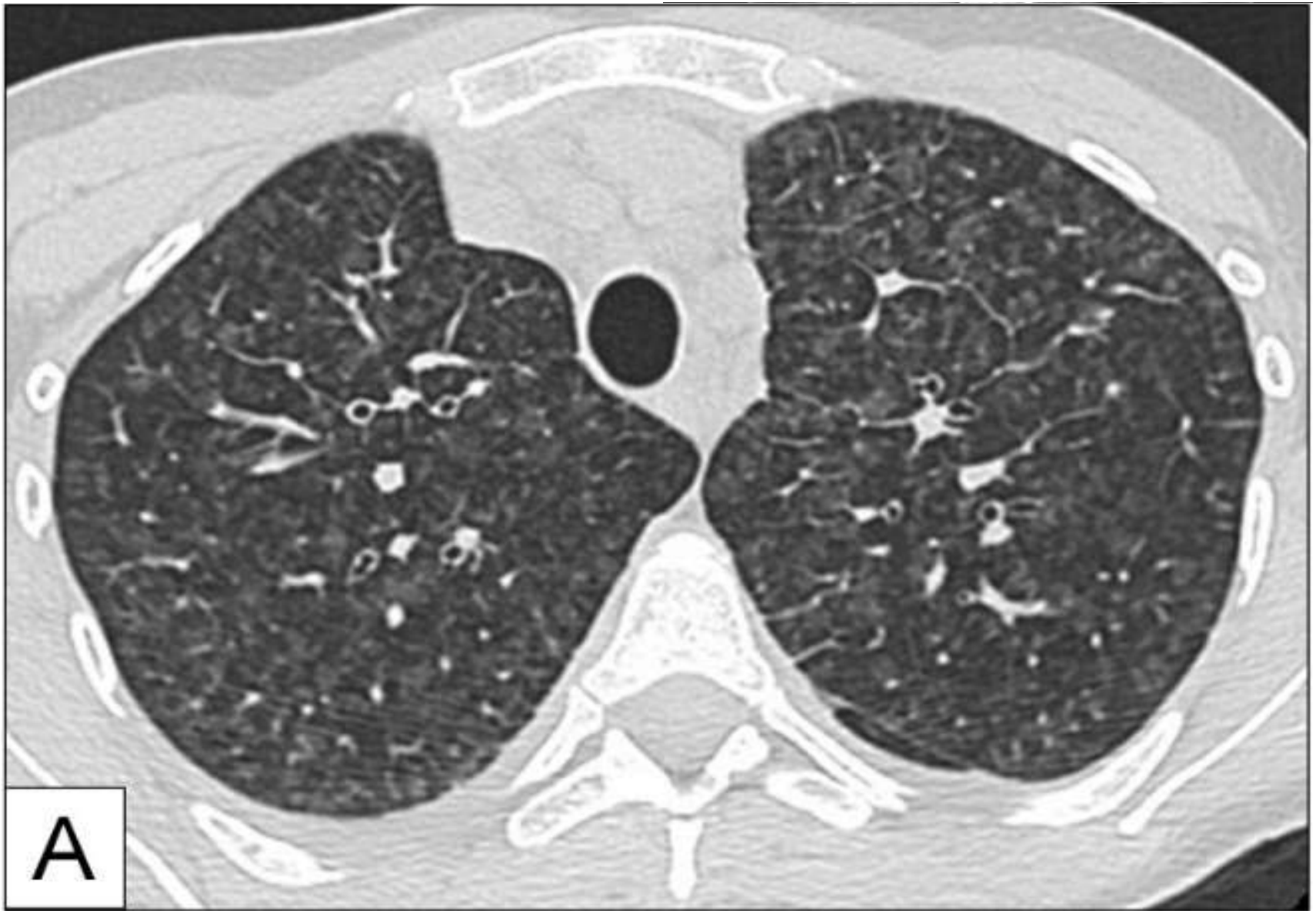
Pulmonary Hypertension:
CT of the Chest in Pulmonary Venoocclusive Disease

American Journal of Roentgenology 2004

Arnaud Resten[1]
Sophie Maitre[1]
Marc Humbert[2]
Anne Rabiller[2]
Olivier Sitbon[2]
Frédérique Capron[3]
Gérald Simonneau[2]
Dominique Musset[1]

- 15 PVOD patients vs 15 iPAH patients
- 3 radiologic abnormalities associated with PVOD:
  - Lymph node enlargement
  - Septal lines
  - Centrilobular ground-glass opacities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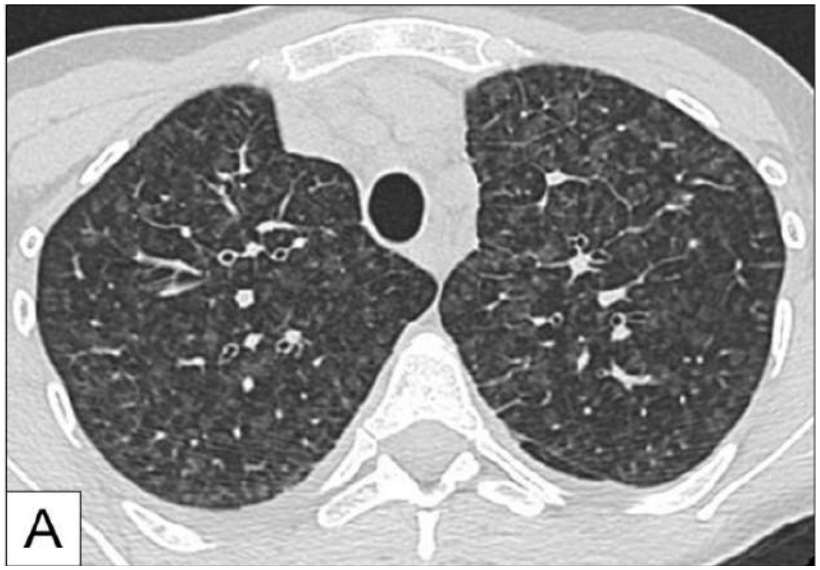
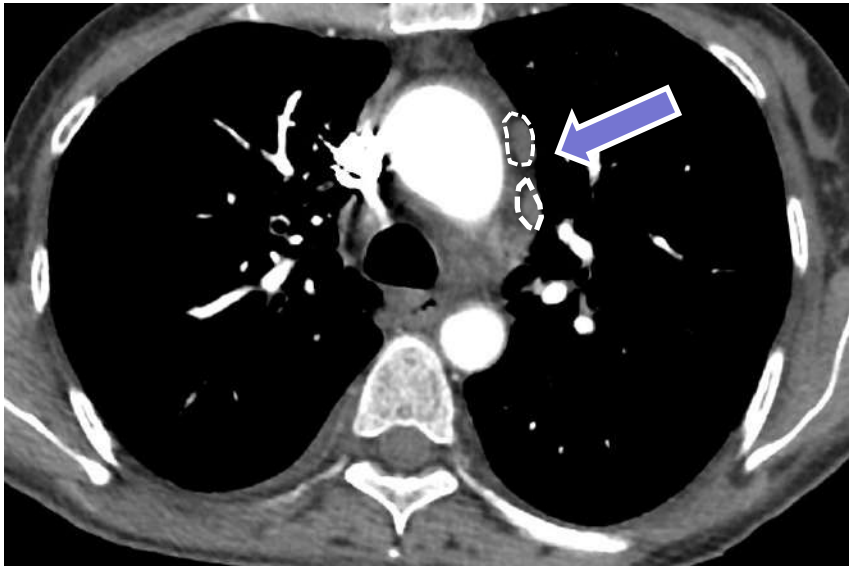
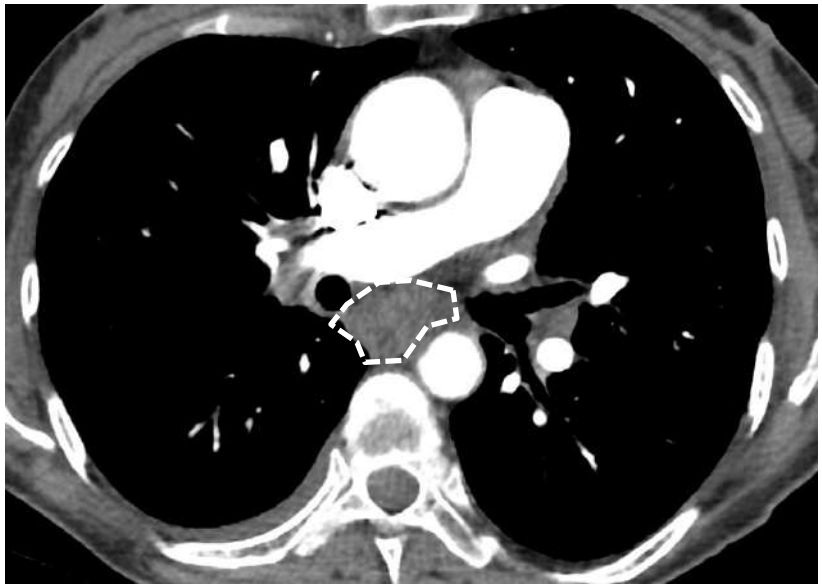
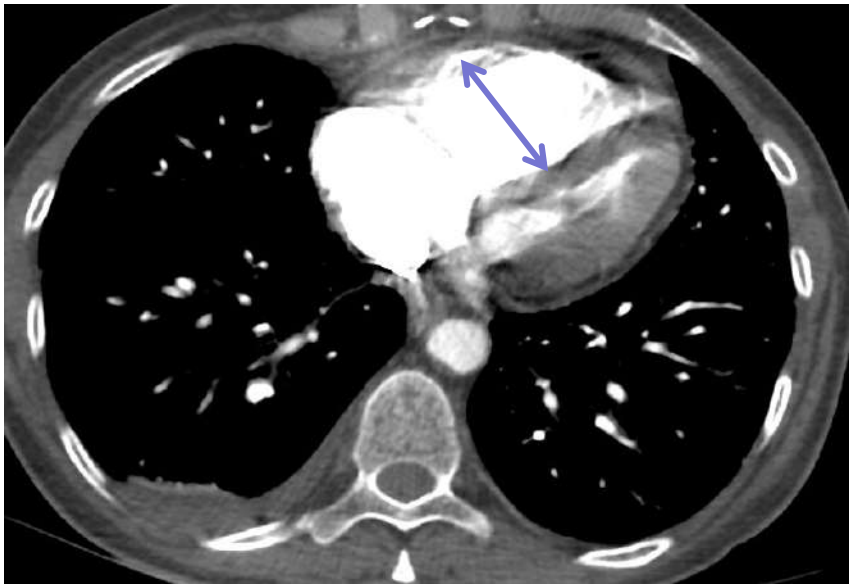
HRCT of the CHEST



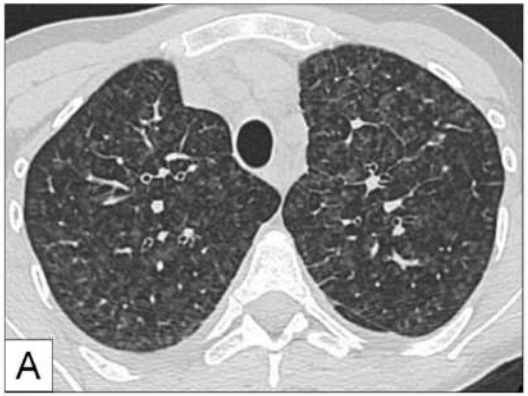


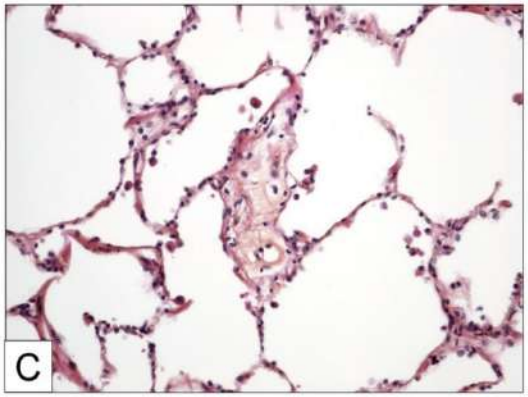


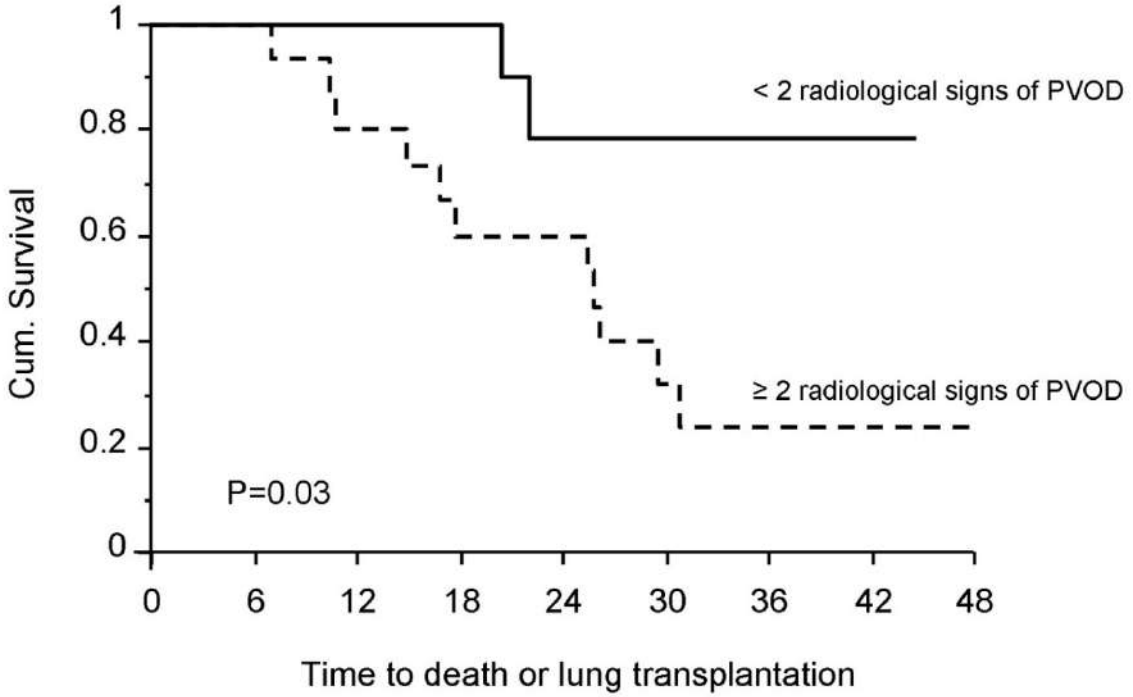


HRCT of the CHEST in SCLERODERMA

Computed Tomography Findings of Pulmonary Venoocclusive Disease in Scleroderma Patients Presenting With Precapillary Pulmonary Hypertension







Gunther et al, *Arthr & Rheum* 2012

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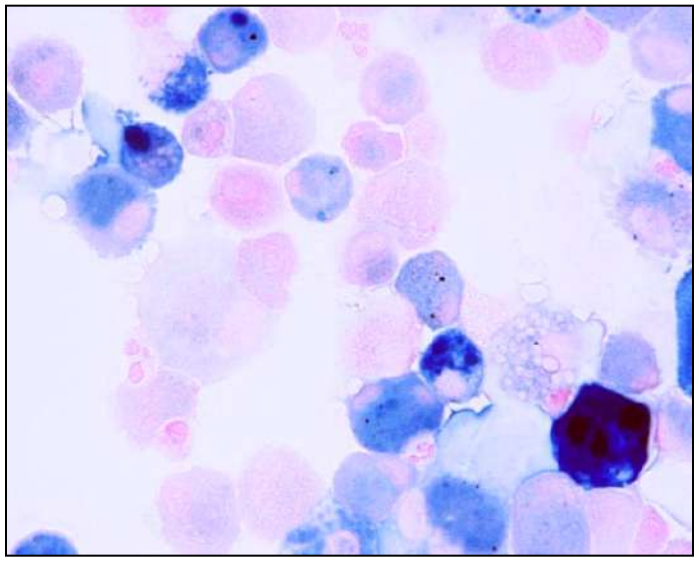
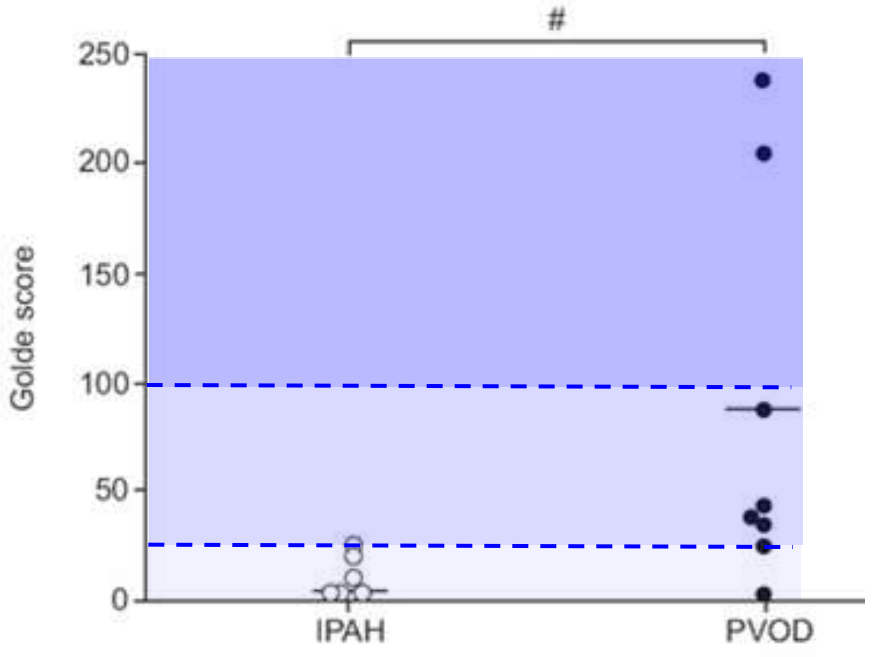
Possible occult alveolar haemorrhage

<50% of PVOD patients but uncommon in iPAH



Haemosiderin-laden macrophages



Golde score

Difficult to perform because of severe hypoxemia

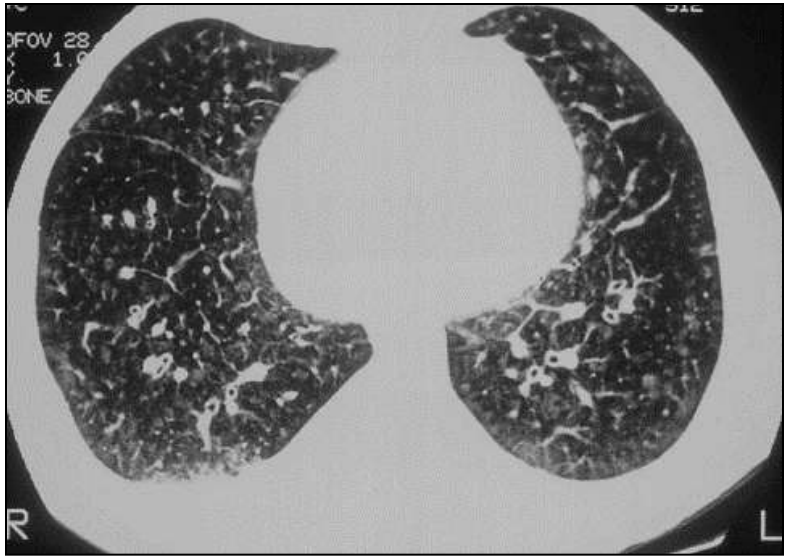
Rabiller, *Eur Respir J* 2006

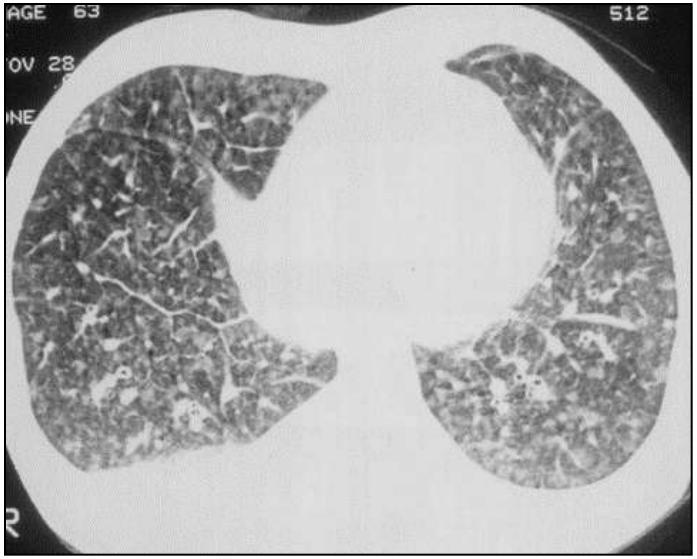
Management of PVOD

MANAGEMENT OF PVOD

- Risk of pulmonary edema with <u>all PAH therapies</u>
  - Risk with all specific PAH therapies ≠ class effect
  - Mechanism : Increase of blood flow with no modification of post-capillary resistance
  - Pulmonary edema confirms the diagnosis of PVOD

Epoprostenol





Humbert, AJRCCM 1998

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MANAGEMENT OF PVOD

- Risk of pulmonary edema with all PAH therapies
  - Risk with all specific PAH therapies ≠ class effect
  - Mechanism : Increase of blood flow with no modification of post-capillary resistance
  - Pulmonary edema confirms the diagnosis of PVOD

- Poor response to specific PAH therapies:
  - As observed in PAH associated to CTD : poor response associated to venous involvement ?

- Lung transplantation remains the treatment of choice.

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MANAGEMENT OF PVOD

- High-dose diuretics
- Anticoagulation : warfarin ?
  - No data confirming interest in this subgroup of PAH
  - No recommendation
  - No specific complications described even in the presence of occult alveolar hemorrage.
- Oxygen supplementation:
  - patients frequently hypoxemic
- Cautious use of specific PAH therapies:
  - Risk of pulmonary edema
  - Possible haemodynamic improvement with epoprostenol (1)
  - Oral therapy ? Stabilization with sildenafil (2)

(1) Okumura H *et al*. Chest. 2002;122:1096-8.
(2) Barreto AC *et al*. Braz J Med Biol Res 2005;38:185-95.

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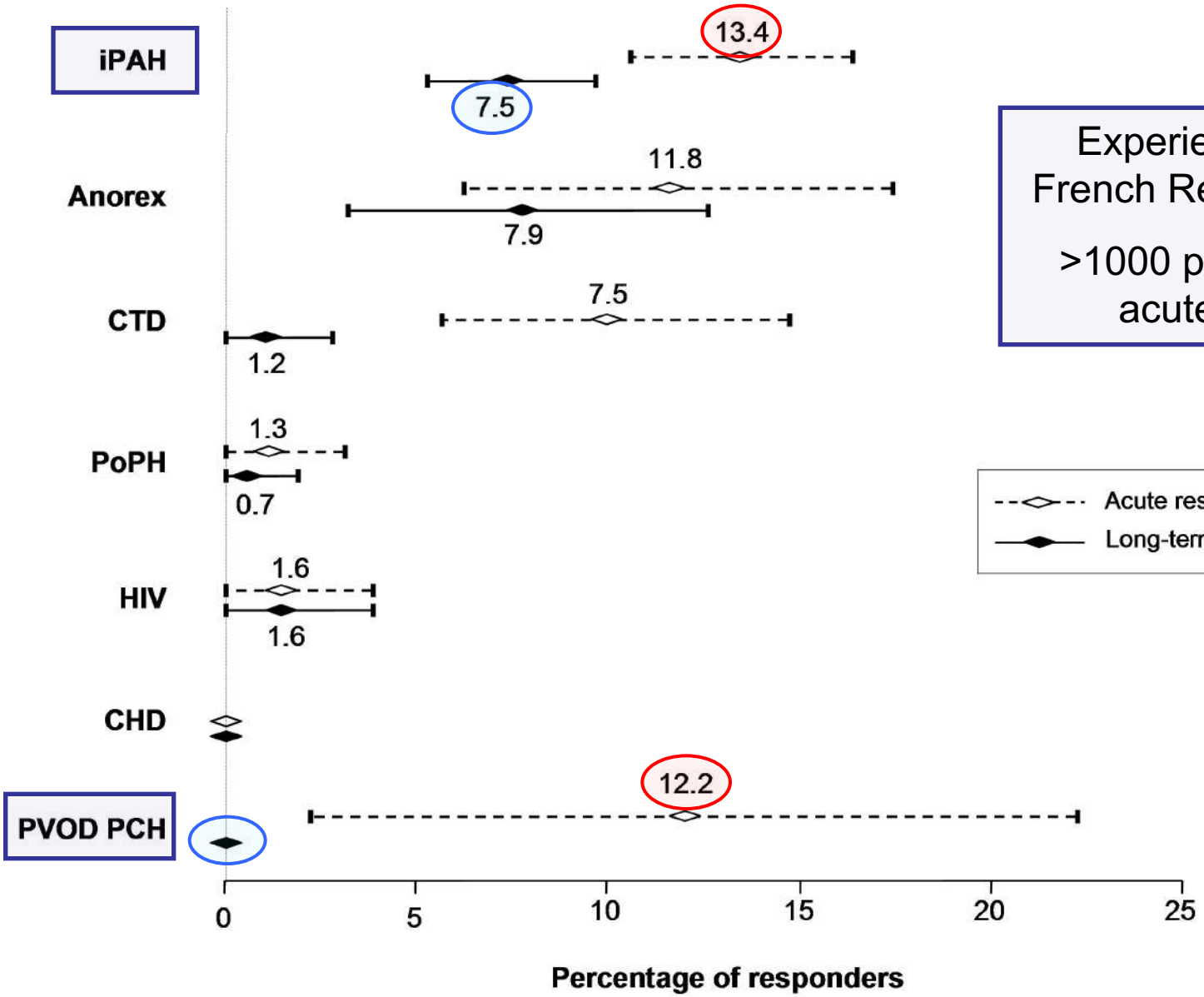
ACUTE VASODILATOR TESTING

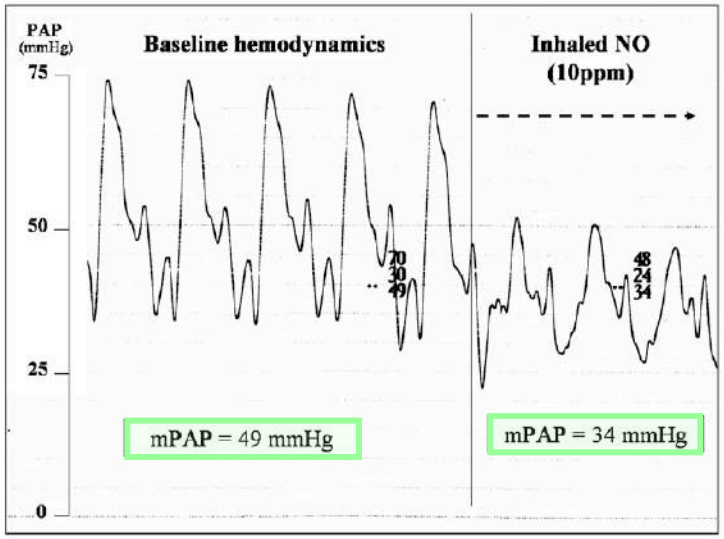


Experience of the French Referral centre

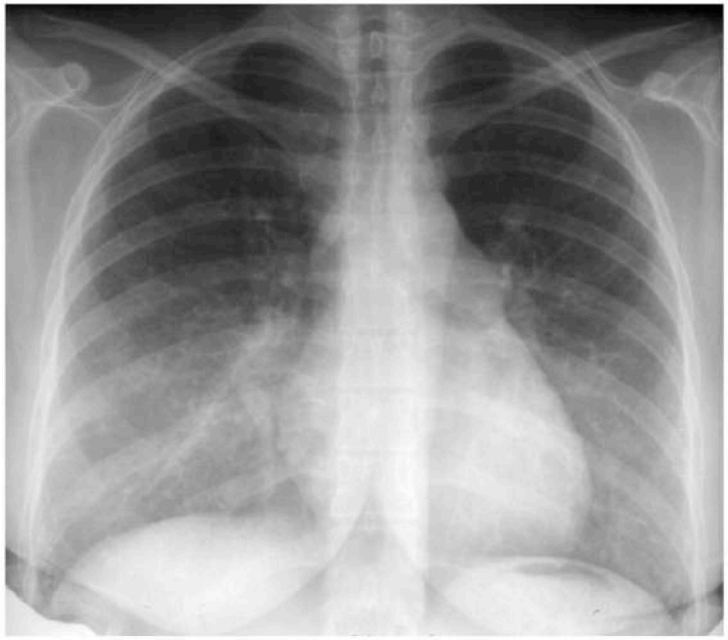
>1000 patients with acute testing

Montani D, *Eur Heart J 2010*.

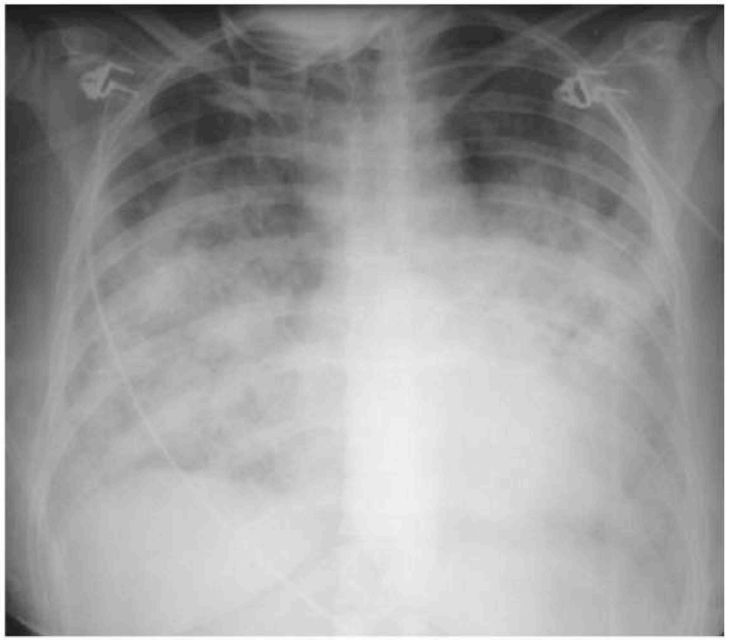
ACUTE NO TESTING AND CCBs



CCBs are contraindicated even in the presence of acute vasodilator response



Prior to diltiazem therapy

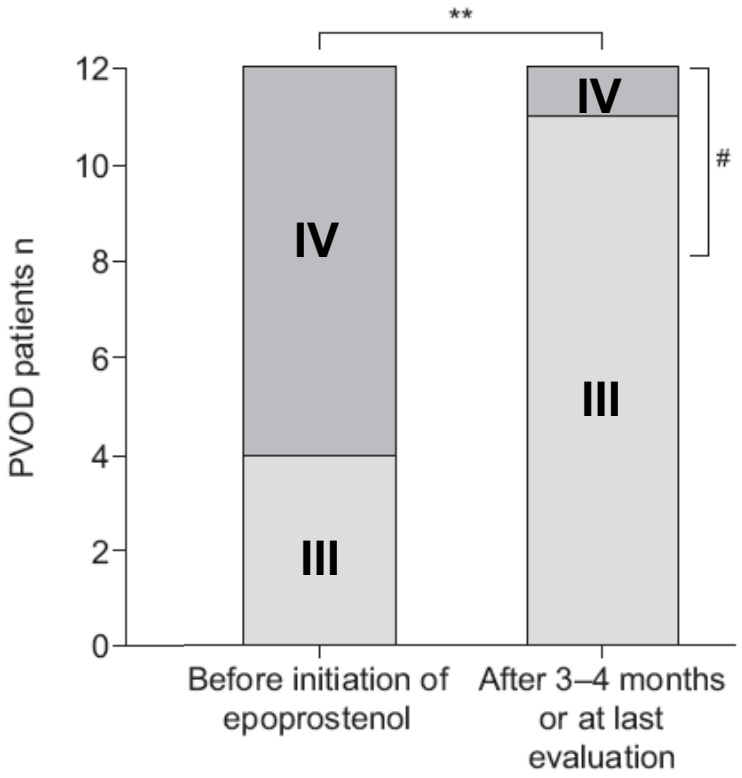


After 2 days of diltiazem therapy

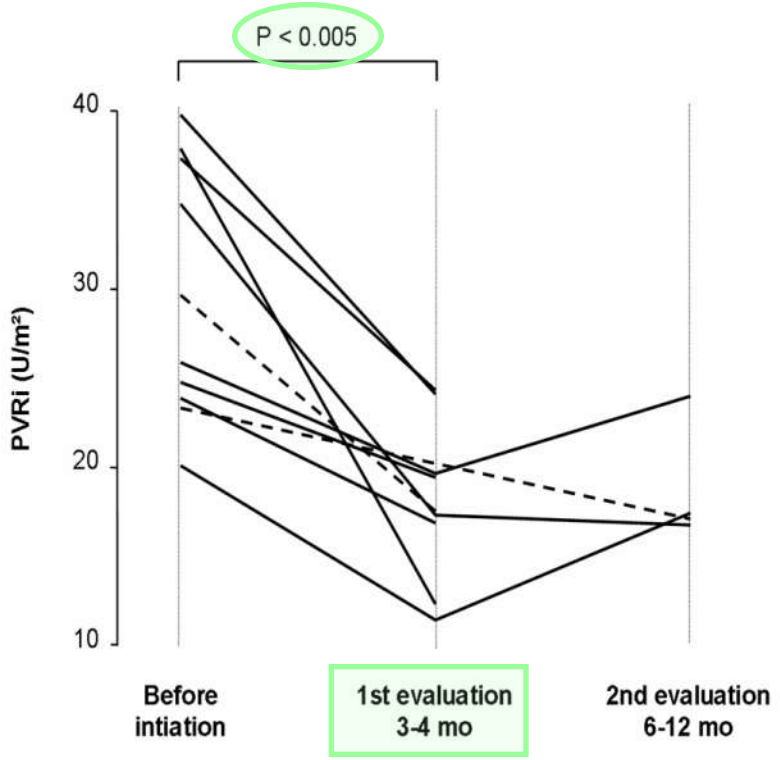
Is there any place for specific PAH therapy?

Epoprostenol may be a bridge-therapy to LTx

Cautious use (low dose, slow increase, high-dose diuretics)



NYHA functional class



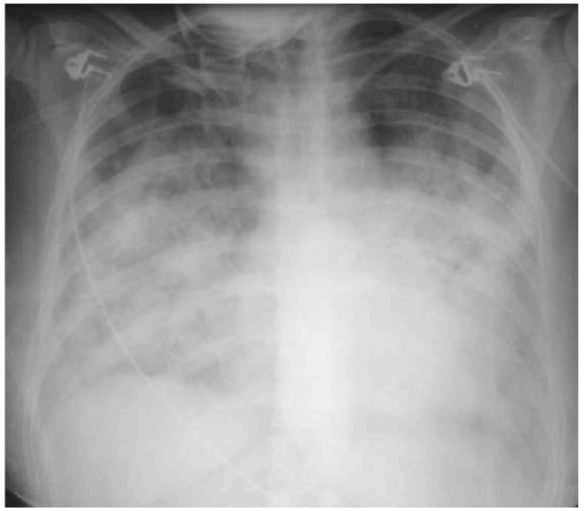
Pulmonary vascular resistance

Montani D, *Eur Respir J, 2009.*

Experience of the French Referral Centre (n=64)

12 (20%) experienced pulmonary edema

2 were listed for urgent LTx



	Baseline	second evaluation	P-value
EIF2AK4 bi-allelic mutations, Y/N	17/47		
Gender, female/male (ratio)	20/44		
NYHA functional class, n (%)			
II	6 (9·5)	15 (23·5)	0·10
III	46 (72)	38 (59·5)	
IV	12 (18·5)	11 (17)	
Six-minute walk distance, *m*	289 (160)	321 (157)	0·0142
mPAP, *mmHg, mean (SD)*	46 (10)	46 (12)	0·87
CI, *L/min/m², mean (SD)*	2·43 (0·76)	2·84 (0·74)	<0·0001
PVR, *WU, mean (SD)*	9·7 (4·7)	8·1 (5·0)	0·0002
PAH medical therapy			
ERA	-	45	
PDE5i	-	7	
Prostacyclin derivative	-	9	

Montani D *et al*. Lancet Respir Med (Epub)

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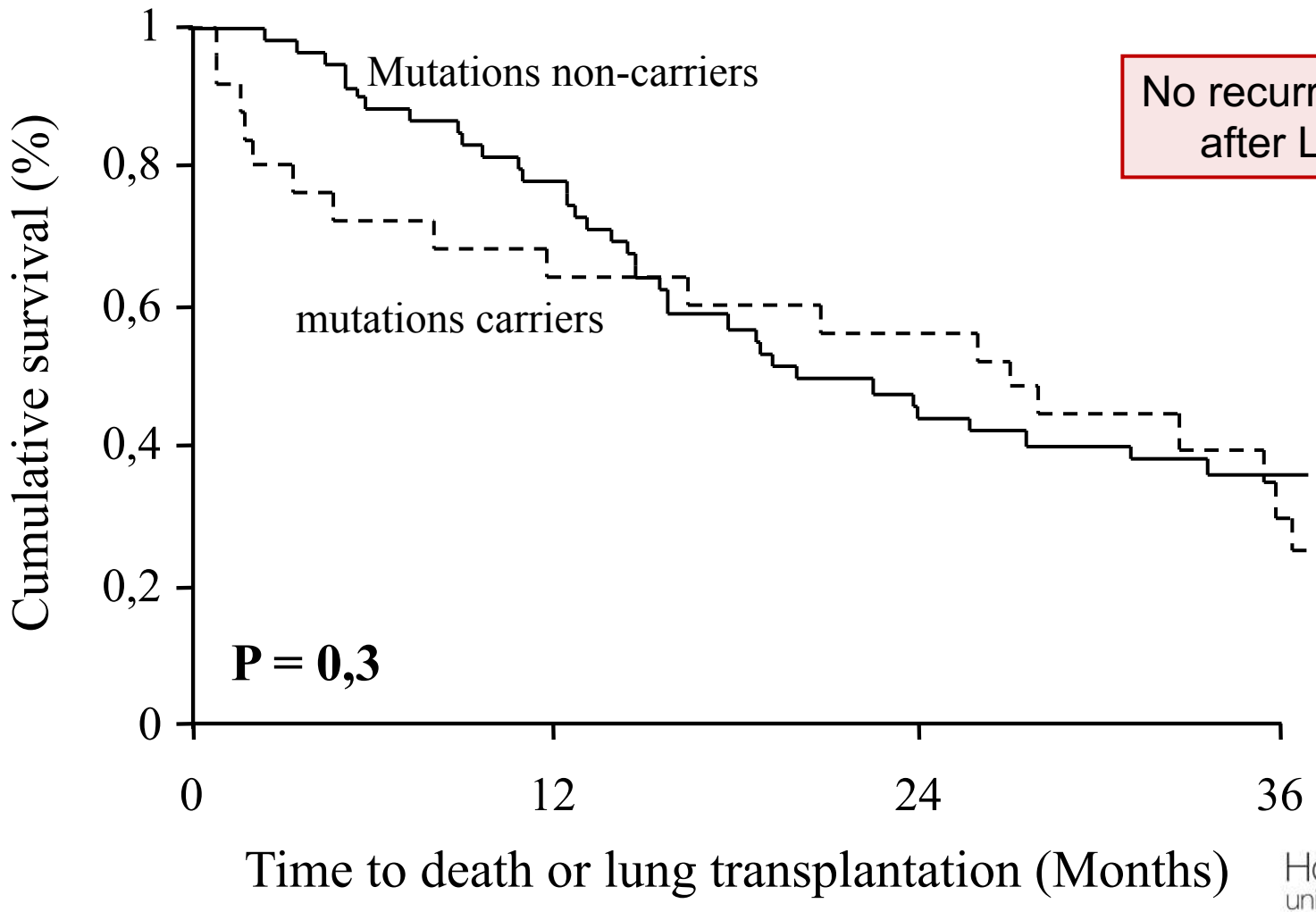
Survival in PVOD

Time to death or lung transplantation



No recurrence after LTx

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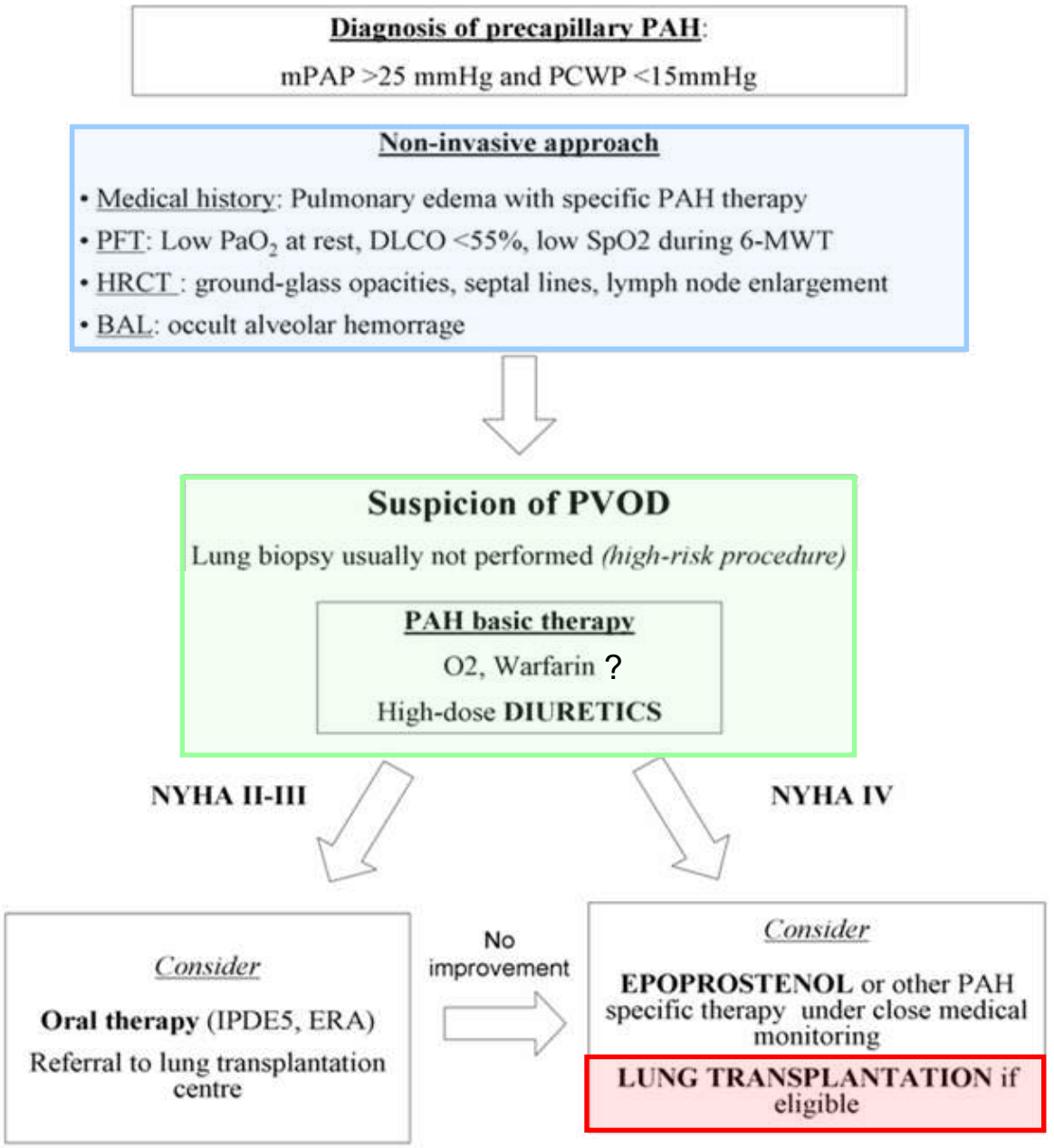
CONCLUSION


Diagnosis of precapillary PAH:
mPAP >25 mmHg and PCWP <15mmHg
Non-invasive approach
• Medical history: Pulmonary edema with specific PAH therapy
• PFT: Low PaO2 at rest, DLCO <55%, low SpO2 during 6-MWT
• HRCT : ground-glass opacities, septal lines, lymph node enlargement
• BAL: occult alveolar hemorrage
Suspicion of PVOD
Lung biopsy usually not performed (high-risk procedure)
PAH basic therapy
O2, Warfarin ?
High-dose DIURETICS
NYHA II-III
NYHA IV
Consider
Oral therapy (IPDE5, ERA)
Referral to lung transplantation centre
No improvement
Consider
EPOPROSTENOL or other PAH specific therapy under close medical monitoring
LUNG TRANSPLANTATION if eligible

CONCLUSION

Diagnosis of precapillary PAH:

mPAP >25 mmHg and PCWP <15mmHg

Non-invasive approach

- Medical history: Pulmonary edema with specific PAH therapy
- PFT: Low PaO_2 at rest, DLCO <55%, low SpO2 during 6-MWT
- HRCT : ground-glass opacities, septal lines, lymph node enlargement
- BAL: occult alveolar hemorrage

Suspicion of PVOD

Lung biopsy usually not performed *(high-risk procedure)*

PAH basic therapy

O2, Warfarin ?

High-dose **DIURETICS**

Better understanding of the role of EIF2AK4/GCN2 may be helpful to find **innovative therapeutic targets** in this devasting condition.

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Back-up Slides

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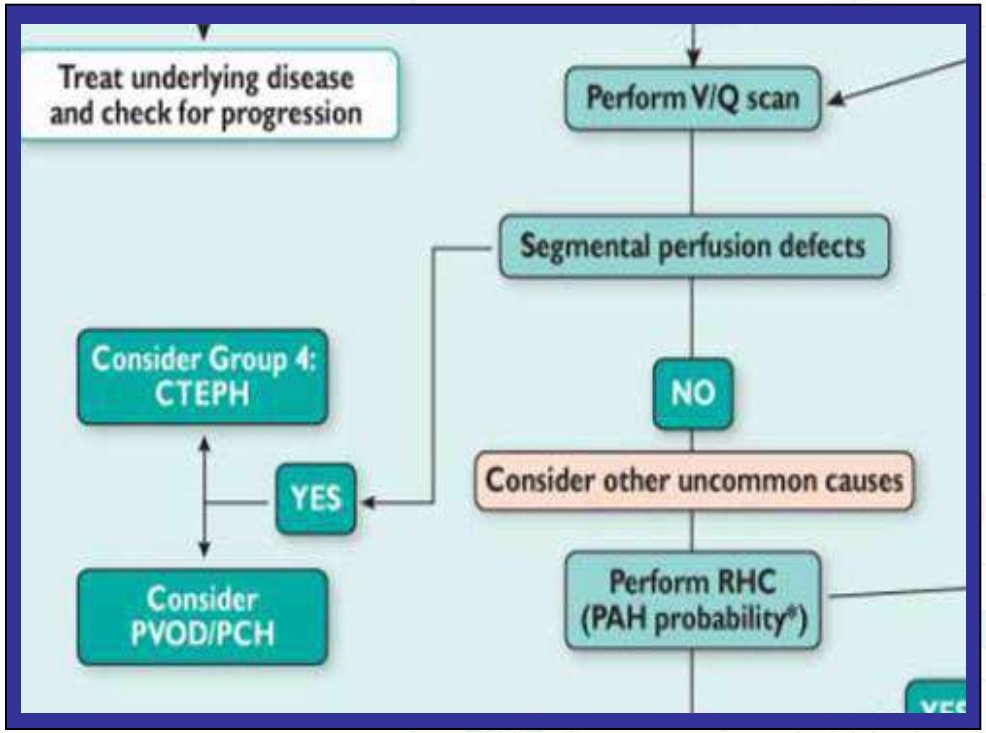
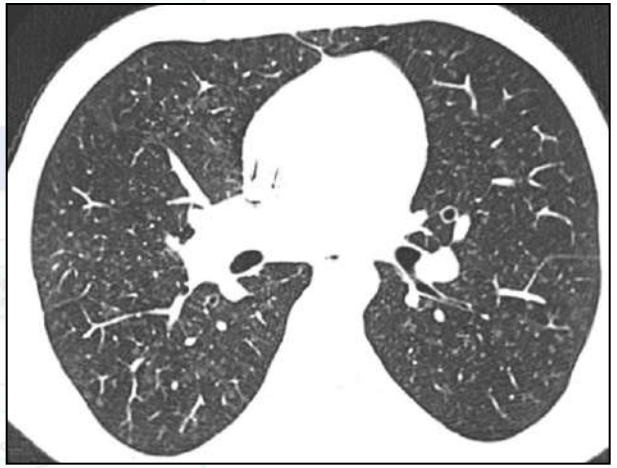
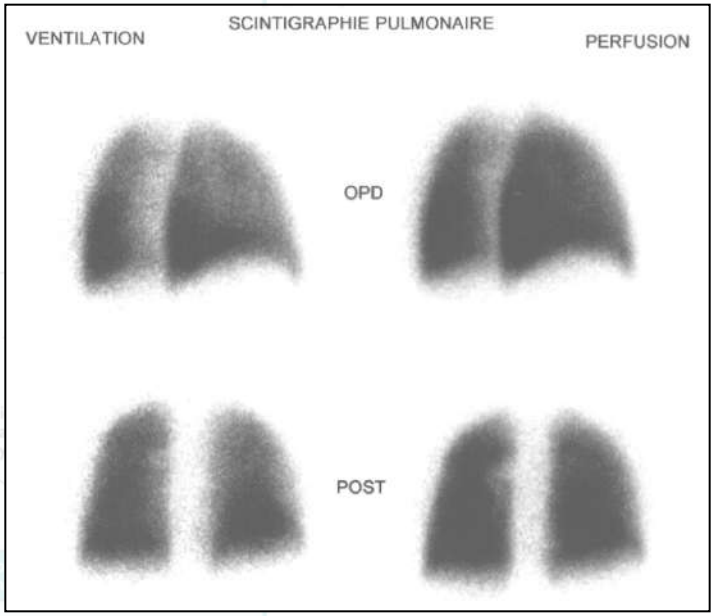
PERFUSION / VENTILATION LUNG SCAN

ERS/ESC Guidelines







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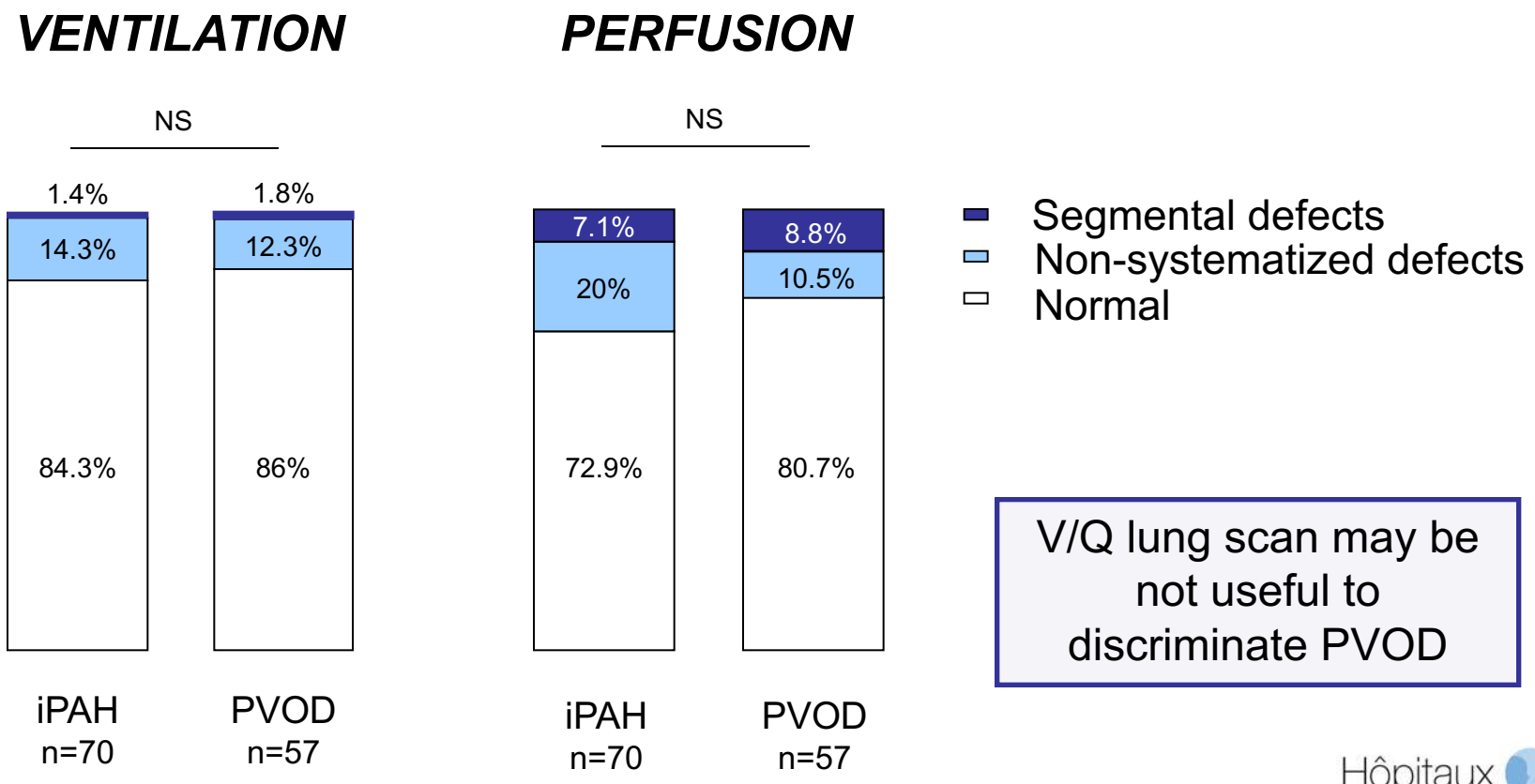
PERFUSION / VENTILATION LUNG SCAN

- Experience in the French Referral Centre:

  ⇒ 70 iPAH and 57 PVOD *(30 confirmed)*.



V/Q lung scan may be not useful to discriminate PVOD

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GCN2 and liver disease

Am J Physiol Endocrinol Metab 305: E1124–E1133, 2013.
First published September 3, 2013; doi:10.1152/ajpendo.00080.2013.

The eukaryotic initiation factor 2 kinase GCN2 protects against hepatotoxicity during asparaginase treatment

Gabriel J. Wilson,[1] Piyawan Bunpo,[2] Judy K. Cundiff,[2] Ronald C. Wek,[3] and Tracy G. Anthony[1,2]

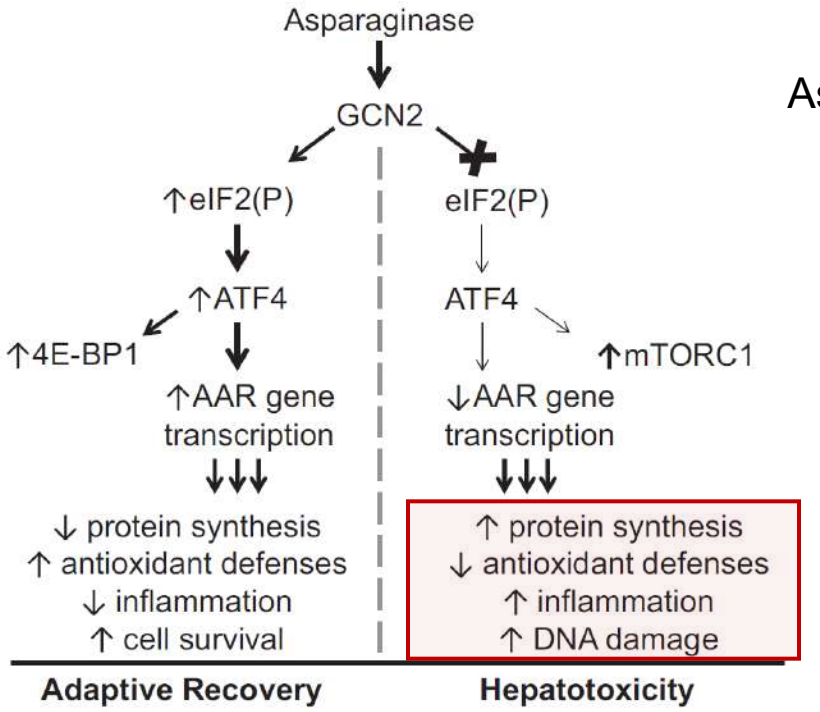

Fig. 5. The GCN2-initiated AAR promotes liver recovery during asparaginase treatment. The current working model shows that, in the absence of GCN2, both a premature restoration of protein synthesis alongside a failure to induce gene transcription by ATF4 alters the cellular redox environment, favoring a proinflammatory state and facilitating DNA damage and cell death.

Asparaginase

Gcn2$^{-/-}$ mice

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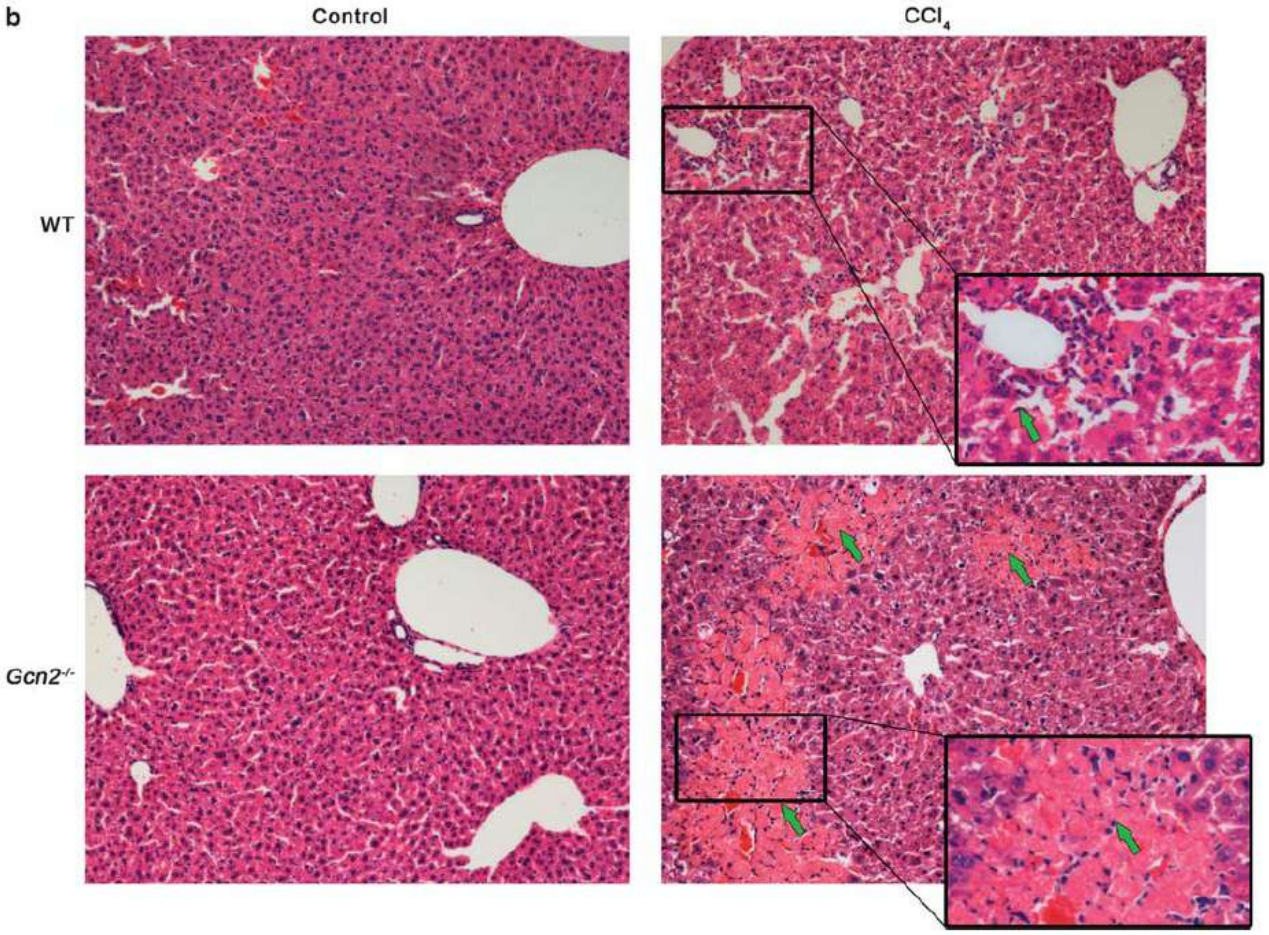
GCN2 kinase is a key regulator of fibrogenesis and acute and chronic liver injury induced by carbon tetrachloride in mice

Laboratory Investigation (2013) 93, 303–310

Elena Arriazu[1], Marina Ruiz de Galarreta[1], María J López-Zabalza[1], Tung Ming Leung[2], Natalia Nieto[2] and María J Iraburu[1]



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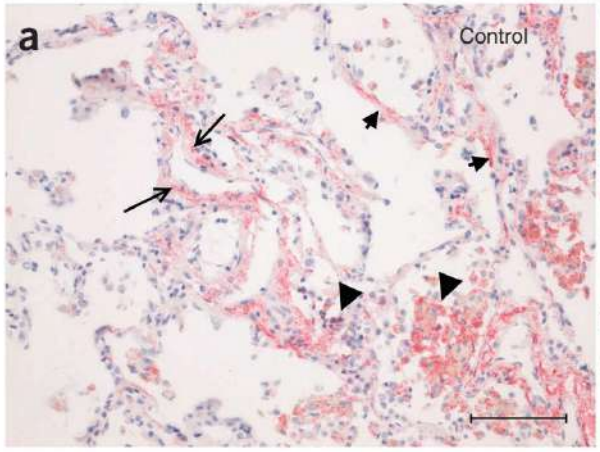
BASIC RESEARCH

Role of GCN2

- *EIF2AK4* gene codes for **GCN2** (general control nonderepressible 2)
- GCN2 is a **serine-threonine kinase** present in all eukaryotes that can induce changes in gene expression in response to aminoacid deprivation
- Role and expression of GCN2 in pulmonary vasculature is unknown

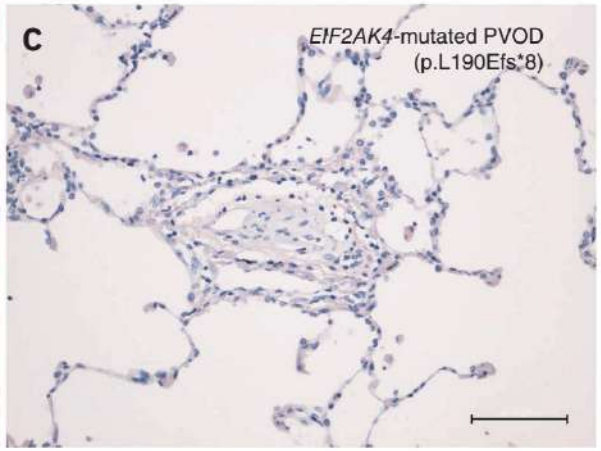
Immunohistochemical staining for GCN2

Control



Staining of smooth muscle cells and macrophages

EIF2AK4 mutated PVOD

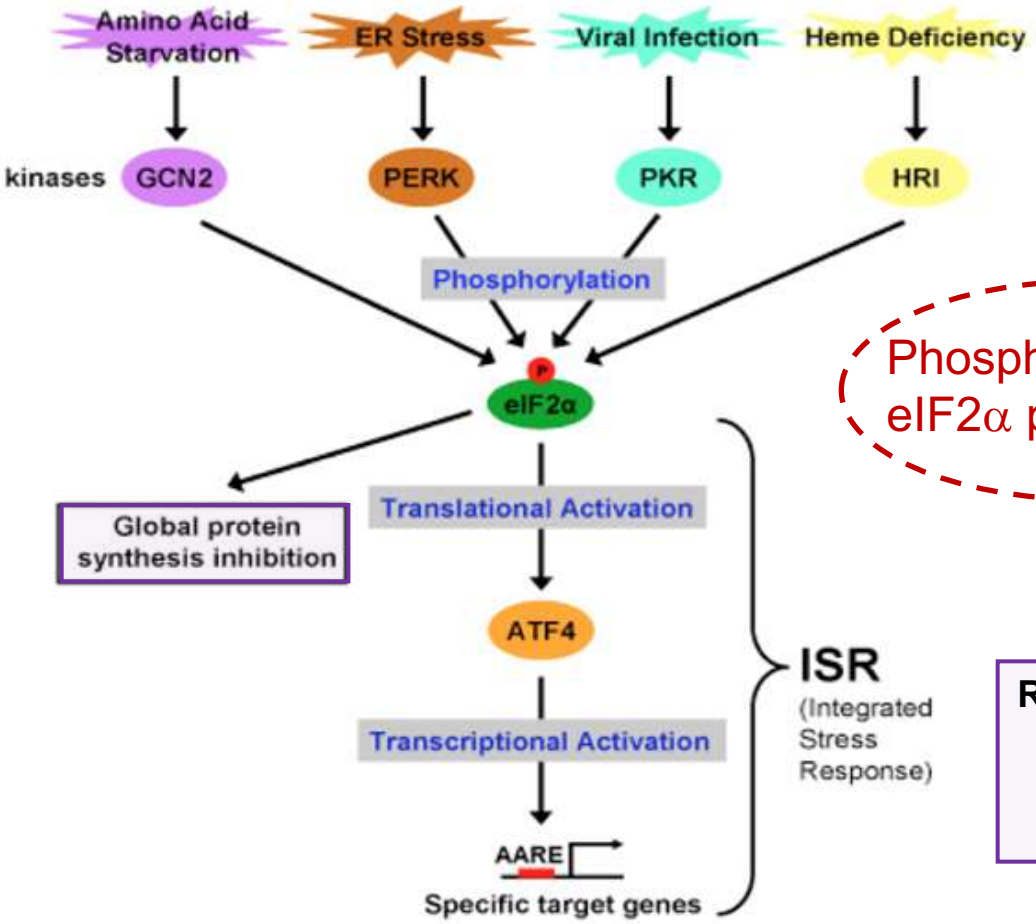


No staining

Eyries et al, *Nature Genetics* 2014

Role of GCN2

- GCN2 belongs to a family of 4 kinases which phosphorylate eIF2α
- eIF2α induce or inhibit the transcription of several target genes mediating **Integrated Stress Response (ISR)**

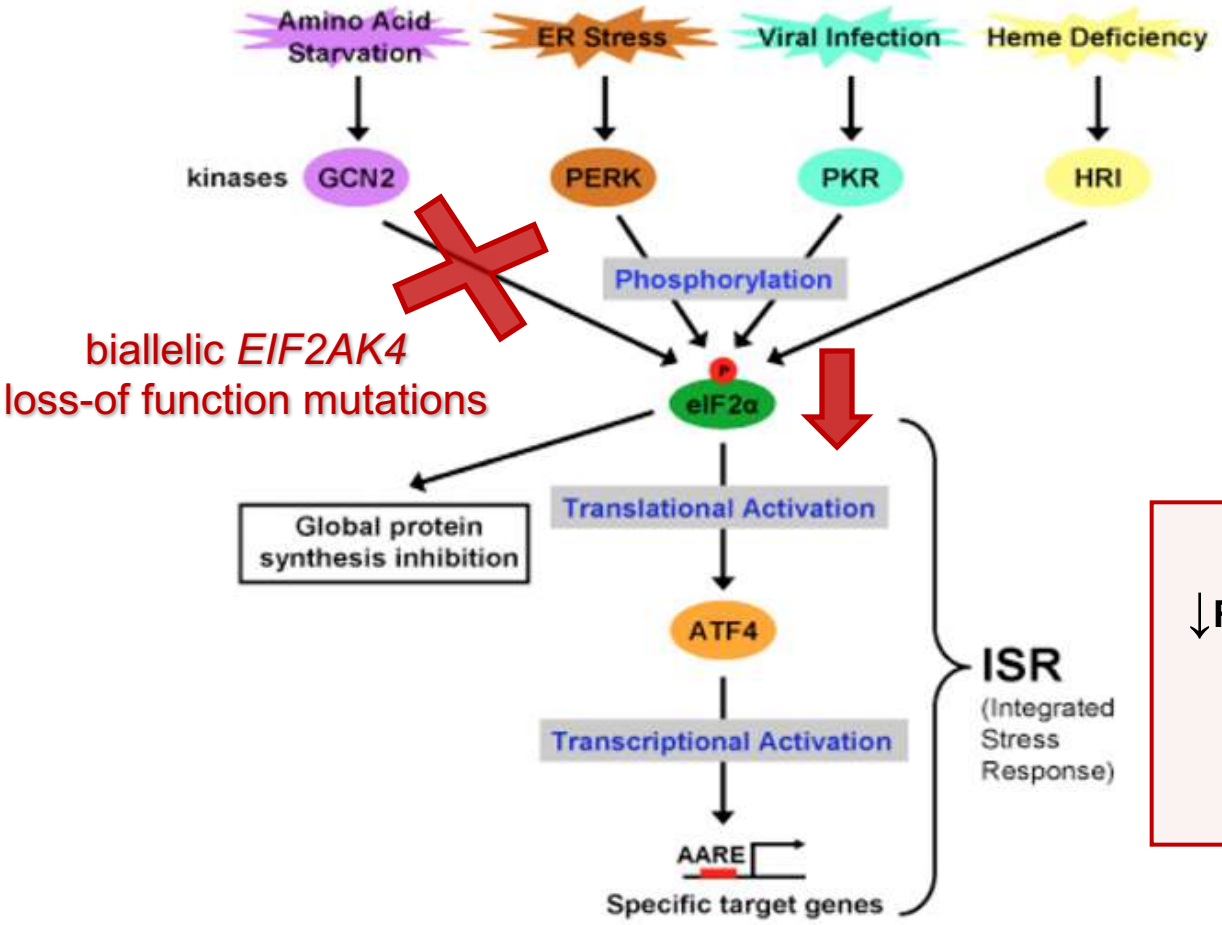


Phosphorylation of eIF2α protects cells

Resistance to oxydative stress
Decrease of inflammation
Cell survival
Angiogenesis (VEGF)

Role of GCN2

- At present, eIF2α is the only charcaterized substrate of GCN2
- Link between biallelic *EIF2AK4* loss-of function mutations and remodeling of lung vessels remains elusive.



↑ **Protein synthesis**

↓**Resistance to oxydative stress**

↑ **Inflammation**

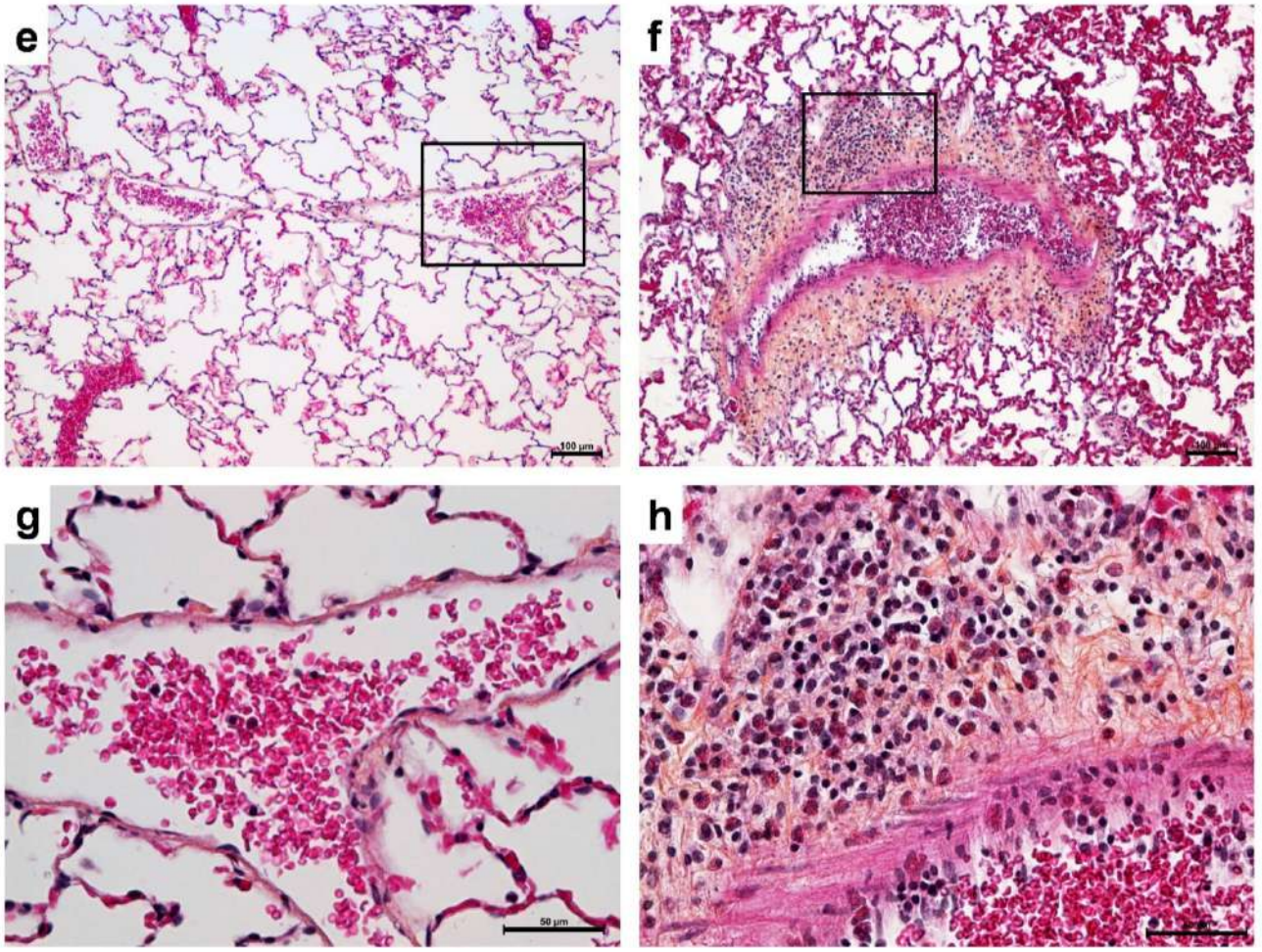
↓ **Cell survival**

↓ **Angiogenesis**

Cyclophosphamide associated PH

Venous remodeling + inflammation

Control | Cyclophosphamide



Ranchoux B, *Am J Pathol* 2014 Epub

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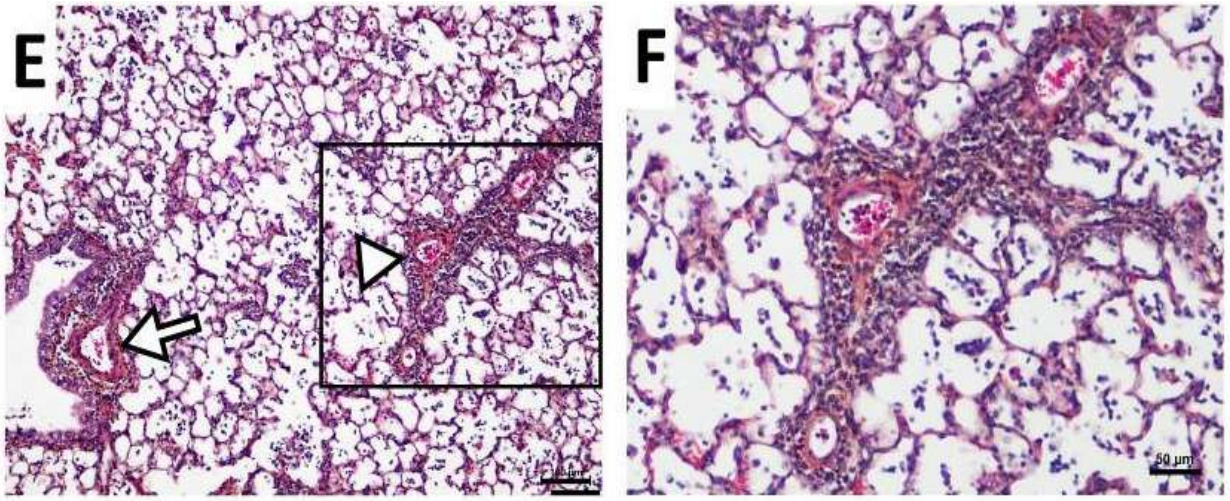
Mitomycin associated PVOD

MMC-rats

venular remodeling

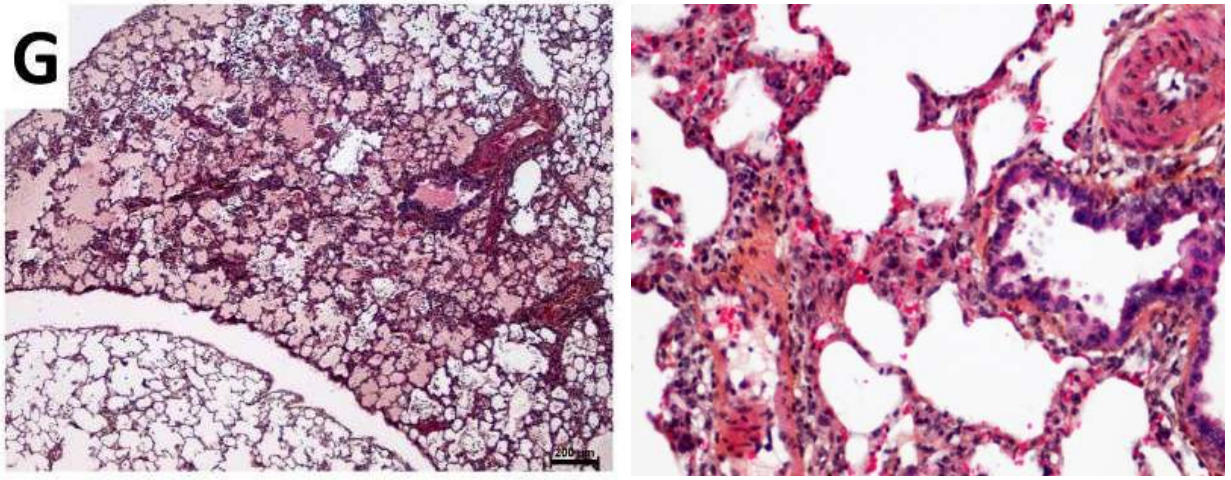
inflammation



MMC-rats

capillary proliferation

pulmonary edeam



Perros, *Circulation* 2015