GRCI 2017
France

6 AU 8 DÉCEMBRE 2017
Novotel Paris Tour Eiffel

Passion Communication Education

Epidémiologie et Diagnostic de l'HTP post-embolique

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Centre de Compétences Maladies Rares Pulmonaires

INSERM UMR-S 1140

DÉCLARATION DE LIENS D'INTÉRÊT AVEC LA PRÉSENTATION

Intervenant : Olivier Sanchez, Paris

☑ Je déclare les liens d'intérêt suivants :

MSD, BAYER, ACTELION, BMS, PFIZER, DAIICHI SANKYO

Classification des hypertensions pulmonaires

1. Hypertension artérielle pulmonaire

- 1.1 Idiopathique
- 1.2 Héritable
  - 1.2.1 Mutations *BMPR2*
  - 1.2.2 Autres mutations
- 1.3 Induite par des médicaments, des toxiques
- 1.4 Associée à
  - 1.4.1 Connectivite
  - 1.4.2 Infection VIH
  - 1.4.3 Hypertension portale
  - 1.4.4 Cardiopathie congénitale
  - 1.4.5 Bilharziose

1'. Maladie veino-occlusive pulmonaire et/ou hémangiomatose capillaire pulmonaire

- 1'.1 Idiopathique
- 1'.2 Héritable
  - 1'.2.1 Mutations *EIF2AK4*
  - 1'.2.2 Autres mutations
- 1'.3 Induite par des médicaments, des toxiques, ou les radiations
- 1'.4 Associée à
  - 1'.4.1 Connectivite
  - 1'.4.2 Infection VIH

1''. Hypertension pulmonaire persistante du nouveau-né

2. Hypertension pulmonaire due à des maladies du cœur gauche

- 2.1 Dysfonction ventriculaire gauche systolique
- 2.2 Dysfonction ventriculaire gauche diastolique
- 2.3 Valvulopathies
- 2.4 Obstacle gauche congénital ou acquis et cardiomyopathies
- 2.5 Sténoses veineuses pulmonaires congénitales ou acquises

3. Hypertension pulmonaire due à des maladies respiratoires chroniques et/ou à une hypoxie

- 3.1 Bronchopneumopathie chronique obstructive
- 3.2 Pneumopathies interstitielles
- 3.3 Autres maladies respiratoires restrictives et/ou obstructives
- 3.4 Syndrome d'apnée du sommeil
- 3.5 Syndromes d'hypoventilation alvéolaire
- 3.6 Séjour prolongé en altitude
- 3.7 Anomalies du développement

4. Hypertension pulmonaire thromboembolique chronique et autres obstructions artérielles pulmonaires

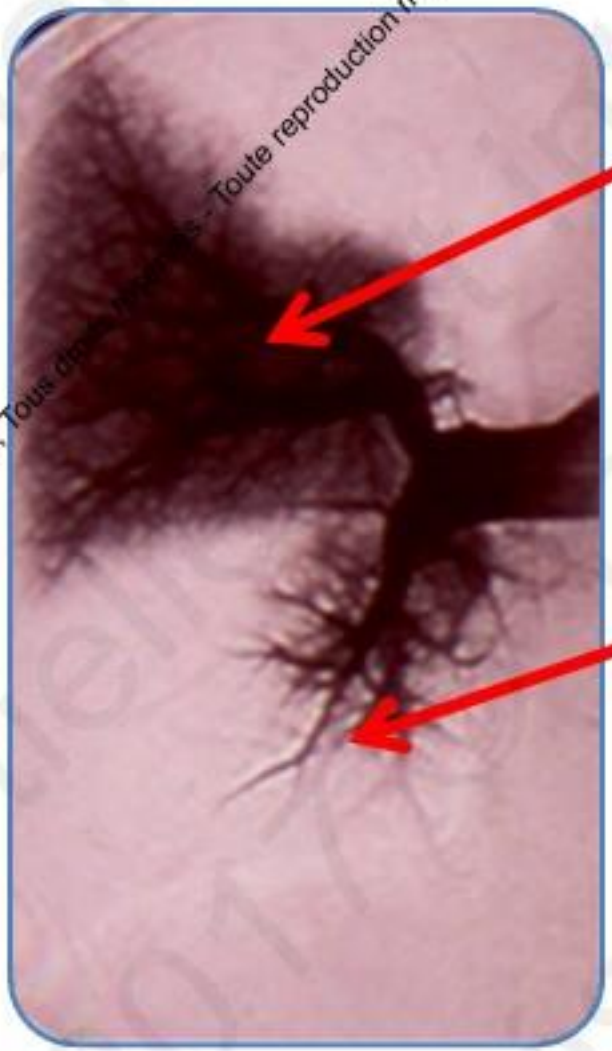
- 4.1 Hypertension pulmonaire thromboembolique chronique
- 4.2 Autres obstructions artérielles pulmonaires
  - 4.2.1 Angiosarcome
  - 4.2.2 Autres tumeurs intravasculaires
  - 4.2.3 Artérite
  - 4.2.4 Sténoses artérielles pulmonaires congénitales
  - 4.2.5 Parasites (hydatidose)

5. Hypertension pulmonaire de mécanisme peu clair ou multifactoriel

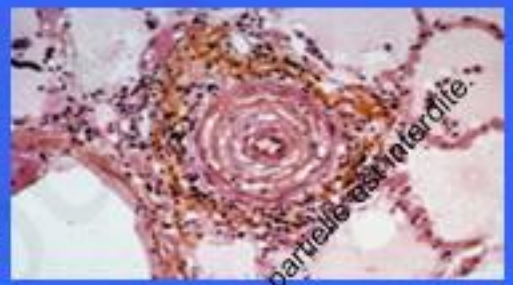
- 5.1 Maladies hématologiques : anémies hémolytiques chroniques, syndromes myéloprolifératifs, splénectomie
- 5.2 Maladies systémiques : sarcoïdose, histiocytose langerhansienne pulmonaire, lymphangioléiomyomatose, neurofibromatose
- 5.3 Maladies métaboliques : glycogénose, maladie de Gaucher, dysthyroïdie
- 5.4 Autres maladies : microangiopathie thrombotique tumorale pulmonaire, fibrose médiastinale, insuffisance rénale chronique (dialysée ou non), hypertension pulmonaire segmentaire

D'après Galiè N et al., Eur Respir J 2015;46(4):903-75

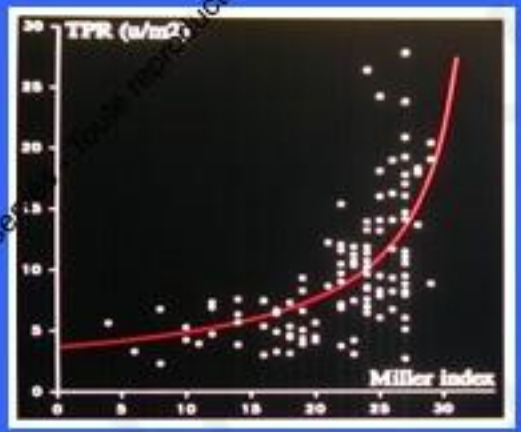
Physiopathologie



Remodelage



Obstruction



CTEPH and previous VTE: data from the International CTEPH Registry[1]

	All patients N=679	Operable patients N=427	Nonoperable patients N=247	p
Confirmed previous acute PE	**74.8%**	77.5%	70.0%	0.034
Recurrent PE	32.8%	35.0%	28.8%	0.214
PE reported as « massive »	40.8%	47.1%	29.4%	0.009
Confirmed previous DVT	56.1%	60.4%	49.0%	0.029
Thrombolytic treatment	14.4%	18.5%	6.6%	0.0009

[1] Pepke Zaba Circulation 2011;124:1973-81

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Clinical conditions predisposing for CTEPH

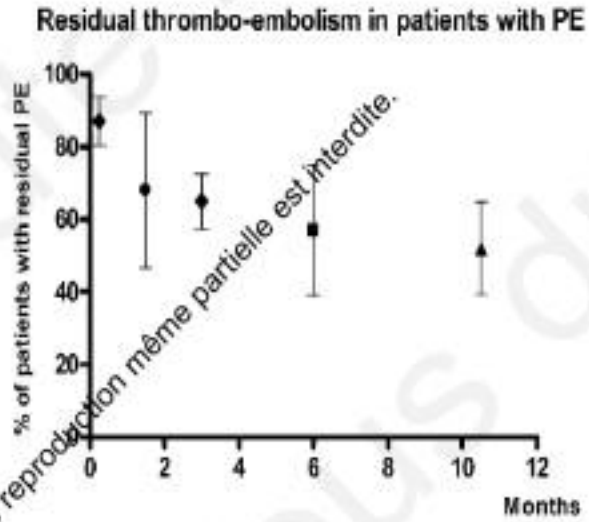
Retrospective study comparing
433 patients with CTEPH vs 254 patients with other non thromboembolic PH

Condition	OR (95% CI)	p
Ventriculo-atrial shunt or infected pace-maker	76.40 (7.67-10350.62)	<0.001
Splenectomy	17.87 (1.56-2438.07)	0.017
Thyroid hormone replacement	6.10 (2.73-15.05)	<0.001
APA / LAC	4.20 (1.56-12.21)	0.004
Malignancy	3.76 (1.47-10.43)	0.005
Previous VTE	4.52 (2.35-9.12)	<0.001
Recurrent VTE	14.49 (5.40-43.08)	<0.001

Bonderman ERJ 2009;33:325-331

From acute PE to CTEPH

- In patients who survive a PE
  - Resolution of the clots (physiological fibrinolysis) => restoration of blood flow and normal haemodynamic parameters in 10-21 days[1]
- 30 to 50% of patients have residual pulmonary vascular obstruction on V/Q scan 1 year after a PE[2,3]
- 44% of patients have persistent right ventricular dysfunction 1 year after a PE[4]
- 56% of patients have persistent complaints of dyspnea after a PE [5]
  - The majority of them developed new or worsened dyspnea after PE
- Patients with residual pulmonary vascular obstruction are more dyspneic, have functional limitation (↓ 6MWT) and higher sPAP [2]



[1] Dalen *et al* N Engl J Med 1969

[2] Nijkeuter *et al* Chest 2006

[3] Sanchez *et al* JTH 2010

[4] Ribeiro *et al* Circulation 1999

[5] Klok *et al* Eur J Intern Med 2008

Incidence of Chronic Thromboembolic Pulmonary Hypertension after Pulmonary Embolism

Vittorio Pengo, M.D., Anthonie W.A. Lensing, M.D., Martin H. Prins, M.D.,

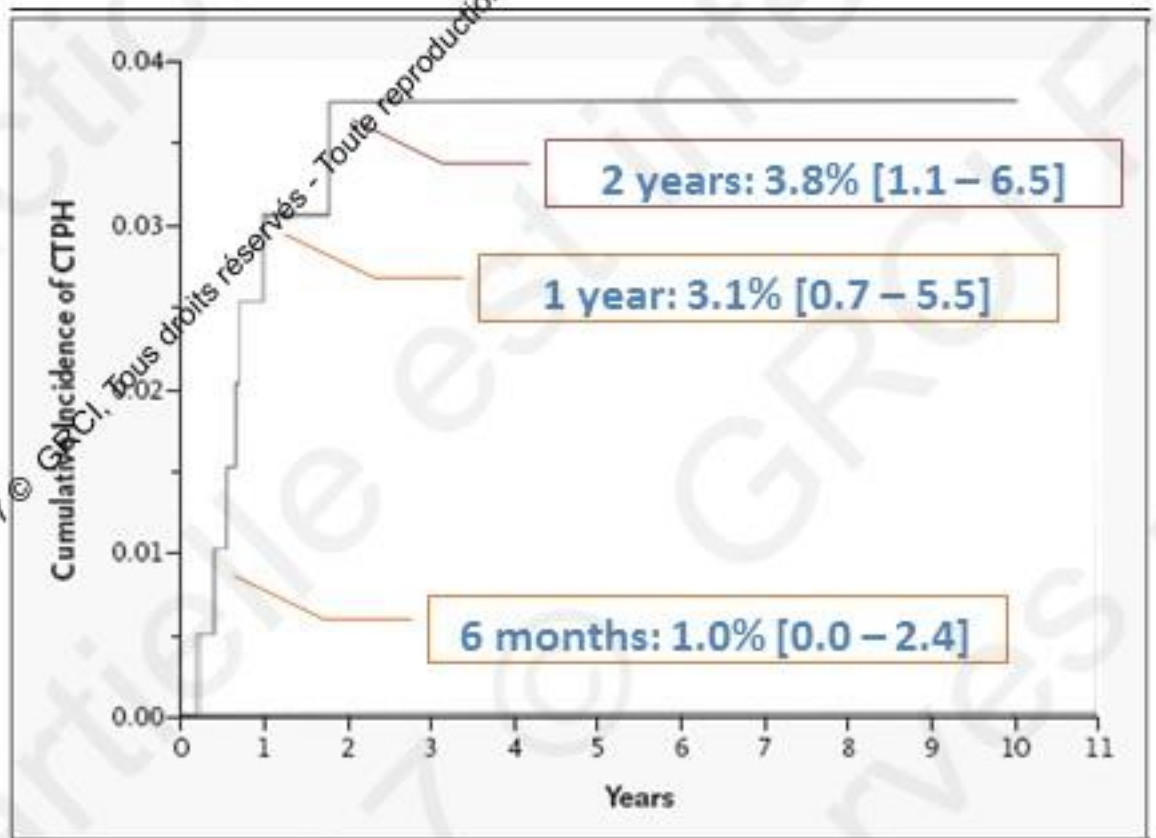


Figure 2. The Cumulative Incidence of CTPH after a First Episode of Pulmonary Embolism without Prior Deep-Vein Thrombosis.

- Risk factors for CTEPH
  - Age
  - Previous VTE
  - « Idiopathic » PE
  - Proximal PE

N Engl J Med 2004;350:2257-64.

Incidence of Chronic Thromboembolic Pulmonary Hypertension after Pulmonary Embolism

Vittorio Pengo, M.D., Anthonie W.A. Lensing, M.D., Martin H. Prins, M.D.,

Patient No.	Age at Time of Qualifying PE	Time from Qualifying PE to Symptoms Suggestive of CTPH	Time from Symptoms to Diagnosis of CTPH	Findings at Diagnosis of CTPH			
				Mean PAP	Systolic PAP	Residual Perfusion	NYHA Class
	yr	*mo*	*mo*	*mm Hg*		*%*	
PE as first episode of VTE							
1	68	21	0	34	65	54	II
2	69	6	2	44	80	48	II
3	37	5	1	25	55	60	II
4	52	2	1	34	60	43	II
5	72	3	2	50	90	38	III
6	53	5	3	35	85	50	II
7	20	10	2	50	90	39	III

N Engl J Med 2004;350:2257-64.

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	yr	*mo*	*mo*	*mm Hg*		*%*	
PE as first episode of VTE							
1	68	21			6[illegible]	64	II
2	69	6		2[illegible]			II
3	37	5					
4	52	2					
5	72	3					
6	53	5					II
7	20	10	2			39	

Absence of initial hemodynamic data at the time of acute PE diagnosis

N Engl J Med 2004;350:2257-64.

Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

Thromb Haemost 2014; 112:

Prevalence of CTEPH after pulmonary embolism

Laurent Guérin[1]; Francis Couturaud[2]; Florence Parent[3]; Marie-Pierre Revel[4]; Florence Gillaizeau[5]; Benjamin Planquette[1]; Daniel Pozzi[1]; Marie Guégan[2]; Gérald Simonneau[3]; Guy Meyer[1,6]; Olivier Sanchez[1,6]

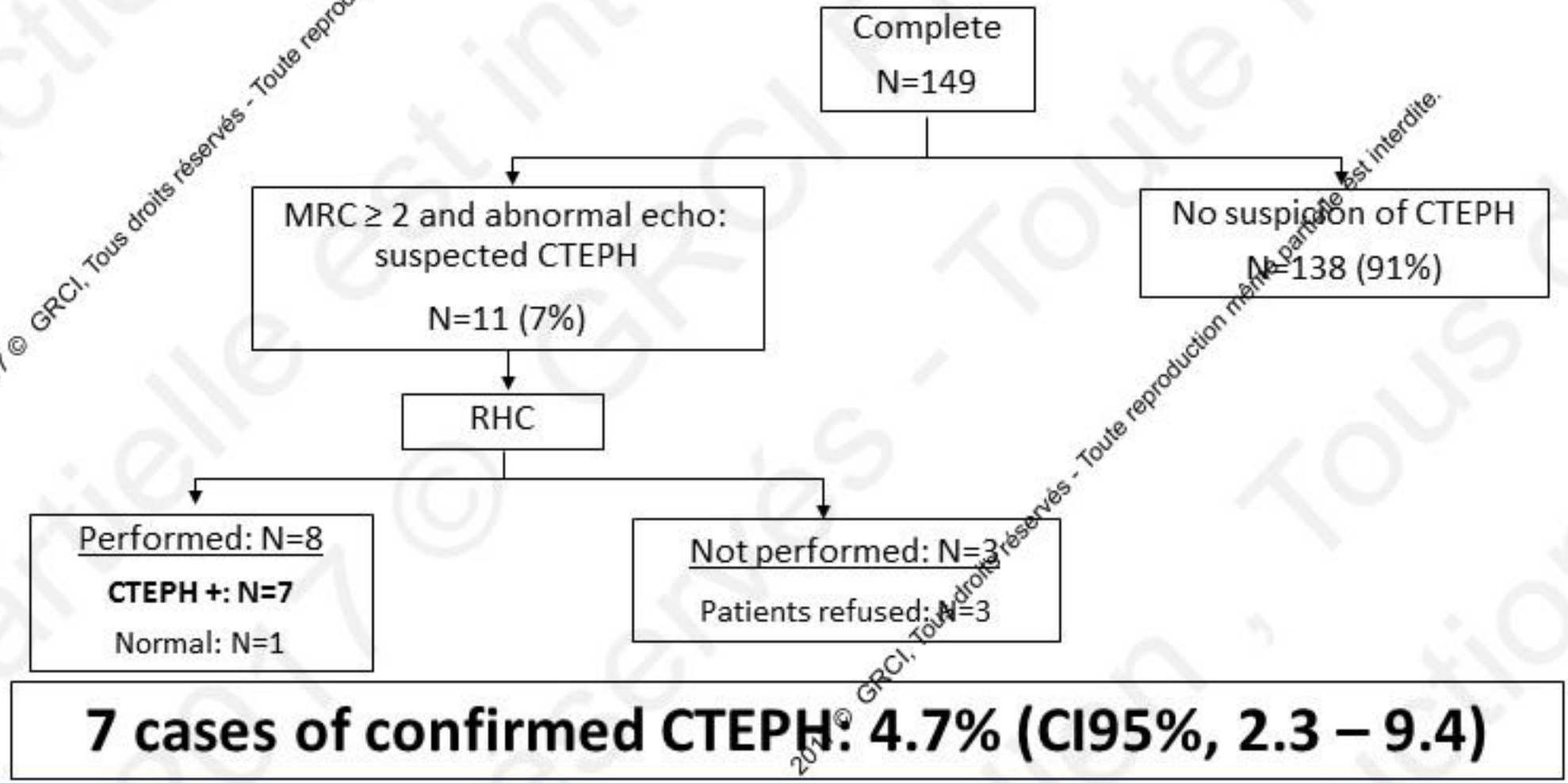
- At the time of acute PE diagnosis
  - Echocardiography: RV/LV, sPAP
  - BNP, NT-proBNP
- Patients alive after an acute PE
- Prospective follow-up during a maximum of 2 years
  - Assessment of persistent dyspnea (MRC scale)
  - Echocardiography: V_{TR} V_{PR} RV/LV
  - Right heart catheterization in case of dyspnea MRC ≥ 2 AND abnormal echocardiography
  - CTEPH: mPAP ≥ 25 PcwP < 15 + abnormal V/Q scan

Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

Thromb Haemost 2014; 112:

Prevalence of CTEPH after pulmonary embolism

Laurent Guérin[1]; Francis Couturaud[2]; Florence Parent[3]; Marie-Pierre Revel[4]; Florence Gillaizeau[5]; Benjamin Planquette[1]; Daniel Pontal[1]; Marie Guillon[2]; Gérald Simonneau[3]; Guy Meyer[1,6]; Olivier Sanchez[1,6]



7 cases of confirmed CTEPH: 4.7% (CI95%, 2.3 – 9.4)

Individual characteristics of 7 CTEPH

Patient	Initial PE			During follow-up								
	Age (years)	sPAP (mmHg)	RV/LV	MRC	VTR (m/s)	sPAP (mmHg)	RV/LV	Time to RHC (months)	RAP (mmHg)	mPAP (mmHg)	CO (l/min)	PVR (UI)
1	71	45	0.9	2	3.8	73	1.1	27	11	54	4.9	8.8
2	74	70	1.1	3	5.4	132	1.3	7.2	10	58	3.2	16.1
3	81	81	1.3	5	4.7	100	1.4	7.4	7	52	3.1	11.6
4	77	84	1.1	2	3.5	58	NA	10	7	30	6.2	2.9
5	70	43	0.5	2	4.2	75	0.7	22.7	4	36	5.7	4.6
6	75	62	0.5	2	2.8	56	0.72	3	3	30	3.7	6.1
7	72	102	0.8	2	4	81	1.1	6.6	4	53	4.5	10.7
Mean	**75**	**75**	**0.97**					**13.7**	**7**	**45**	**4.5**	**7.5**
± SD	**4**	**20**	**0.3**					**9**	**3**	**12**	**1.2**	**3.5**

The Hemodynamic Response to Pulmonary Embolism in Patients Without Prior Cardiopulmonary Disease

McIntyre et al. Am J Cardiol 1971; 28: 288-94

- 20 patients
- No prior cardiopulmonary disease
- PE angiographically proven
  - Pulmonary vascular obstruction (Miller index): 13 – 68%
- RHC

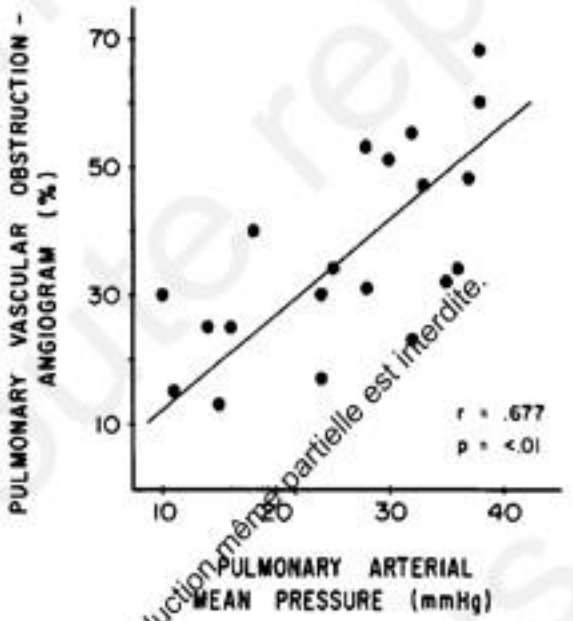


Figure 2. A highly significant relation existed between mean pulmonary arterial pressure **(abscissa)** and estimated angiographic obstruction **(ordinate).**

Mean PAP never exceed 40 mmHg (sPAP ≈ 60 mmHg) despite massive obstruction in some patients suggesting that this level approximates the maximal pressure response of a previously normal right ventricle.

➔ **mPAP > 40 mmHg during acute PE should suggest either prior CTEPH or non embolic causes of PH**

CT Signs of CTEPH at the time of acute PE

Among 120 patients who had spiralCT for diagnosis of acute PE

	CTEPH + (n=7)	CTEPH – (n=99)
Organised mural thrombi, yes / no, (%)	6 (86) / 1(14)	20 (20) / 79 (80)
Arterial webs or bands, yes / no, (%)	4 (57) / 3 (43)	3 (3) / 96 (97)
Dilated bronchial arteries, yes / no, (%)	1 (25) / 3 (75)1	13 (13) / 76 (87)
Mosaic parenchymal perfusion pattern, yes / no, (%)	6 (86) / 1 (14)	27 (27) / 70 (73)
Presence of at least two CT signs, yes / no, (%)	7 (100) / 0 (0)	19 (19) / 80 (81)

[1]Due to the quality of injections in bronchial arteries, this sign was interpretable in only 4 out the 7 CT.

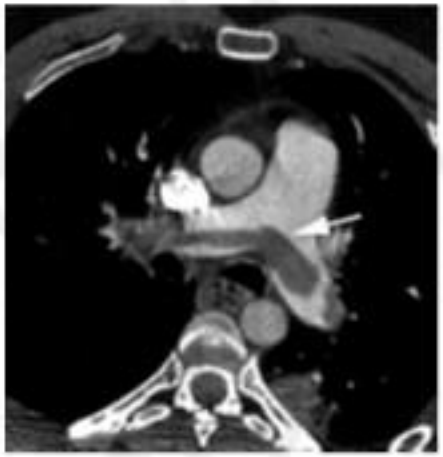
Differentiating acute from chronic thromboemboli on CT

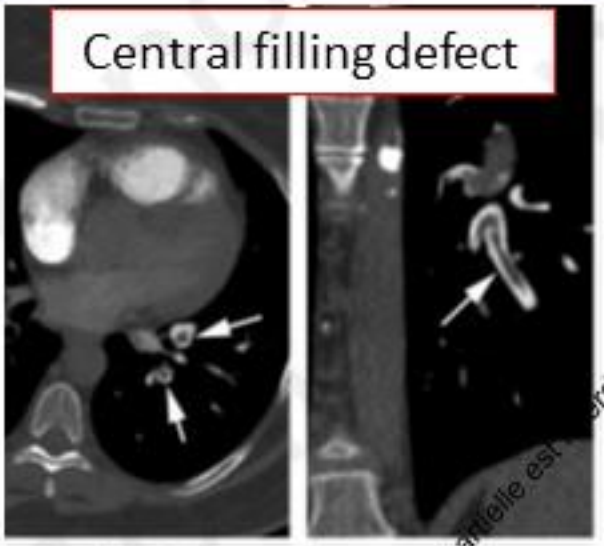
	Acute	Chronic
Direct features	Preserved calibre of the vessel Central or eccentric filling defect	Vessel narrowing Calibre change Intimal irregularities Laminated thrombus Webs / Bands Complete amputation of the vessel
Indirect features	Right ventricular enlargement (if PE is severe)	Increased calibre of main pulmonary artery Right ventricular enlargement and hypertrophy Prominence of bronchial arteries
Parenchymal features	Triangular subpleural consolidation or groud glass with fine reticular changes	Mosaic perfusion Subpleural scar / cavitation Focal pleural thickening

Ruggiero Clinical Radiol 2017

Direct features

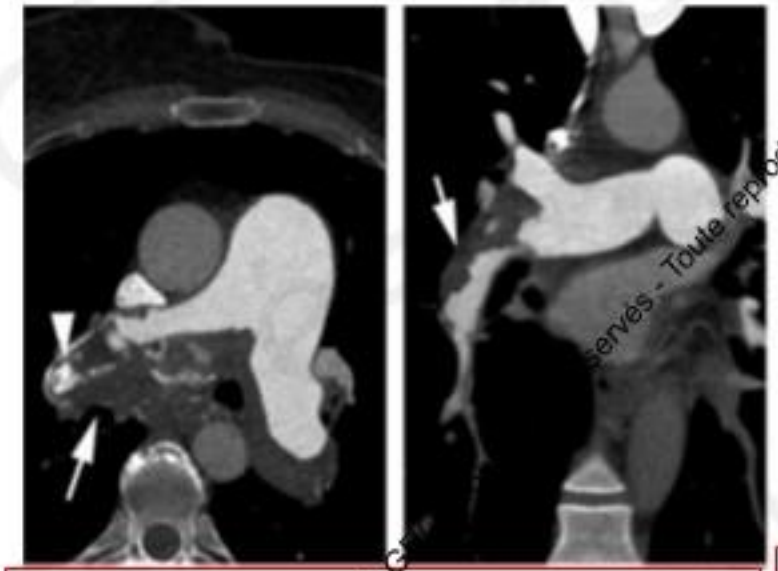
Acute PE



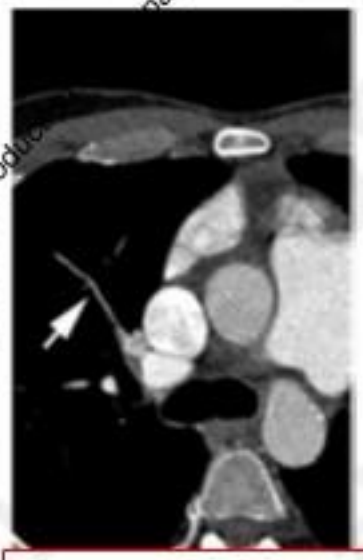


Central filling defect

CTEPH



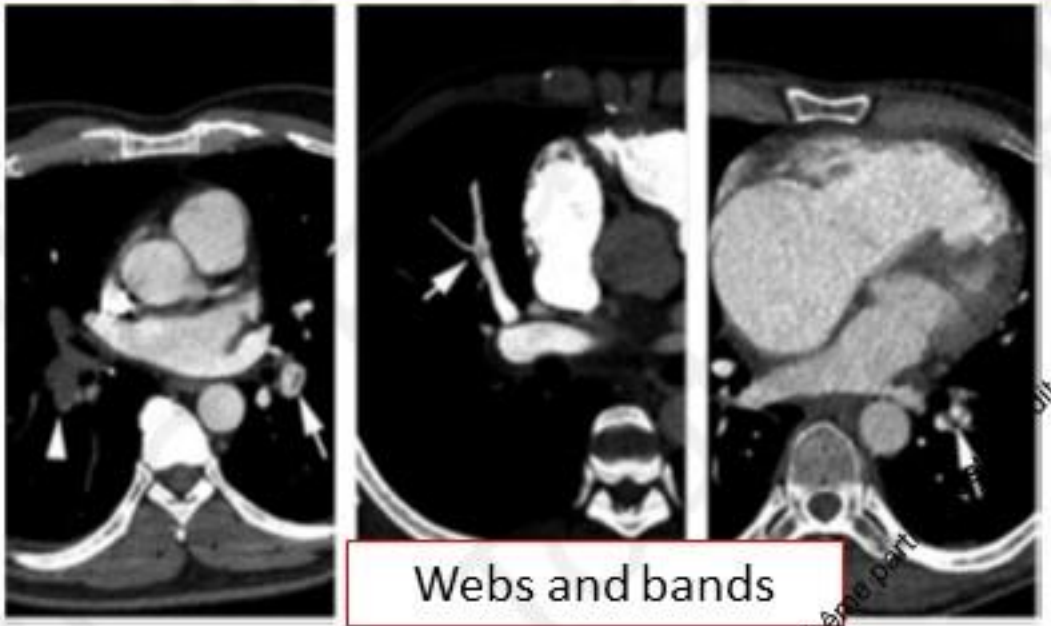
Chronic large pulmonary embolus



Marked reduction in calibre of PA

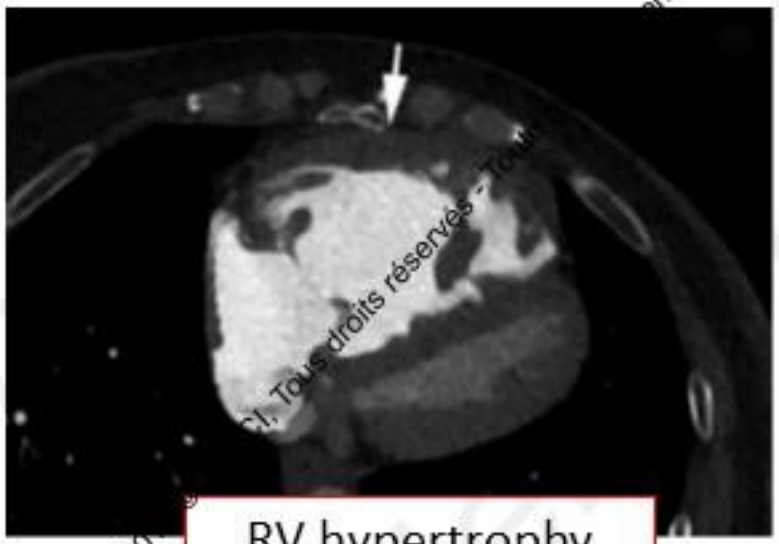
Indirect features

CTEPH



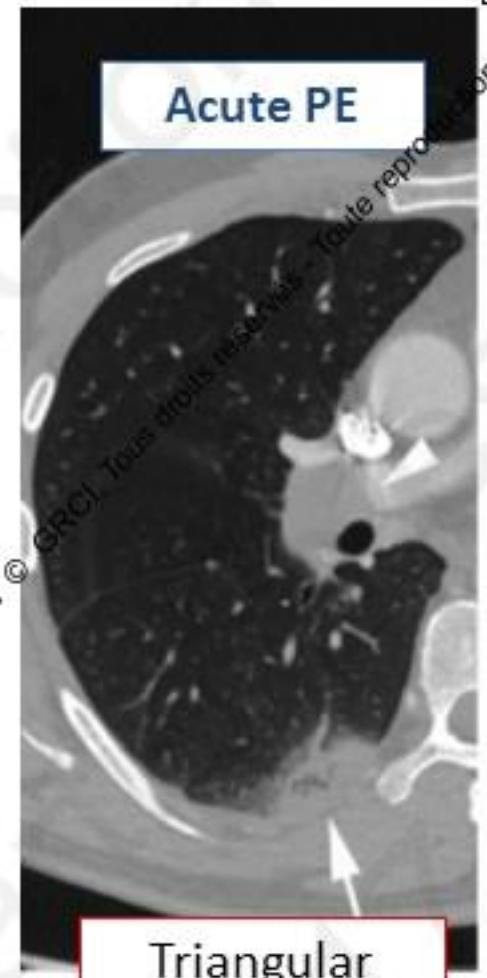
Webs and bands

CTEPH

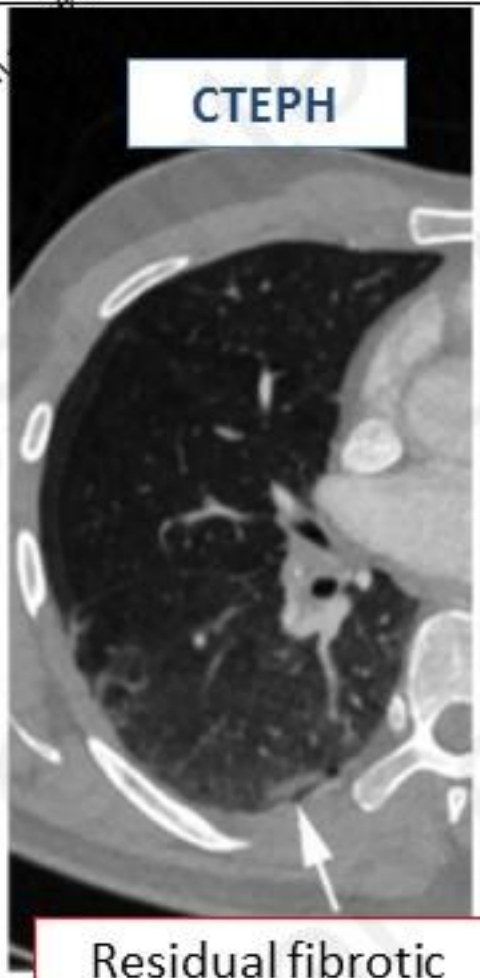


RV hypertrophy

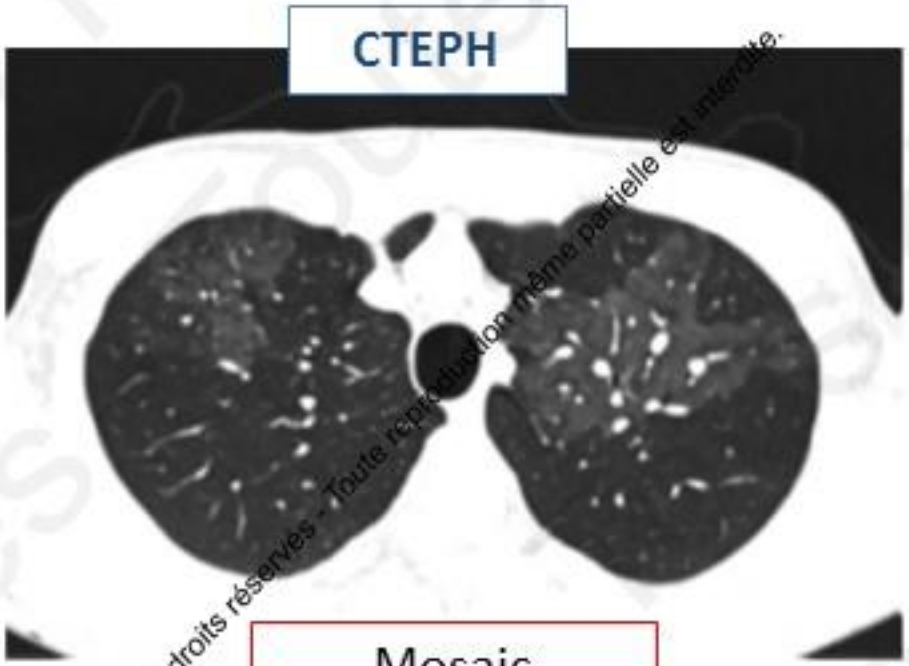
Parenchymal features



Triangular subpleural consolidation



Residual fibrotic band & pleura thrickening



Mosaic perfusion

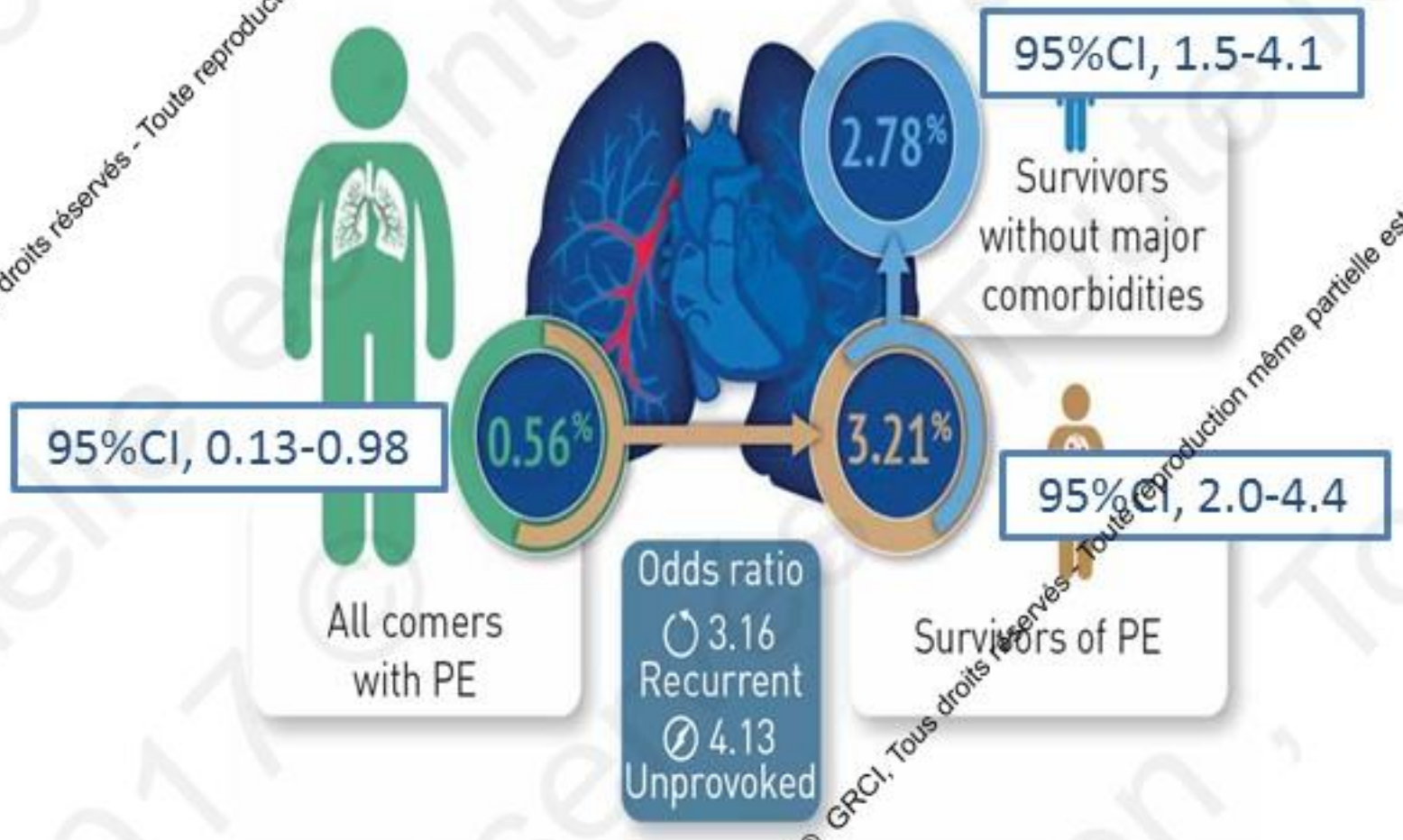
Incidence of CTEPH after PE systematic review and meta-analysis

- To assess the cumulative incidence of CTEPH after PE
  - 3 pre-defined sub-categories
    - All comers
    - Survivors
    - Survivors without comorbidities
  - RHC vs Echo
- To assess risk factors of CTEPH

	Studies (n=15)	Patients (n=3963)
All comers	2	1186
Survivors	4	999
Survivors without comorbidities	9	1775

- Ende-Verhaar YM *et al. Eur Respir J* 2017;49:1601792.

Incidence of CTEPH after PE



- Ende-Verhaar YM *et al. Eur Respir J* 2017;49:1601792

Risk factors for CTEPH after PE

Risk factor	Odds Ratio	95% CI
Unprovoked PE	4.1	2.1–8.2
Recurrent VTE	3.2	1.7–5.9

- Ende-Verhaar YM *et al. Eur Respir J* 2017;49:1601792.

Incidence of CTEPH after PE echo vs RHC studies

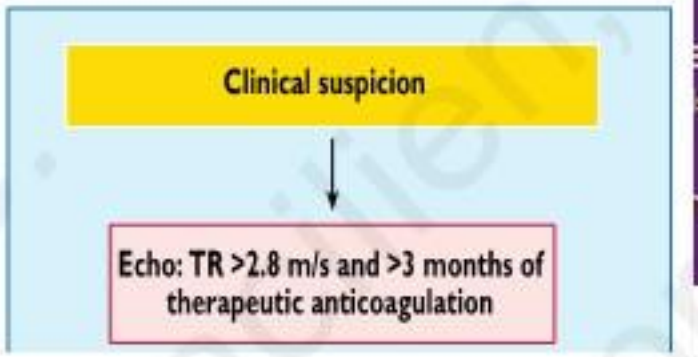
Diagnosis of CTEPH	Incidence	95% CI
Echo only (6 studies)	9.1%	4.1-14.0
RHC (9 studies)	2.8%	1.5-4.1

- Ende-Verhaar YM *et al. Eur Respir J* 2017;49:1601792

ESC 2015 guidelines

Recommendations	Class[a]	Level[b]
In PE survivors with persistent dyspnoea, diagnostic evaluation for CTEPH should be considered.	IIa	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended.	III	C

Galiè Eur Heart J 2016;37:67-119



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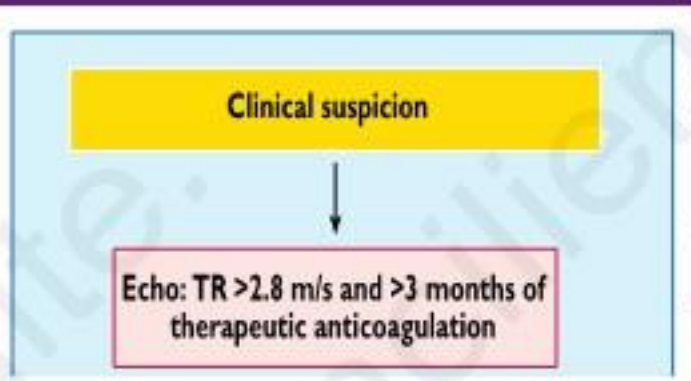
Galiè Eur Heart J 2016;37:67-119



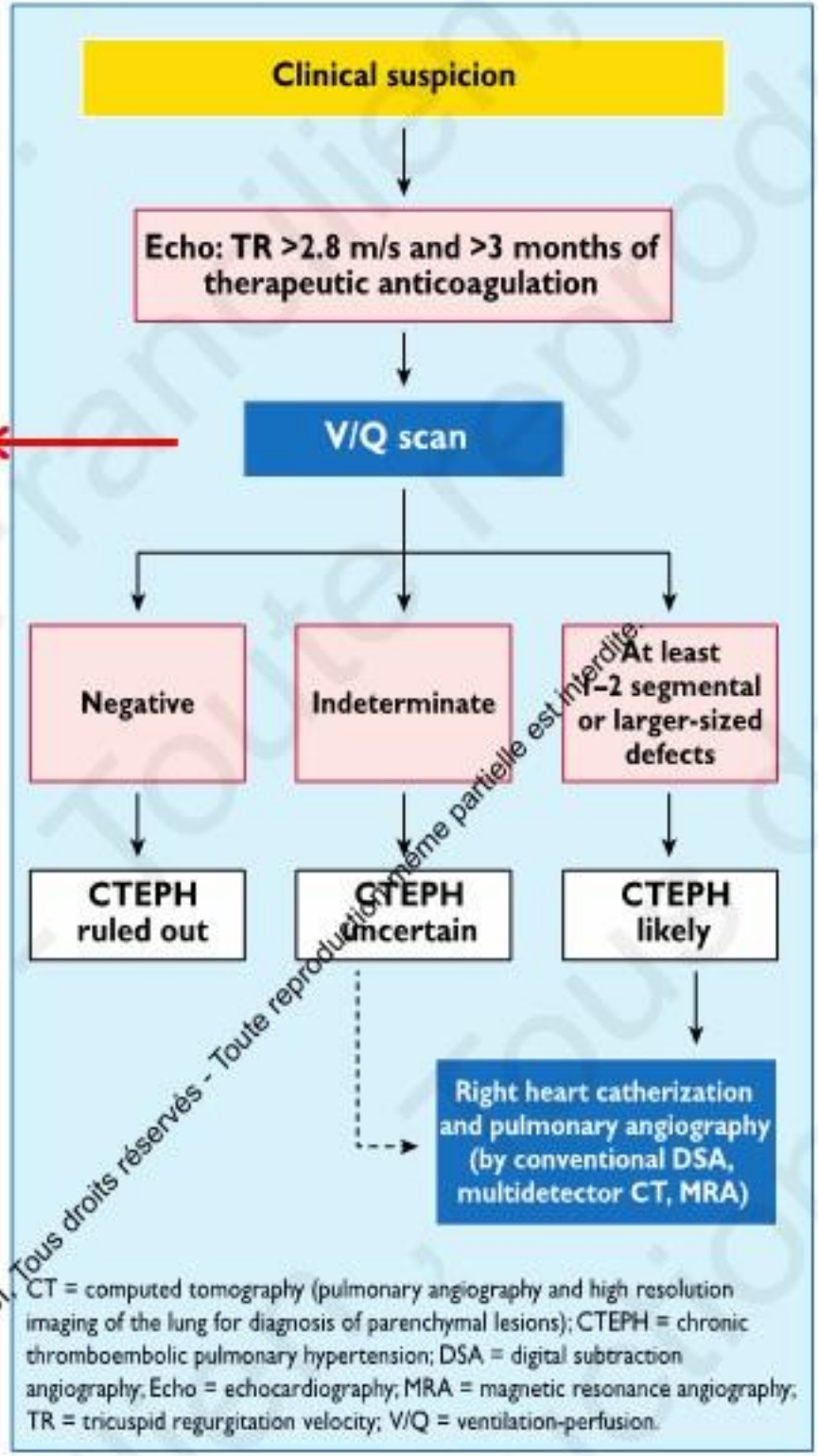
Vitesse d'insuffisance tricuspide (m/s)	Autres signes échographiques d'HTP	Probabilité d'HTP à l'échographie cardiaque
≤ 2,8 ou non mesurable	Non	Bas
≤ 2,8 ou non mesurable	Oui	Intermédiaire
2,9-3,4	Non	
2,9-3,4	Oui	Haut
> 3,4	Non requis	

A. Ventricules	B. Artère pulmonaire	C. Veine cave et Oreillette Droite
Rapport du diamètre basal ventricule droit / ventricule gauche (VG) > 1,0	Temps d'accélération du flux d'éjection pulmonaire < 105 m/s et/ou "notch" (encoche) mésosystolique	Diamètre de la veine cave inférieure > 21 mm ***avec*** diminution de son collapsus inspiratoire (< 50 % lors du "sniff test" ou < 20 % en inspiration normale)
Inversion ou aplatissement de la courbure du septum interventriculaire (index d'excentricité du VG > 1,1 en systole et/ou en diastole)	Vitesse protodiastolique de régurgitation pulmonaire > 2,2 m/s	Surface de l'oreillette droite (télésystole) > 18 cm^2
	Diamètre de l'artère pulmonaire > 25 mm	

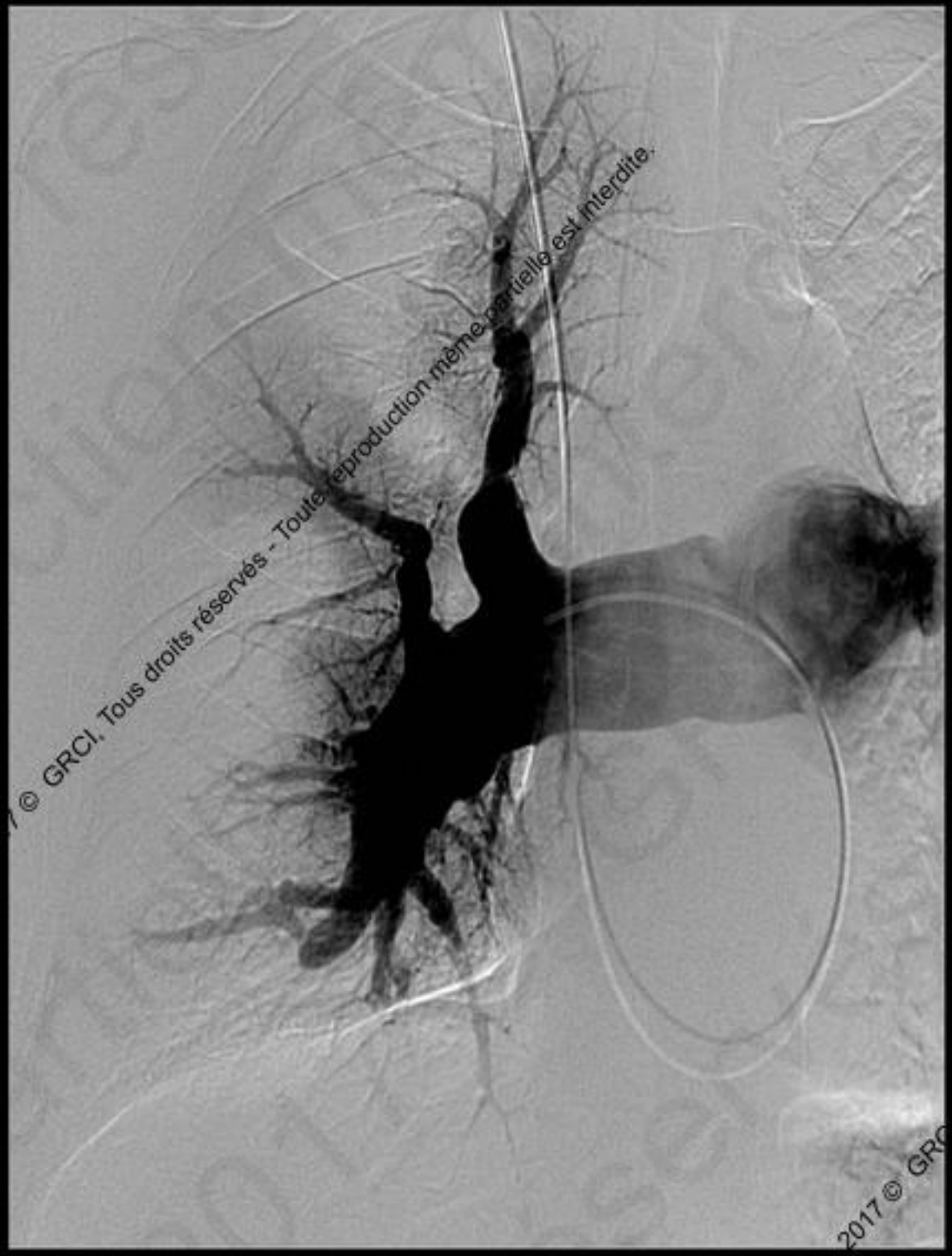
Galiè Eur Heart J 2016;37:67-119

Indicator	Scintigraphy V/Q (1)*	Scintigraphy V/Q (2)†	CTPA
Sensitivity (%)	97.4	96.2	51.3
Specificity (%)	90	94.6	99.3
Accuracy (%)	92.5	95.2	82.8
NPV (%)	98.5	97.9	79.7
PPV (%)	83.5	90.3	97.6

*Intermediate with high-probability scans as indicative of CTEPH.
†Only high-probability scans as indicative of CTEPH.
NPV = negative predictive value; PPV = positive predictive value.

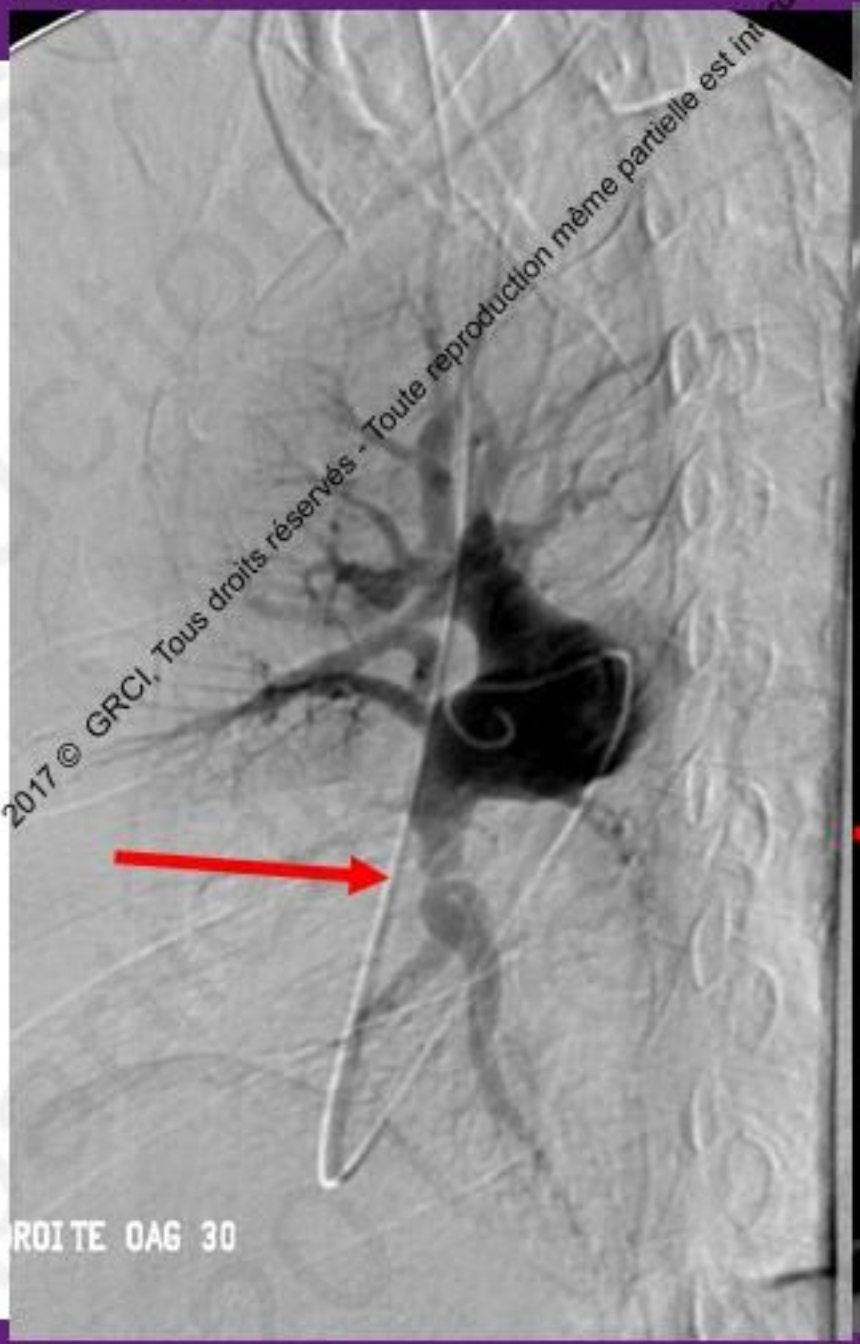


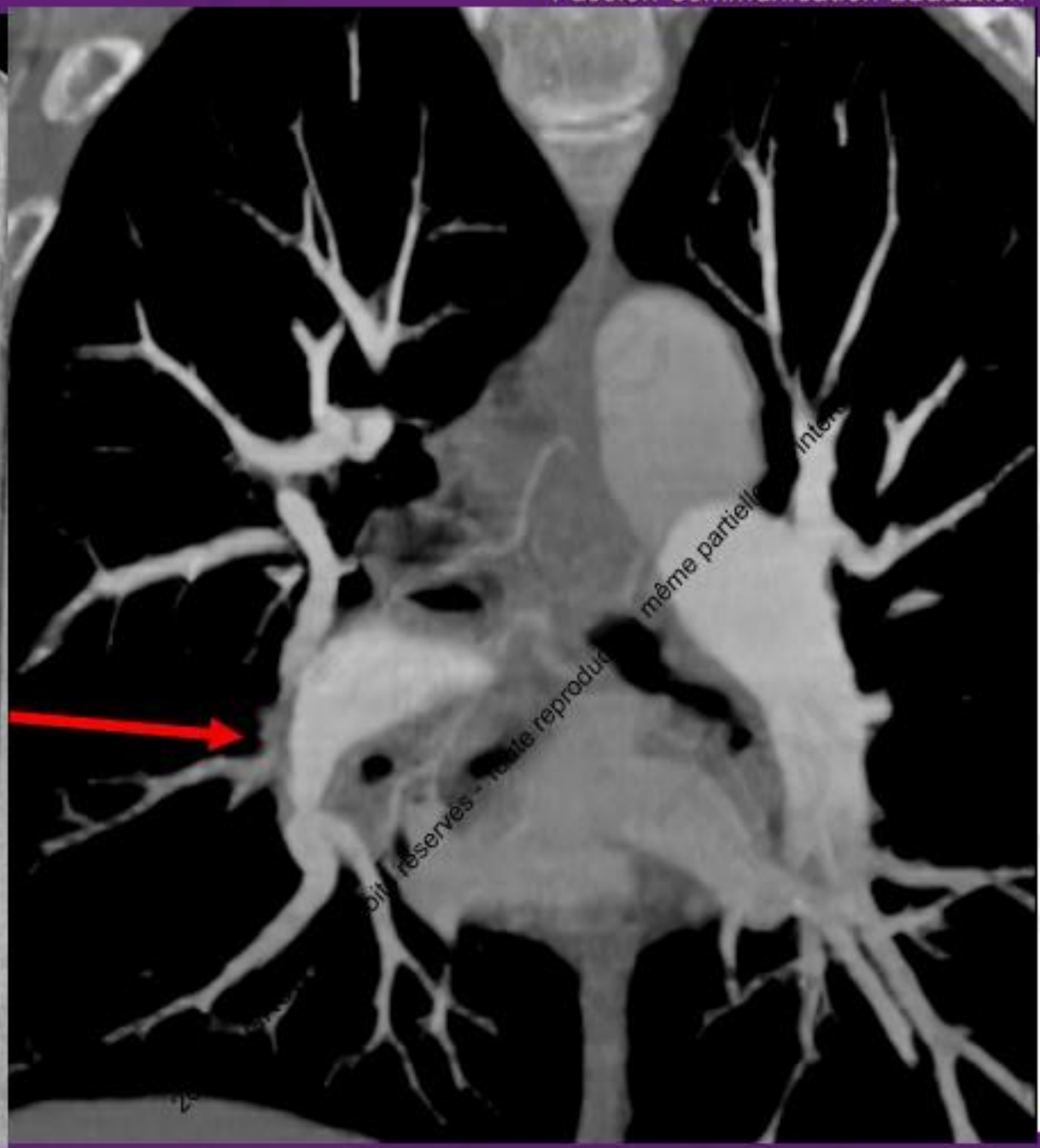
Tunariu J Nucl Med 2007;48:680-4
Galiè Eur Heart J 2016;37:67-119



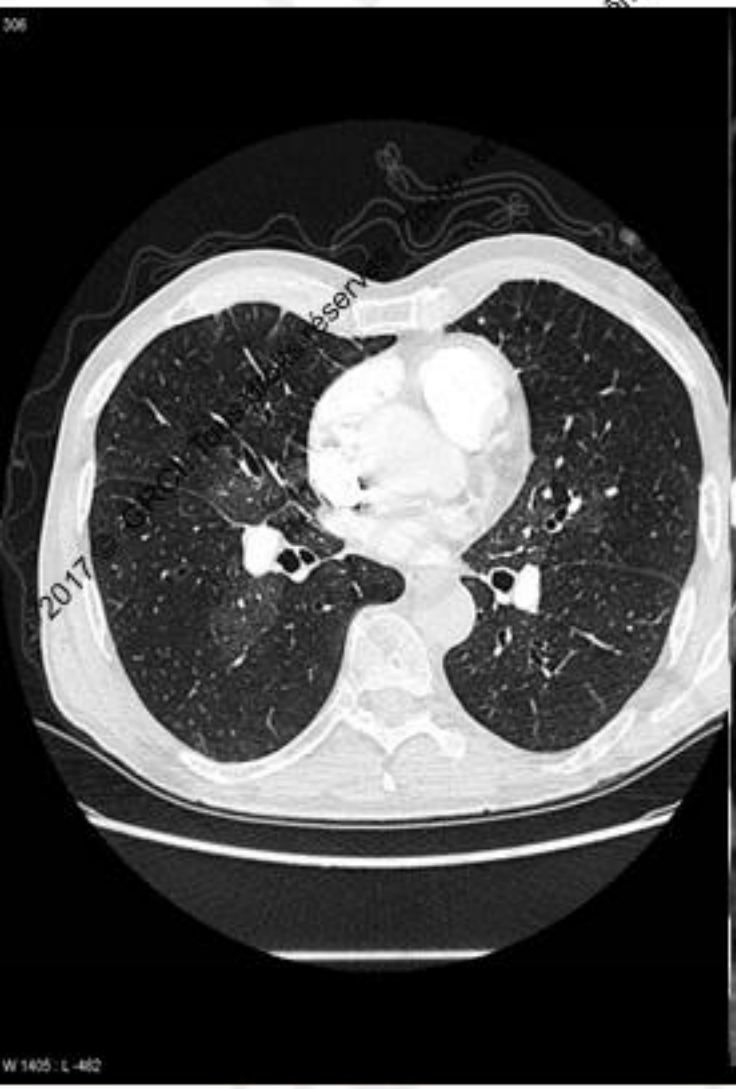
Angiographie pulmonaire

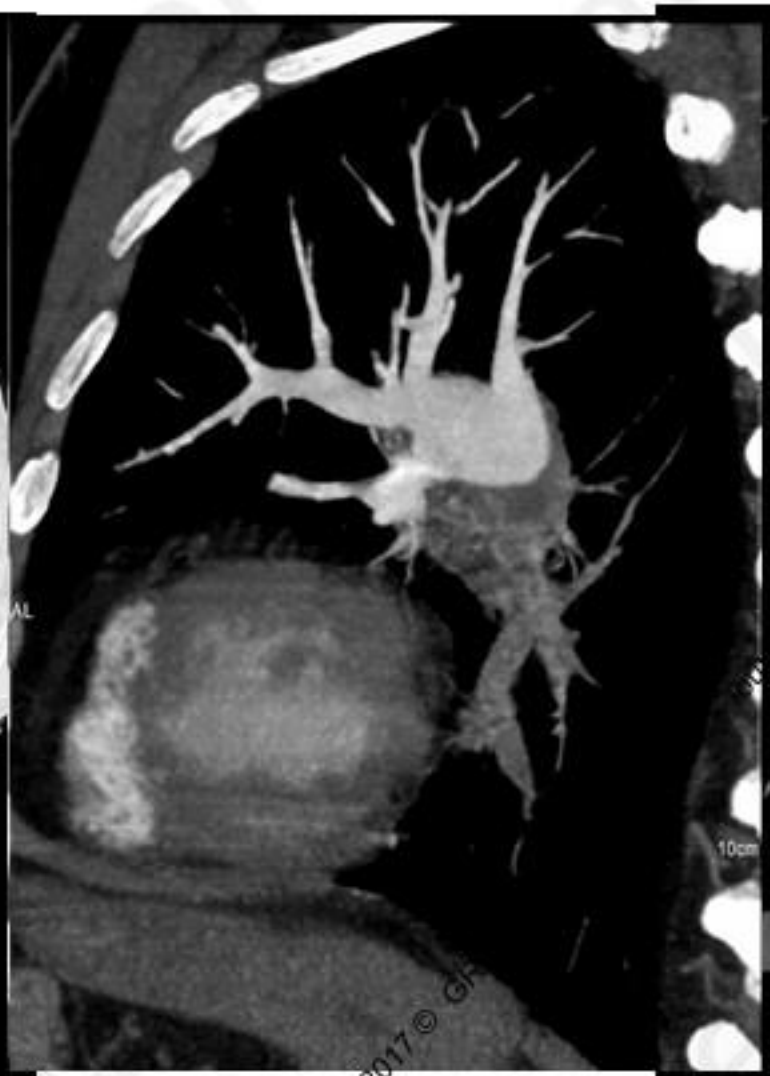
- Technique rigoureuse
- Plusieurs incidences
  - Face droite
  - Profil droit
  - OAG
  - Profil gauche

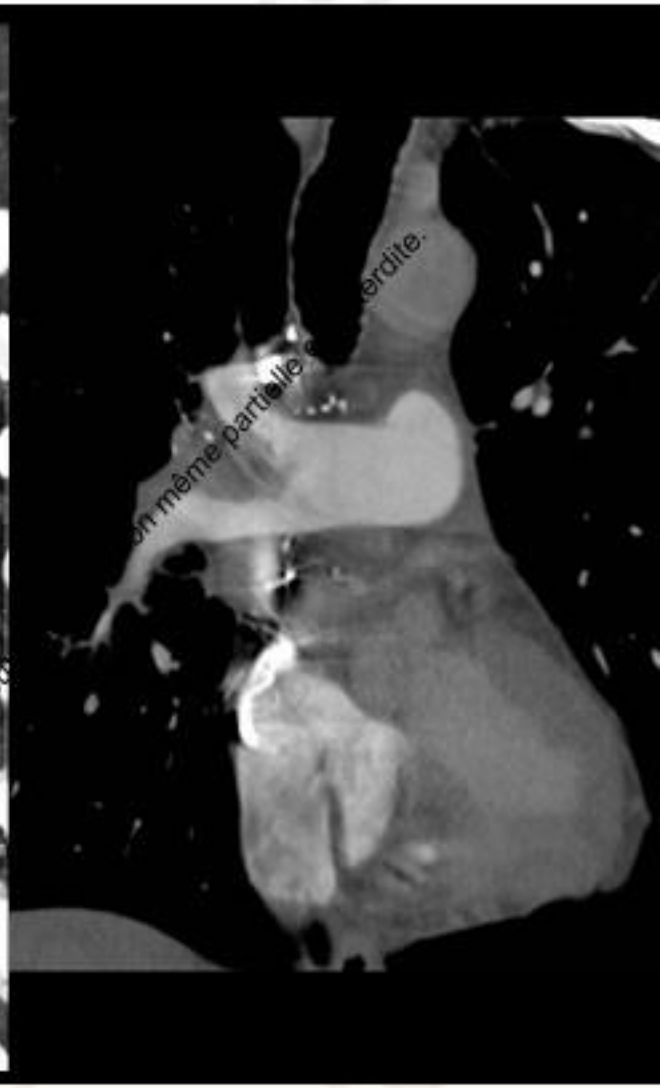




Angioscanner thoracique







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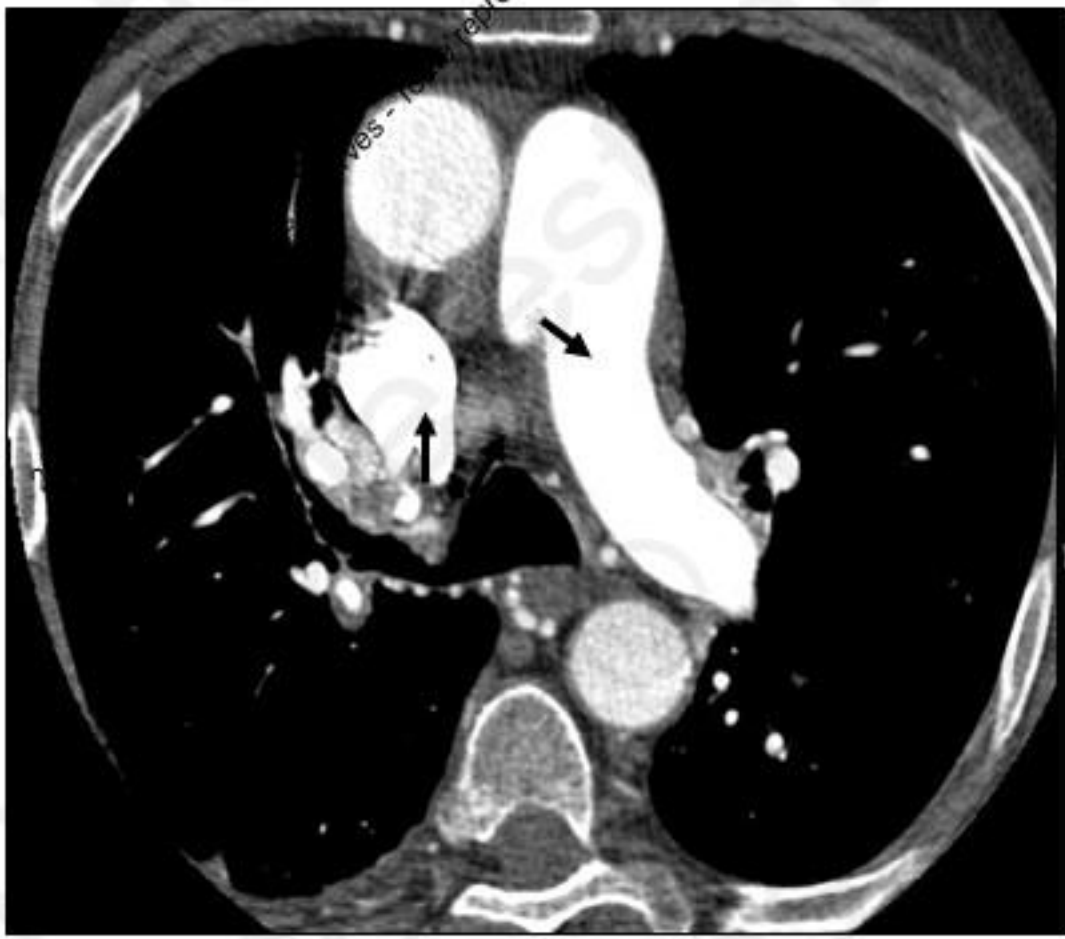
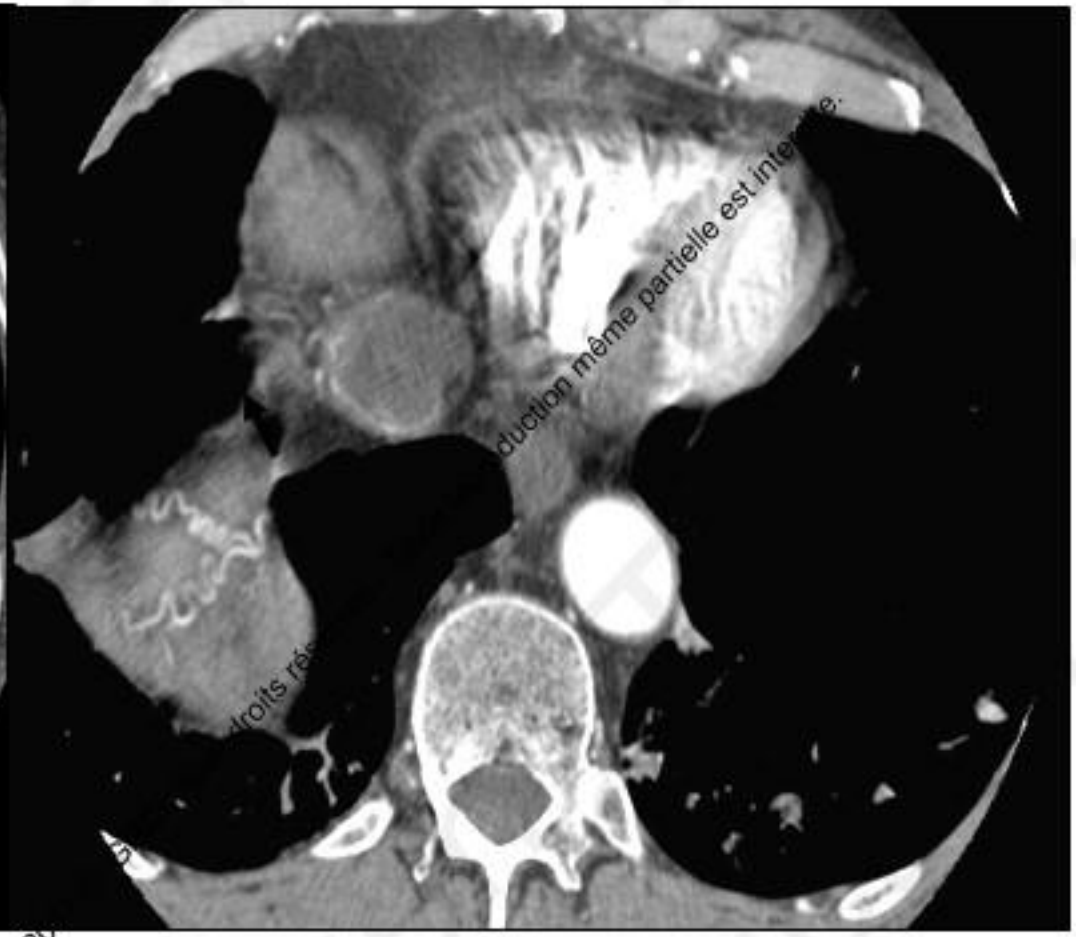
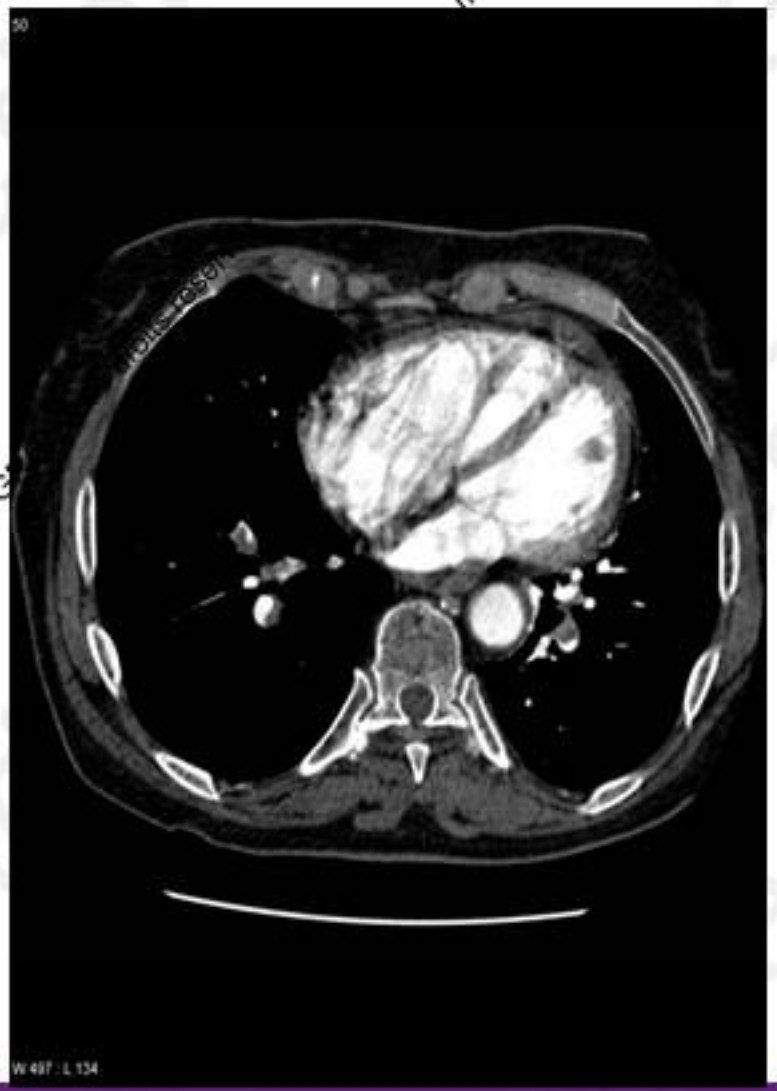
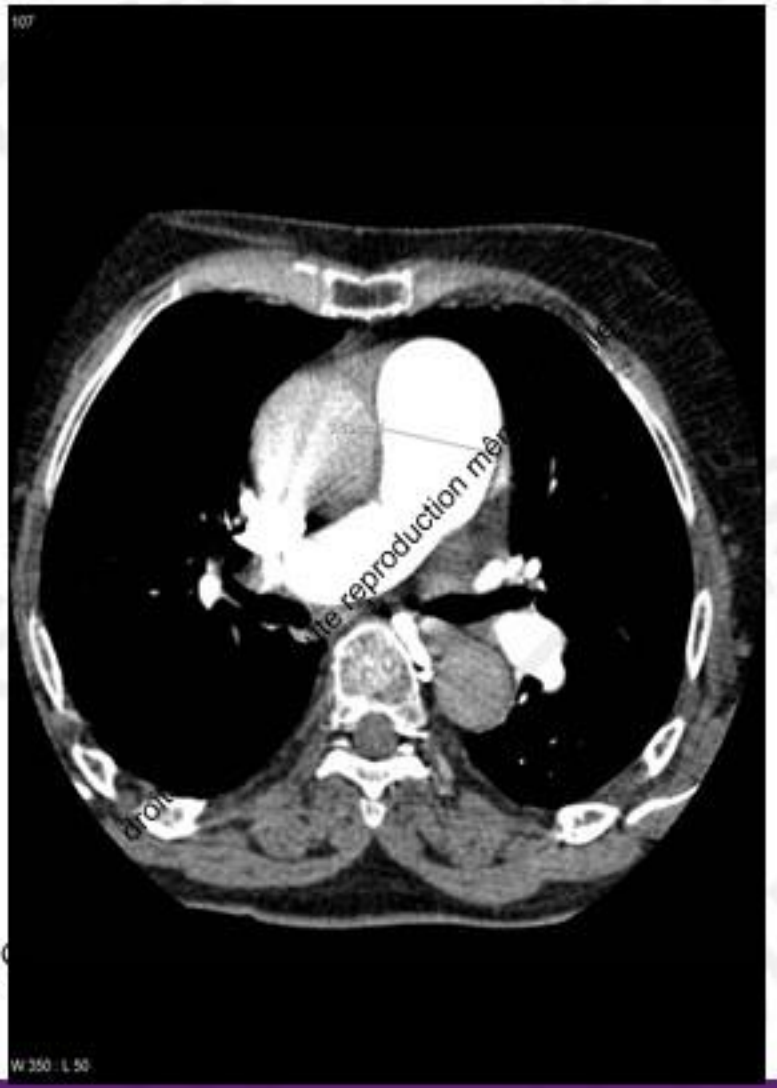




Angioscanner thoracique



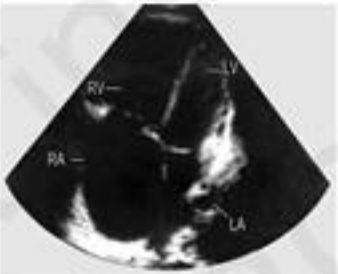


Diagnostic

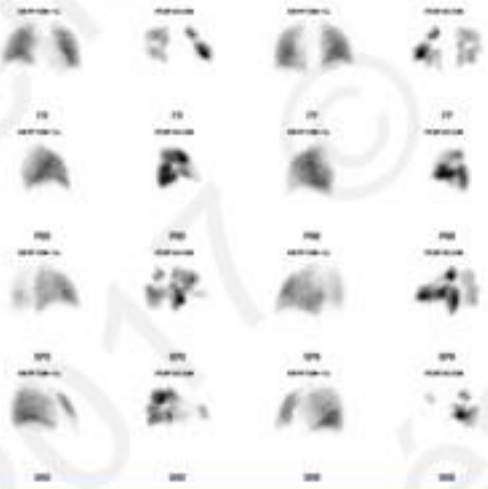
- Après une EP aiguë ou récidivante:
  - Lune de miel
  - **Dyspnée d'effort**
  - Hémoptysie
  - Signes d'insuffisance cardiaque droite
  - Souffles thoraciques +++
  - **La première présentation d'une HTPPE peut mimer celle d'une EP « aiguë » (TDM+++/ PAPs+++)**
- Sans antécédent connu d'EP:
  - Diagnostic fait dans le cadre du bilan d'une HTAP

Dépistage

- Echocardiographie
  - Dilatation VD
  - PAPs
  - FEVG



- Scintigraphie V/Q
  - Défects perfusionels systématisés



Confirmation

- KT droit
  - HTP pré-capillaire

- Angiographie pulmonaire
- Angio TDM thoracique