CHRONIC THROMBO-EMBOLIC PULMONARY HYPERTENSION (CTEPH)

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PULMONARY CIRCULATION

Ala-al-din abu Al-Hassan Ali ibn Abi-Hazm al-Qarshi al-Dimashqi known as **Ibn al-Nafis** was an Arab physician in the 13th century mostly famous for being the first to describe the pulmonary circulation of the blood. The work of Al-Nafis regarding the right sided (pulmonary) circulation pre-date the much later work (1628) of William Harvey's *De motu cordis*. Both theories attempt to explain circulation.

The opening page of one of Ibn al-Nafis's medical works. This is probably a copy made in India during the 17th or 18th century.

PULMONARY CIRCULATION

Based on his anatomical knowledge, Al-Nafis stated: "Blood from the right chamber of the heart must arrive at the left chamber, but there is no direct pathway between them. The thick septum of the heart is not perforated and does not have visible pores as some people thought or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa (pulmonary artery) to the lungs, spread through its substances, be mingled there with air, pass through the arteria venosa (pulmonary vein) to reach the left chamber of the heart, and there form the vital spirit..."

DEFINITION

- Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure ≥25 mm Hg at rest, measured during right heart catheterization.
- There is still insufficient evidence to add an exercise criterion to this definition.

Definitions and Diagnosis of Pulmonary Hypertension

Marius M. Hoeper et al Journal of the American College of Cardiology Volume 62, Issue 25, Supplement, 24 December 2013, Pages D42–D50

Table 1. Classification of pulmonary hypertension

1 Pulmonary arterial hypertension
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 Bone morphogenetic protein receptor type II
  - 1.2.2 Activin receptor-like kinase 1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drug and toxin induced
- 1.4 Associated pulmonary arterial hypertension
  - 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
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 Pulmonary hypertension with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans' cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorder: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

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DEFINITION

- CTEPH represents the 4th category of the Nice pulmonary hypertension classification.
- Elevated pre-capillary pulmonary artery pressure (PAP) – mean >25mmHg.
- At least one segmental perfusion defect (scintigraphy, CTPA, MR - angiography or conventional angiography)
- 3 months of anti-coagulation
- Usually a consequence of incomplete resolution of acute pulmonary emboli

EPIDEMIOLOGY

- 19% of patients referred to general pulmonary hypertension centres
- Incidence 5 per million/year
- Prevalence up to 38.4 million

RISK FACTORS

- History of Venous Thrombo-Embolism, especially massive and recurrent embolism
- 25% of CTEPH patients have no history of previous embolism
- 1-5% of acute PE goes onto CTEPH
- Thrombophilic factors:
  - Elevated circulating factor 8
  - Elevated plasma von Willebrand Factor
  - Circulating anti-phospholipid antibodies increased
  - Lupus anti-coagulant increased

RISK FACTORS

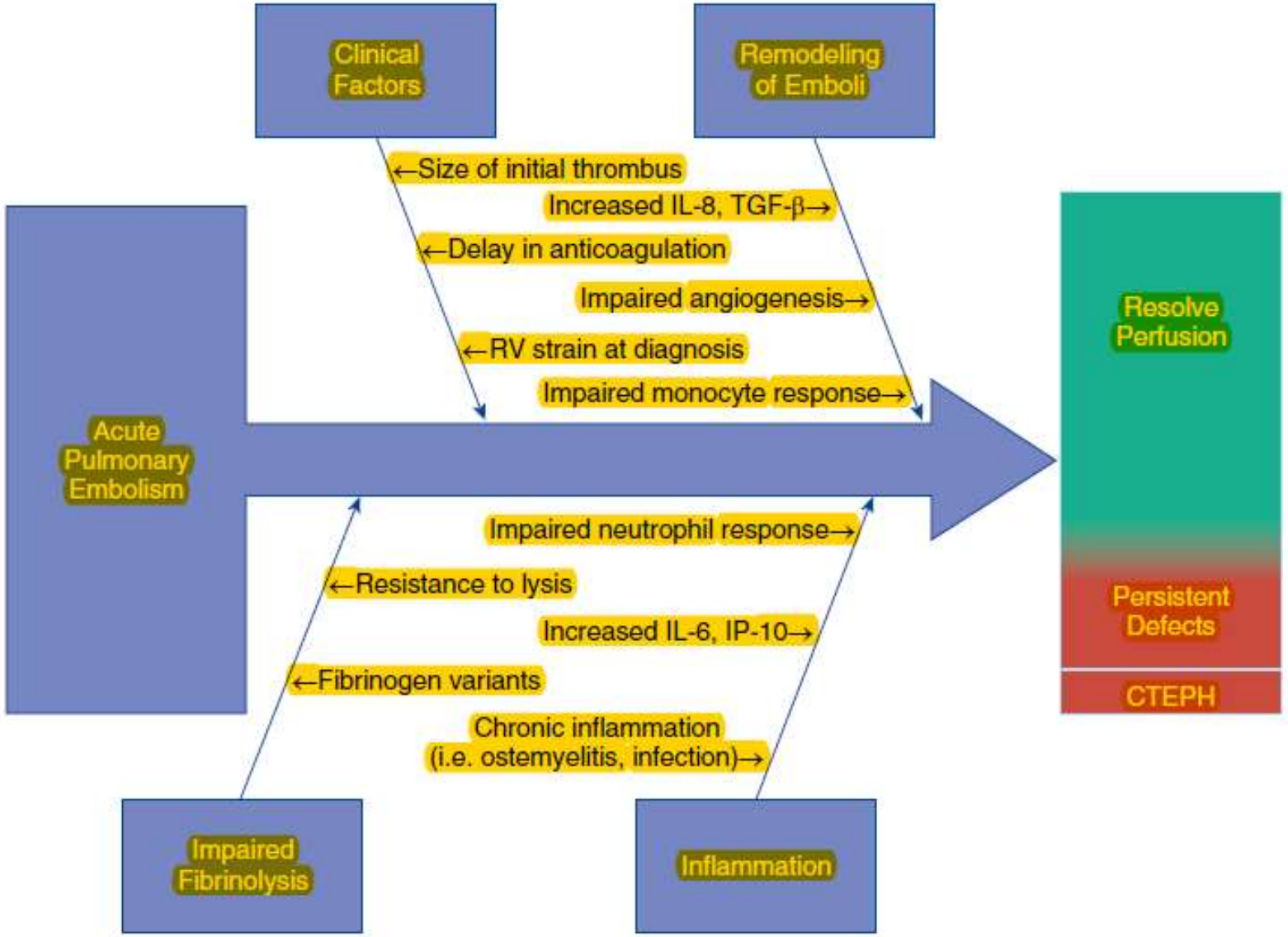
- Elevated prevalence of chronic inflammatory disorders and infections
- Splenectomy
- V-A shunts
- Cancer
- Non-O Blood groups
- Older age

PATHOPHYSIOLOGY

- After acute embolism – recovery of perfusion occurs
- Time to reperfusion varies – usually 3 weeks but residual defects can be found up to 1 year
- Higher risk of CTEPH if defects found after 3 months of anti-coagulation
- Persistent perfusion defects are remodeled into intravascular fibrotic scars
- If a significant portion of the vascular bed is involved that leads to CTEPH

PATHOPHYSIOLOGY

- Resistance to fibrinolysis possible
- Thrombolytic therapy at presentation of acute PE does not preclude CTEPH
- Neutrophils help in thrombolysis whereas chronic inflammation is mainly monocyte driven
- Inhibition of angiogenesis


Clinical Factors
Remodeling of Emboli
←Size of initial thrombus
Increased IL-8, TGF-β→
←Delay in anticoagulation
Impaired angiogenesis→
←RV strain at diagnosis
Impaired monocyte response→
Acute Pulmonary Embolism
Resolve Perfusion
Persistent Defects
CTEPH
Impaired neutrophil response→
←Resistance to lysis
Increased IL-6, IP-10→
←Fibrinogen variants
Chronic inflammation (i.e. ostemyelitis, infection)→
Impaired Fibrinolysis
Inflammation

SYMPTOMS

- Dyspnoea – usually exertional
- Decline in exercise tolerance
- Atypical chest pain
- Non productive cough
- Episodic Haemoptysis
- Syncope

SIGNS

- Pulmonary hypertension
  - Loud P2
  - S4 gallop
  - Tricuspid regurgitation murmur
  - Praecordial right ventricular lift
- RV failure
  - Pedal oedema
  - Elevated JVP
  - Pulsatile Liver
  - Ascites
  - Right sided S3
- Pulmonary Flow murmurs

DIAGNOSIS

- Chest X-Ray- Cardiomegaly, Oligemia, Right descending pulmonary artery dilatation >20mm, pleural effusion, parenchymal scarring
- V/Q Scan – procedure of choice 96-97 % sensitivity and 90-95% specificity
- CTPA- 51% sensitivity and 99% specificity
- SPECT Scanning
- Catheter based Pulmonary Angiography
- Dual energy CT
- Contrast Enhanced-MRA – similar to V/Q
- Dynamic Contrast-Enhanced MRI
- Optical Coherence Tomography (OCT)- 2 dimensional, invasive, catheter based

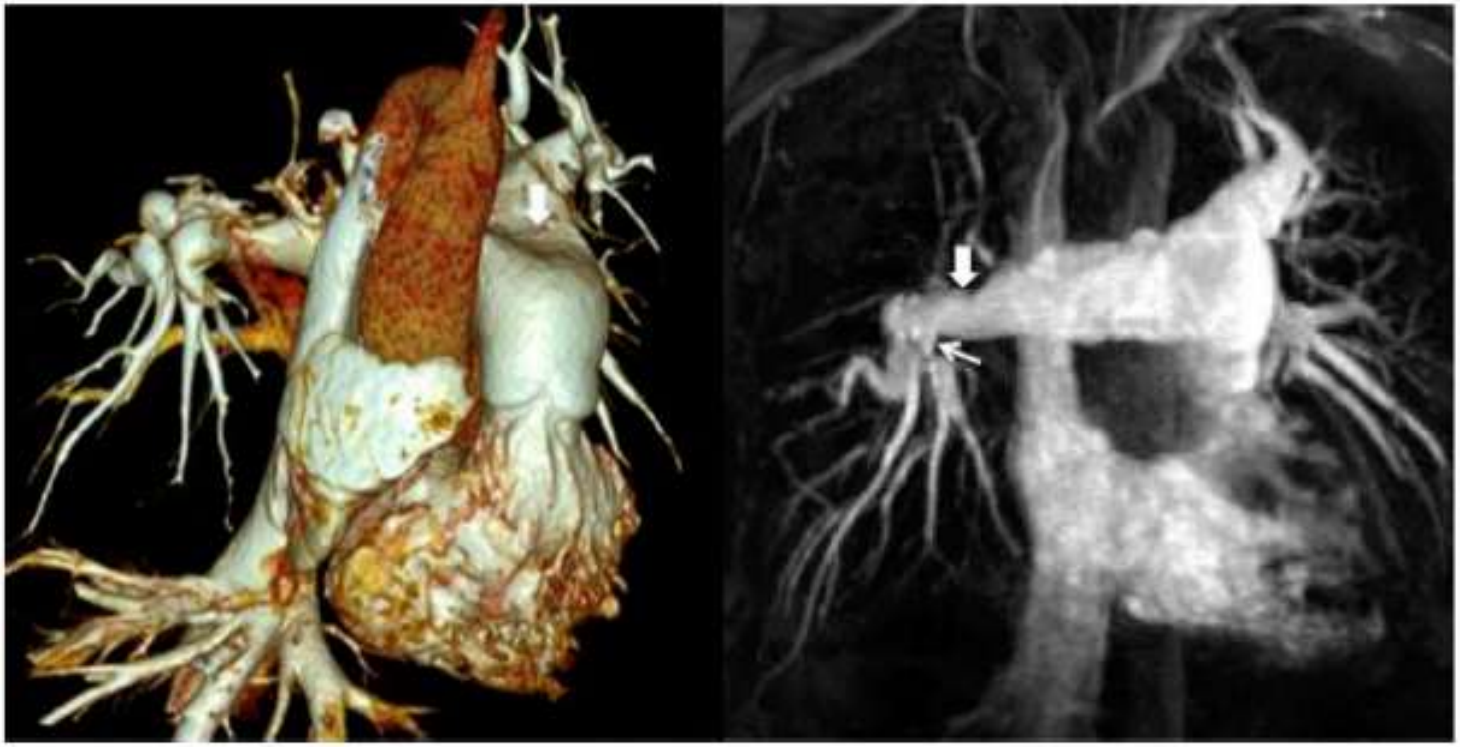


Figure 9. A 50-year-old male with proximal chronic thromboembolic pulmonary hypertension. Computed tomographic volume rendering (*left*) and a still image of magnetic resonance pulmonary angiography (*right*) demonstrate good disease correlation. There is a proximal thrombus in the main and right pulmonary artery (*thick arrows*) with occlusion of the right upper and middle lobes, and a complex trifurcation web (*thin arrow*) in the lower lobe.

ASSESSMENT OF HAEMODYNAMICS

- Echocardiography
- CT
- MRI
- Right Heart Cath – procedure of choice

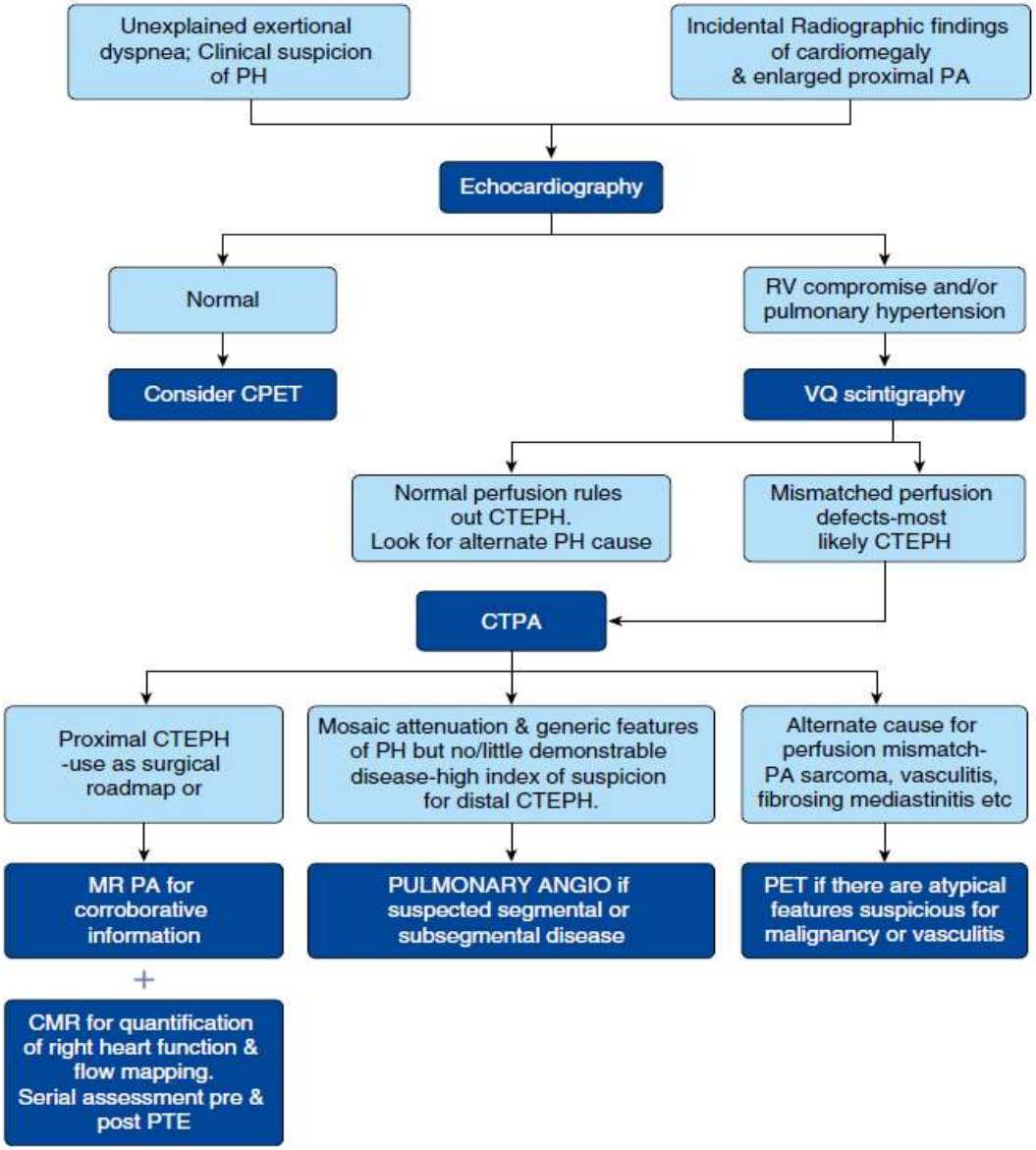


Figure 14. Suggested diagnostic algorithm for the evaluation of patients with suspected chronic thromboembolic disease. CMR = cardiovascular magnetic resonance; CPET = cardiopulmonary exercise testing; CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomographic pulmonary angiography; MR PA = magnetic resonance pulmonary angiography; PA = pulmonary artery; PET = positron emission tomography; PH = pulmonary hypertension; PTE = pulmonary thromboendarterectomy; RV = right ventricle; VQ = ventilation–perfusion.

PROGNOSIS

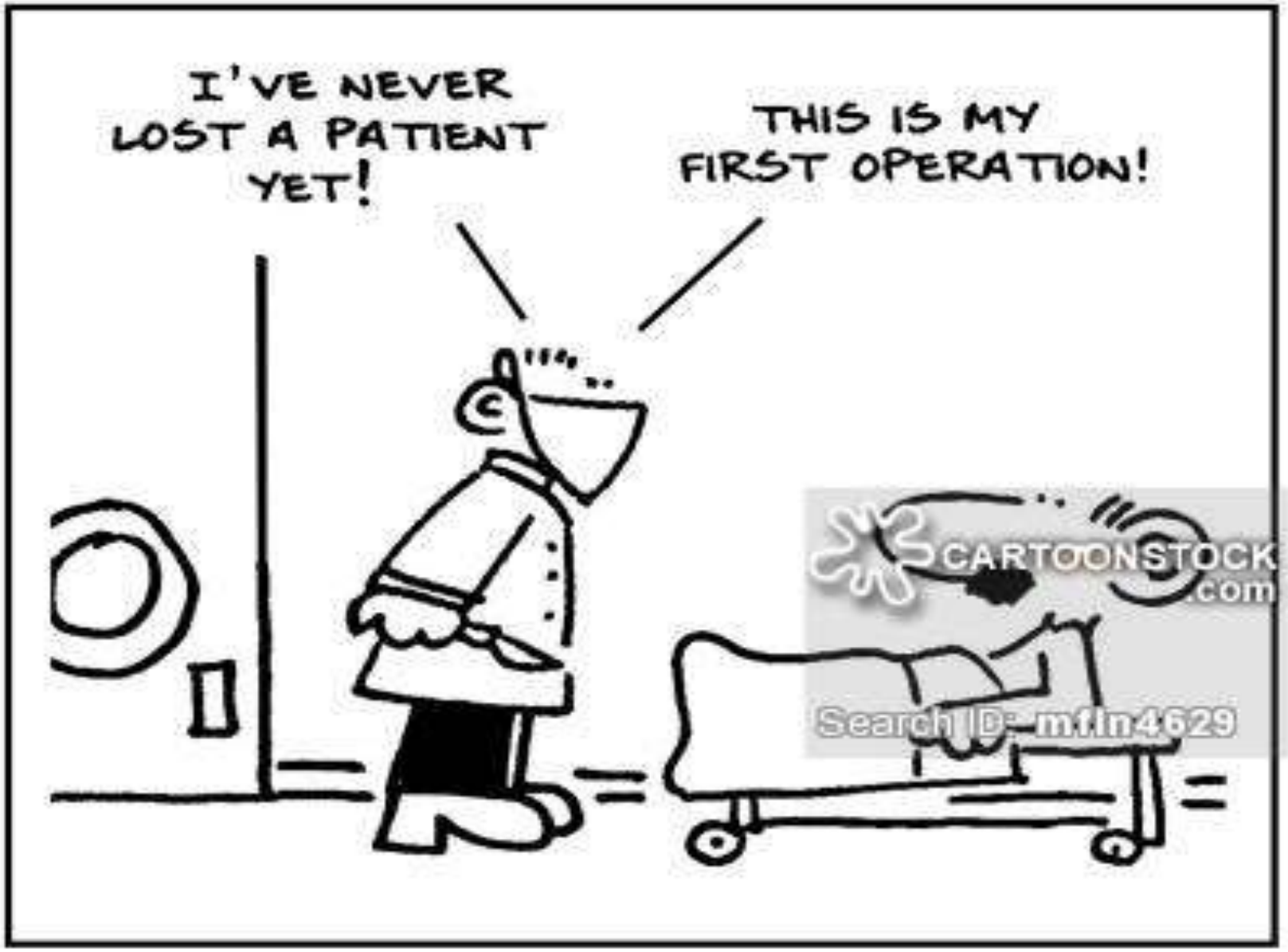
- 30% 3-Year Survival without treatment

TREATMENT

- Pulmonary endarterectomy
- Medical therapy
- Balloon Pulmonary Angioplasty

SURGICAL TREATMENT

- Pulmonary endarterectomy is the treatment of choice
- However it is a difficult procedure requiring expertise
- Should be performed in centres of experience
- Need an experienced interdisciplinary team
- Majority but not all patients are eligible


I'VE NEVER LOST A PATIENT YET!
THIS IS MY FIRST OPERATION!
CARTOONSTOCK .com
Search ID: mfin4629

SURGICAL TREATMENT

- Treatment is guided by:
  - Severity of symptoms-WHO Class iii or iv
  - Severity of pulmonary hypertension and right heart dysfunction
  - Extent and level of obstruction- Main and proximal vessels preferable
  - Correlation between PH and degree of obstruction
  - Co-morbidities- e.g. Emphysema, concomitant coronary artery disease, Severe LV systolic dysfunction
  - Technical factors – Chest wall abnormalities
  - Risk/benefit ratio

SURGICAL TREATMENT

- The endarterectomy procedure follows four basic principles:
  - The endarterectomy must be bilateral, therefore a median sternotomy is done
  - Perfect visualization is essential by use of C-P bypass and 20 minutes circulatory arrest with cooling to 20°C
  - Identification of the correct dissection plane is crucial
  - A complete endarterectomy is essential

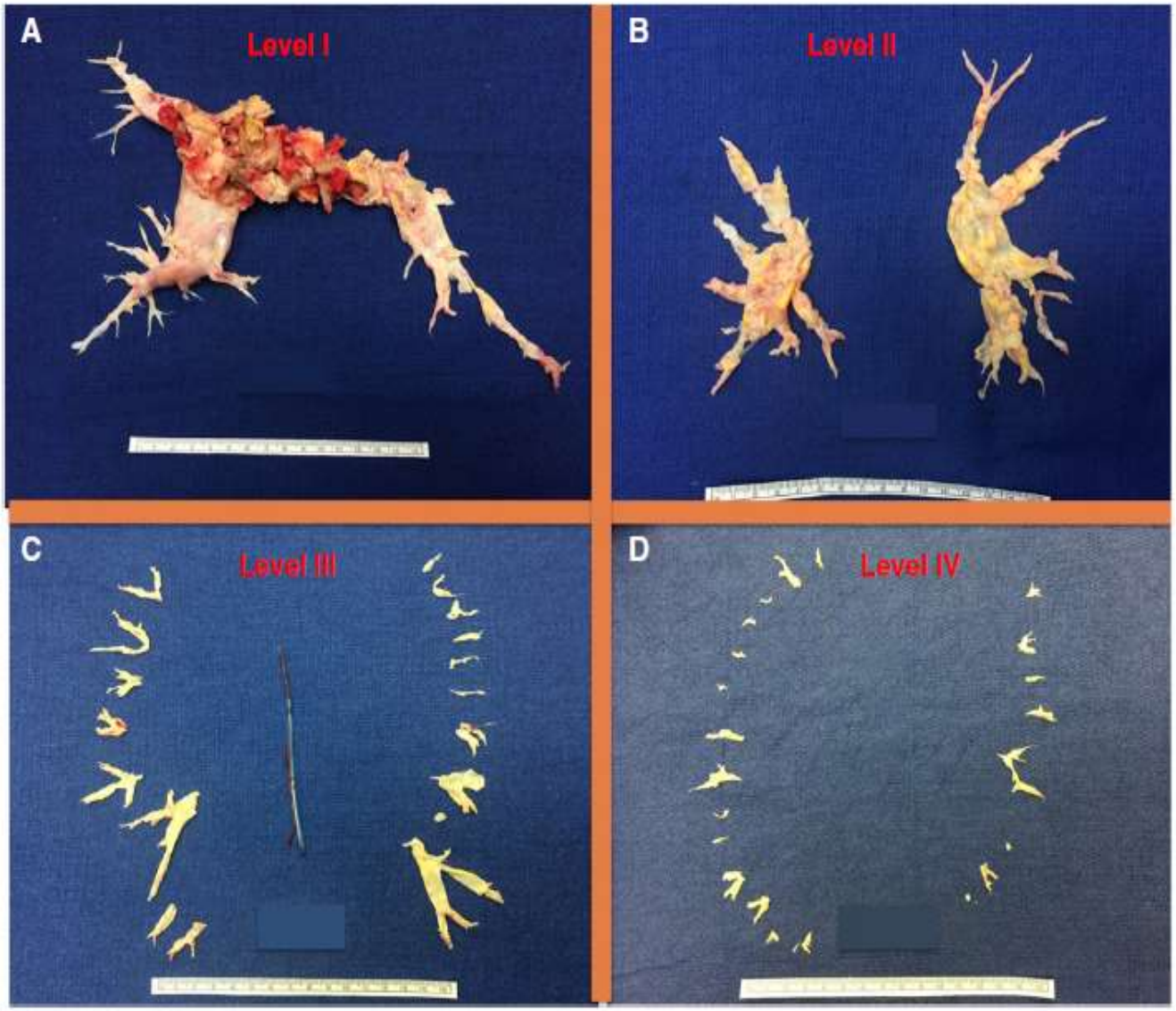


Figure 5. University of California, San Diego classification of pulmonary endarterectomy disease levels. This figure illustrates typical surgical specimens classified based on the most proximal level of obstruction, levels I to IV.

SURGICAL TREATMENT

- In hospital mortality is between 2-5 %
- Endarterectomy results in 3-year survival of 89% [1]
- Residual Pulmonary hypertension occurs in 35% of patients [2,3]
- Recurrent Thrombo-Embolism does occur

1. Delcroix M, et al Circulation 2016;133:859-871
2. Concliffe R et al. AJRCCM 2008;177:1122-1127
3. Freed DH et al. J Thorac Cardiovasc Surg 2011;141: 383-387

MEDICAL TREATMENT

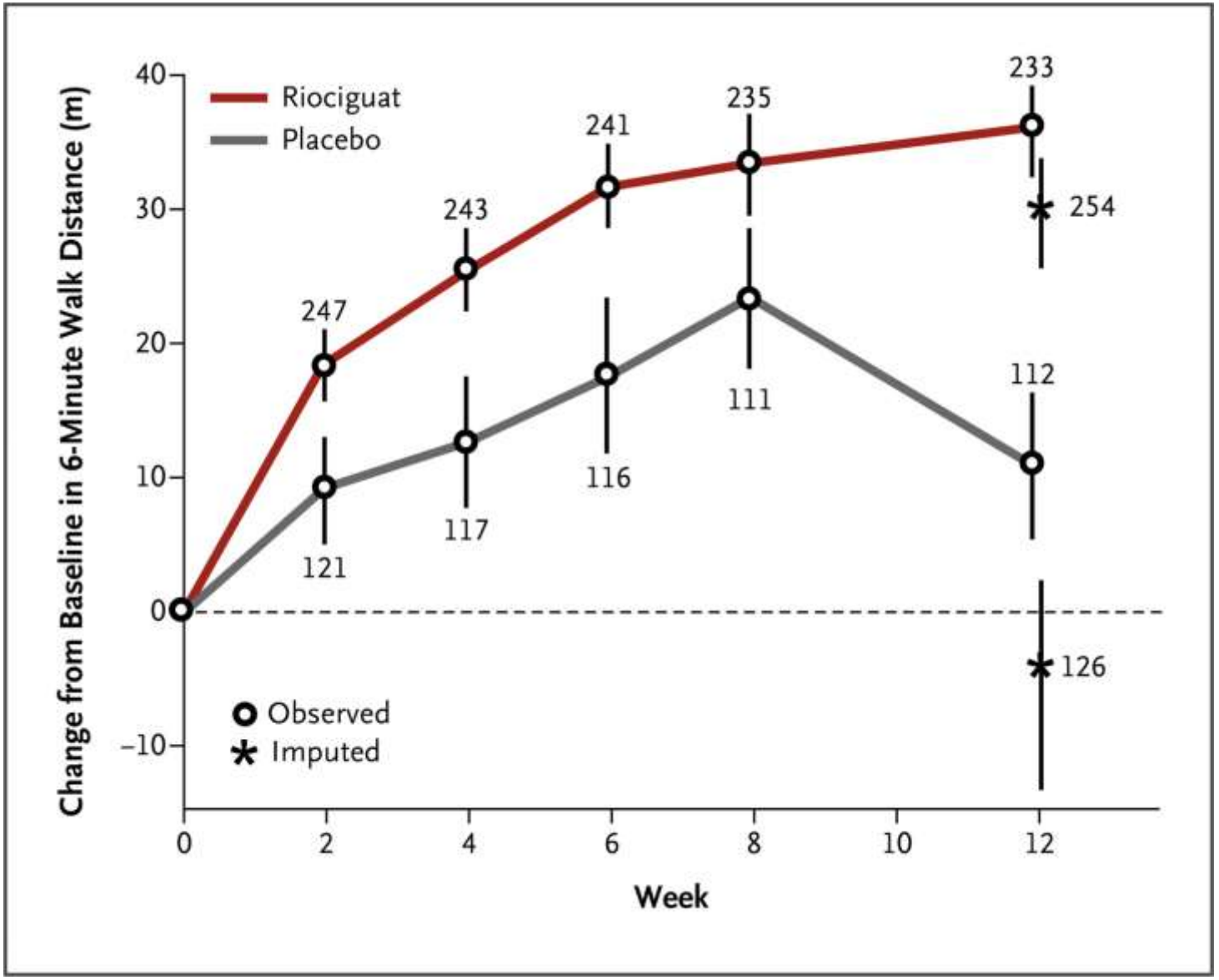
- For Inoperable Cases
  - Distal Disease
  - Co-morbidities
- Residual Pulmonary Hypertension
- Bridging therapy to endarterectomy in patients with severe haemodynamic parameters


WHEN WE TESTED THIS DRUG ON MICE, NOBODY NOTICED ANY SIDE EFFECTS.
SCHWADRON

MEDICAL TREATMENT

- Traditional Medical therapy:
  - Anticoagulants- Role of NOACS to be determined
  - Diuretics
  - Oxygen
- Specific PAH therapy
  - Prostanoids
  - PDE-5 Inhibitors
  - Endothelin Receptor Antagonists
  - Soluble Guanylate Cyclase Stimulators – Riociguat[1]

1. Chest1- Ghofrani et al NEJM 2013; 369:319-329


Change from Baseline in 6-Minute Walk Distance (m)
40
30
20
10
0
−10
Riociguat
Placebo
Observed
Imputed
247
243
241
235
233
254
121
117
116
111
112
126
0
2
4
6
8
10
12
Week

BALLOON PULMONARY ANGIOPLASTY

- First trials in Japan in 2001
- Used in inoperable CTEPH
- Role in Distal Disease and combination with endarterectomy and Medical treatment needs to be worked out

CATHETER DIRECTED THROMBOLYSIS

From: Percutaneous Transluminal Pulmonary Angioplasty for Central-Type Chronic Thromboembolic Pulmonary Hypertension

J Am Coll Cardiol Intv. 2013;6(11):1212-1213. doi:10.1016/j.jcin.2013.03.025

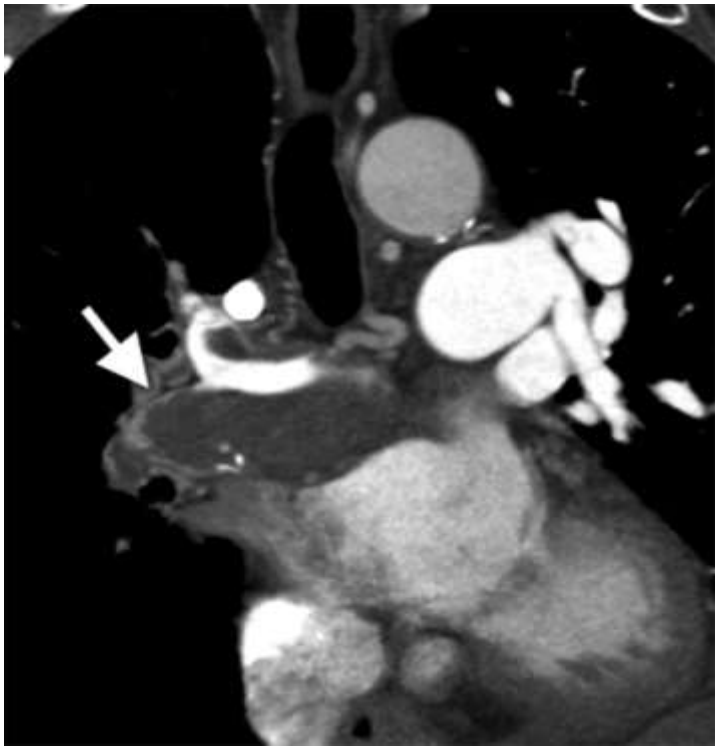


Figure Legend:

Chest Computed Tomography Before PTPA

Arrow indicate a large thrombosis in the main tract. PTPA = percutaneous transluminal pulmonary angioplasty (Online Video 1).

From: Percutaneous Transluminal Pulmonary Angioplasty for Central-Type Chronic Thromboembolic Pulmonary Hypertension

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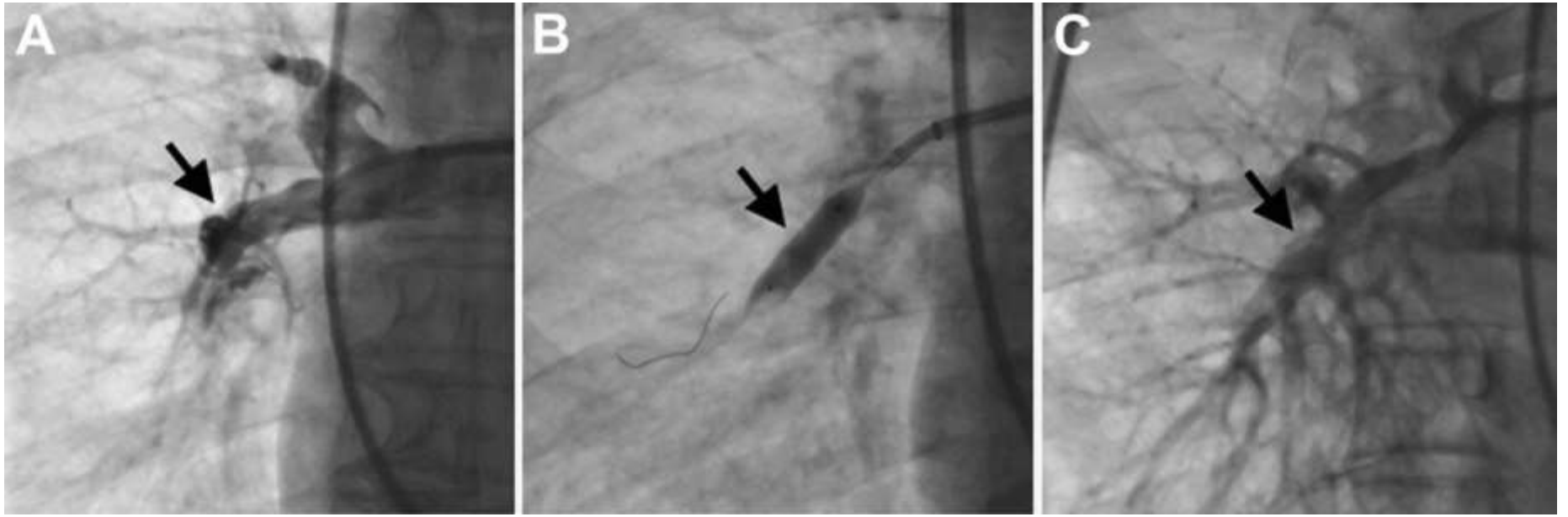

Figure Legend:

Angiographies at the First Session

Angiographies before PTPA (A), during dilation of the target lesion by the small-size balloon catheter (B), and after the first session of PTPA (C). Abbreviations as in Figure 1.

From: Percutaneous Transluminal Pulmonary Angioplasty for Central-Type Chronic Thromboembolic Pulmonary Hypertension

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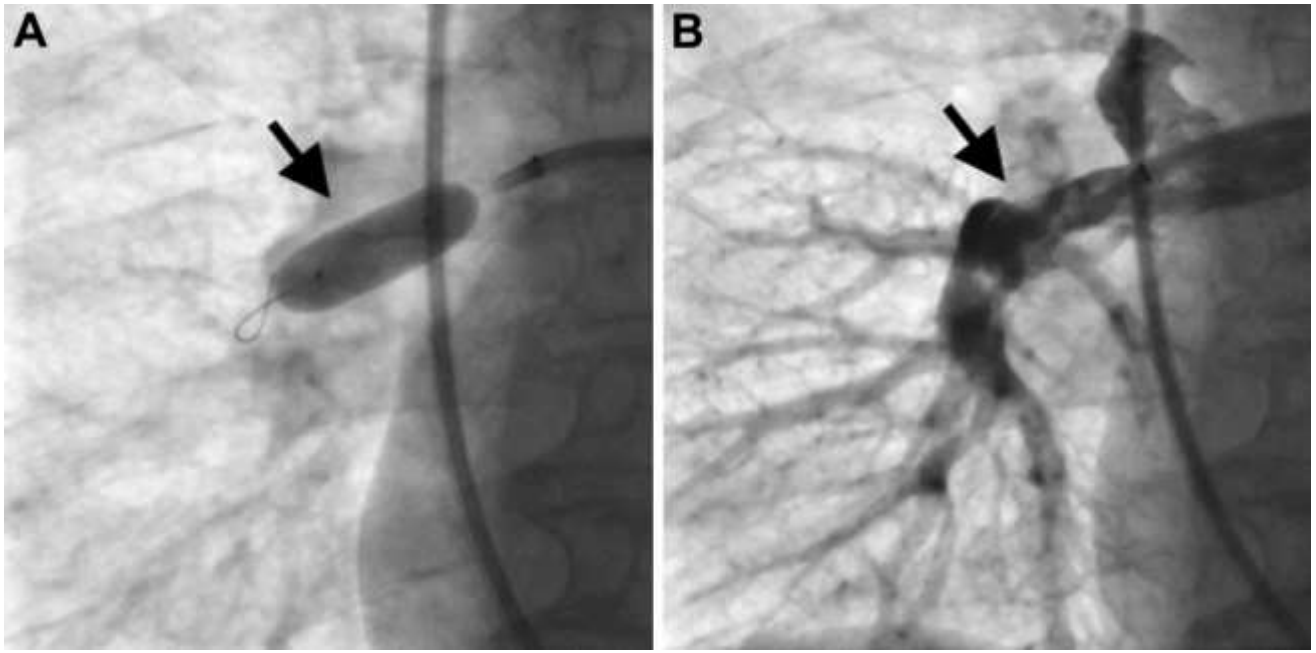

Figure Legend:

Angiographies at the Second Session

Angiographies during dilation by a larger balloon catheter (A) and after the second session of PTPA (B). Abbreviations as in Figure 1 (Online Video 2).

THANK YOU

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