ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΜΕΛΕΤΗΣ ΤΗΣ ΠΝΕΥΜΟΝΙΚΗΣ ΥΠΕΡΤΑΣΗΣ

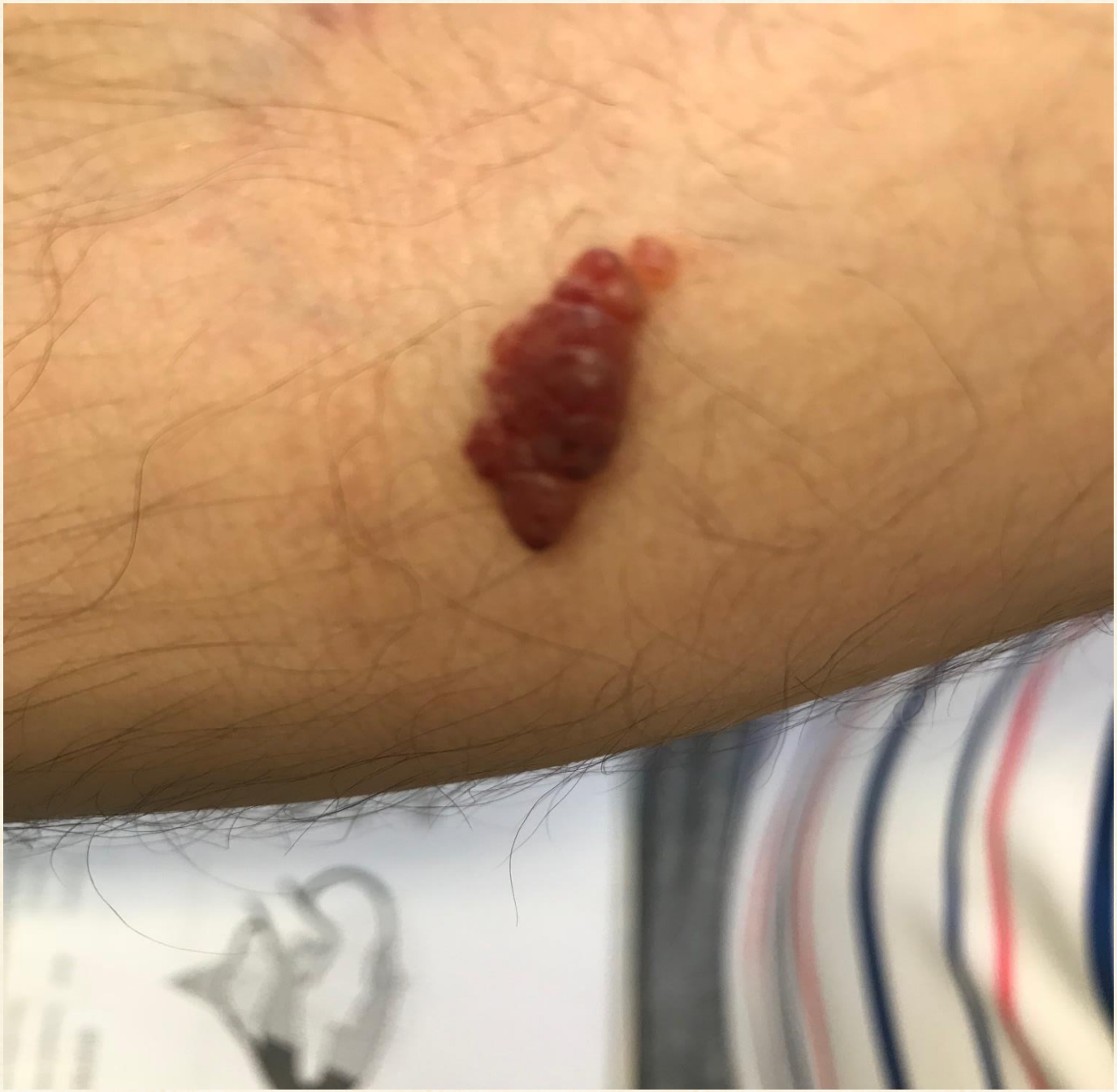
2° ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ ΠΝΕΥΜΟΝΙΚΗΣ ΥΠΕΡΤΑΣΗΣ

Πνευμονική υπέρταση σε ασθενή με πολλαπλά αιμαγγειώματα

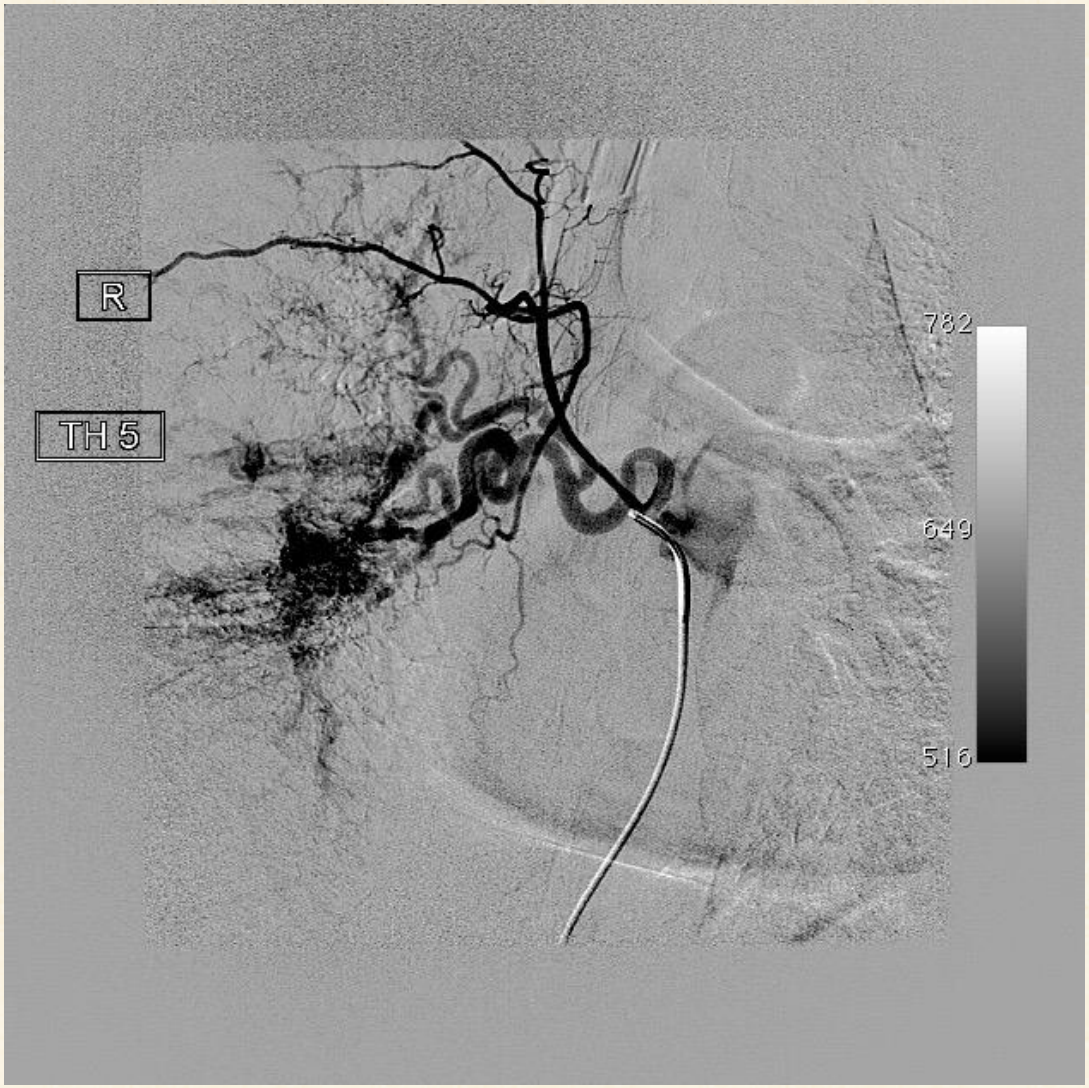
Φραντζέσκα Φραντζεσκάκη
Πνευμονολόγος – Εντατικολόγος
ΜΕΘ ΠΓΝ «ΑΤΤΙΚΟΝ»
Διακλινικό Ιατρείο Πνευμονικής Υπέρτασης

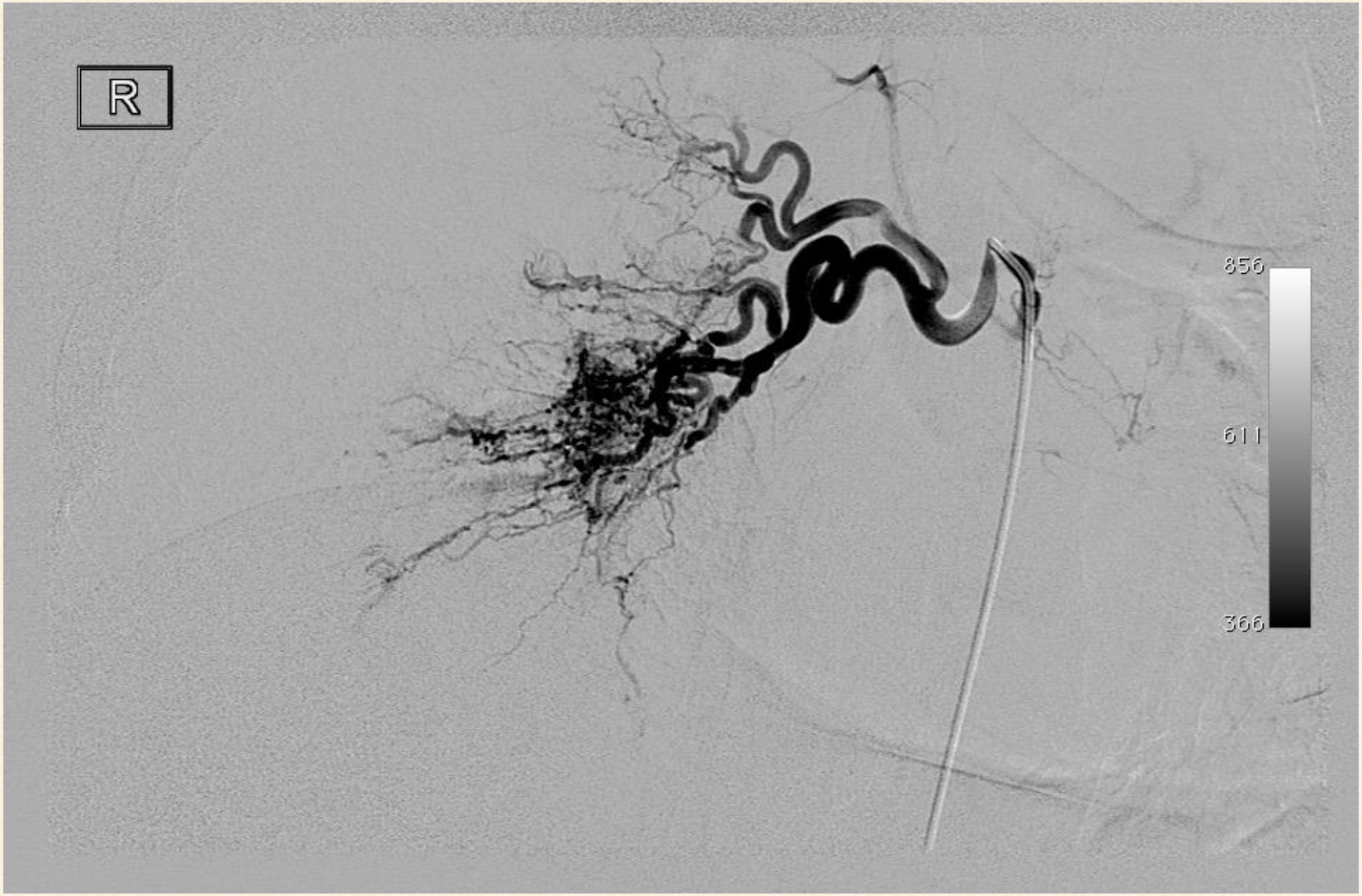
Case report

- Male 33 yo (March 2018)
- Exertional dyspnea, exercise intolerance (since 3 mo) (WHO-FC: III)
- Medical history:
  - Multiple hemangiomas (T7-T9, liver, spleen)
  - Resection of a costal hemangioma at left T6 (1999)
  - Splenectomy (2000)
  - Progressive gait difficulty
  - Pyramidal signs in lower limbs
  - Proximal lower limbs weakness
  - Urinary dysfunction-Loss of erection
  - Thoracic myelopathy



DSA 2/2015 Hemangioma T4

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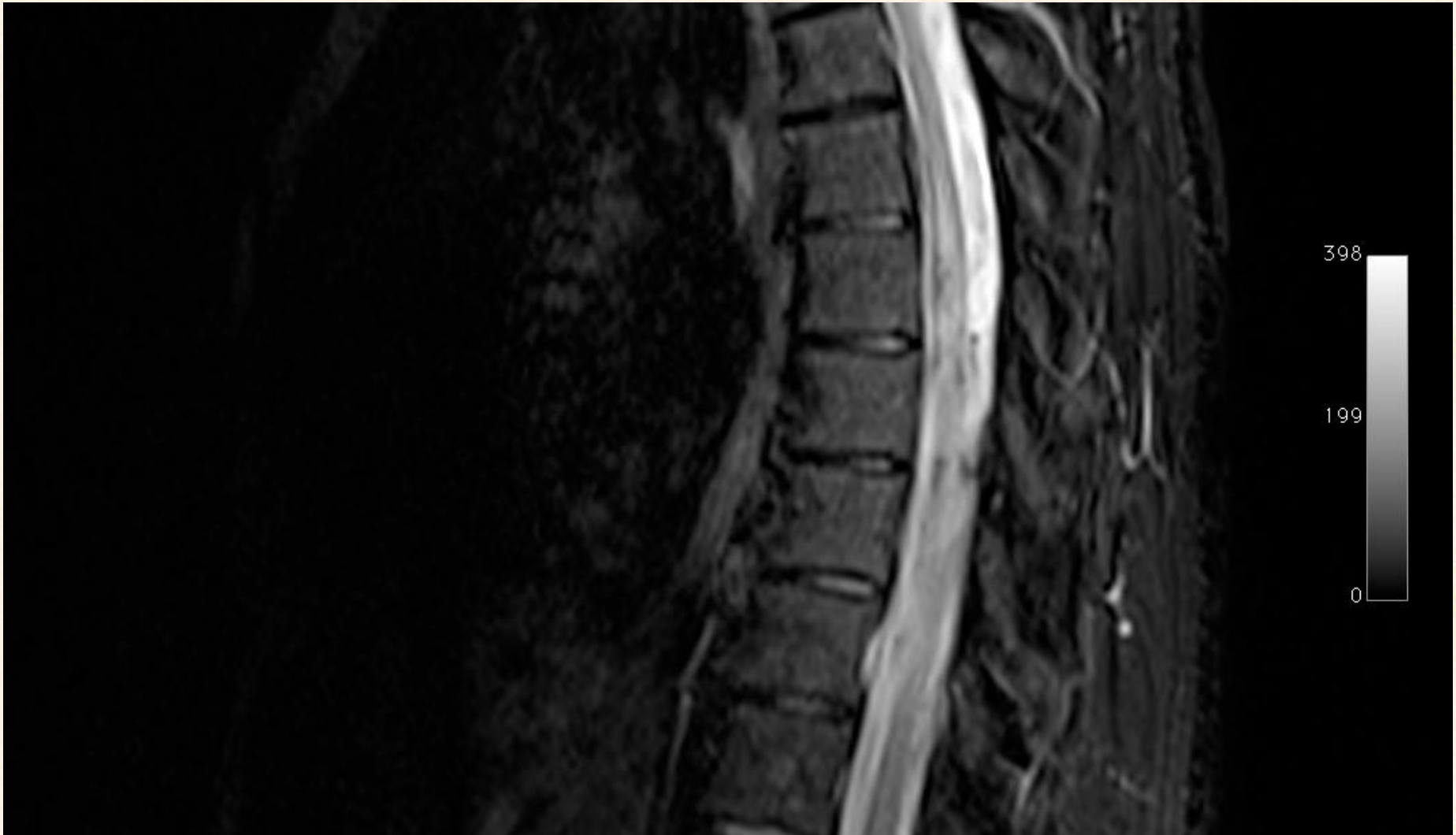
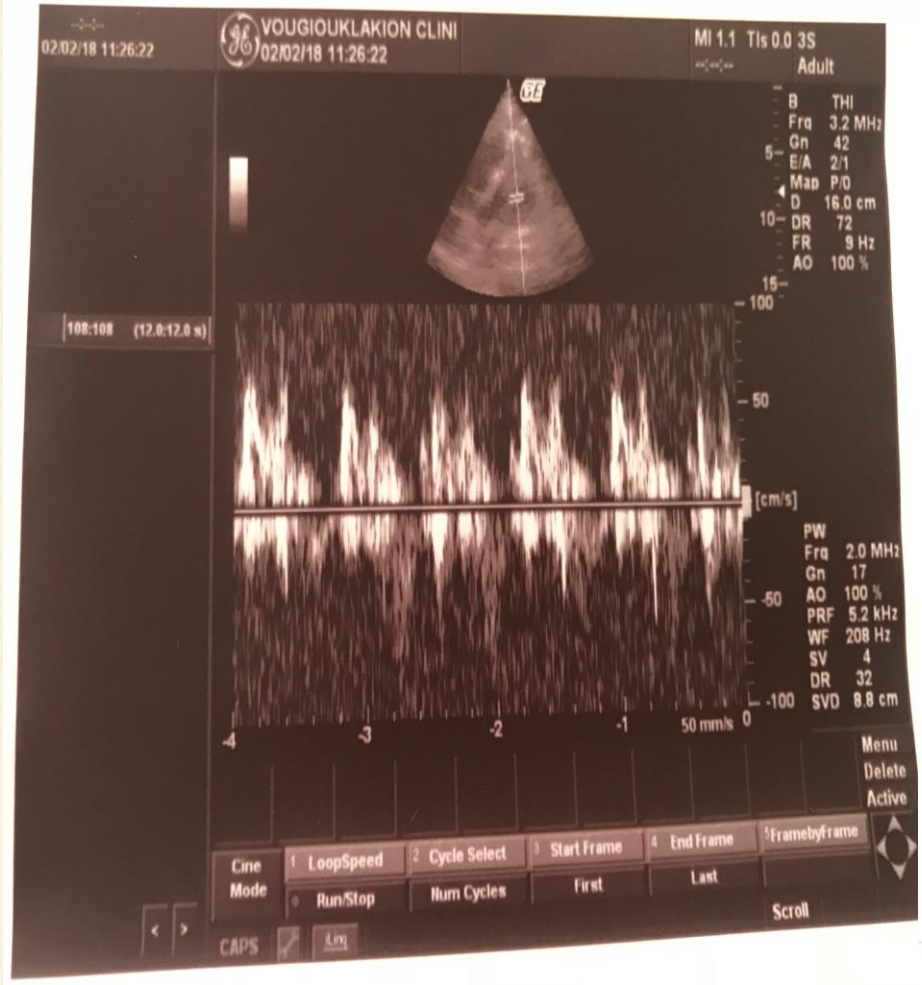
Serial Spinal MRAs (2/2016):Progressive worsening myelopathy due to potential venous congestion

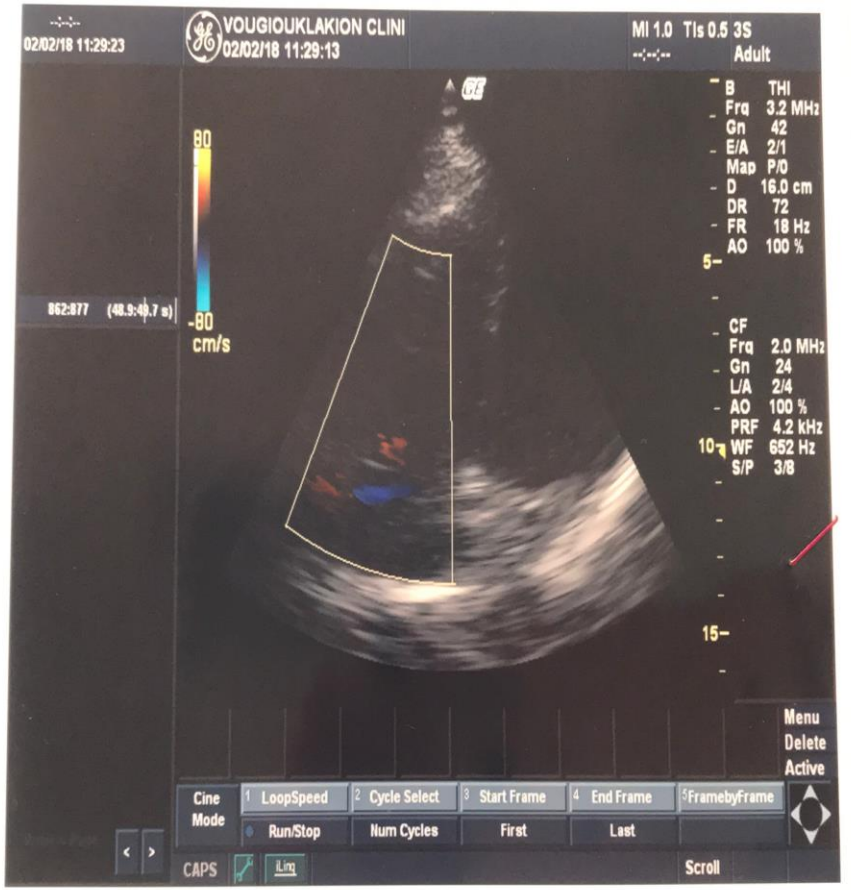


Echocardiography (15/03/2018)

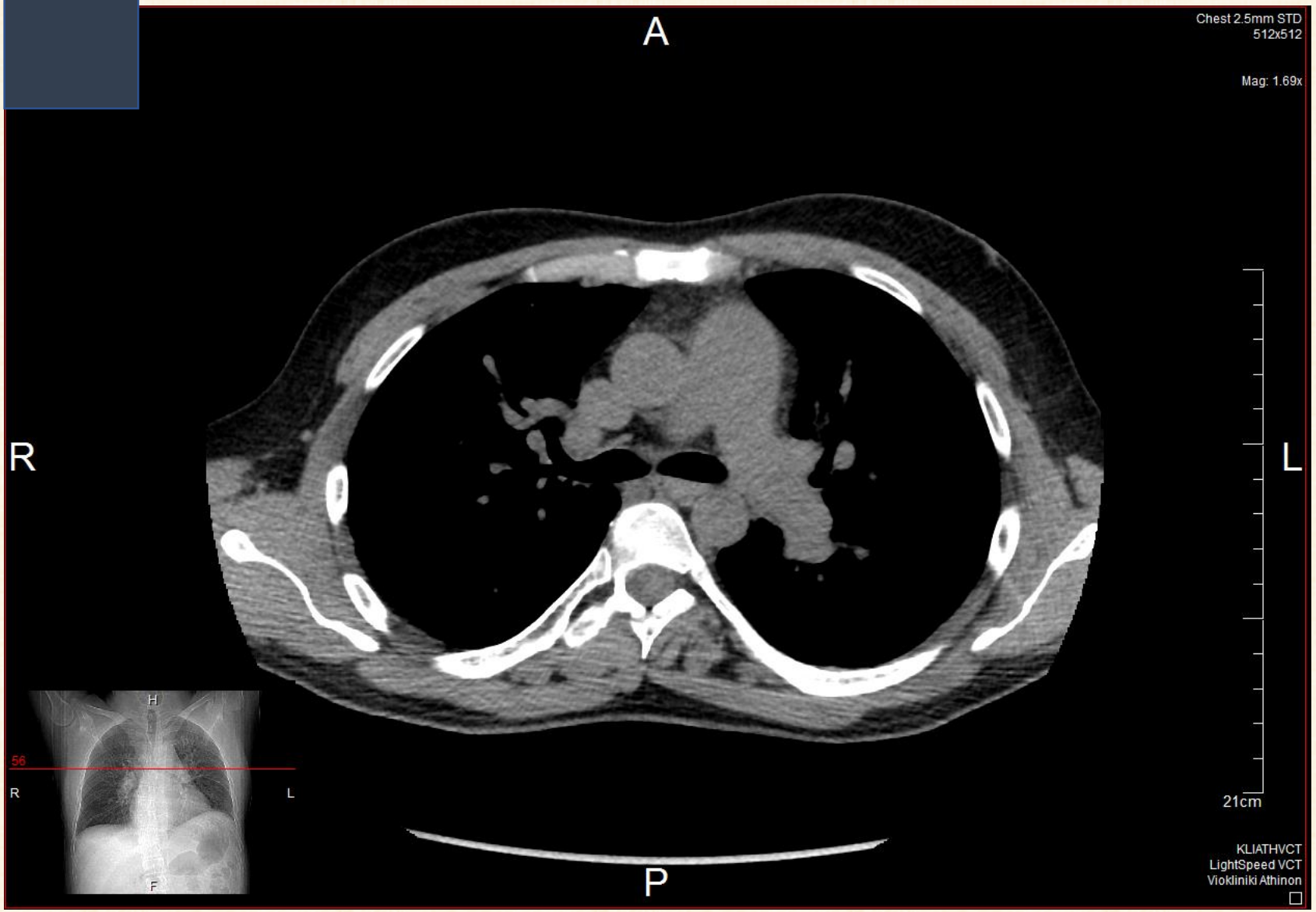
- RA dilatation
- RV dilatation (42mm) diffuse hypokinesis, severe dysfunction (TAPSE: 17mm, S-TDI:9 cm/sec)
- Main pulmonary artery dilation (30 mm)
- Tricuspid valve regurgitation – VmaxTG:4,7 m/sec (PASP: 91mm)

Echocardiography (15/03/2018)





HRCT 22/01/2018



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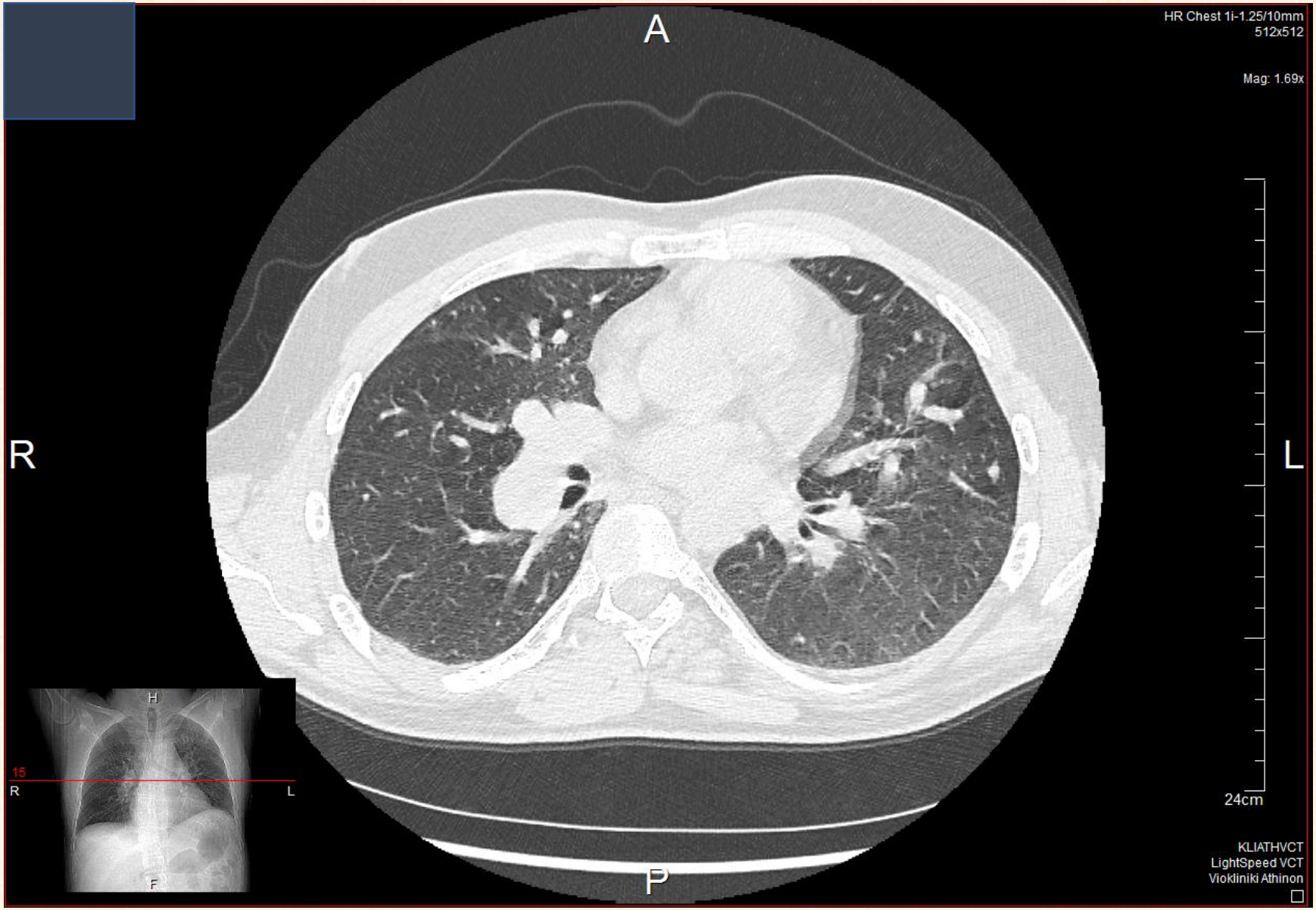
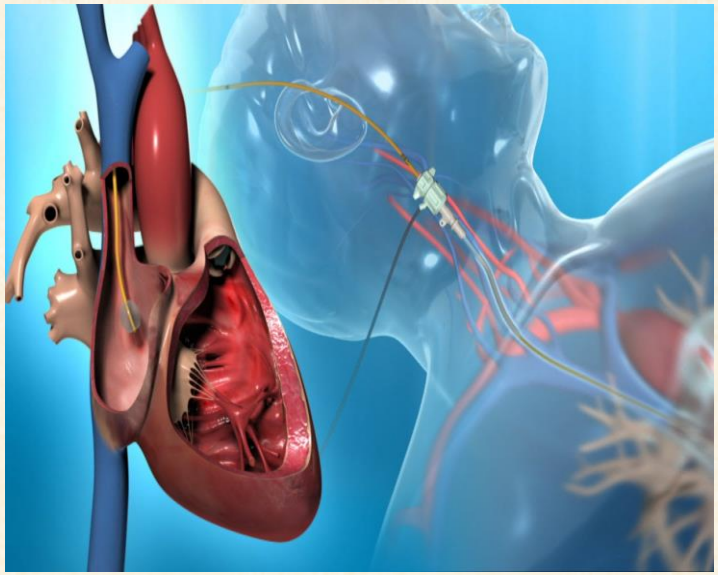


RHC: 11/04/2018

- RAP: 4mmHg
- PAP:92/41/58 mmHg (S/D/M)
- Pwedge: 11 mmHg
- CO:5 L/min, CI:2,4 L/min/m^2
- PVR: 9,4 Wood Units
- SVO_2: 73%



Laboratory tests

- Serological testing for CTD and thrombophilia screening: Negative
- SaO_2 : 94%
- **Lung function tests**: normal, DLCO:63,7%
- **NT-proBNP**: 489 ng/L
- Doppler Ultrasonography of lower extremity veins:

No thrombosis

Ποια είναι η πιθανή διάγνωση?

1. Πνευμονική αρτηριακή υπέρταση
2. Πνευμονική υπέρταση στα πλαίσια πνευμονικής νόσου
3. Πνευμονική υπέρταση από αριστερή καρδιακή νόσο
4. Πνευμονική υπέρταση κατηγορίας 5
5. Χρειάζονται επιπρόσθετες εξετάσεις

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

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

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

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

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

- 3.1 Chronic obstructive pulmonary disease
- 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 lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

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

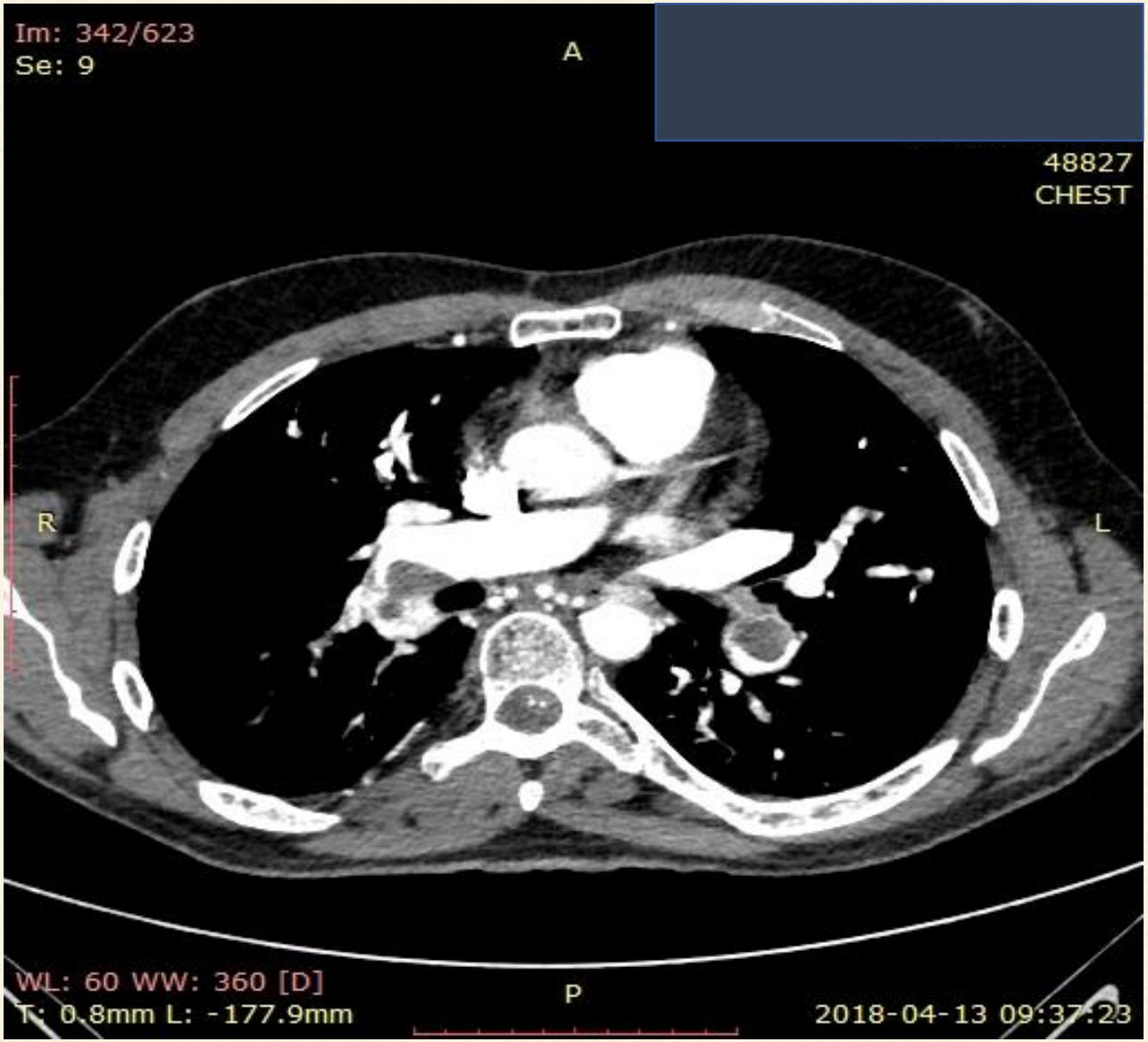
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 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

Τι άλλες εξετάσεις θα ζητάγατε?

1. Υπολογιστική αγγειογραφία πνευμονικής αρτηρίας (CTPA)
2. Σπινθηρογράφημα αιμάτωσης πνευμόνων
3. Μαγνητική τομογραφία καρδίας
4. Καρδιοαναπνευστική κόπωση

CTPA 13/04/2018



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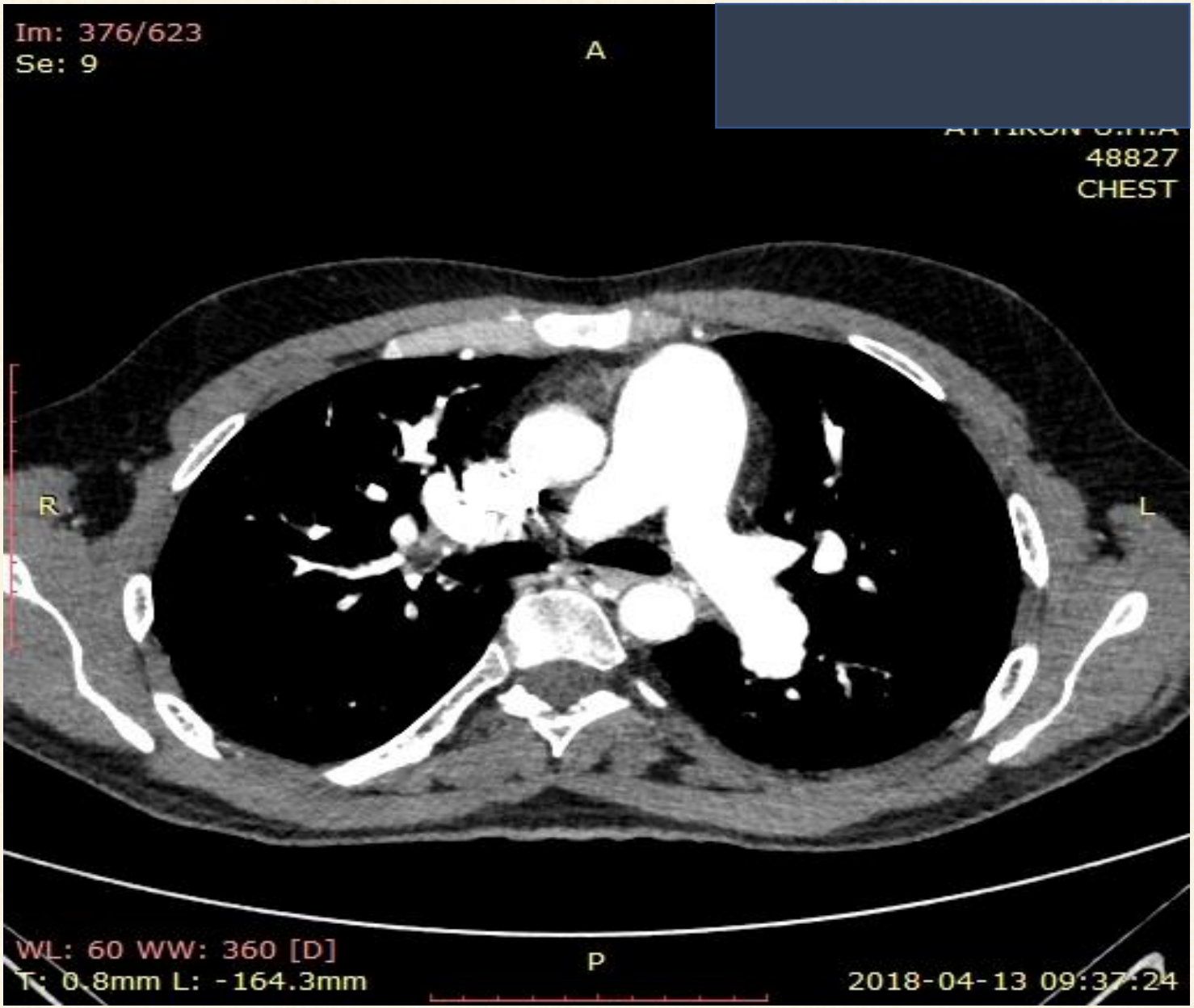

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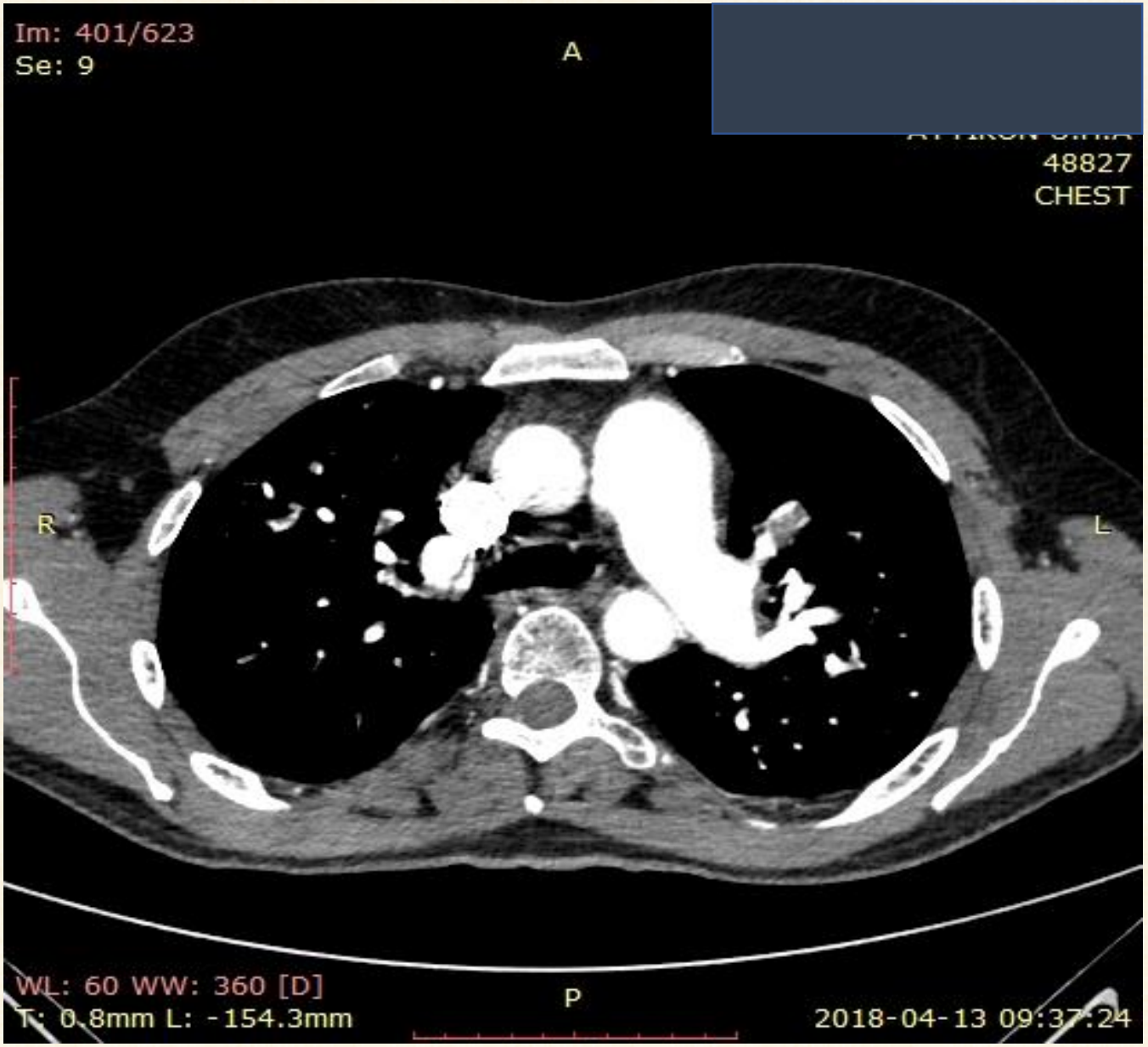

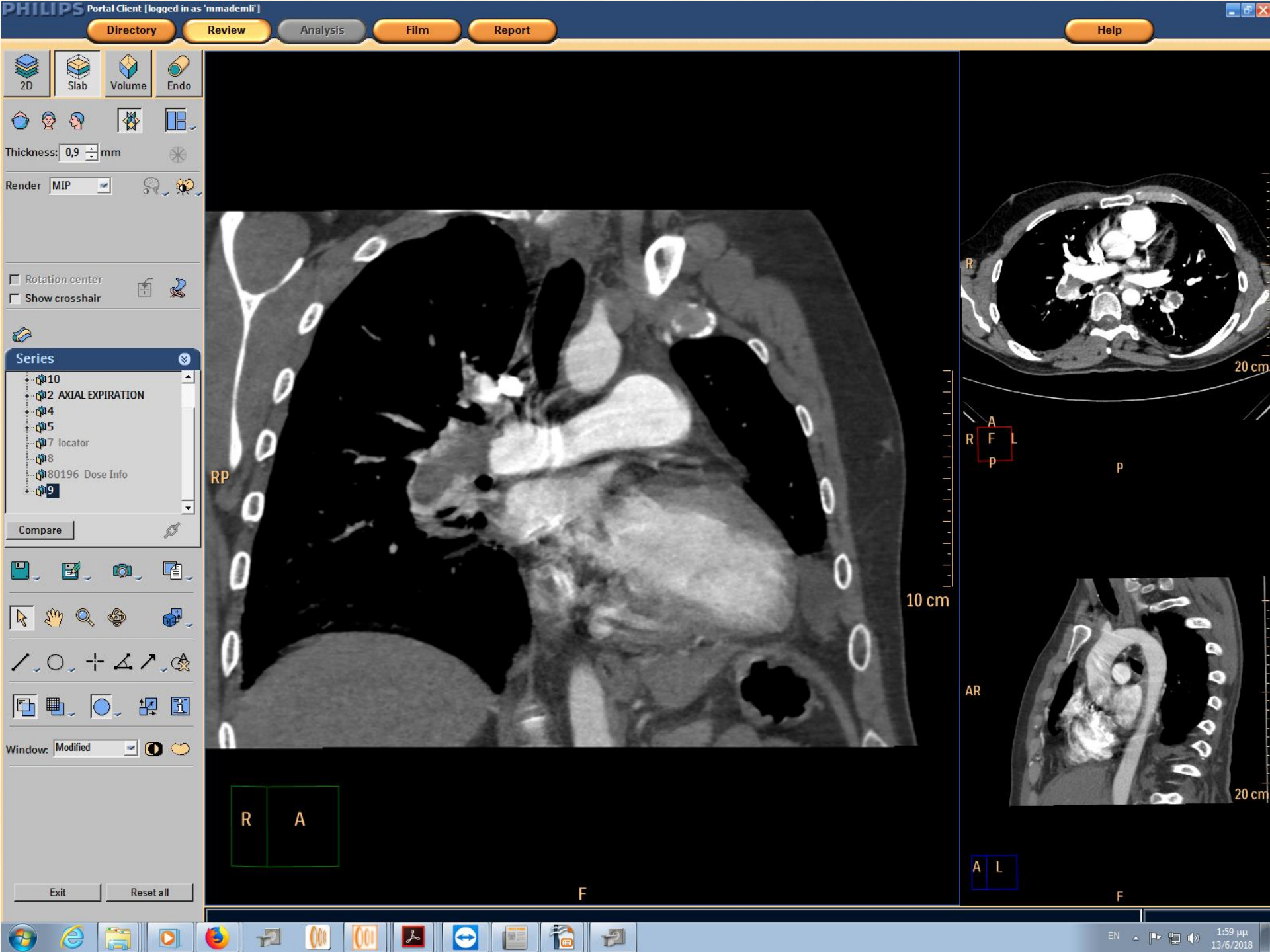
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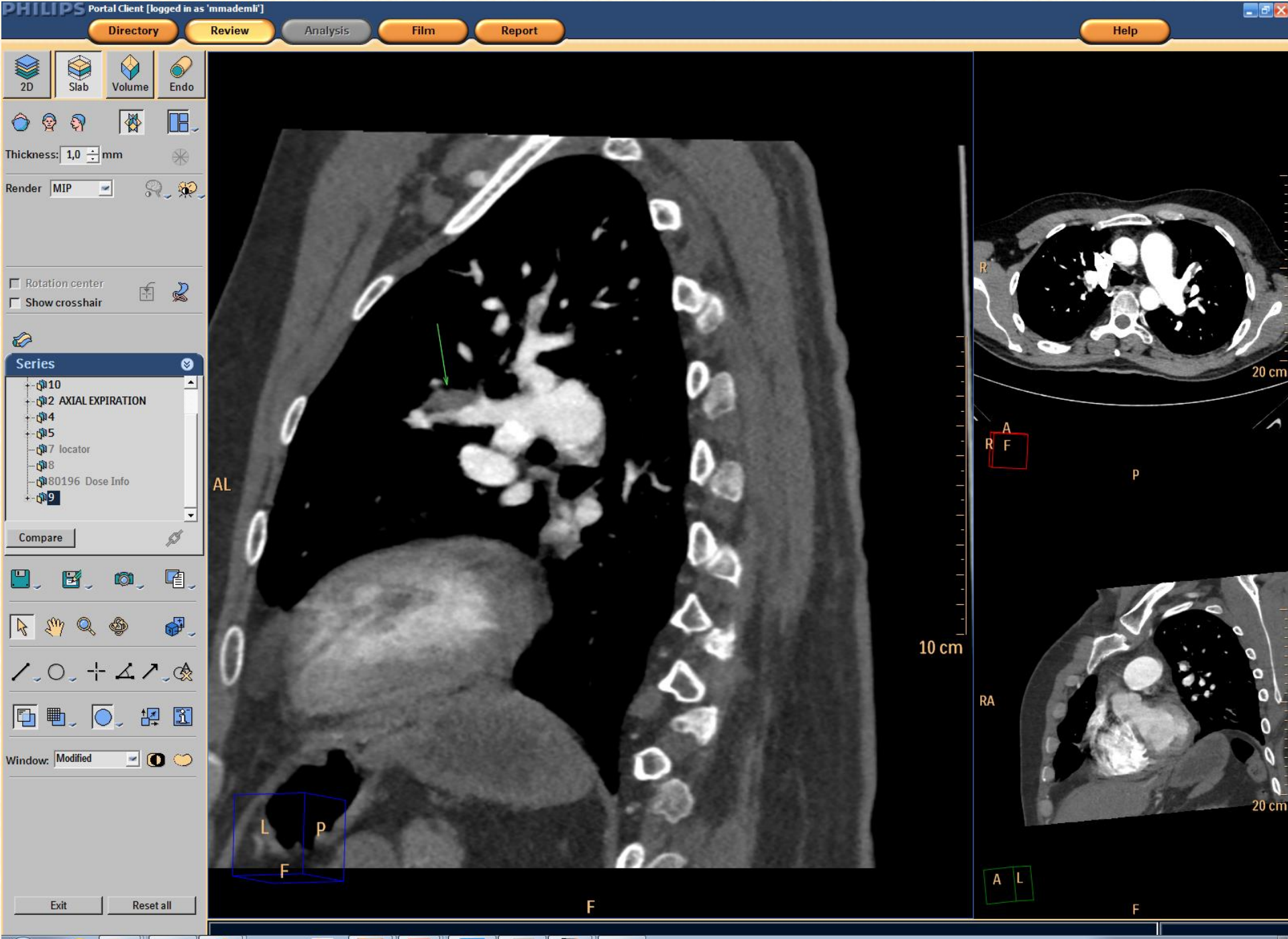
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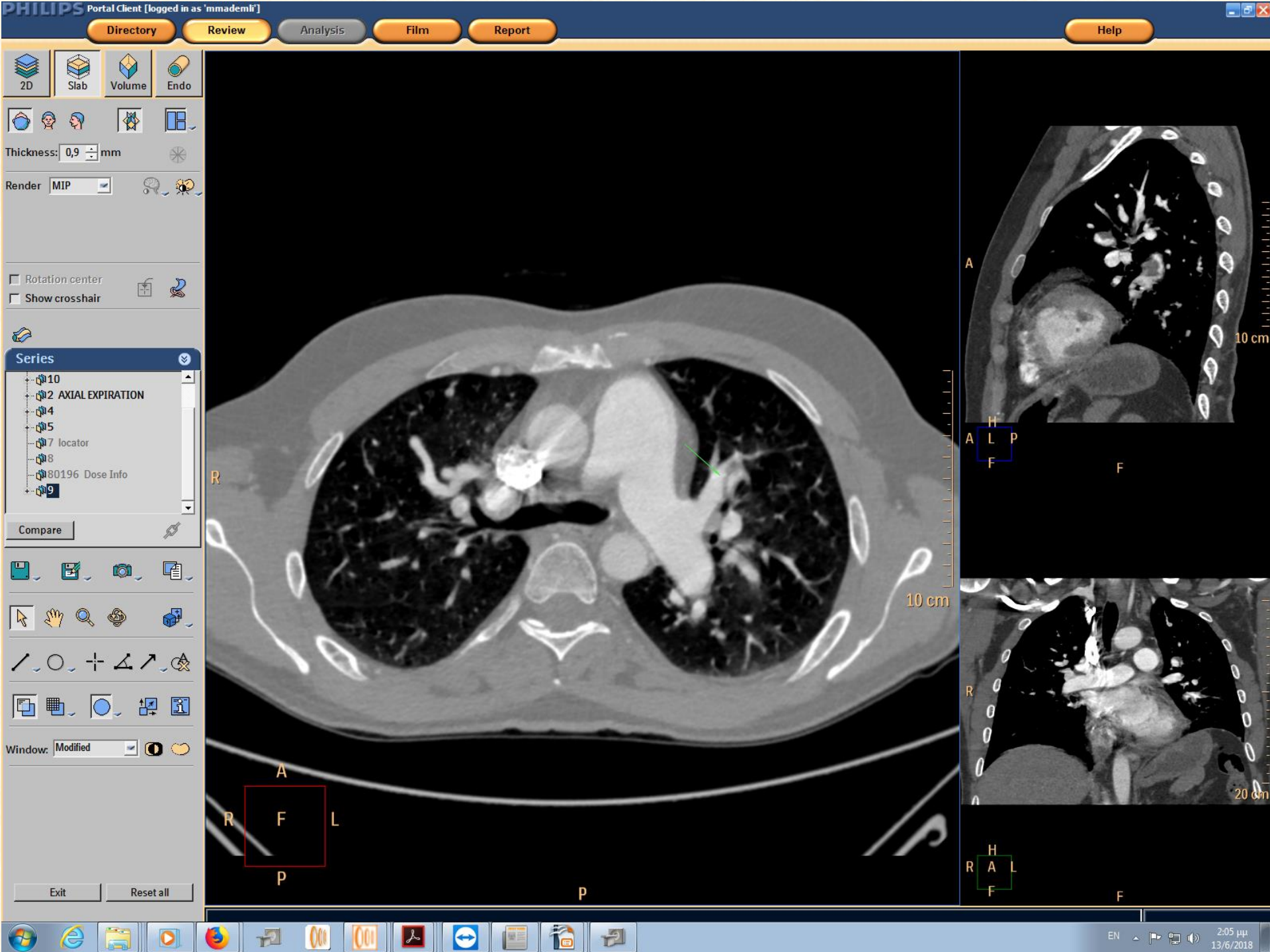
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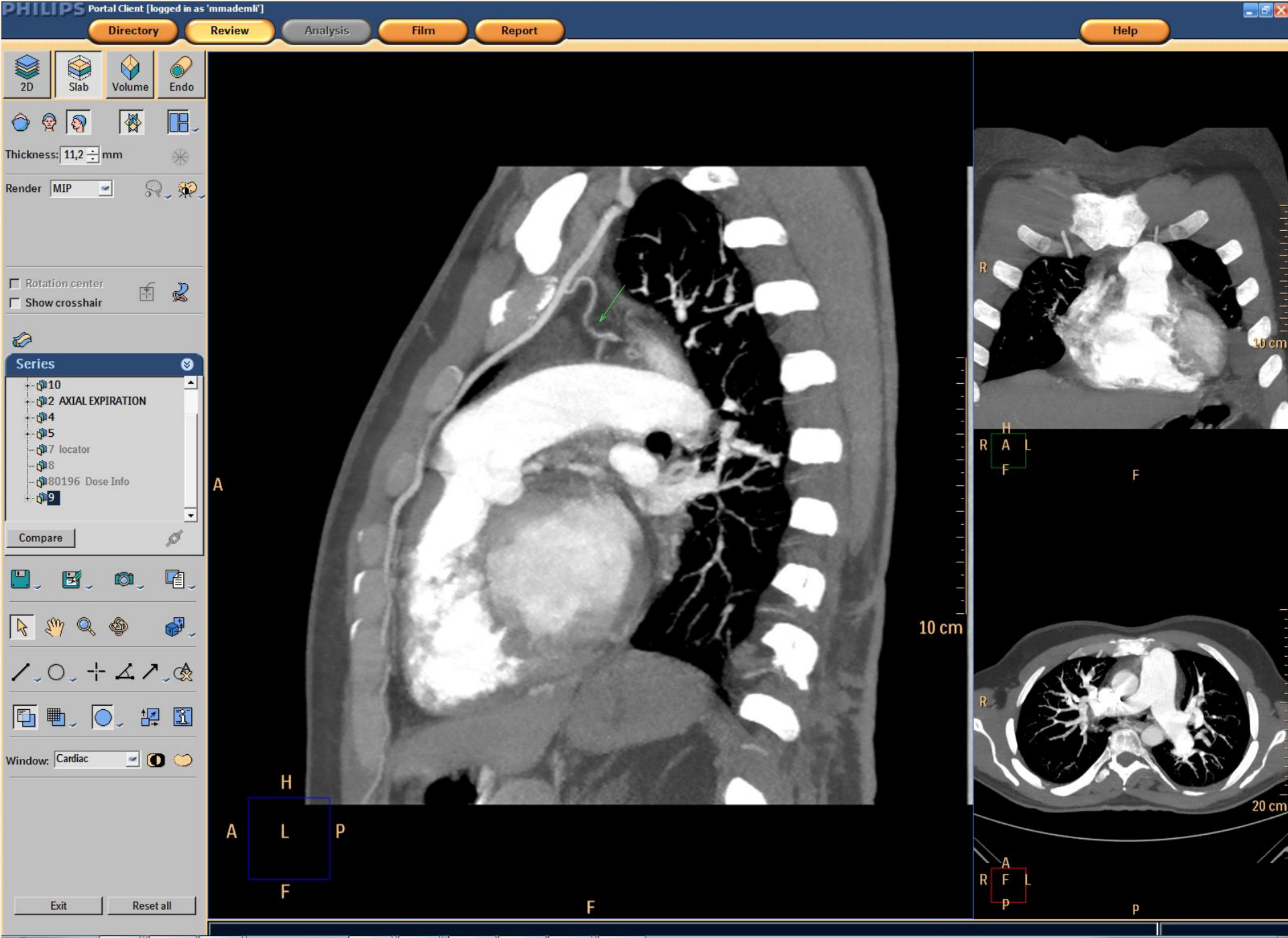
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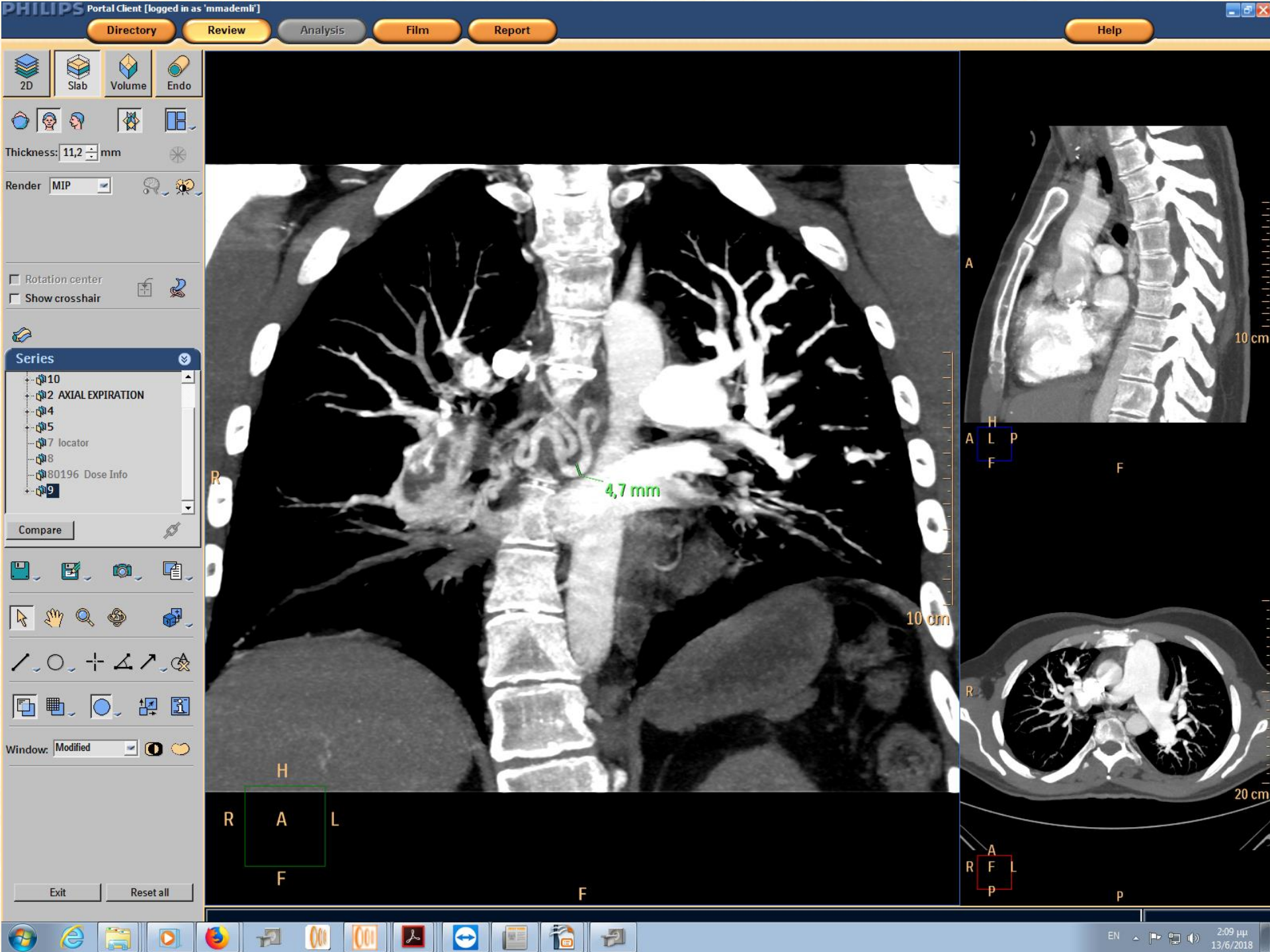
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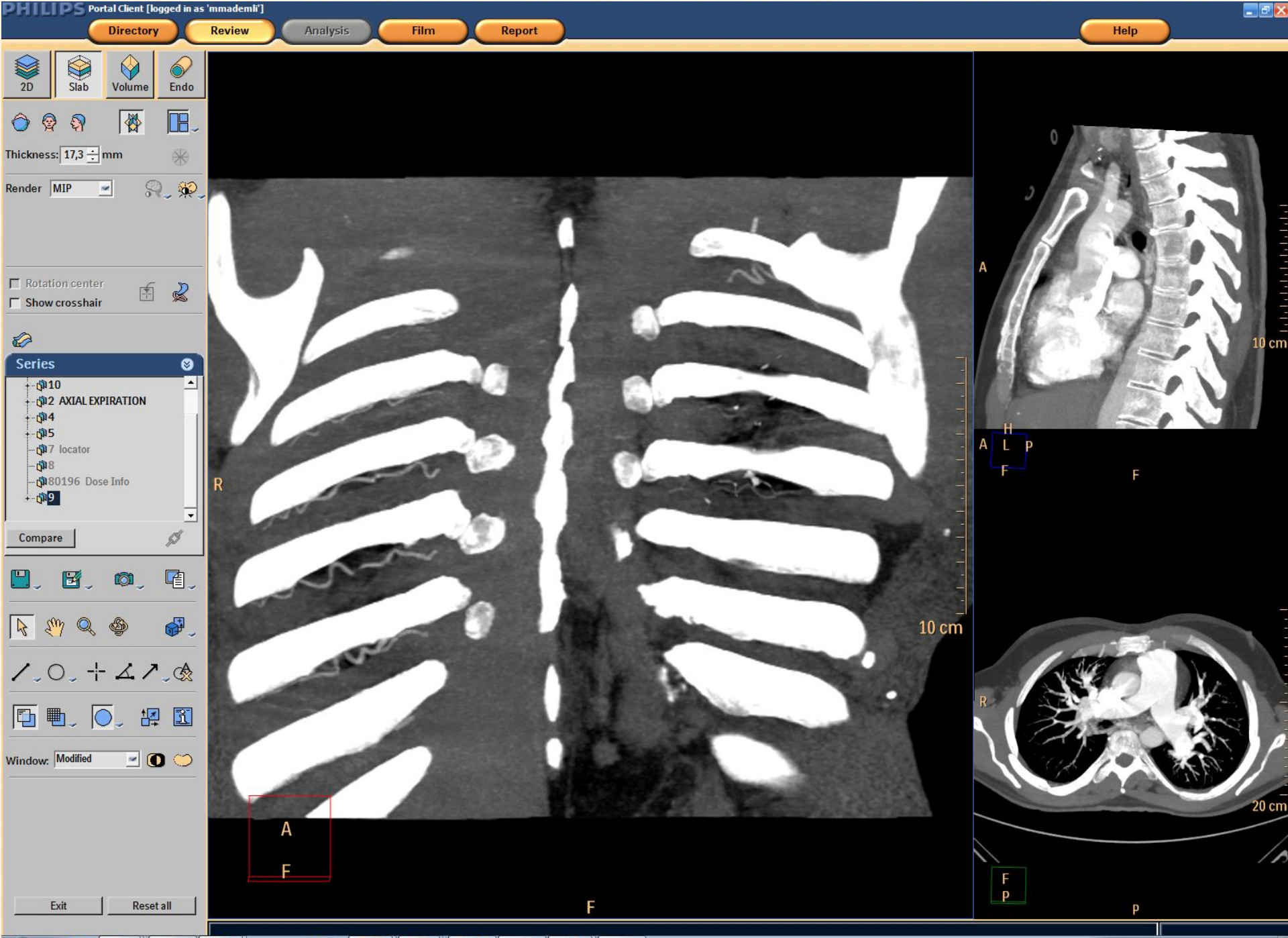
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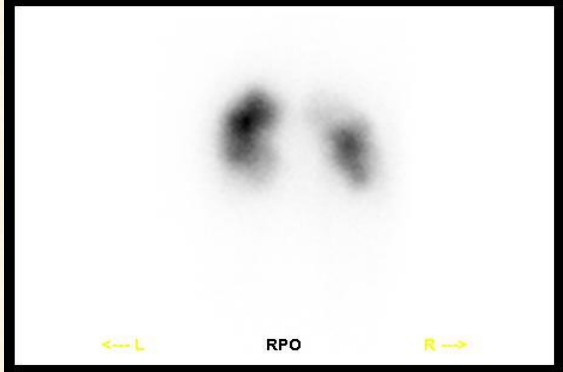
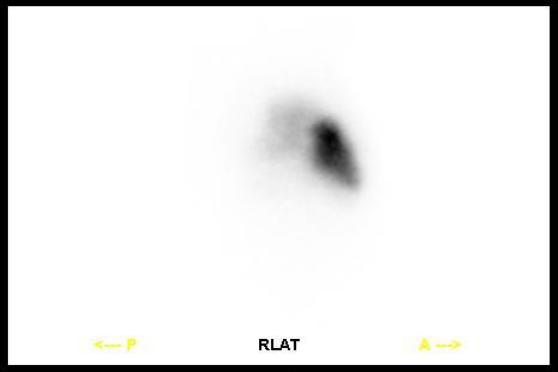
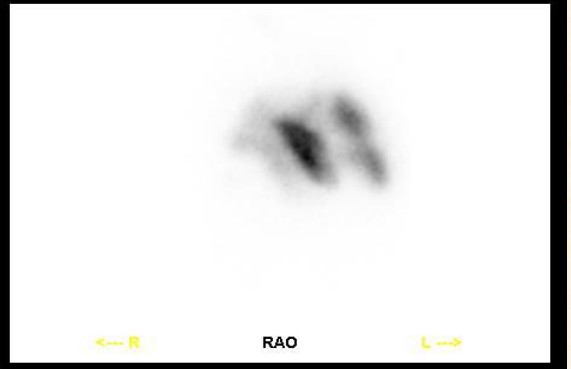
Study Name: Lung perfusion

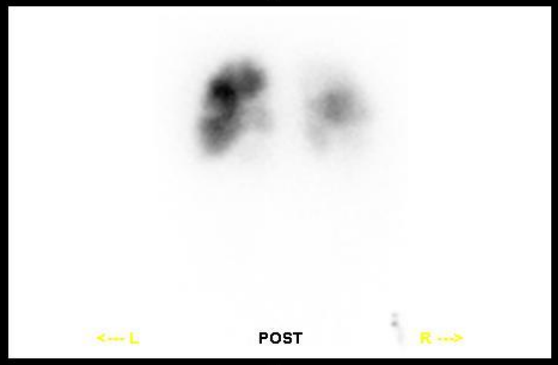
Date & Time: 4/17/2018

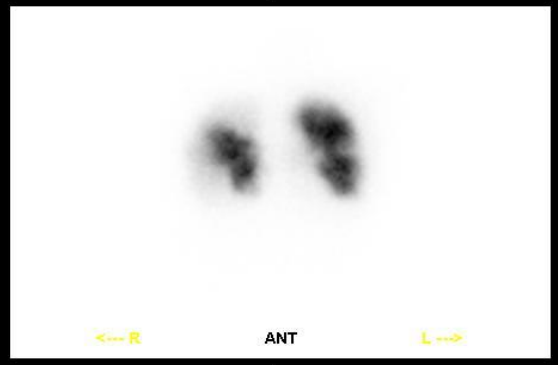
Manufacturer Model: MILLENNIUM MPR

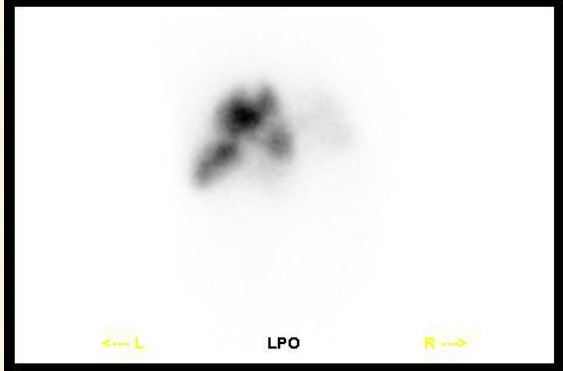


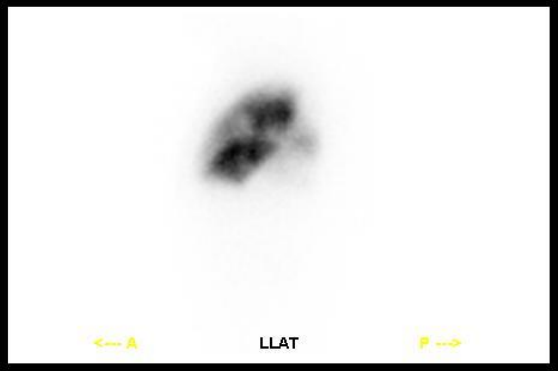


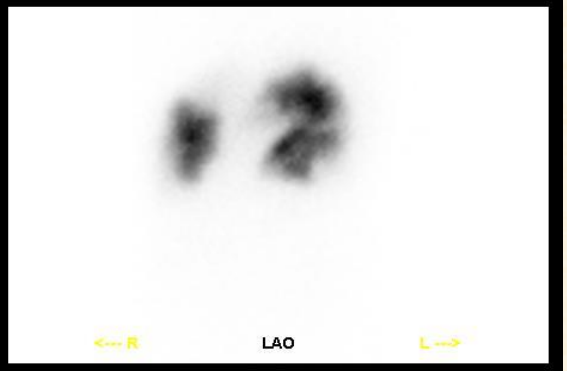












Τι θεραπεία θα επιλέγατε?

1. Αντιπηκτική αγωγή εφ'όρου ζωής
2. Riociguat
3. Καρδιοχειρουργική εκτίμηση για πιθανή ενδαρτηρεκτομή
4. Όλα τα παραπάνω

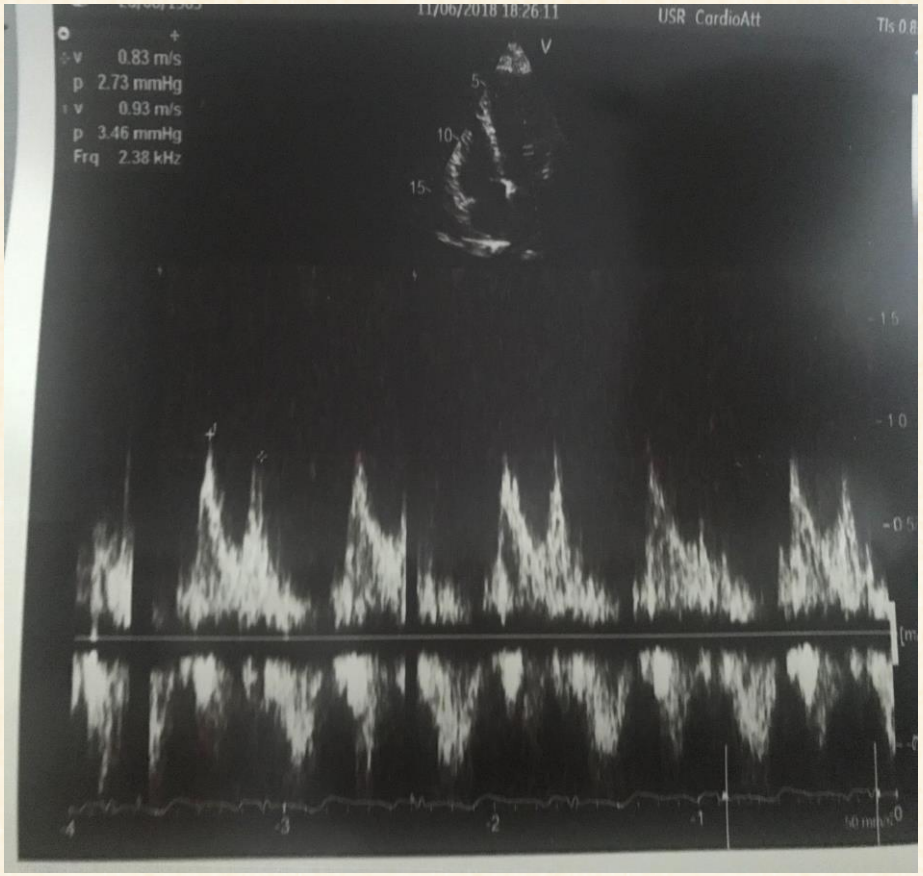
Θεραπευτική προσέγγιση

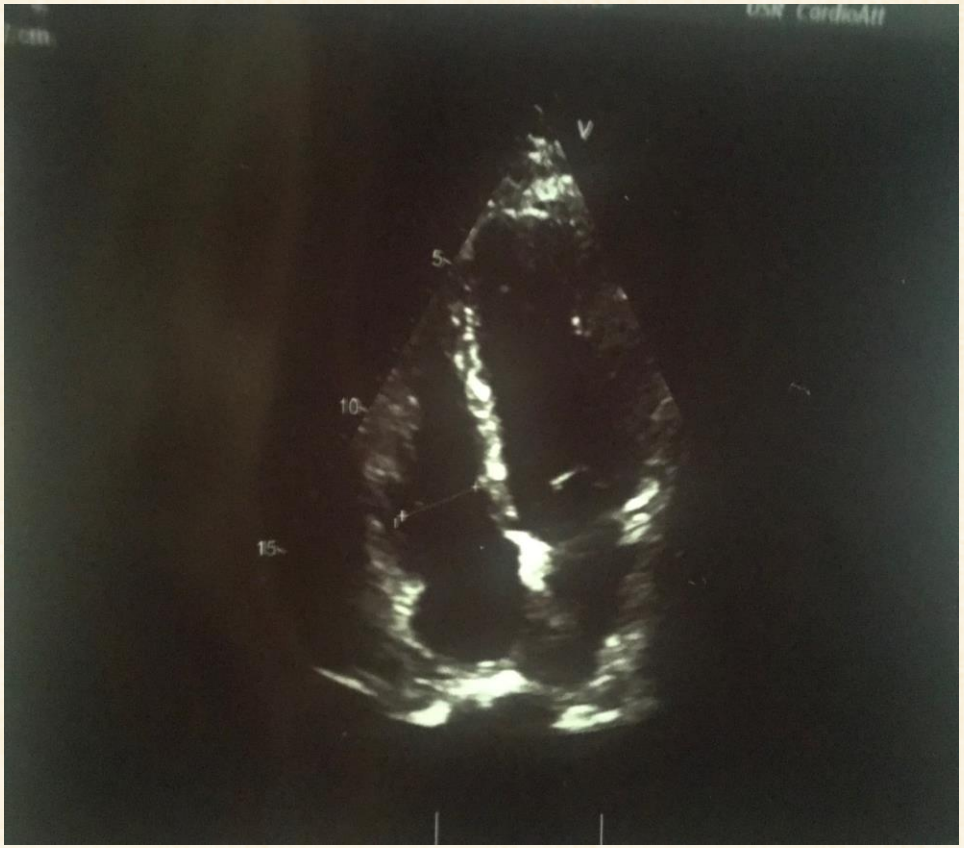
- Έναρξη αντιπηκτικής αγωγής αρχικά με LMWH και στη συνέχεια με ασενοκουμαρόλη με στόχο INR 2.5-3
- Διουρητικά
- Έναρξη riociguat σε προοδευτικά αυξανόμενη δόση μέχρι 2.5 mg x 3
- Καρδιοχειρουργική εκτίμηση για πνευμονική ενδαρτηρεκτομή σε εξειδικευμένο κέντρο μετά από τρεις μήνες αντιπηκτικής αγωγής

Echocardiography (13/06/2018)

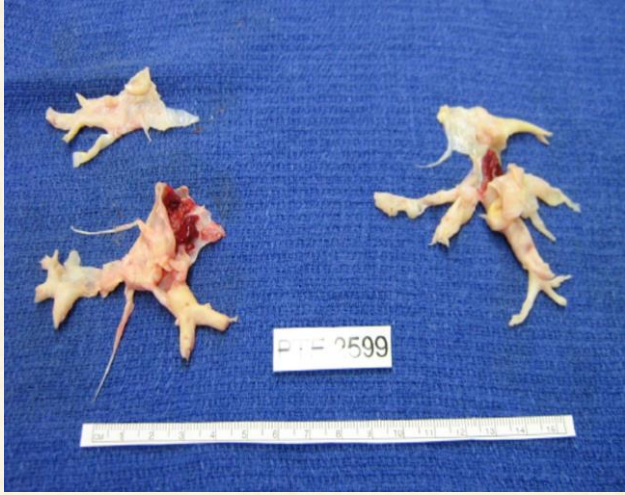
- Normal dimensions of RA and RV with satisfactory systolic function
- Main pulmonary artery dilation (30 mm)
- Tricuspid valve regurgitation – VmaxTG: 3 m/sec (PASP: 40 mm)

Echocardiography (13/06/2018)



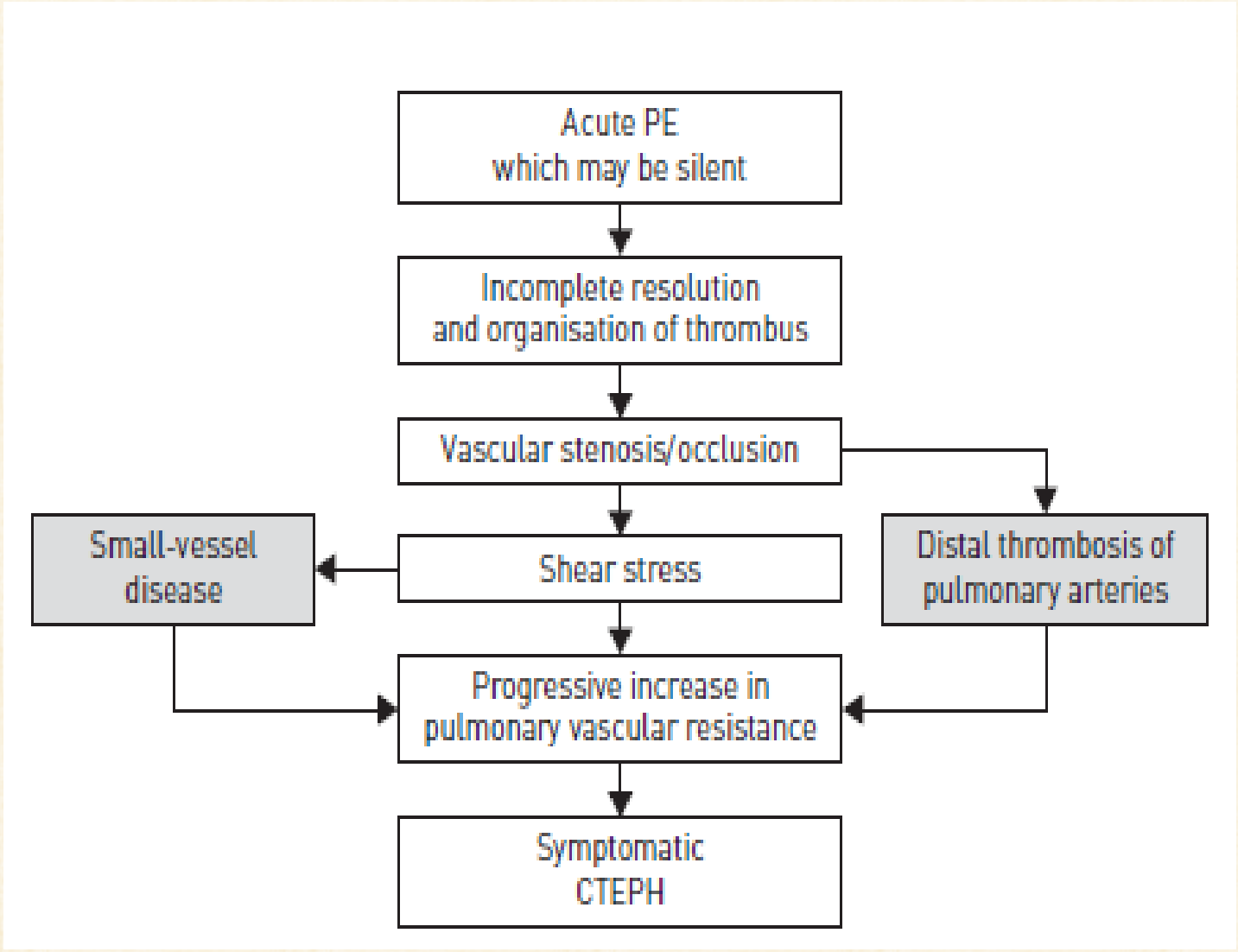


CTEPH

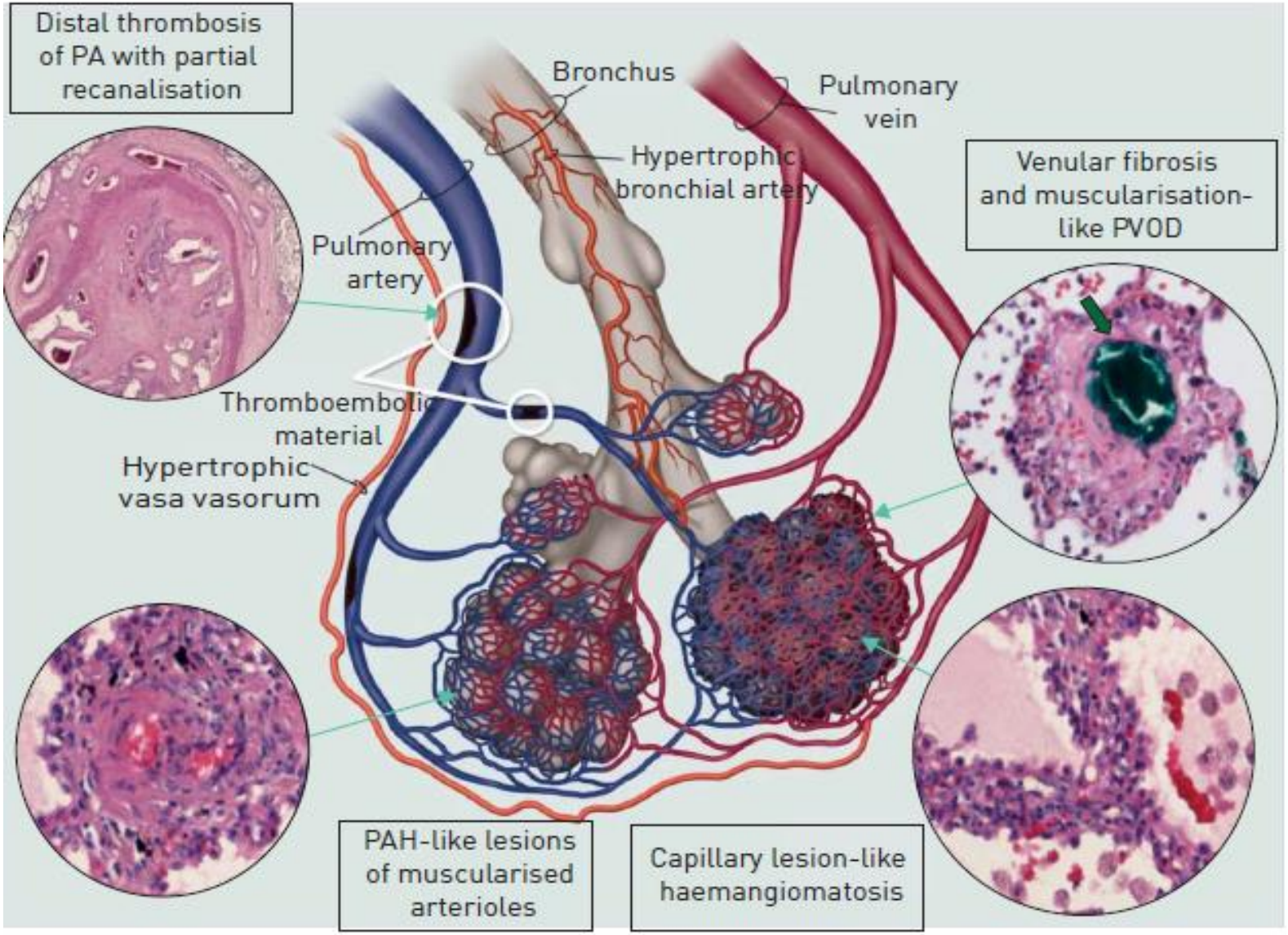


- Group 4 of the present clinical classification
- Rare and late complication of PE
- Thrombi in proximal pulmonary arteries
- Small vessel disease
- “Honeymoon period”
- Incidence after symptomatic PE: 0.4-6.2% (3.4%)
- Systematic V/Q scanning after PE: Not recommended

Simonneau et al. *Eur Respir Rev* 2017;26



Simonneau et al. *Eur Respir Rev* 2017;26



Simonneau et al. *Eur Respir Rev* 2017;26

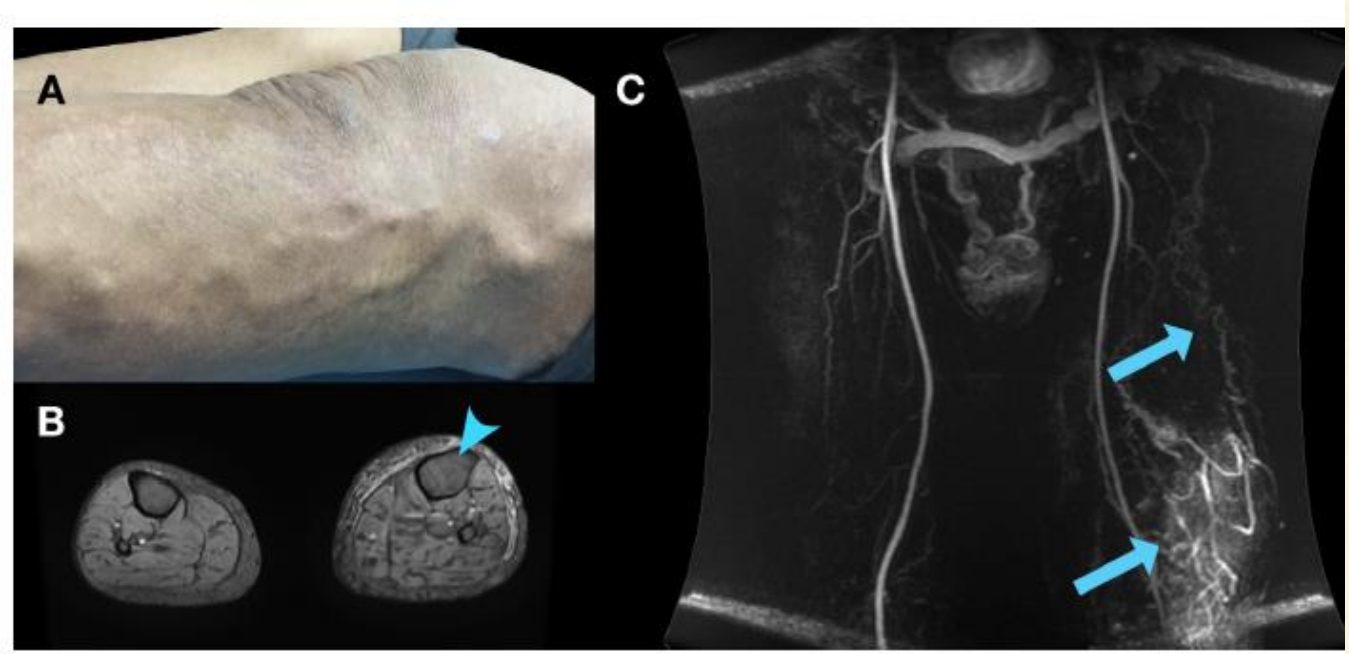
TABLE 1 Risk Factors for the Development of CTEPH

Acute pulmonary embolism
Recurrent pulmonary embolic events
Large perfusion defect
Higher pulmonary artery pressure at time of initial PE diagnosis
Idiopathic (unprovoked) pulmonary embolus
Hemostatic risk factors
Elevated factor VIII, von Willebrand factor, type 1 plasminogen activator inhibitor
Abnormal fibrinogen structure
Antiphospholipid antibodies and lupus anticoagulant
Non–type-O blood groups
Elevated lipoprotein(a)
Associated medical conditions
Splenectomy
Ventriculoatrial shunt
Infected intravenous catheters/devices
Chronic inflammatory disorders
Hypothyroidism
Malignancy

Mahmud et al. *JACC* 2018; 71(21)

Vascular malformations might be associated with CTEPH

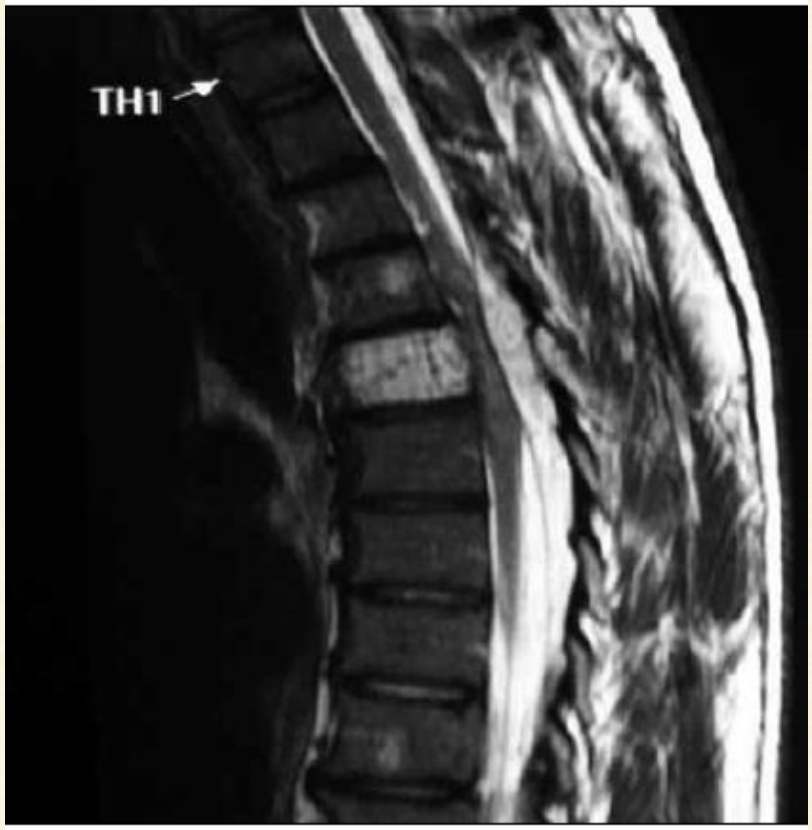
<u>Klippel-Trenaunay-Weber Syndrome</u>: VM of capillary, venous, lymphatic type, disturbed growth of the bones of extremities – 8-22% thromboembolism



Chenbhanich et al. *BMJ Case Rep* 2018

Thoracic Vertebral Hemangioma Causing Paraplegia in Klippel-Trenaunay-Weber Syndrome: Case Report

Turkish Neurosurgery 2012, Vol: 23, No: 4, 518-520



- No limb hypertrophy
- Hyperpigmented lesions
- Hemangioma on the thoracic vertebra
- Multiple hemangiomas of T3,T4
- DVT

Vascular malformations as underlying cause of chronic thromboembolism and pulmonary hypertension

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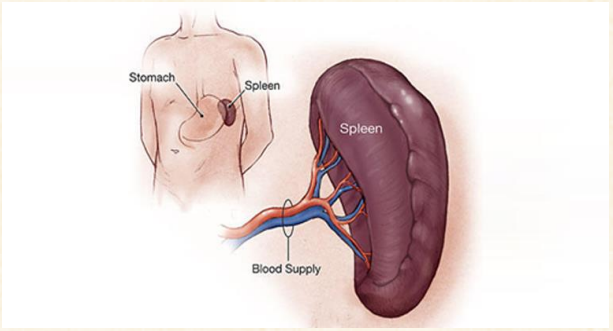
Journal of Plastic, Reconstructive & Aesthetic Surgery (2009) 62, 684–689

4 pts with low-flow VM and CTEPH without other risk factors

- Blood stagnation – activation of coagulation
- Coagulopathy correlated with the extent of malformation

Mazoyer et al. *Clin Lab Haematol* 2002;24:243-51

Splenectomy and thrombosis



- Arterial thrombosis: coronary, cerebral, extremity vessels
- Stroke, vascular dementia, limb ischemia
- Venous thrombosis: portal, splenic, LA, priapism, PE, CTEPH (VTE: 10.7%)
- Spleen: Important role in coagulation homeostasis

Kimmig L and al. *Ann Am Thorac Soc*, 2016: 13(6)

Risk factors for chronic thromboembolic pulmonary hypertension

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Condition	Marginal effects	
	OR (95% CI)	p-value
Thyroid hormone replacement	5.41 (2.70–12.23)	<0.001
Malignancy	1.99 (1.01–4.26)	0.046
Previous VTE	19.36 (11.66–33.79)	<0.001
Recurrent VTE	45.02 (21.00–114.73)	<0.001
Chronic venous ulcers	3.17 (1.45–8.17)	0.003
APA/LAC	3.28 (1.58–7.50)	0.001
Systemic lupus erythematosus	0.06 (0.00–0.48)	0.005
VA shunt or infected pacemaker	19.49 (2.47–2520.10)	0.001
Inflammatory bowel disease	2.21 (0.69–9.05)	0.189
Splenectomy	22.09 (2.97–2824.53)	<0.001
Abnormal haemoglobins	7.97 (0.98–1035.53)	0.054
COPD	0.26 (0.09–0.73)	0.012
Osteomyelofibrosis	1.47 (0.28–14.65)	0.673

Retrospective cohort analysis
4 Eur PEA centers
687 pt-11y

Eur Respir J 2009; 33: 325–331

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Results From an International Prospective Registry

Joanna Pepke-Zaba, MD; Marion Delcroix, MD; Irene Lang, MD; Eckhard Mayer, MD; Pavel Jansa, MD; David Ambroz, MD; Carmen Treacy, BSc; Andrea M. D'Armini, MD; Marco Morsolini, MD; Repke Snijder, MD; Paul Bresser, MD; Adam Torbicki, MD; Bent Kristensen, MD; Jerzy Lewczuk, MD; Iveta Simkova, MD; Joan A. Barberà, MD; Marc de Perrot, MD; Marius M. Hoeper, MD; Sean Gaine, MD; Rudolf Speich, MD; Miguel A. Gomez-Sanchez, MD; Gabor Kovacs, MD; Abdul Monem Hamid, MD; Xavier Jaïs, MD; Gérald Simonneau, MD

	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)	*P* (Exploratory)
Associated conditions, % (n)	78.4 (677)	77.0 (426)	80.6 (247)	0.2878
Thrombophilic disorder, %	31.9	37.1	23.5	0.0003
Previous major surgery, %	21.7	18.8	26.7	0.0197
Varicose veins, %		20.4	21.1	0.8440
Obesity, %			19.0	0.4623
Chronic venous insufficiency, %			14.6	0.6596
Prolonged hospitalization, %			15.8	1.0000
History of cancer, %			16.6	0.0156
Coronary disease and/or myocardial infarction, %	11.8		13.4	0.3883
Thyroid disorder and hormone replacement therapy, %	8.4	7.7	9.3	0.4732
Family history of DVT or PE, %	6.6	8.2	4.0	0.0382
Fracture, %	5.5	5.9	4.5	0.4815
Non–insulin-dependent diabetes mellitus, %	5.2	5.4	4.9	0.8580
Congestive heart failure, %	4.6	2.8	7.7	0.0065
Splenectomy, %	3.4	1.9	5.7	0.0118

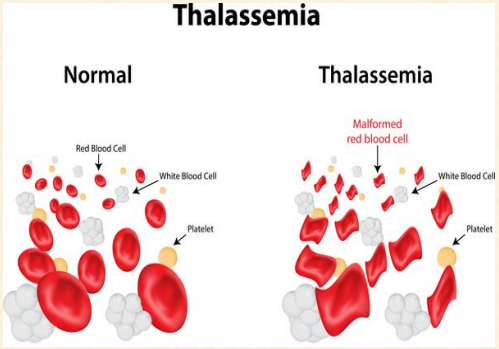
Distal type CTEPH?
Comorbidities?

Pathophysiologic mechanism-microparticles

- Microparticles (MP): 100-1000nm vesicles, with cell –surface proteins, RNA and DNA
- Erythrocyte, platelet, endothelial-derived
- Platelet derived: 50-100 higher procoagulant activity than platelets
- Spleen: clearing circulating microparticles
- High MP levels: VTE
- Elevated in PH Group I, III, IV
- Inflammatory modulation-Vascular remodeling

Bucciarelliet al. *Thromb Res* 2012; 129
Amabile et al. *Am J Crit Care Med* 2008;177
Amabile et al. *Eur Respir J* 2013;42

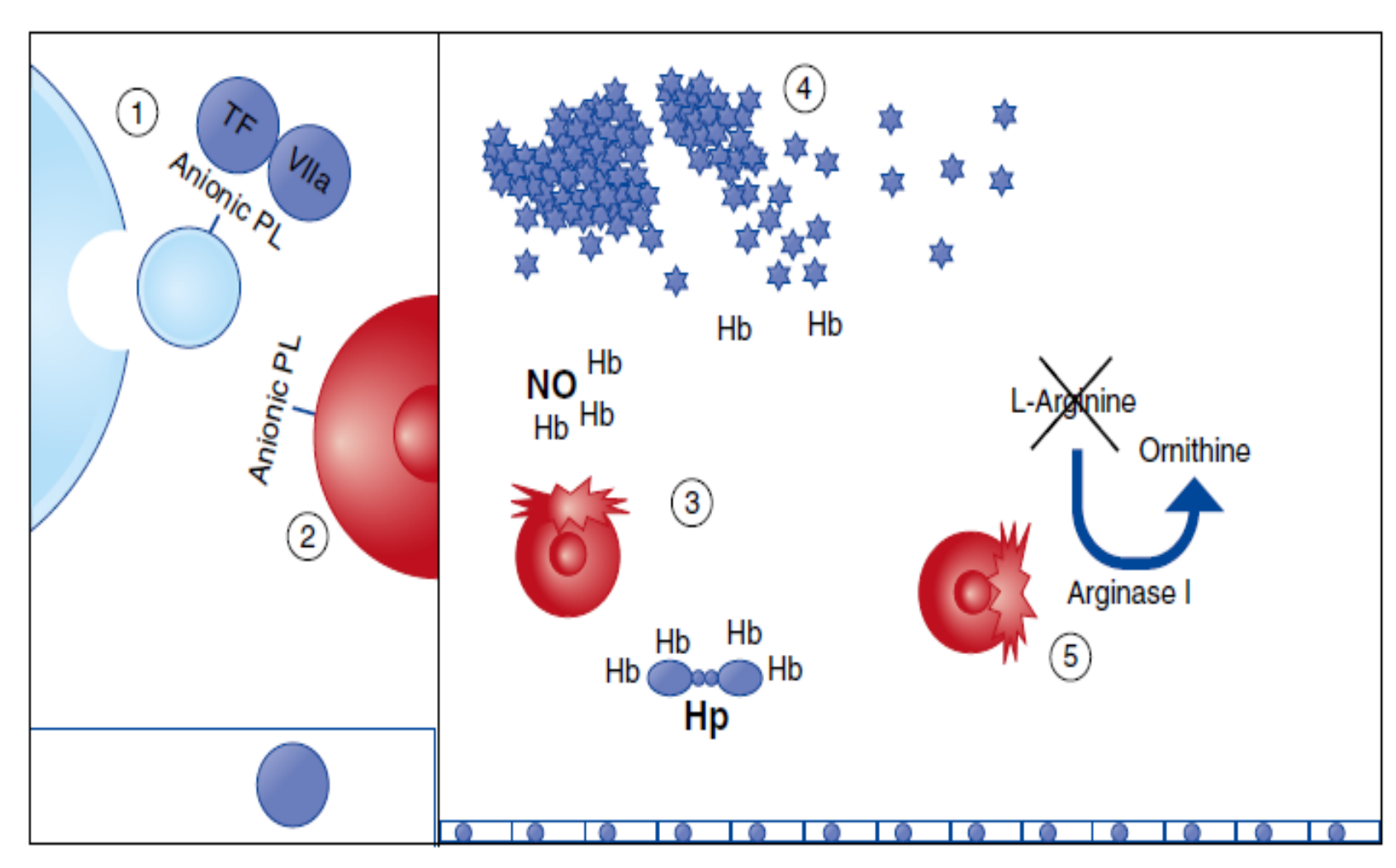
Other mechanisms of post-splenectomy procoagulant state



- Post – splenectomy thrombocytosis?
- Elevated PAI-1, fibrinogen, D-dimers
- More reactive platelets
- Red blood cell membrane asymmetry-thalassemia

Watters JM et al. *Am J Surg* 2010;199
Frey MK et al. *J Am Heart Assoc* 2014;3

Splenectomy and thrombosis



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Take home messages

- Vascular malformations are a rare cause of CTEPH
- Splenectomy is a significant risk factor for the development of CTEPH
- PE might be followed by a PV remodeling process modified by various immune phenomena
- Essential to detect and treat CTEPH before small vessel disease


Ευχαριστώ !!!