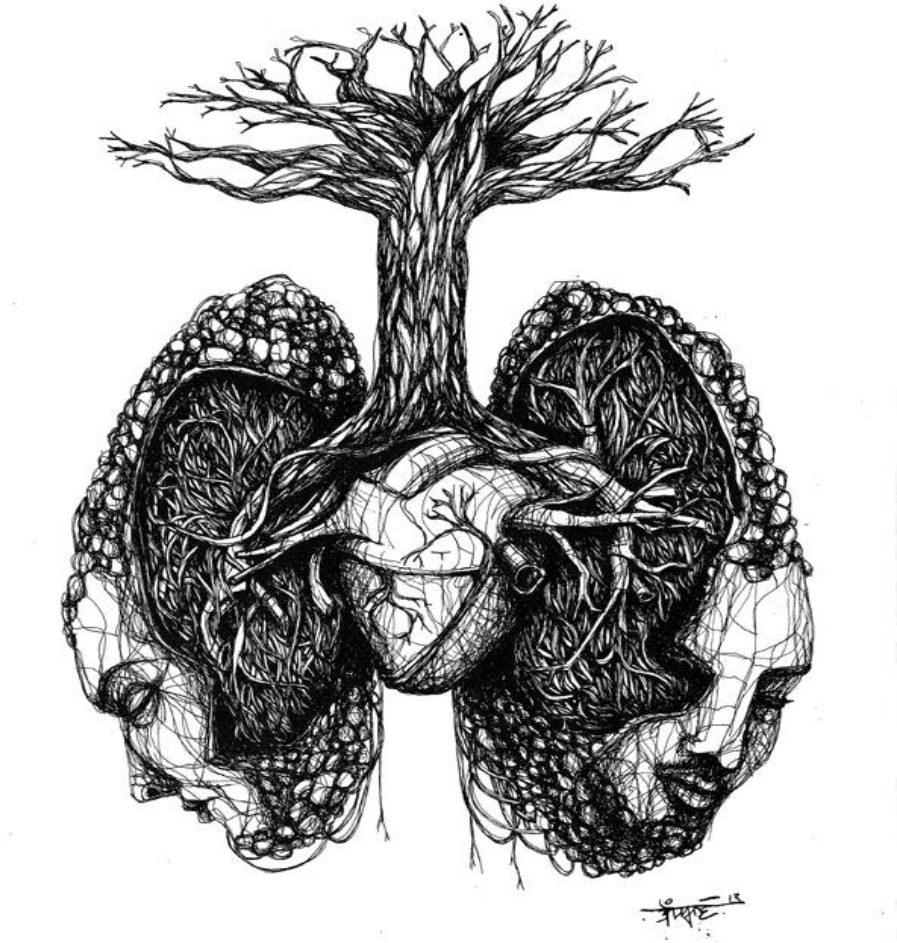
ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ
ΑΤΤΙΚΟΝ

Πνευμονική Υπέρταση

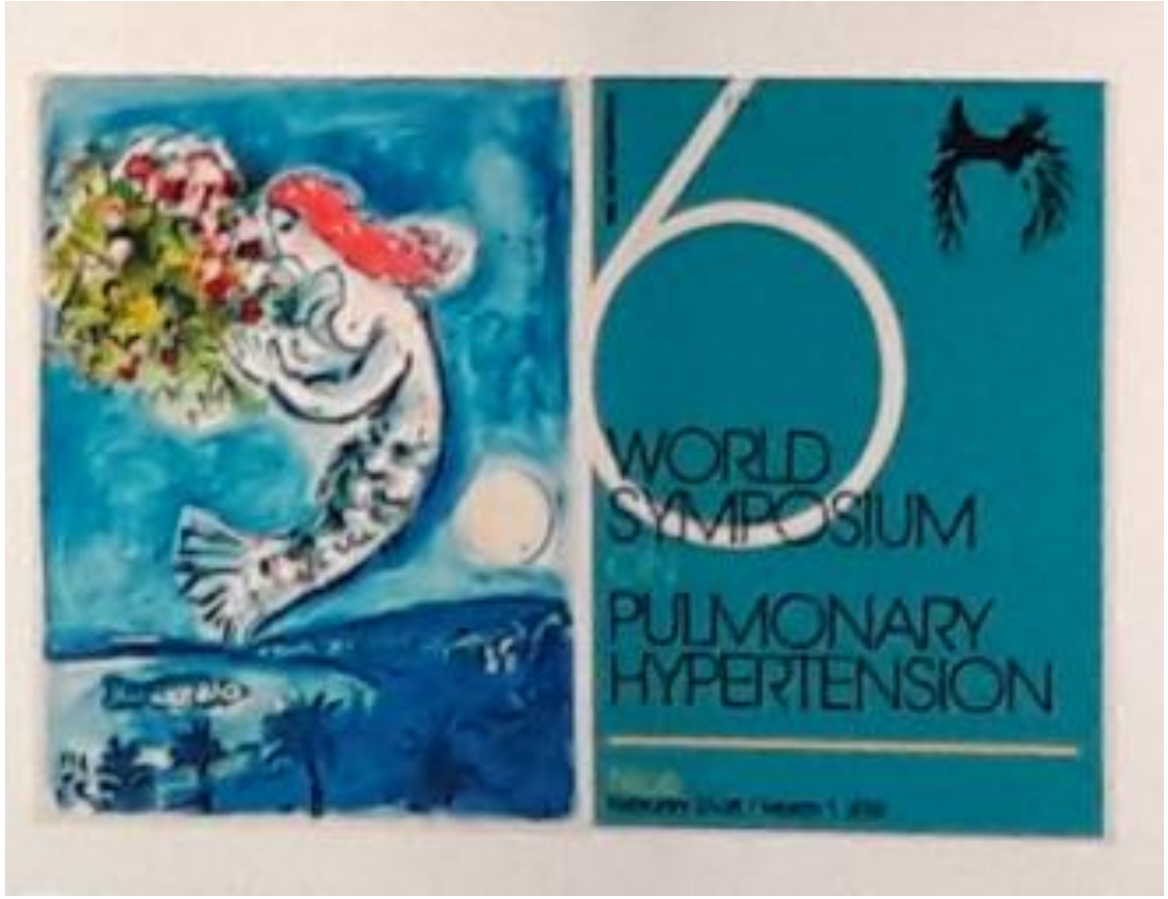


Σταγάκη Ελένη, Πνευμονολόγος

Σισμανόγλειο ΓΝΑ

Η Πνευμονική Υπέρταση το 2018

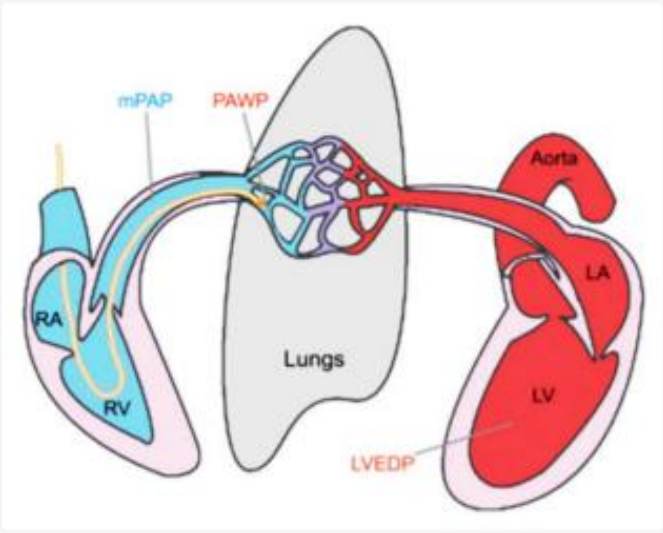
1. Φυσιολογία- Παθοφυσιολογία
2. Ορισμός
3. Ταξινόμηση
4. Διάγνωση
5. Διαστρωμάτωση κινδύνου
6. Βασικές αρχές θεραπείας

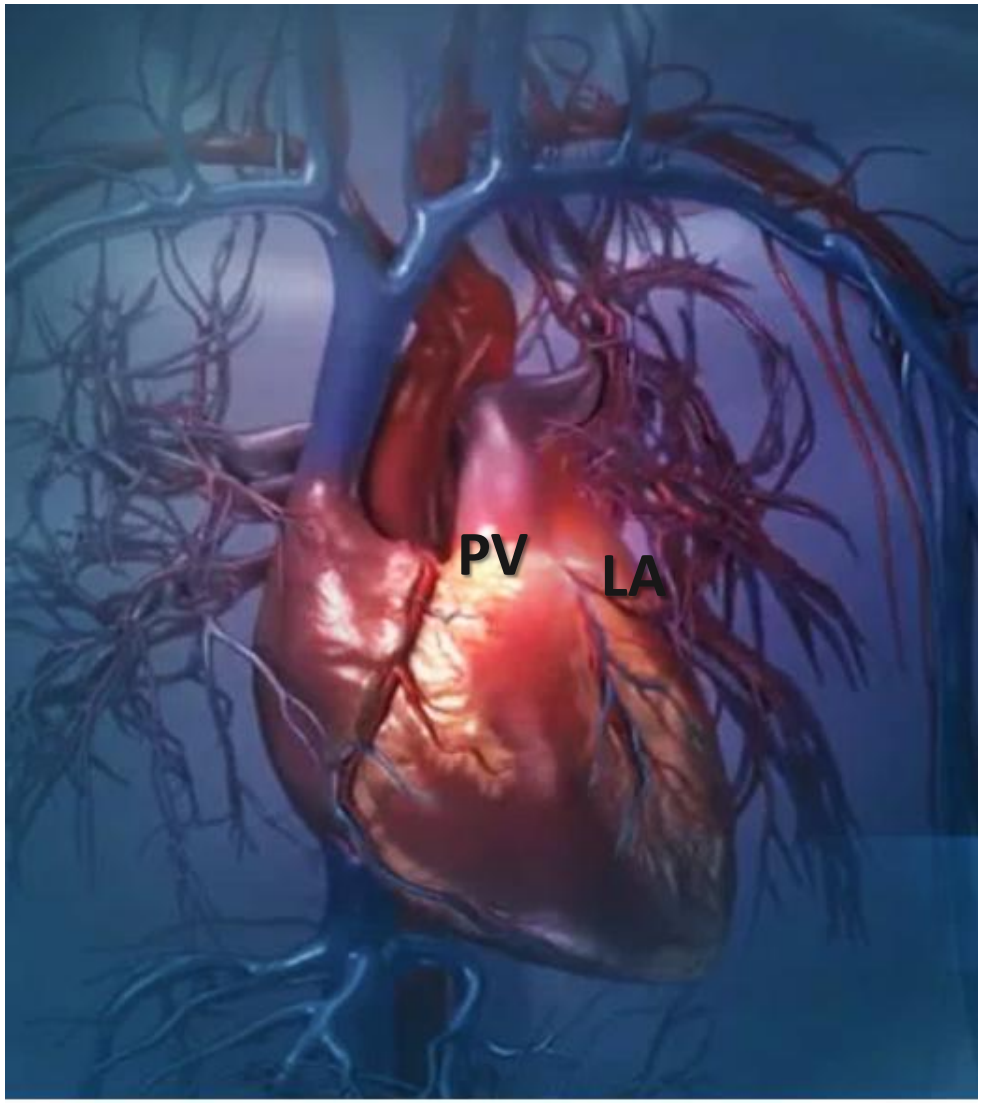


1. Φυσιολογία- Παθοφυσιολογία

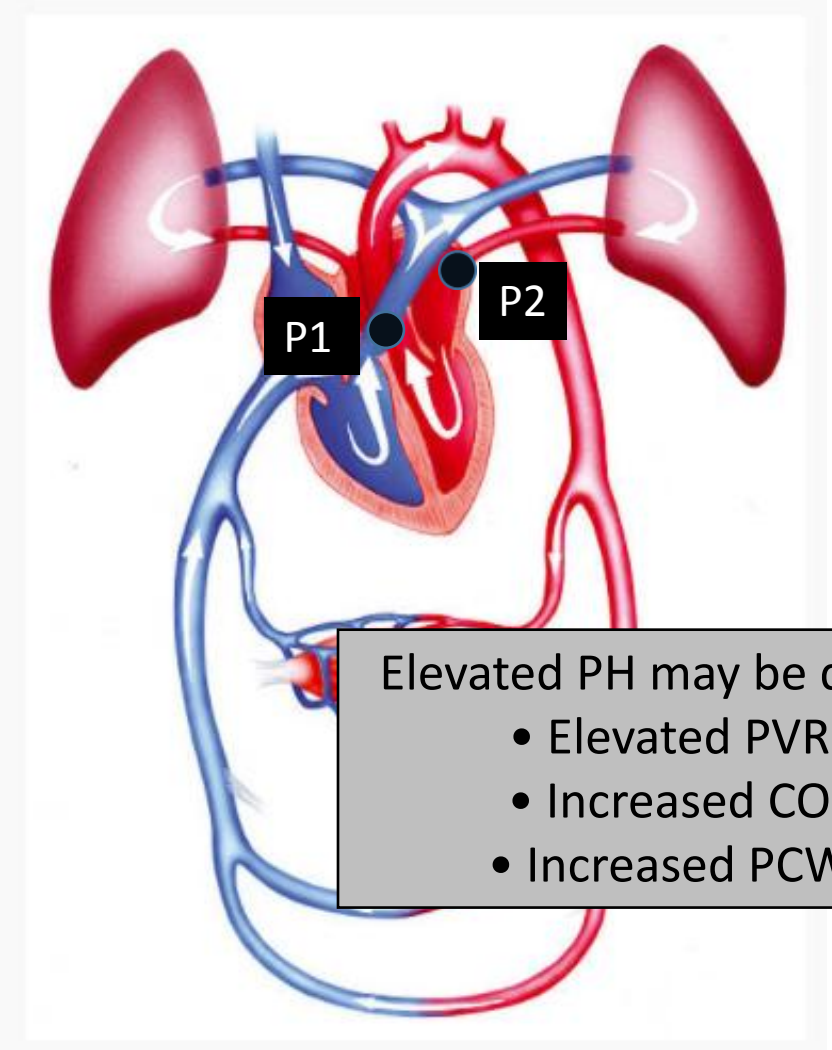
Πνευμονική κυκλοφορία

Ορίζεται σαν το αγγειακό δίκτυο που εκτείνεται
από την Πνευμονική Βαλβίδα(PV)
έως τον αριστερό κόλπο(LA)





Πνευμονική κυκλοφορία



Βασικές αρχές

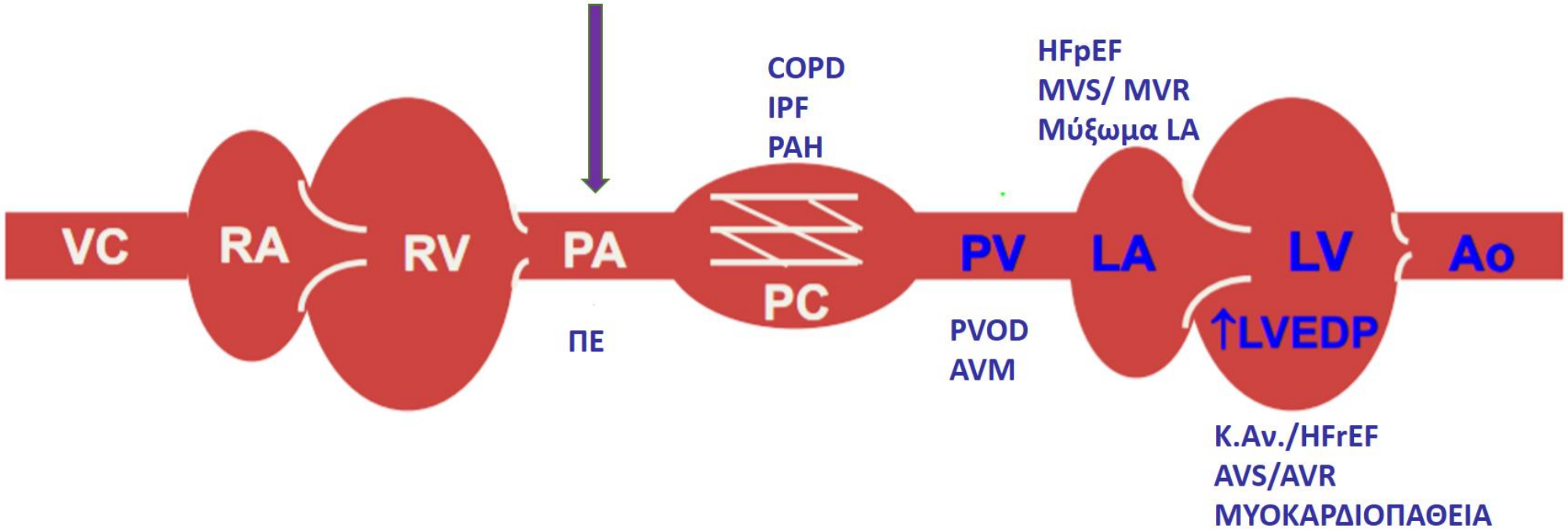
- Όλος ο όγκος παλμού /όλη η καρδιακή παροχή (CO) «άγεται» με πολύ χαμηλές πιέσεις
- Οδηγός πίεση P1-P2→ mPAP-PCWP
- Πνευμονικές αγγειακές αντιστάσεις (PVR)
- **mPAP= PAWP+ (CO x PVR)**

  PVR= (mPAP-PCWP)/CO
- Μεγάλο ποσοστό της PVR → μικροκυκλοφορία
- Στρατολόγηση – Διάταση τριχοειδών

2. Ορισμός

Πνευμονική κυκλοφορία

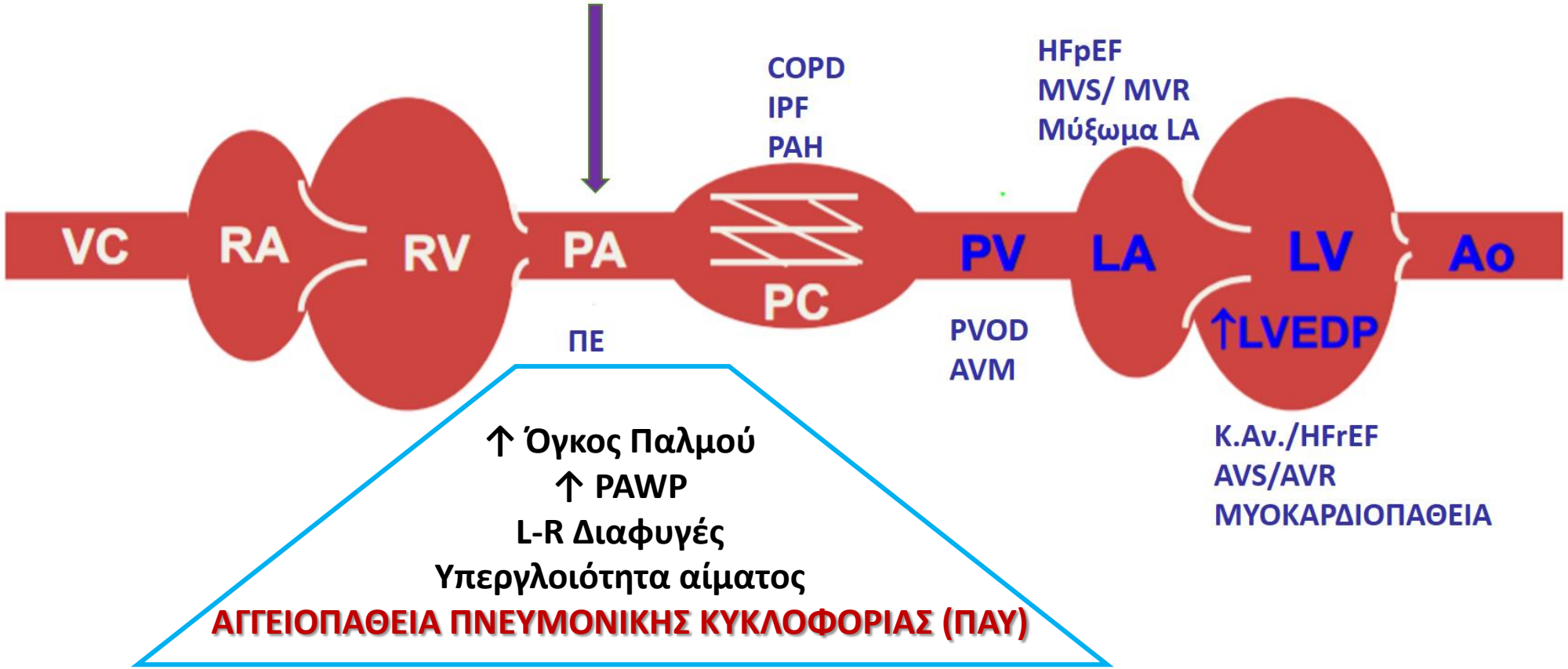
ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ (PH)= ΑΥΞΗΜΕΝΗ ΠΙΕΣΗ ΠΝΕΥΜΟΝΙΚΗΣ ΑΡΤΗΡΙΑΣ ***(mPAP>20 mm Hg)***



Haemodynamic definitions and updated clinical classification of pulmonary hypertension
Gérald Simonneau et al, ERJ Dec 2018,

Πνευμονική κυκλοφορία

ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ (PH)= ΑΥΞΗΜΕΝΗ ΠΙΕΣΗ ΠΝΕΥΜΟΝΙΚΗΣ ΑΡΤΗΡΙΑΣ ***(mPAP>20 mm Hg)***



Haemodynamic definitions and updated clinical classification of pulmonary hypertension
Gérald Simonneau et al, ERJ Dec 2018,

ERJ Express. Published on December 13, 2018 as doi: 10.1183/13993003.01913-2018

SERIES
WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

Haemodynamic definitions and updated clinical classification of pulmonary hypertension

TABLE 1 Haemodynamic definitions of pulmonary hypertension (PH)

Definitions	Characteristics	Clinical groups#
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR ⩾3 WU	1, 3, 4 and 5
Isolated post-capillary PH (IpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR <3 WU	2 and 5
Combined pre- and post-capillary PH (CpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩾3 WU	2 and 5

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units. #: group 1: PAH; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: PH due to pulmonary artery obstructions; group 5: PH with unclear and/or multifactorial mechanisms.

Πνευμονική κυκλοφορία

00:28:20

Normal pulmonary hemodynamics

Systolic PAP, mmHg:	13 – 30	
Diastolic PAP, mmHg:	6 – 15	
Mean PAP, mmHg:	8 – 20	20-25mmHg
PAWP, mmHg	5 – 12	
PPC, mmHg	8-12	
DPG, mmHg:	0 – 5	5-7 mmHg
TPG, mmHg	2 – 12	
RAP, mmHg	0 – 8	
CO, L/min:	4 – 8	
CI, L/min/m2	2.5 - 4.5	
PVR, WU:	0.2 – 1.2	2-3 WU

Naeije R: Pulmonary vascular function. In Pulmonary Circulation. Diseases and their Treatment. 4nd ed. CRC Press, Boca Raton, FL, 2016, chap 2, pp 11-24

Kovacs et al, Eur Respir J 2009; 34: 888-94

GERALD SIMONNEAU 00:02:53

6 WSPH

TF 4: PH Haemodynamic definitions

1. Should we redefine pulmonary hypertension (PH) and pre-capillary pulmonary pulmonary hypertension?

- **A mean PAP>20 mmHg should be considered as upper normal value**

It is not defining a disease but it is only abnormal increase of PAP pressure

- **Pre-capillary pulmonary hypertension could be defined as**

mean PAP> 20 mm Hg, PAWP < 15 mm Hg and PVR > 3 WU

Πνευμονική Αρτηριακή Υπέρταση(PAH)

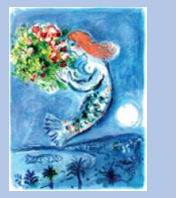
DECEMBER 13, 2018

ERJ Early View

Pulmonary hypertension in chronic lung disease and hypoxia

Steven D. Nathan et al

European Respiratory Journal 2018



2018 Nice

Φυσιολογική mPAP= 14± 3.3 mmHg

Without PH

CLD without PH
mPAP <21mmHg ή mPAP 21- 24 και PVR<3WU

PH

CLD with PH
mPAP 21- 24 και PVR≥3WU ή mPAP≥ 25mmHg

ΣΟΒΑΡΗ PH

mPAP >35mmHg
mPAP≥ 25mmHg παρουσία χαμηλής καρδιακής παροχής (CI <2L/min/m^2)

Am J Respir Crit Care Med.2018

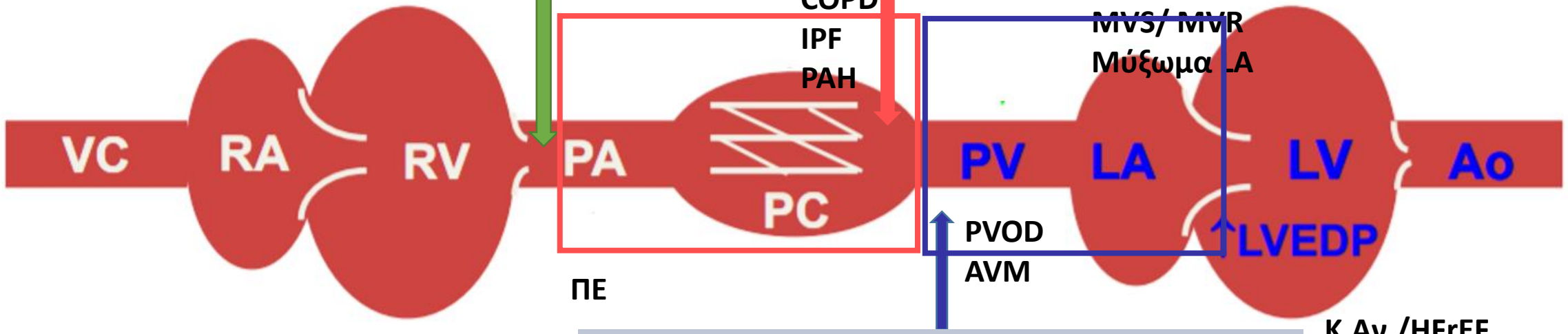
ΠΥ στην ΑΣΚΗΣΗ

Proposed criteria for Exercise – PH (consistent with ERS statement 2017)

- mPAP > 30mmHg AND TPR > 3mmHg per litre CO
- This could be due to
  - (I) Αποκαλύπτει Πνευμονική Αγγειακή Νόσο
  - (II) Αύξηση της πίεσης στον LA (που εκφράζεται με αύξηση της PAWP)
  - (III) Και τα δυο
- How to distinguish?? More research needed…
- Careful exercise-PAWP; Clinical Score for LHD; Exercise Echo/MRI; a good opportunity for AI/machine learning algorithms

Πνευμονική Υπέρταση - PH

ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ (PH)
ΑΥΞΗΜΕΝΗ ΠΙΕΣΗ ΠΝΕΥΜΟΝΙΚΗΣ ΑΡΤΗΡΙΑΣ
(mPAP>20 mm Hg)



Pre-capillary PH — mPAP >20 mmHg, PAWP ⩽15 mmHg, PVR ⩾3 WU

COPD
IPF
PAH

ΠΕ

HFpEF
MVS/ MVR
Μύξωμα LA

PVOD
AVM

Isolated post-capillary PH (IpcPH) — mPAP >20 mmHg, PAWP >15 mmHg, PVR <3 WU

Combined pre- and post-capillary PH (CpcPH) — mPAP >20 mmHg, PAWP >15 mmHg, PVR ⩾3 WU

K.Av./HFrEF
AVS/AVR
ΜΥΟΚΑΡΔΙΟΠΑΘΕΙΑ

$$Q \times PVR = \Delta P \text{ ή } PVR = \frac{\Delta P=(P1-P2)=\textbf{mPAP-PCWP}}{Q}$$

DPG=Diastolic Pressure Gradient= DPAP- PAWP

3. Ταξινόμηση

Αγγειοδραστικότητα και PVOD/PCH

DAVID MONTANI 00:03:14

CLINICAL CLASSIFICATION OF PH

1. Pulmonary Arterial Hypertension

1.1 Idiopathic PAH
1.2 PAH with vasoreactivity (Table 1)
1.3 Heritable PAH (Table 2)
1.4 Drugs and toxins induced (Table 3)
1.5 Associated with:
1.5.1 Connective tissue disease
1.5.2 HIV infection
1.5.3 Portal hypertension
1.5.4 Congenital heart disease (Table 4)
1.5.5 Schistosomiasis
1.6 PAH with overt signs of venous/capillaries (PVOD/PCH) involvement (Table 5)
1.7 Persistent PH of the Newborn syndrome (Table P1)

2. PH due to left heart disease

2.1 PH due to heart failure with preserved E.F
2.2 PH due to heart failure with reduced E.F
2.3 Valvular heart disease
2.4 Congenital post-capillary obstructive lesions (Table P2)

3. PH due to lung diseases and/or hypoxia (Table 6)

3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders (Table P3)

4. PH due to pulmonary artery obstruction

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions (Table 7)

5. PH with unclear mechanisms (Table 8)

5.1 Haematologic disorders
5.2 Systemic disorders
5.3 Others
5.4 Complex congenital heart disease (Table P4)

ΚΛΙΝΙΚΗ ΤΑΞΙΝΟΜΗΣΗ ΤΗΣ ΠΝΕΥΜΟΝΙΚΗΣ ΥΠΕΡΤΑΣΗΣ

NICE 2018

1. Πνευμονική Αρτηριακή Υπέρταση (ΠΑΥ)

1.1 Ιδιοπαθής ΠΑΥ
1.2 Κληρονομική ΠΑΥ
1.3 Προκαλούμενη από φάρμακα και τοξίνες
1.4 Σχετιζόμενη με
- 1.4.1 Νοσήματα του συνδετικού ιστού
- 1.4.2 Λοίμωξη από HIV
- 1.4.3 Πυλαία Υπέρταση
- 1.4.4 Συγγενείς καρδιοπάθειες 1.5.5
- 1.4.5.Σχιστοσωμίαση

1.5 ΠΑΥ με μακροχρόνια αγγειοδραστικότητα
1.6 Πνευμονική Φλεβοαποφρακτική νόσος-πνευμονική τριχοειδική αμαγγειωμάτωση (PVOD/PCH)
1.7 Εμμένουσα Πνευμονική Υπέρταση νεογνού

2. ΠΥ λόγω αριστερής καρδιακής νόσου

1. ΠΥ λόγω Κ.Αν. με διατηρημένο EF
2. ΠΥ λόγω Κ.Αν. με ελαττωμένο EF
3. Βαλβιδοπάθειες
4. Συγγενείς μετατριχοειδικές αποφρακτικές βλάβες

3. Πνευμονική Υπέρταση (ΠΥ) λόγω αναπνευστικών νοσημάτων και/ή υποξία

3.1 Αποφρακτικά πνευμονικά νοσήματα
3.2 Περιοριστικά πνευμονικά νοσήματα
3.3 Άλλα πνευμονικά νοσήματα με μικτό Αποφρακτικό/Περιοριστικό πρότυπο
3.4 Υποξία χωρίς πνευμονική πάθηση
3.5 Νοσήματα του πνεύμονα κατά την ανάπτυξη

4. ΠΥ λόγω απόφραξης της πνευμονικής αρτηρίας

4.1 Χρόνια Θροεμβοεμβολική ΠΥ
4.2 Άλλες αιτίες απόφραξης της πνευμονικής αρτηρίας

5. ΠΥ ασαφούς αιτιολογίας

5.1 Αιματολογιά νοσήματα
5.2 Συστηματικά νοσήματα
5.3 Άλλα νοσήματα
5.4 Σύμπλοκες συγγενείς καρδιοπάθειες

Comprehensive clinical c mPAP≥ 20mmHg ulmonary hypertension

1. Pulmonary arterial hypertension

ΚΑΤΗΓΟΡΙΑ 1

ΡΑΗ
ΕΙΔΙΚΗ ΑΓΓΕΙΟΔΙΑΣΤΑΛΤΙΚΗ ΑΓΩΓΗ

- iPAH
- CTD- (Σκληρόδερμα)
- CHD
- Drugs and Toxins

PVR>3
PAWP≤ 15mmHg

2. Pulmonary hypertension due to left heart disease

ΚΑΤΗΓΟΡΙΑ 2

- ΑΡΙΣΤΕΡΗ ΚΑΡΔΙΑΚΗ ΝΟΣΟΣ

PAWP>15mmHg
Isolated post or pre + post

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

ΚΑΤΗΓΟΡΙΑ 3

- ΑΝΑΠΝΕΥΣΤΙΚΑ ΝΟΣΗΜΑΤΑ

PVR>3
PAWP≤ 15mmHg

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

ΚΑΤΗΓΟΡΙΑ 4

- ΧΡΟΝΙΑ ΘΡΟΜΒΟΕΜΒΟΛΙΚΗ ΠΥ ΣΤΕΡΗ

PVR>3
PAWP≤ 15mmHg

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

ΚΑΤΗΓΟΡΙΑ 5

ΣΥΣΤΗΜΑΤΙΚΑ ΝΟΣΗΜΑΤΑ

PAWP>15mmHg
Isolated pre, post or pre + post

ERS EUROPEAN RESPIRATORY SOCIETY

EUROPEAN SOCIETY OF CARDIOLOGY®

www.escardio.org

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

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ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ
mPAP >20mmHg

ΚΑΤΗΓΟΡΙΑ 1
ΡΑΗ
ΕΙΔΙΚΗ ΑΓΓΕΙΟΔΙΑΣΤΑΛΤΙΚΗ ΑΓΩΓΗ

- **iPAH**
- **CTD- (Σκληρόδερμα)**
- **CHD**
- **Drugs and Toxins**

- HIV infection
- Portal hypertension
- Congenital heart disease
- Schistosomiasis
- **WHO Group I'** (pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis)
- **WHO Group I''** (persistent pulmonary hypertension of the newborn)

ΚΑΤΗΓΟΡΙΑ 2
ΑΡΙΣΤΕΡΗ ΚΑΡΔΙΑΚΗ ΝΟΣΟΣ

dysfunction
- Left ventricular diastolic dysfunction
- Valvular heart disease
- Specific congenital abnormalities

ΚΑΤΗΓΟΡΙΑ 3
ΑΝΑΠΝΕΥΣΤΙΚΑ ΝΟΣΗΜΑΤΑ

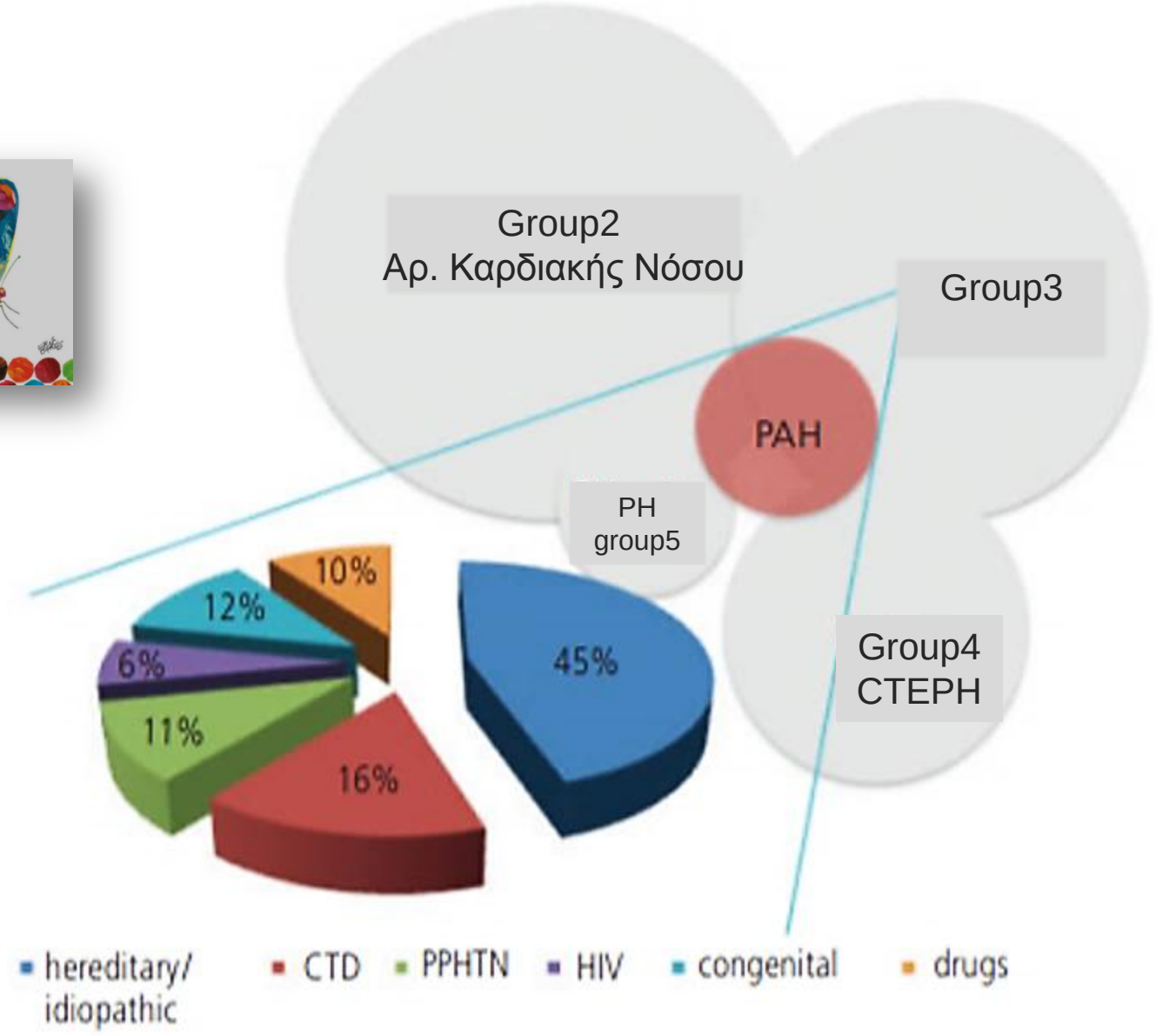
pulmonary disease
- Interstitial lung diseases
- Other mixed restrictive or obstructive lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental lung diseases

ΚΑΤΗΓΟΡΙΑ 4
ΧΡΟΝΙΑ ΘΡΟΜΒΟΕΜΒΟΛΙΚΗ ΠΥ ΣΤΕΡΗ

- Chronic thromboembolic pulmonary hypertension
- Other pulmonary artery obstructions (eg, angiosarcoma, other intravascular tumours, arteritis, congenital stenoses, and parasites)

ΚΑΤΗΓΟΡΙΑ 5
ΣΥΣΤΗΜΑΤΙΚΑ ΝΟΣΗΜΑΤΑ

(eg, sickle cell disease)
- Systemic disorders (eg, sarcoidosis, Langerhans cell granulomatosis)
- Metabolic disorders (eg, Gaucher's disease)
- Others (eg, renal disease)


Group2
Αρ. Καρδιακής Νόσου
Group3
PAH
PH
group5
Group4
CTEPH
10%
12%
6%
11%
16%
45%
hereditary/
idiopathic
CTD
PPHTN
HIV
congenital
drugs

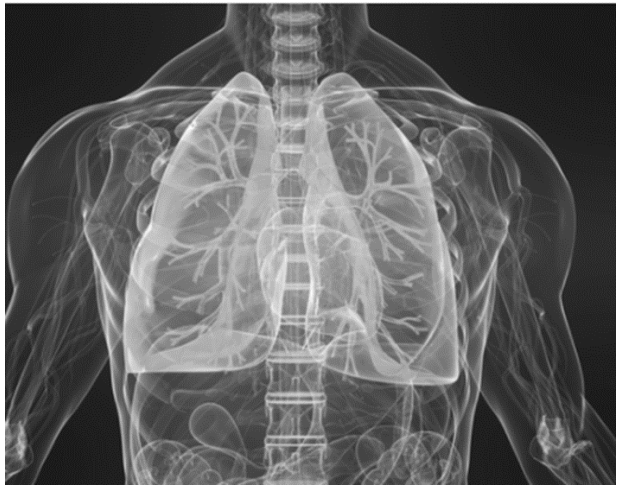
EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Pulmonary hypertension and pulmonary arterial hypertension: a clarification is needed

N. Galiè, M. Palazzini, A. Manes
European Respiratory Journal 2010 36: 986-990; **DOI:** 10.1183/09031936.00038410

- PH IS A HAEMODYNAMIC AND PATHOPHYSIOLOGICAL CONDITION
- PH CAN BE FOUND IN AT LEAST 37 SYNDROMES
- PAH IS A CLINICAL GROUP OF RARE CONDITIONS

- **Πνευμονική Υπέρταση**
- **Πνευμονική Αρτηριακή Υπέρταση**



DAVID MONTANI

CLINICAL CLASSIFICATION OF PH

WSPH

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 diseases (Table 1)
     - 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

3 main issues

- To identify the subgroup of vasoreactive long-term response to calcium channel blockers

Αγγειοδραστική ΠΑΥ

- Αναθεώρηση της λίστας των φαρμάκων- τοξινών

- Διευκρίνηση της κατηγορίας PVOD/PCH

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TABLE 4 Definitions of acute and long-term response

Acute pulmonary vasoreactivity[#] for patients with idiopathic, hereditable or drug-induced PAH	Reduction of mPAP ⩾10 mmHg to reach an absolute value of mPAP ⩽40 mmHg Increased or unchanged cardiac output
Long-term response to CCBs	New York Heart Association Functional Class I/II With sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only

Αγγειοδραστικότητα

ΠΑΥ με Αγγειοδραστικότητα

Table 1. Definition of acute and long-term response

	Definition
1.+Τεστ οξείας Αγγειοδραστικότητας MONO σε iPAH, HPAH, Drug induced	• Ελάττωση mPAP ≥10mmHg όπου φτάνει απόλυτη τιμή mPAP≤40mmHg • Διατήρηση ή αύξηση της καρδιακής παροχής
2. Διατήρηση της ανταπόκρισης σε υψηλές δόσεις CCB	• NYHA I ή II • Με διατήρηση της αιμοδυναμικής βελτίωσης Για τουλάχιστον 1 χρόνο μετά τους CCB

* Nitric oxide (10-20 ppm) is recommended for performing vasoreactivity testing IV epoprostenol is an alternative. Adenosine or inhaled iloprost may be considered as an alternative.

ROBERT NAEIJE

00:12:58

Effects Of Acute Vasodilator Challenge In IPAH

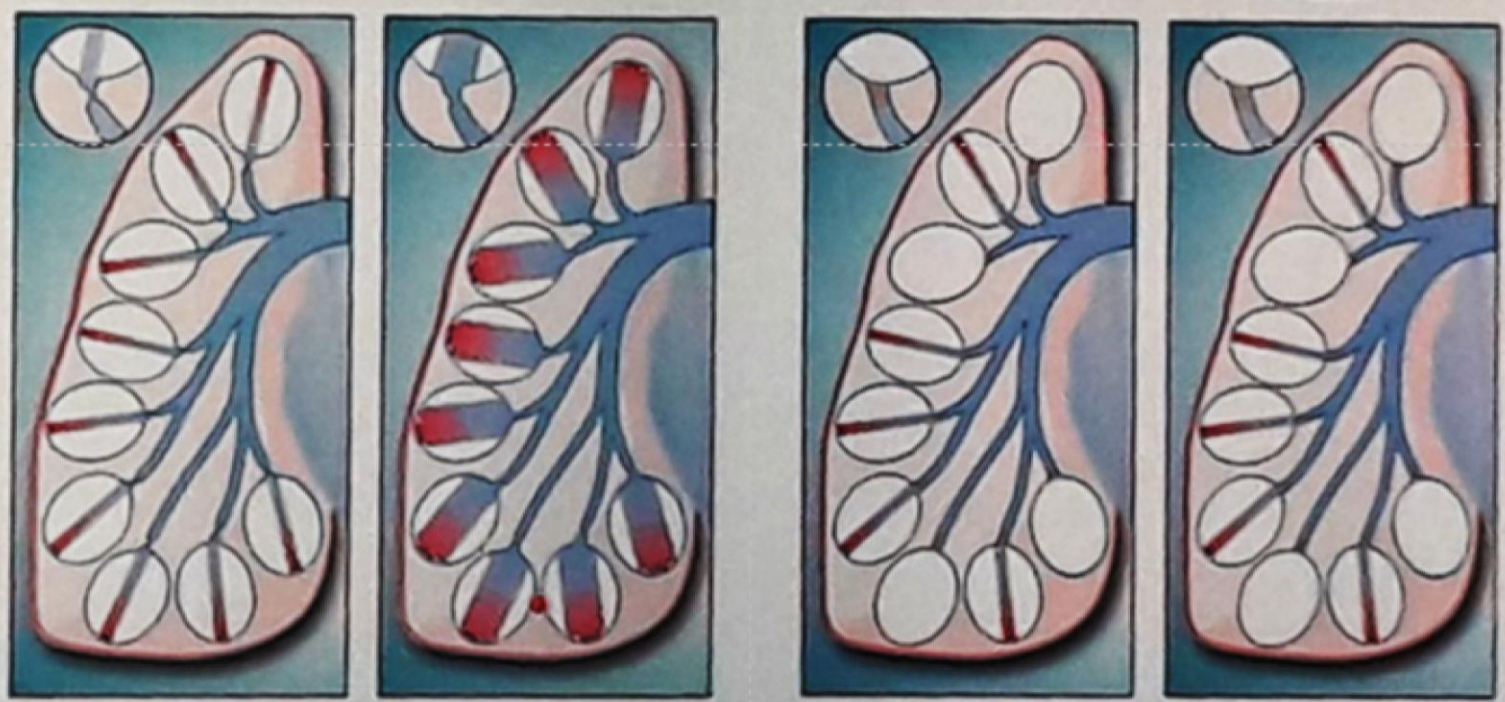
6 WSPH

RESPONDER

PRE POST

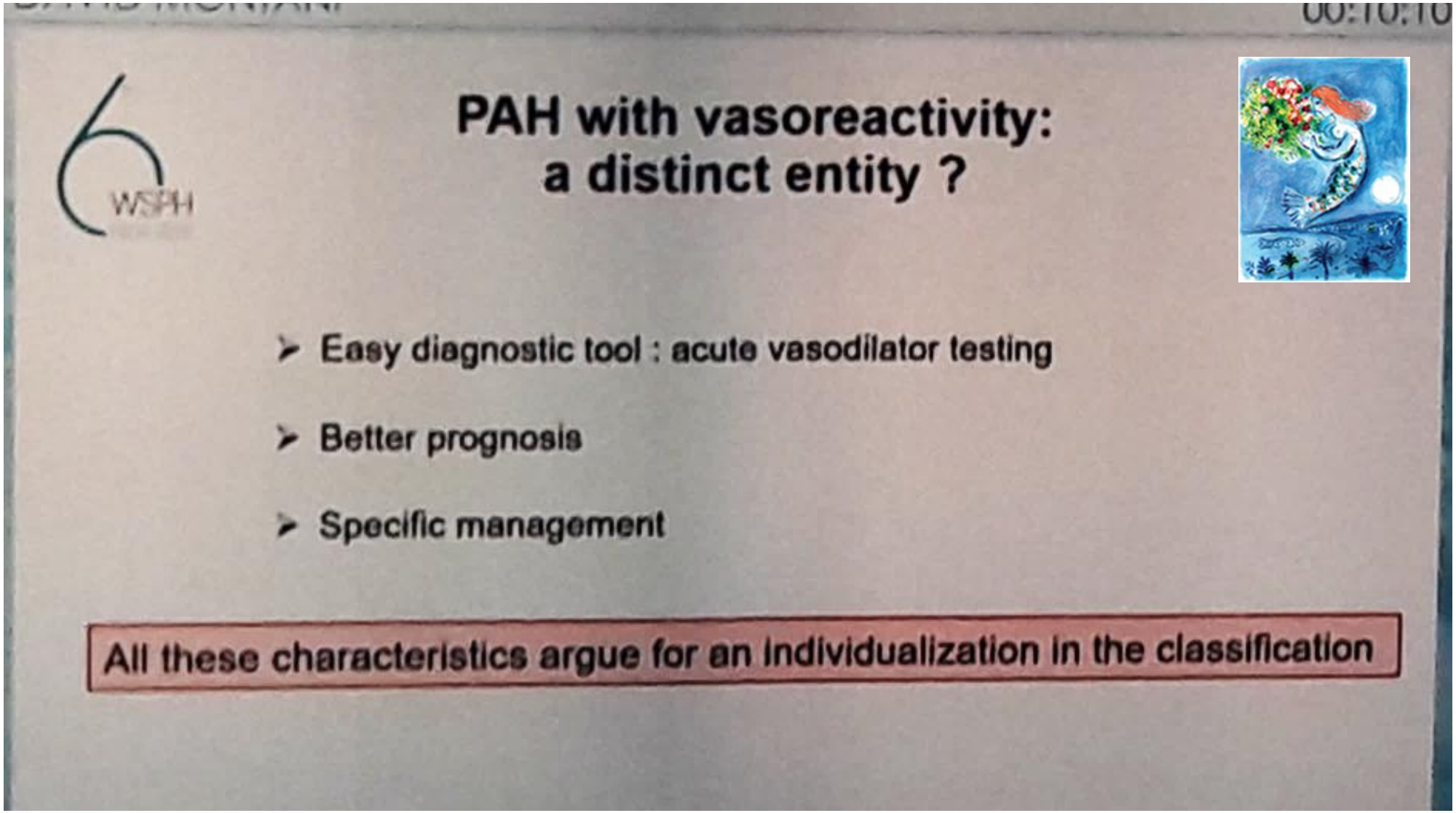
NONRESPONDER

PRE POST



Langleben, Orfanos et al, Ann Intern Med 2015;162:154-6

Αγγειοδραστικότητα



3. Ταξινόμηση

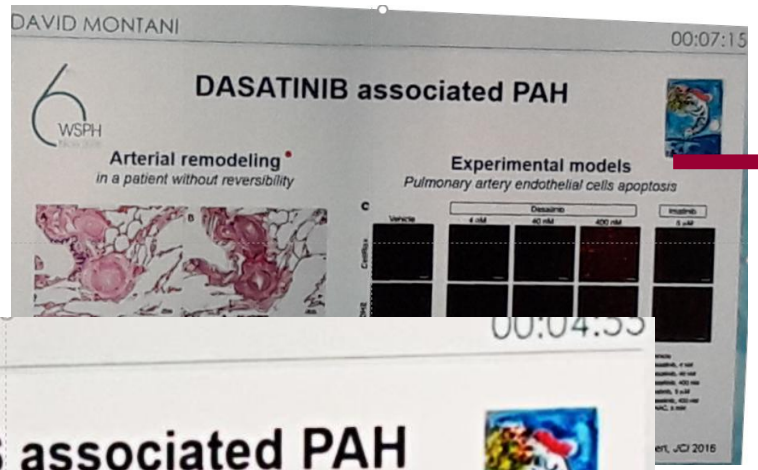
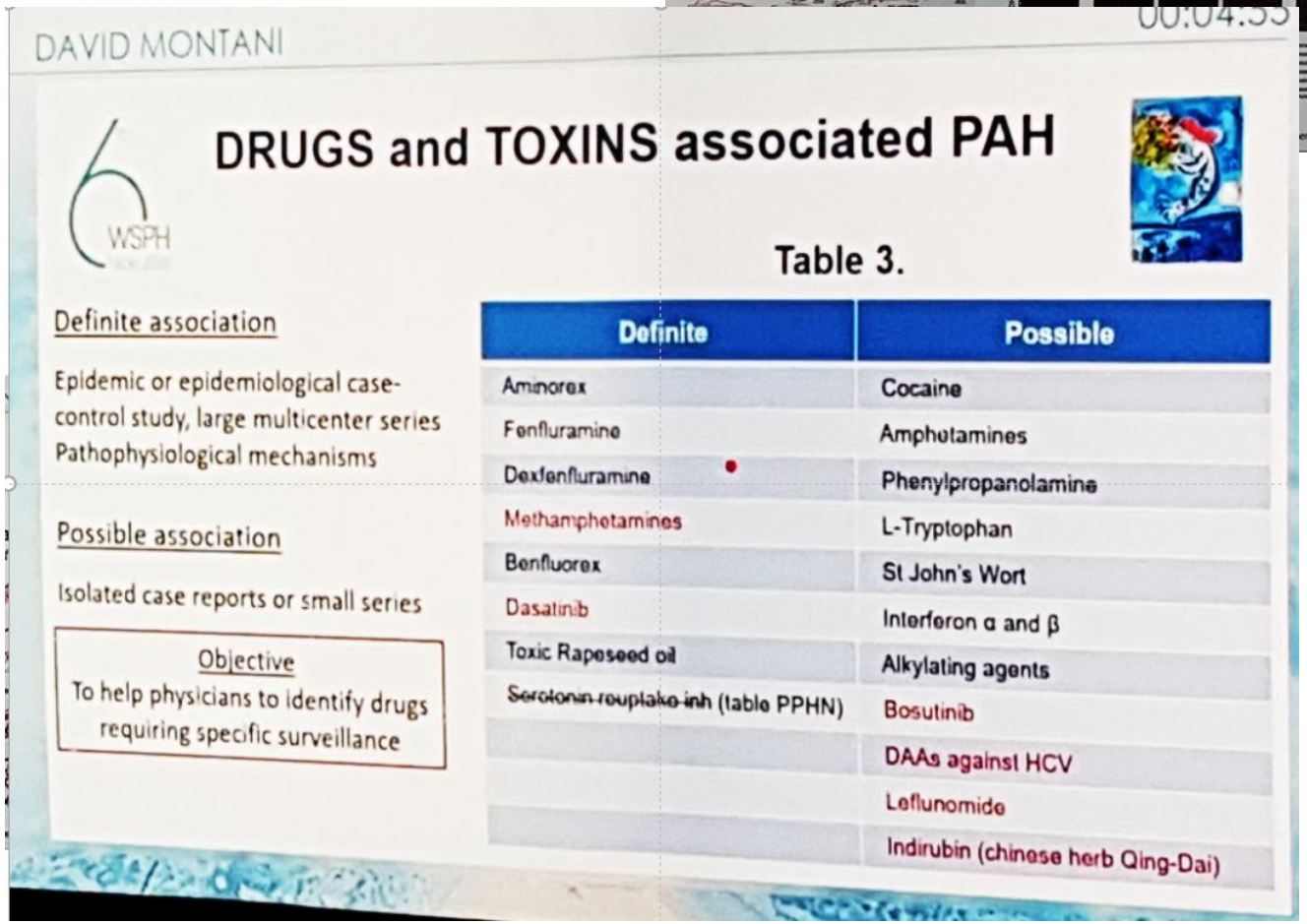
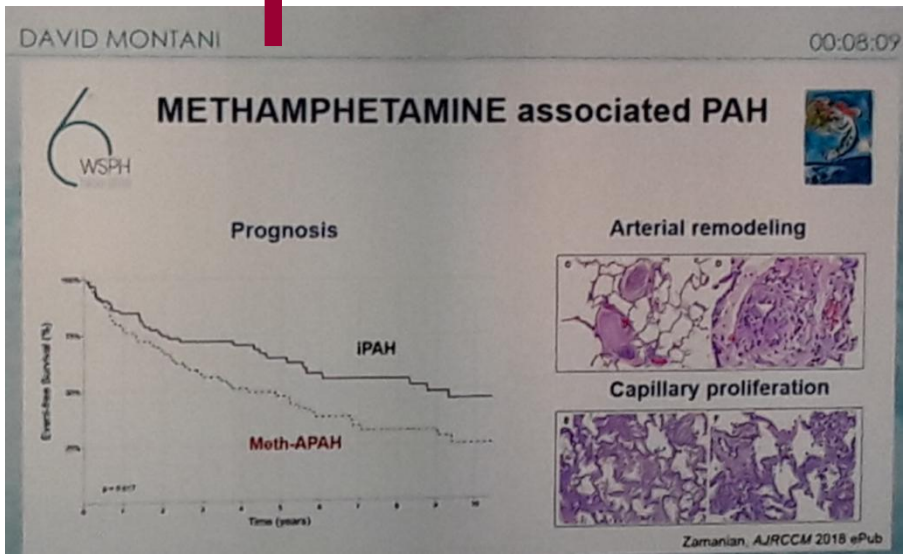


Table 7 Updated risk level of drugs and toxins known to induce pulmonary arterial hypertension

Definite	Likely	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex • Selective serotonin reuptake inhibitors[a]	• Amphetamines • Dasatinib • L-tryptophan • Methamphetamines	• Cocaine • Phenylpropanolamine • St John's Wort • Amphetamine-like drugs • Interferon α and β • Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[b]





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Drugs and Toxins

TABLE 3 Updated classification of drugs and toxins associated with PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	L-tryptophan
Benfluorex	St John's wort
Methamphetamines	Amphetamines
Dasatinib	Interferon-α and -β
Toxic rapeseed oil	Alkylating agents
	Bosutinib
	Direct-acting antiviral agents against hepatitis C virus
	Leflunomide
	Indirubin (Chinese herb Qing-Dai)

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PVOD/PCH

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

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

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Group 4

TABLE 6 Pulmonary hypertension (PH) due to pulmonary artery obstructions

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
- 4.2.1 Sarcoma (high or intermediate grade) or angiosarcoma
- 4.2.2 Other malignant tumours
  - Renal carcinoma
  - Uterine carcinoma
  - Germ cell tumours of the testis
  - Other tumours
- 4.2.3 Non-malignant tumours
  - Uterine leiomyoma
- 4.2.4 Arteritis without connective tissue disease
- 4.2.5 Congenital pulmonary artery stenoses
- 4.2.6 Parasites
  - Hydatidosis

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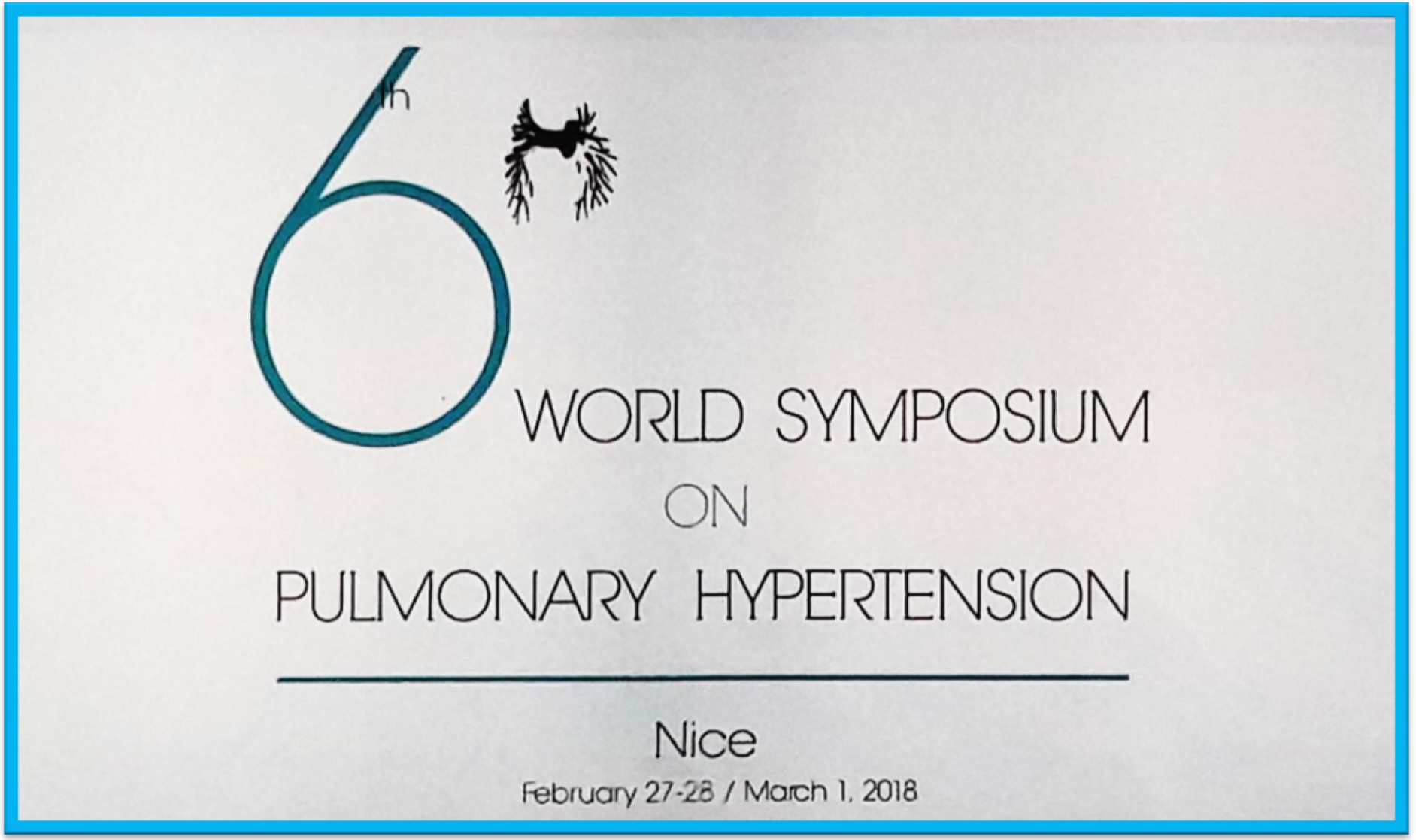
Group 5

TABLE 7 Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders	Chronic haemolytic anaemia Myeloproliferative disorders
5.2 Systemic and metabolic disorders	Pulmonary Langerhans cell histiocytosis Gaucher disease Glycogen storage disease Neurofibromatosis Sarcoidosis
5.3 Others	Chronic renal failure with or without haemodialysis Fibrosing mediastinitis
5.4 Complex congenital heart disease	See the Task Force article by Rosenzweig *et al.* [31] in this issue of the *European Respiratory Journal*

4. Διερεύνηση



4. Διερεύνηση

Diagnostic investigations utilised in patients with PH

- Electrocardiogram
- Chest radiograph
- Echocardiography
- Pulmonary function tests and arterial blood gases
- Ventilation/perfusion lung scan
- High-resolution computed tomography, contrast enhanced computed tomography
- Cardiac magnetic resonance imaging
- Blood tests and immunology
- Abdominal ultrasound scan
- Right heart catheterization and vasoreactivity
- Pulmonary Angiography

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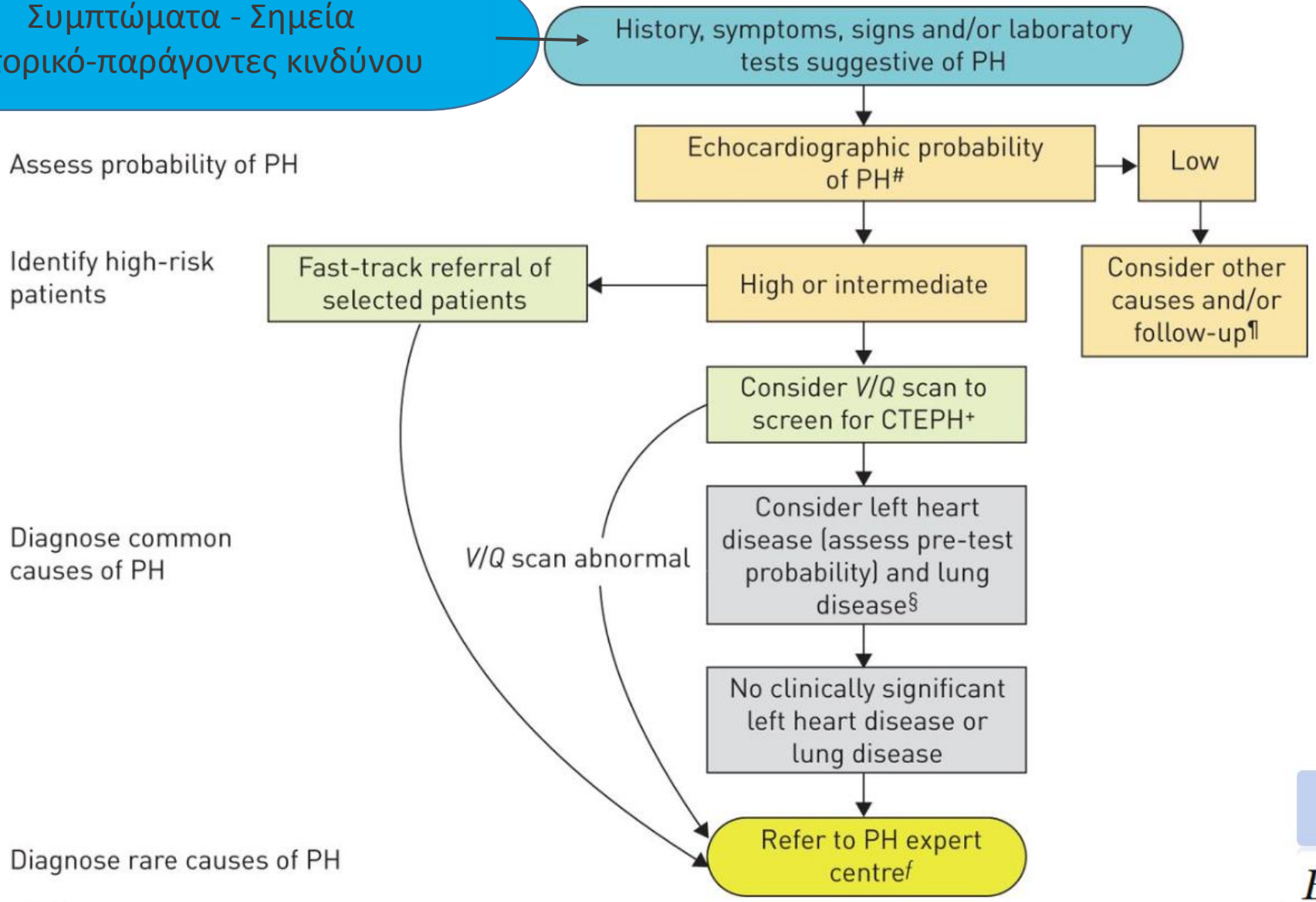
European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Συμπτώματα - Σημεία
Ιστορικό-παράγοντες κινδύνου



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Ιστορικό- παράγοντες κινδύνου

Οικογενειακό ιστορικό (BMPR2/EIF2AK4)
Νόσος συνδετικού ιστού (CREST)
Συγγενής καρδιοπάθεια
Πυλαία υπέρταση
Φλεβική θρόμβωση/ Πνευμονική εμβολή
Χρήση ανορεξιογόνων
HIV
Αιμοσφαιρινοπάθεια
Σπληνεκτομή

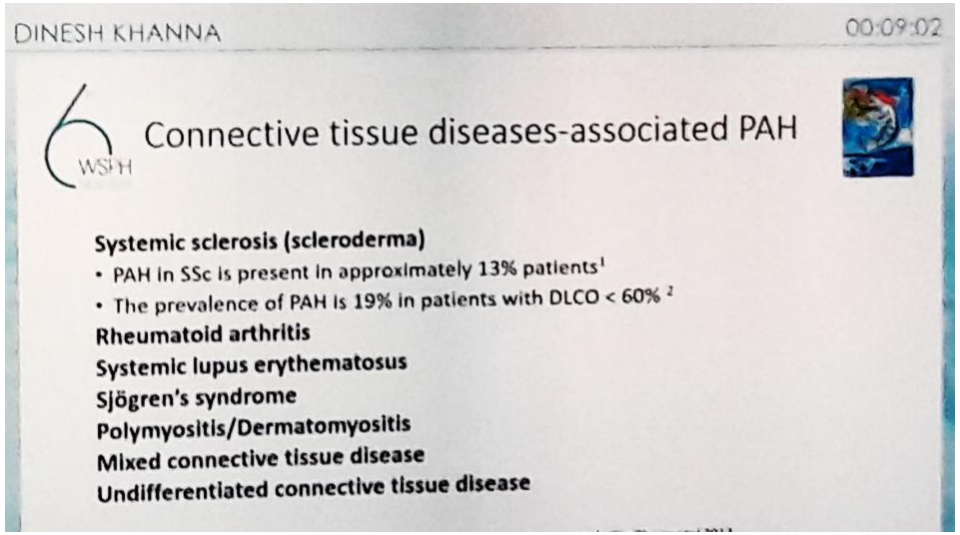

TABLE 3 Updated classification of drugs and toxins associated with PAH

Definite	Possible
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Fenfluramine	Phenylpropanolamine
Dexfenfluramine	L-tryptophan
Benfluorex	St John's wort
Methamphetamines	Amphetamines
Dasatinib	Interferon-α and -β
Toxic rapeseed oil	Alkylating agents
	Bosutinib
	Direct-acting antiviral agents against hepatitis C virus
	Leflunomide
	Indirubin (Chinese herb Qing-Dai)

Κλινική εξέταση

- **Ακτινογραφία**
- **ΗΚΓ**

Ιστορικό- παράγοντες κινδύνου

Οικογενειακό ιστορικό (BMPR2/EIF2AK4)
Νόσος συνδετικού ιστού (CREST)
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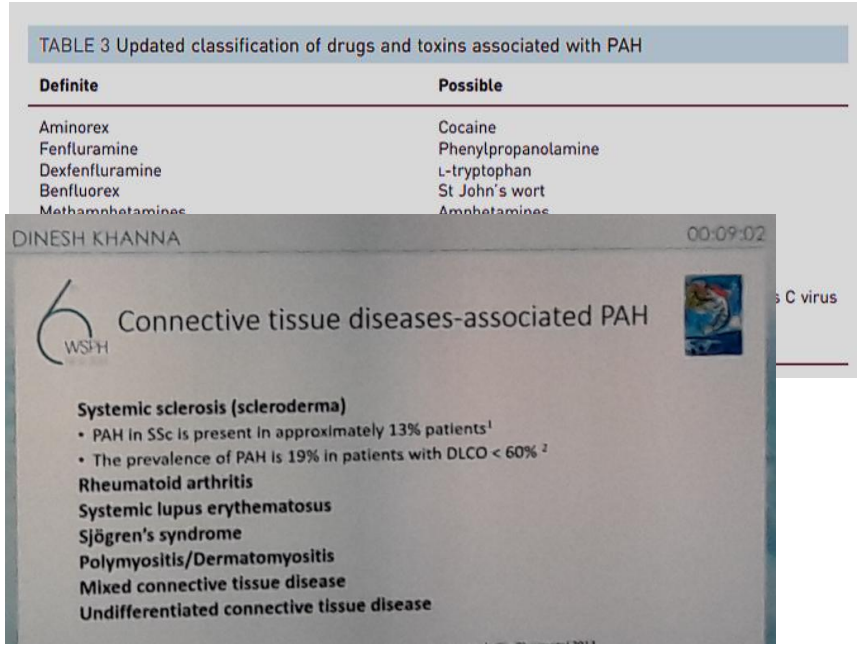
Σπληνεκτομή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Benfluorex	St John's wort
Methamphetamines	Amphetamines

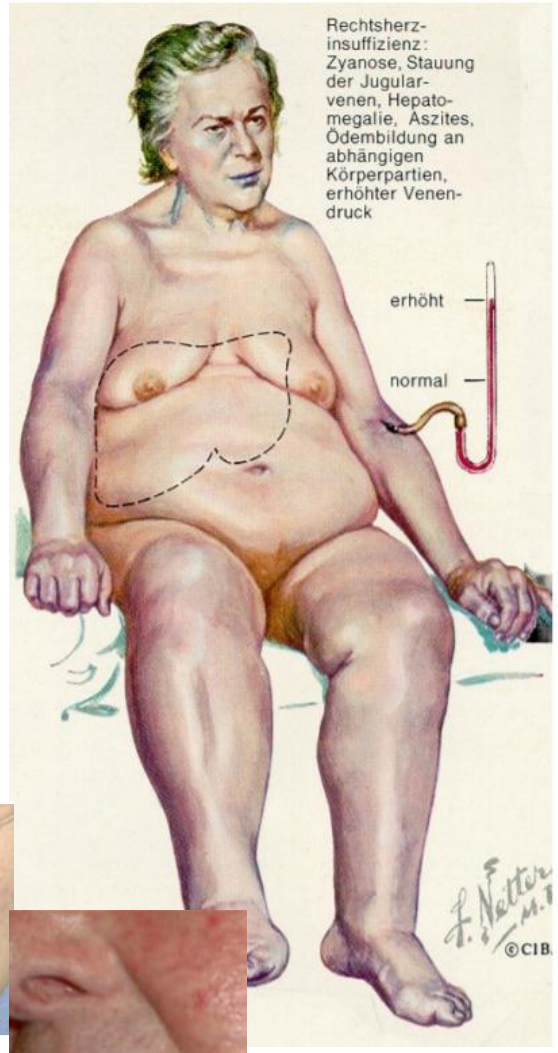
Συχνά μη ειδικά/ καθυστέρηση διάγνωσης (2y)

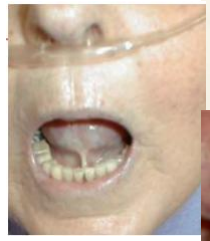
Συμπτώματα

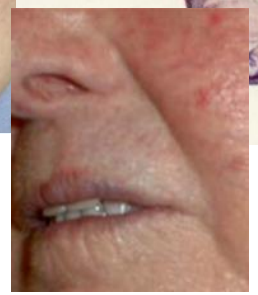
Αρχικά στην άσκηση
Δύσπνοια
Στηθάγχη
Συγκοπτικό επεισόδιο
Αίσθημα παλμών
Φαινόμενο Raynaud
Δυσπεψία
Αιμόπτυση
Βράγχος φωνής

Σημεία

↑P2
Ολοσυστολικό φύσημα
Οίδημα
Ασκίτη
Υποκείμενη νόσος (CTD, ILD, COPD, CHF, HIV)







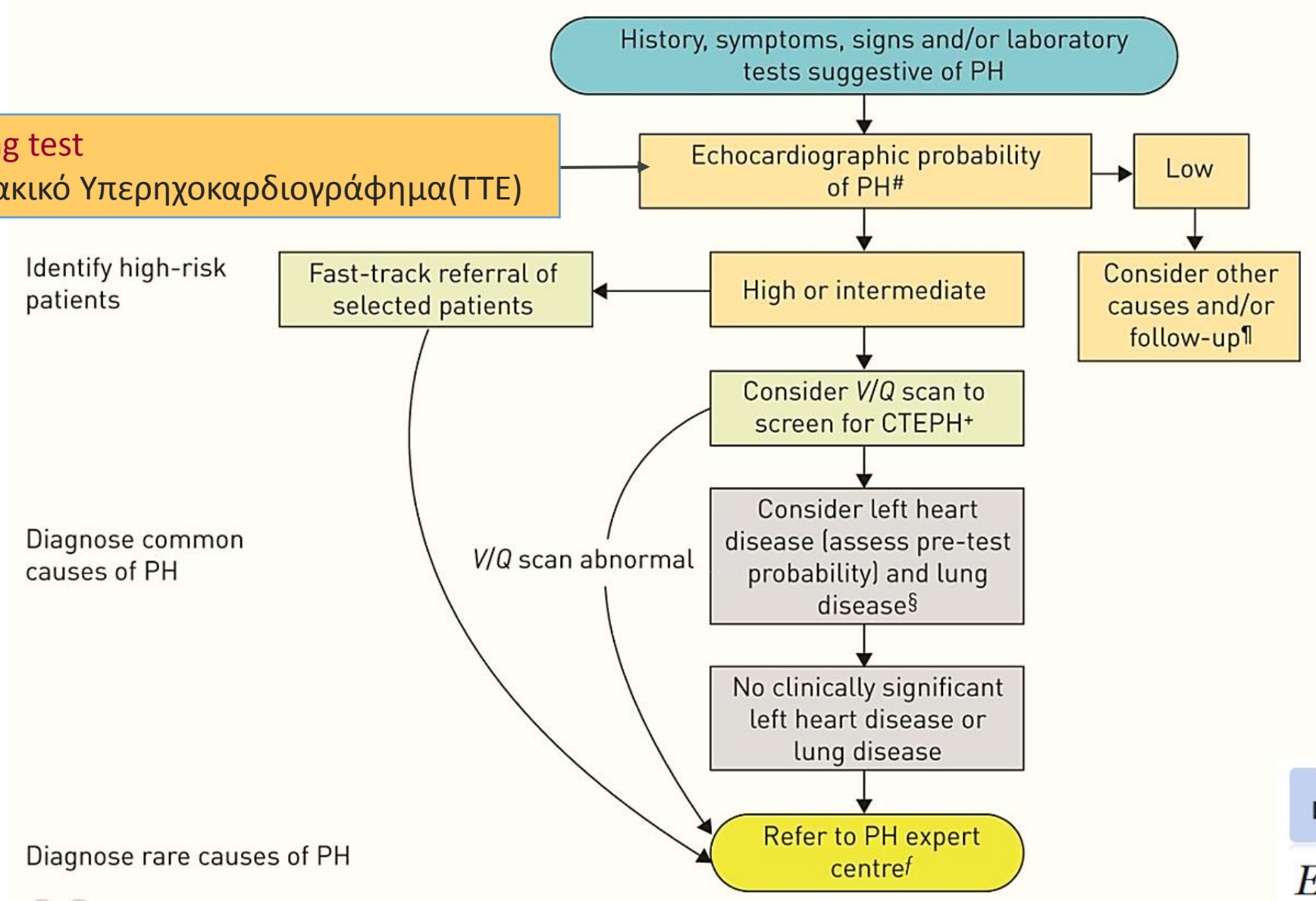
Κλινική εξέταση

- **Ακτινογραφία**
- **ΗΚΓ**

NYHA Functional Class

Class	Patient Symptoms
Class I (Mild) 	No limitation of physical activity. Ordinary physical activity does not cause undue symptoms
Class II (Mild) 	Slight limitation of physical activity. Comfortable at rest, ordinary physical activity results in symptoms.
Class III (Moderate) 	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms.
Class IV (Severe) 	Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Screening test
Διαθωρακικό Υπερηχοκαρδιογράφημα(ΤΤΕ)



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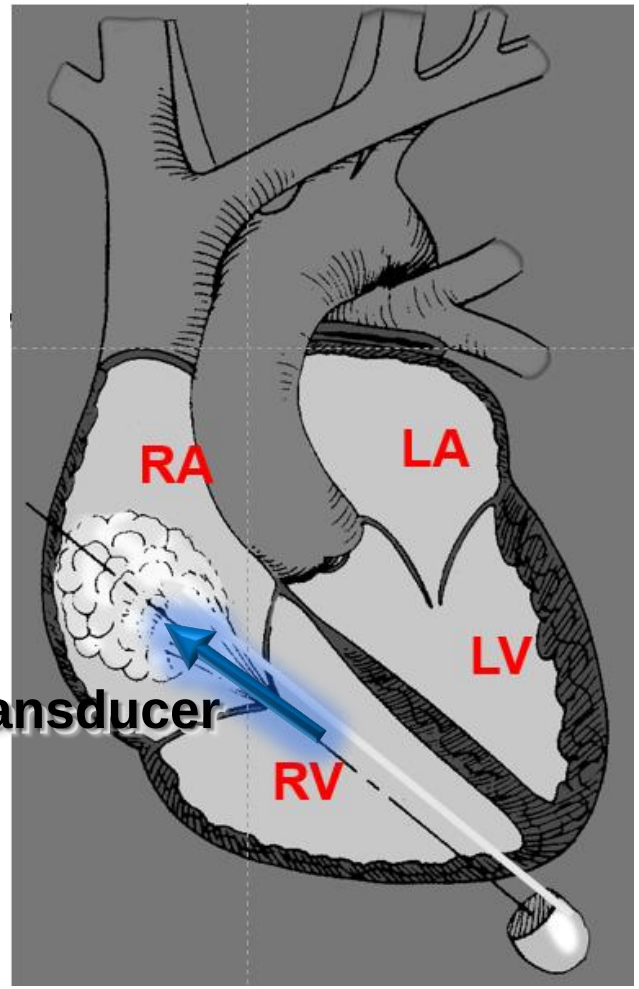
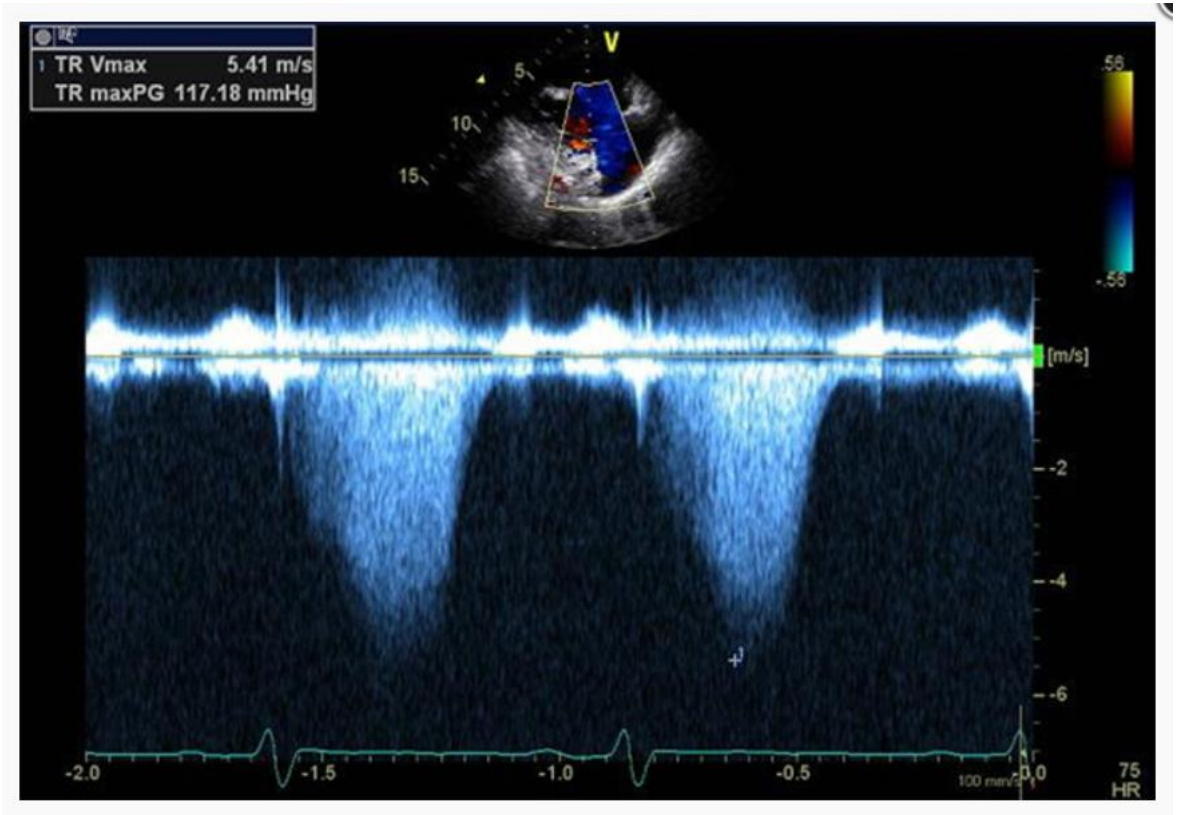
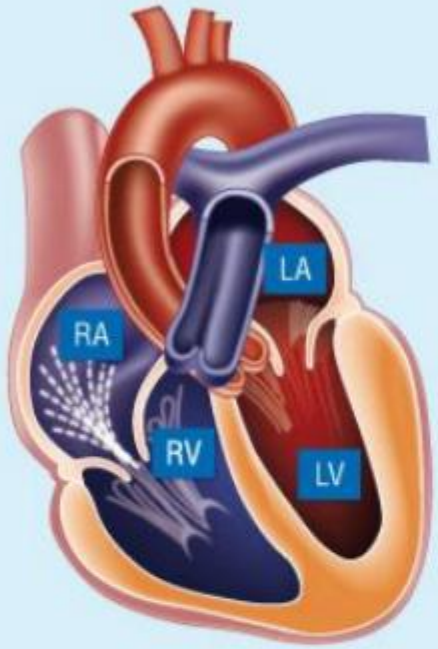
Διαθωρακικό υπερηχοκαρδιογράφημα(TTE) Screening tool

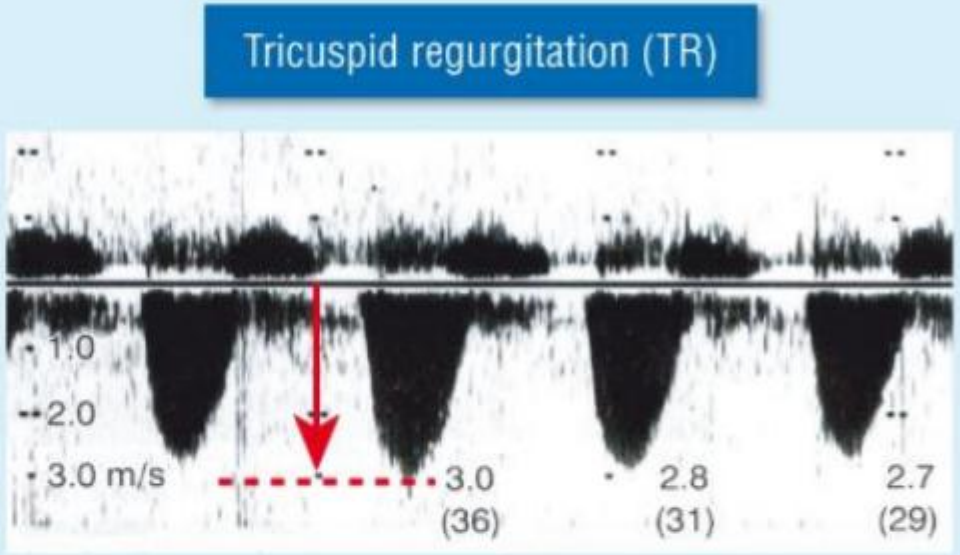


PASP = (4 x [TRVmax]²) + RAP



Διαθωρακικό υπερηχοκαρδιογράφημα(ΤΤΕ) - Screening tool





Syst PAP= Right Ventricular Systolic Pressure

(in absence of pulmonary outflow obstruction)

$RVSP = 4v^2 + RAP^*$

*ESC guidelines. Eur Heart J 2004 Dec;25(24):2243–78.

Υπερηχοκαρδιογραφική εκτίμηση της πιθανότητας για ΠΥ σε συμπτωματικό ασθενή με υποψία Πνευμονικής Υπέρτασης

TRV max

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs"	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

Α. ΚΟΙΛΙΕΣ	Β. ΠΝΕΥΜΟΝΙΚΗ ΑΡΤΗΡΙΑ	Γ. ΚΑΤΩ ΚΟΙΛΗ ΦΛΕΒΑ ΚΑΙ ΔΕ ΚΟΛΠΟ
Right ventricle/ left ventricle basal diameter ratio >1.0.	Right ventricular outlflow Doppler acceleration time <105 m/sec and/or midsystolic notching.	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 %with a sniff or <20 %with quiet inspiration).
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole).	Early diastolic pulmonary regurgitation velocity >2.2 m/sec.	Right atrial area (end-systole) >18 cm^2.
	PA diameter >25 mm..	

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European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

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ECHO

Περικαρδιακή συλλογή

Διάμετρος- Αναπνευστική διακύμανση IVC

Πάχος τοιχώματος RV

Ανεπάρκεια TRV

Tricuspid Annular Plane Systolic Excursion

TAPSE

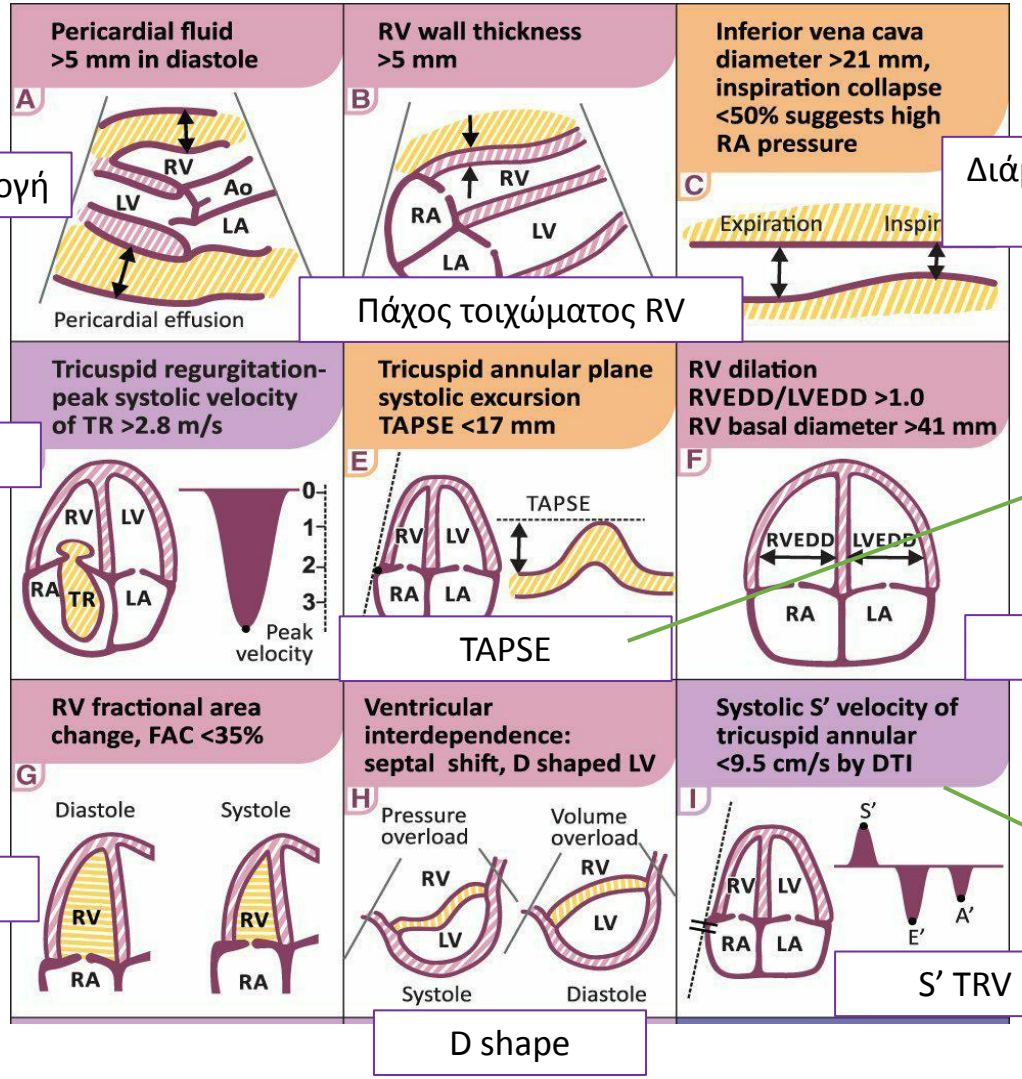
Διάταση RV

EF RV

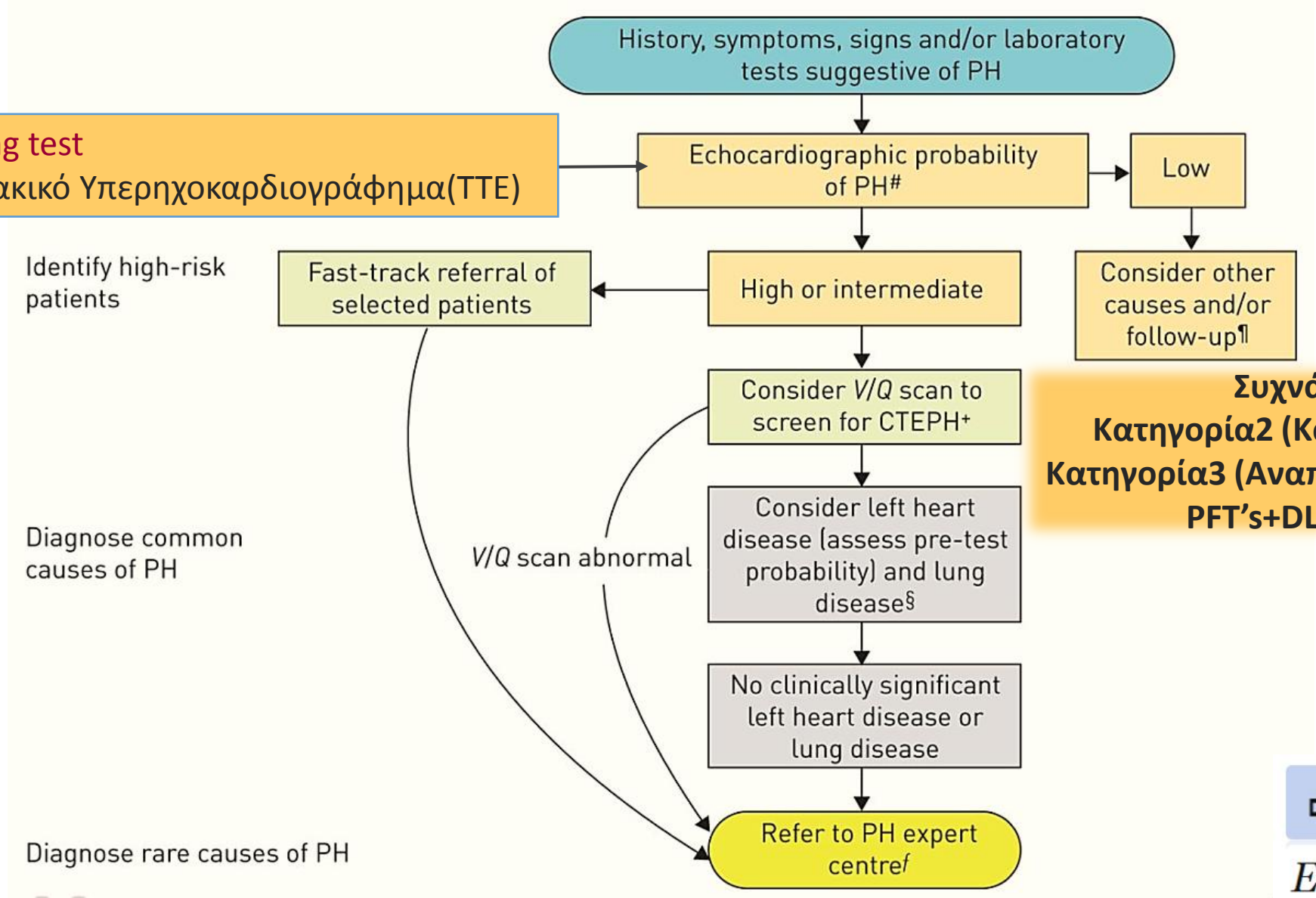
Tricuspid Systolic S' ταχύτητα (cm/s) κίνησης του τριγλωχινικού δακτυλίου

S' TRV

D shape



Screening test
Διαθωρακικό Υπερηχοκαρδιογράφημα(TTE)



Συχνά αίτια
Κατηγορία2 (Καρδιακή νόσος)
Κατηγορία3 (Αναπνευστικό νόσημα)
PFT's+DLCO, HRCT

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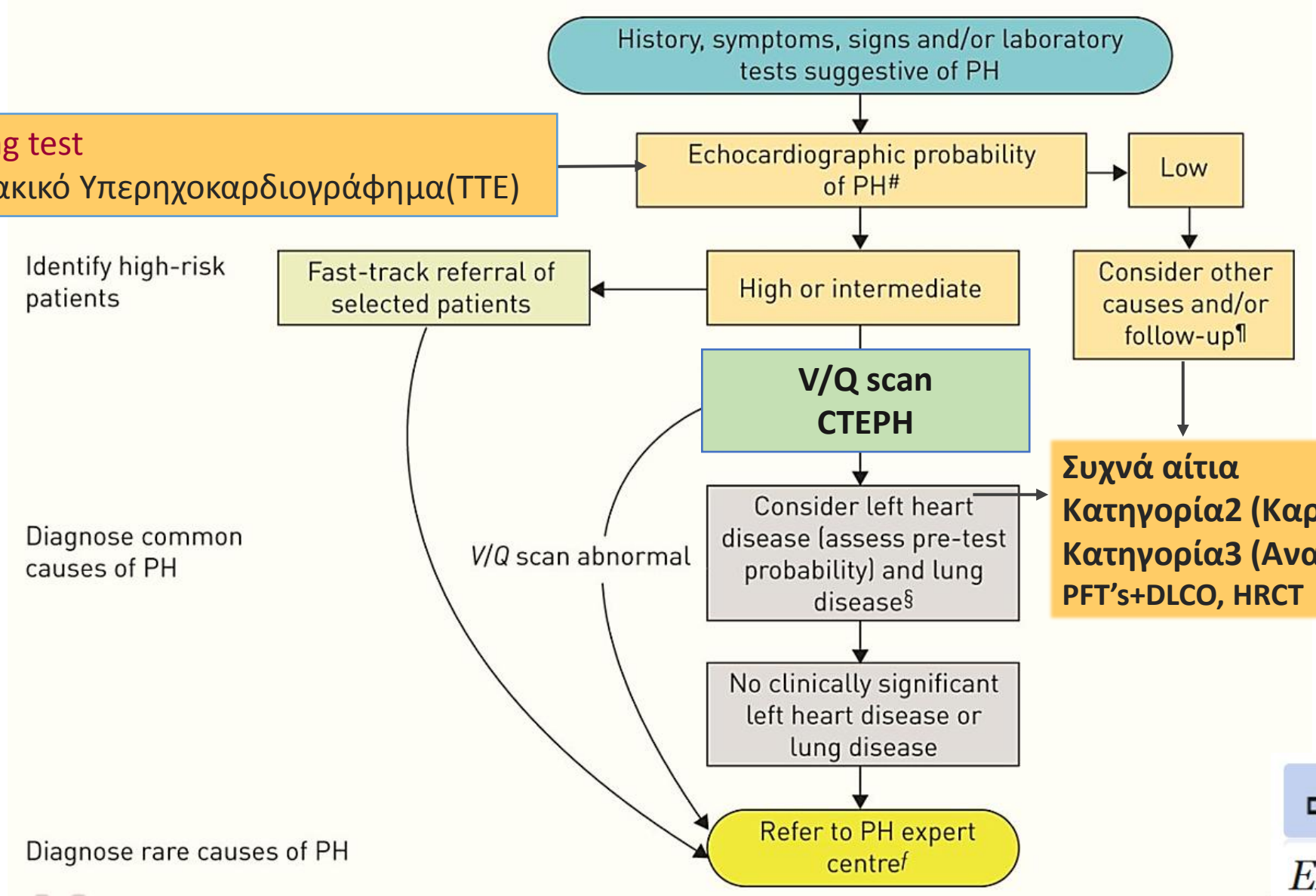
Screening test
Διαθωρακικό Υπερηχοκαρδιογράφημα(ΤΤΕ)



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PFT's+DLCO, HRCT

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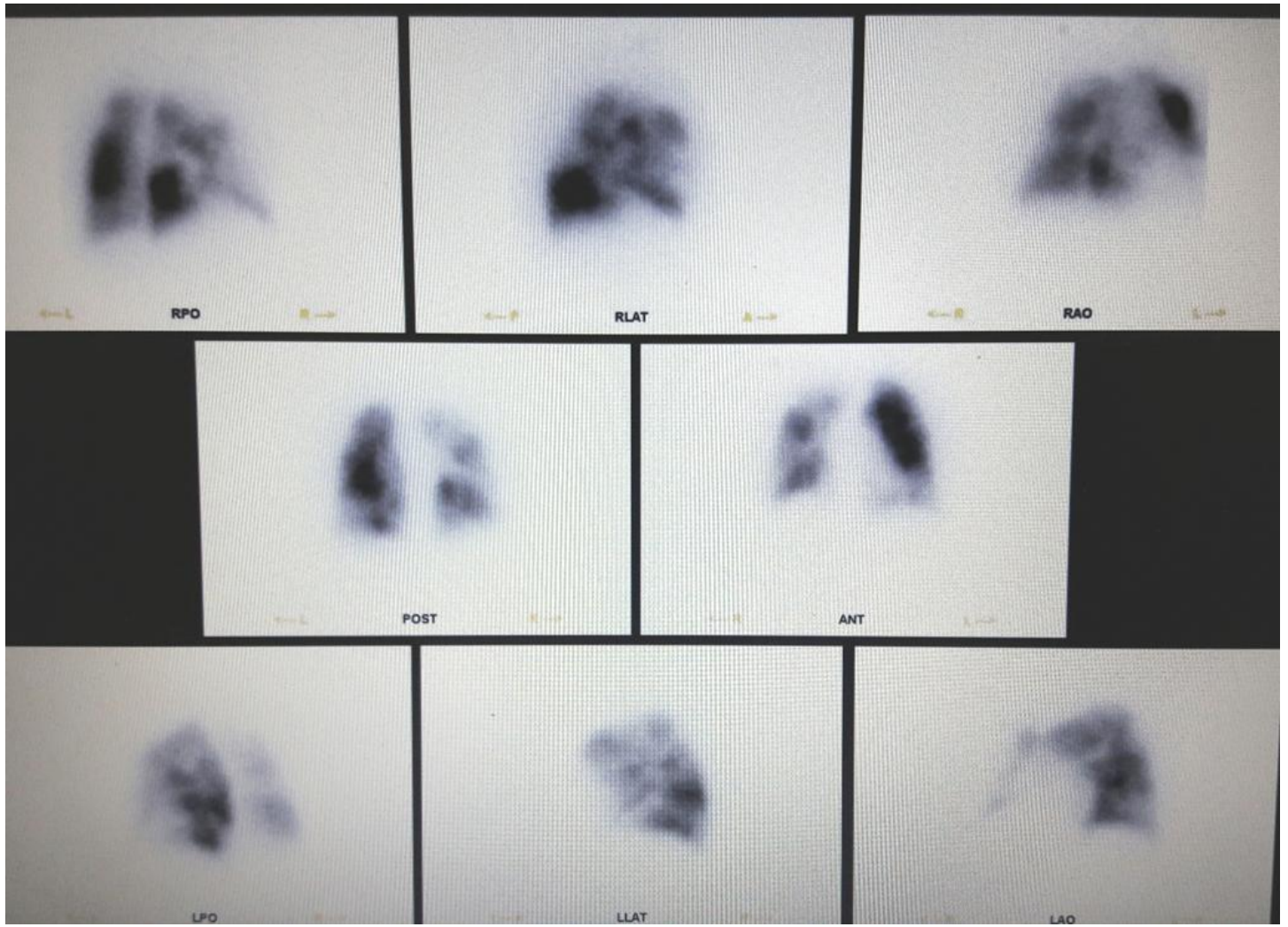
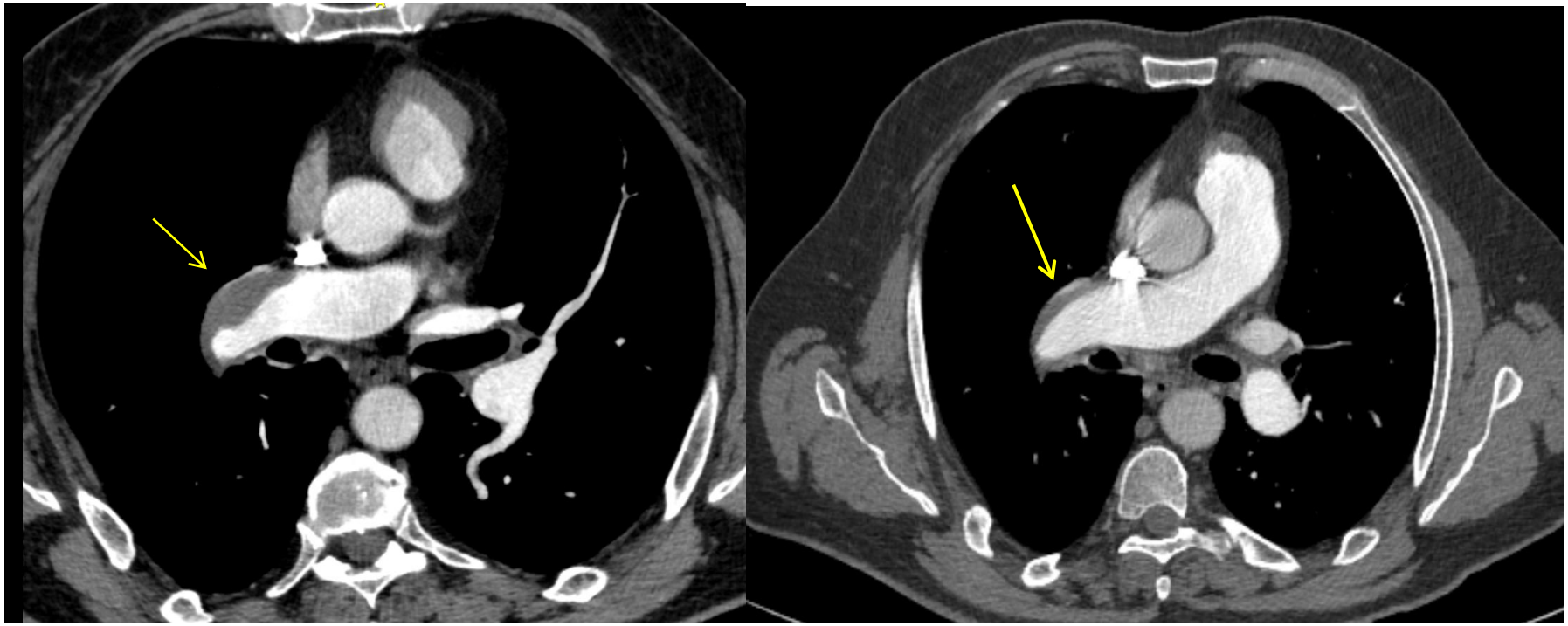
Q scanning πνευμόνων: εικόνα ενδεικτική CTED



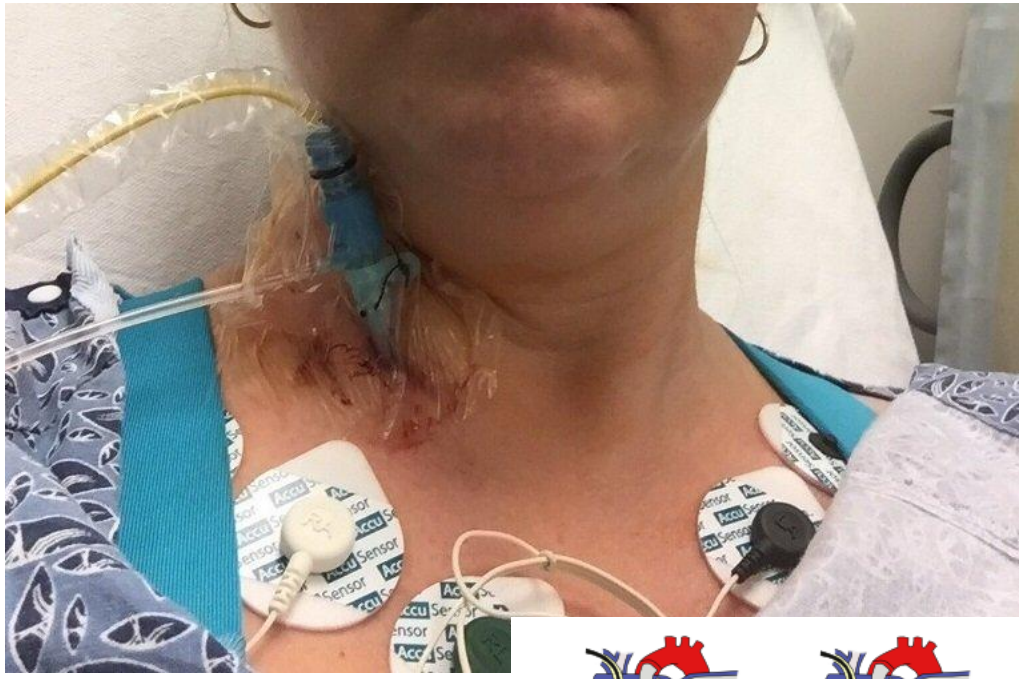
CTPA

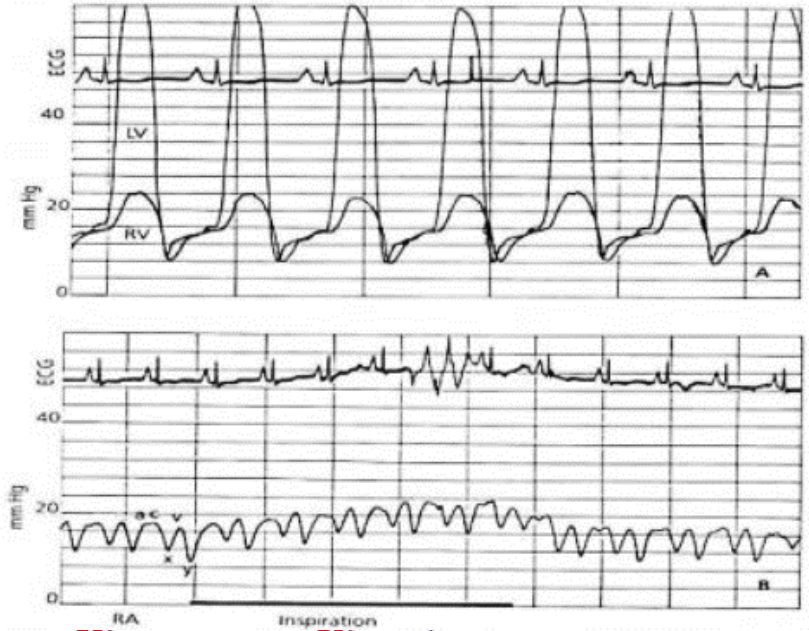


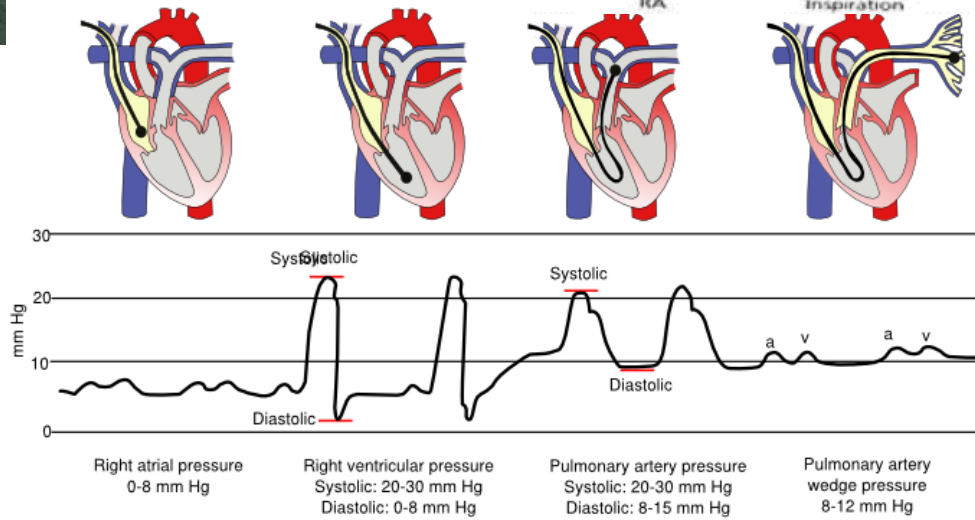
IOYN 2016

IAN 2017

Δεξιός καρδιακός καθετηριασμός- RHC

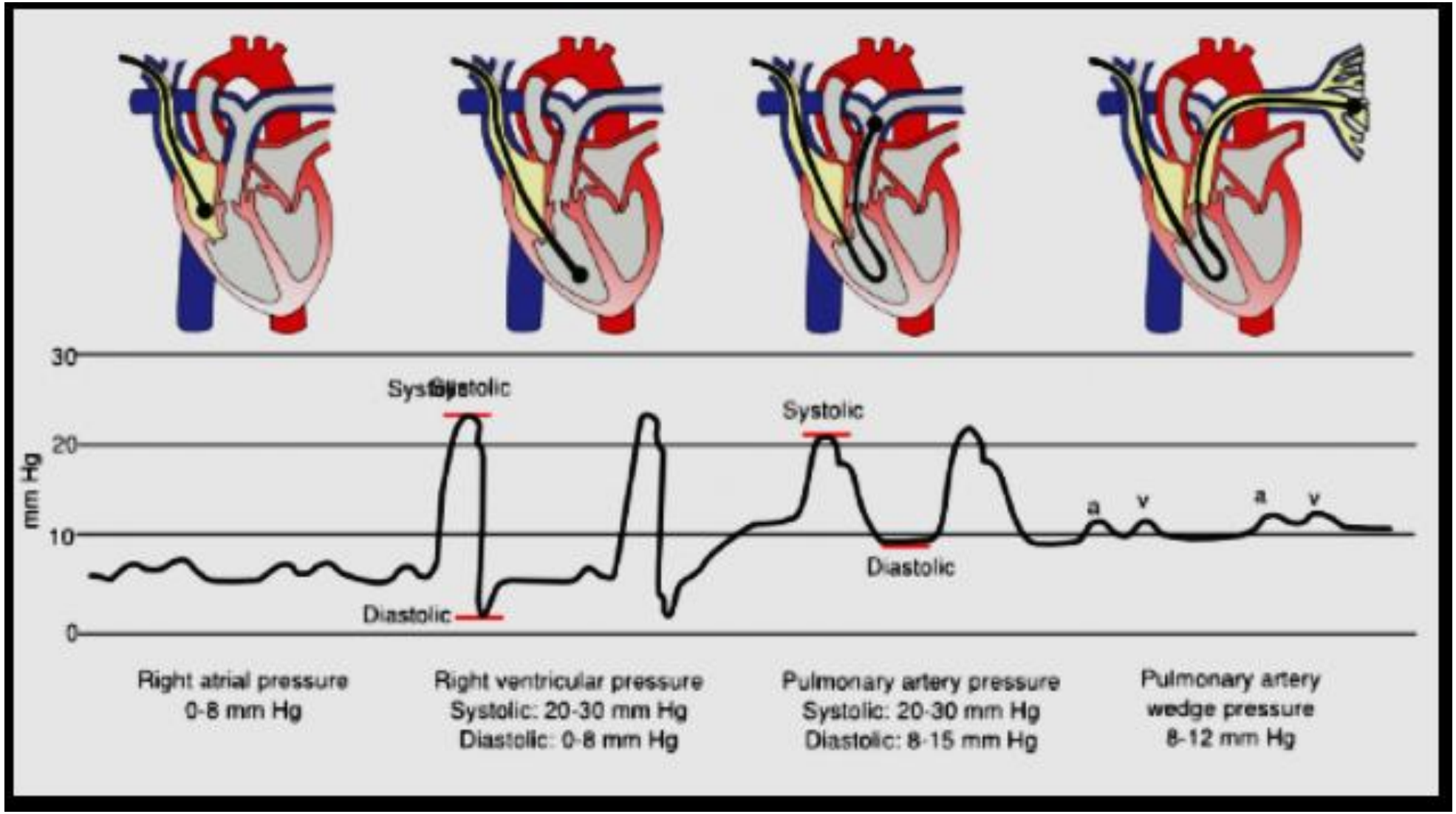


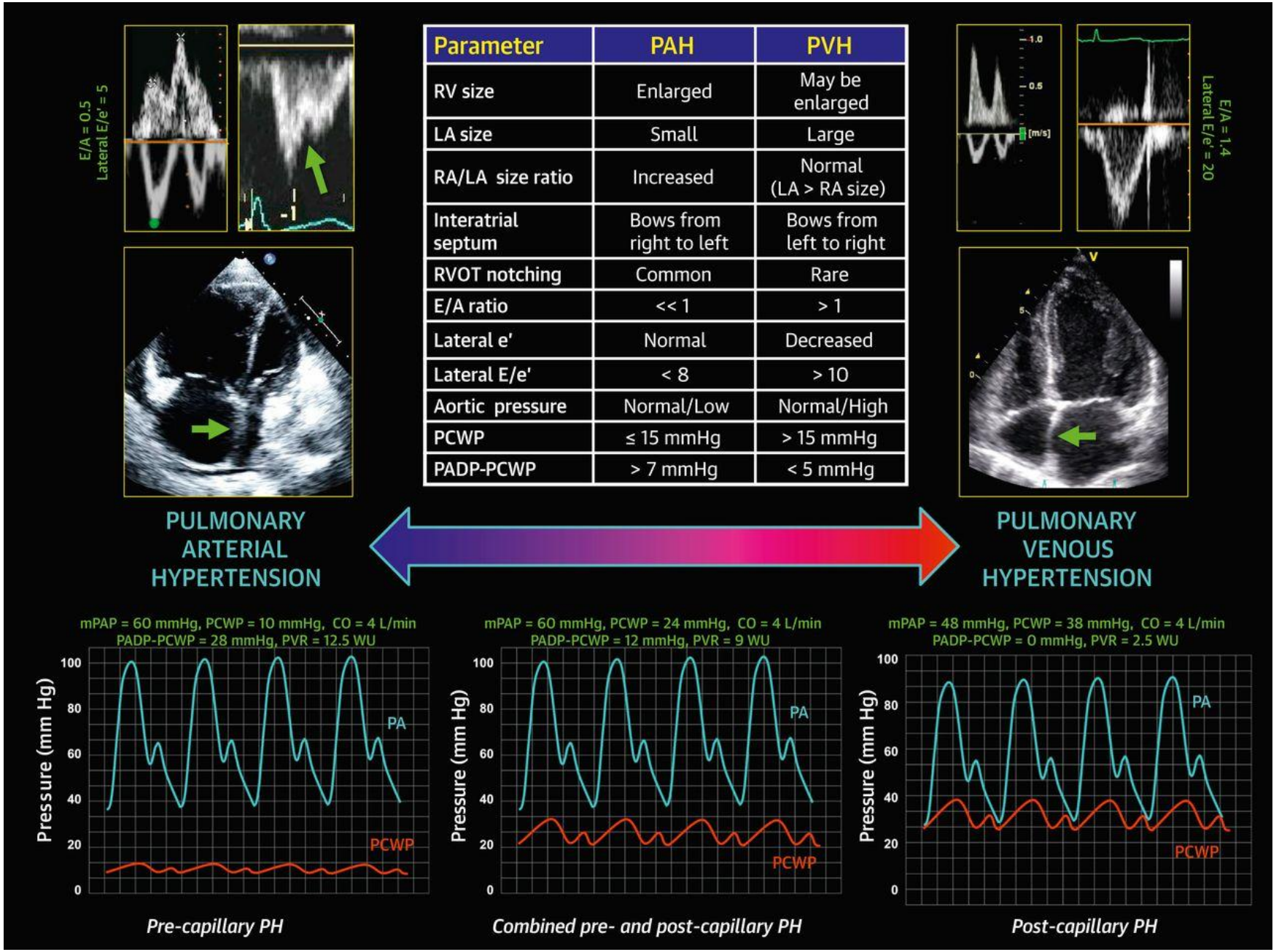




RHC

mPAP≥20mmHg/ PVR>3/ PAWP≤ 15mmHg





Parameter	PAH	PVH
RV size	Enlarged	May be enlarged
LA size	Small	Large
RA/LA size ratio	Increased	Normal (LA > RA size)
Interatrial septum	Bows from right to left	Bows from left to right
RVOT notching	Common	Rare
E/A ratio	<< 1	> 1
Lateral e'	Normal	Decreased
Lateral E/e'	< 8	> 10
Aortic pressure	Normal/Low	Normal/High
PCWP	≤ 15 mmHg	> 15 mmHg
PADP-PCWP	> 7 mmHg	< 5 mmHg

Vallerie V. McLaughlin et al. JACC 2015;65:1976-1997

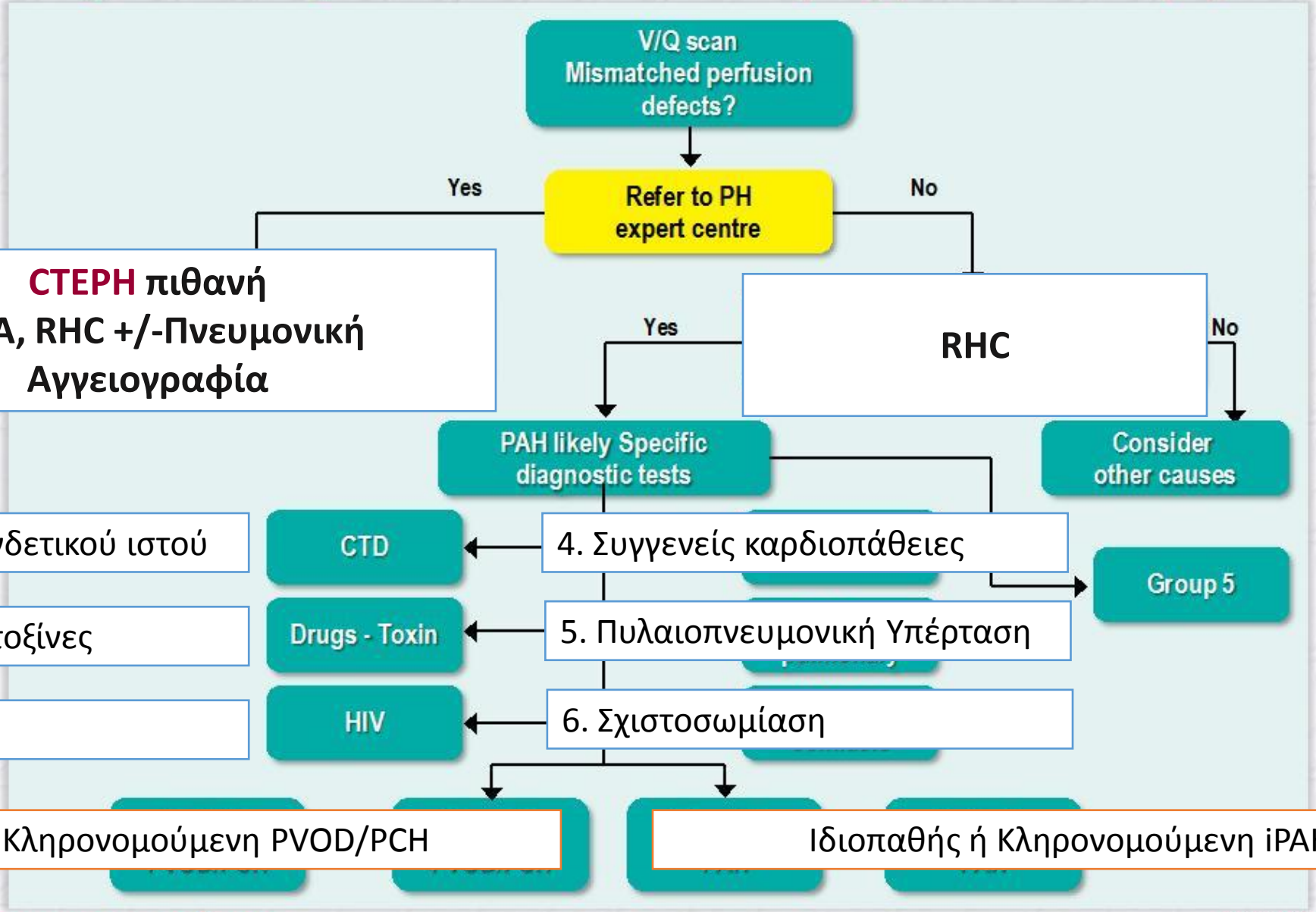
ROBERT NAEIJE 00:04:30

WSPH

Summary of fluid challenge in PH

- The fluid challenge test (FCT) may be standardized as a rapid infusion (< 5 min) of 500 ml of saline
- The ULN of PAWP during a FCT is 20 mmHg
- A FCT can be recommended to assist in the differential diagnosis of PH

Diagnostic Algorithm for Pulmonary Hypertension (2)



CTEPH πιθανή
CTPA, RHC +/-Πνευμονική Αγγειογραφία

1. Νοσήματα συνδετικού ιστού
2. Φάρμακα και τοξίνες
3. HIV
4. Συγγενείς καρδιοπάθειες
5. Πυλαιοπνευμονική Υπέρταση
6. Σχιστοσωμίαση

Ιδιοπαθής ή Κληρονομούμενη PVOD/PCH

Ιδιοπαθής ή Κληρονομούμενη iPAH

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

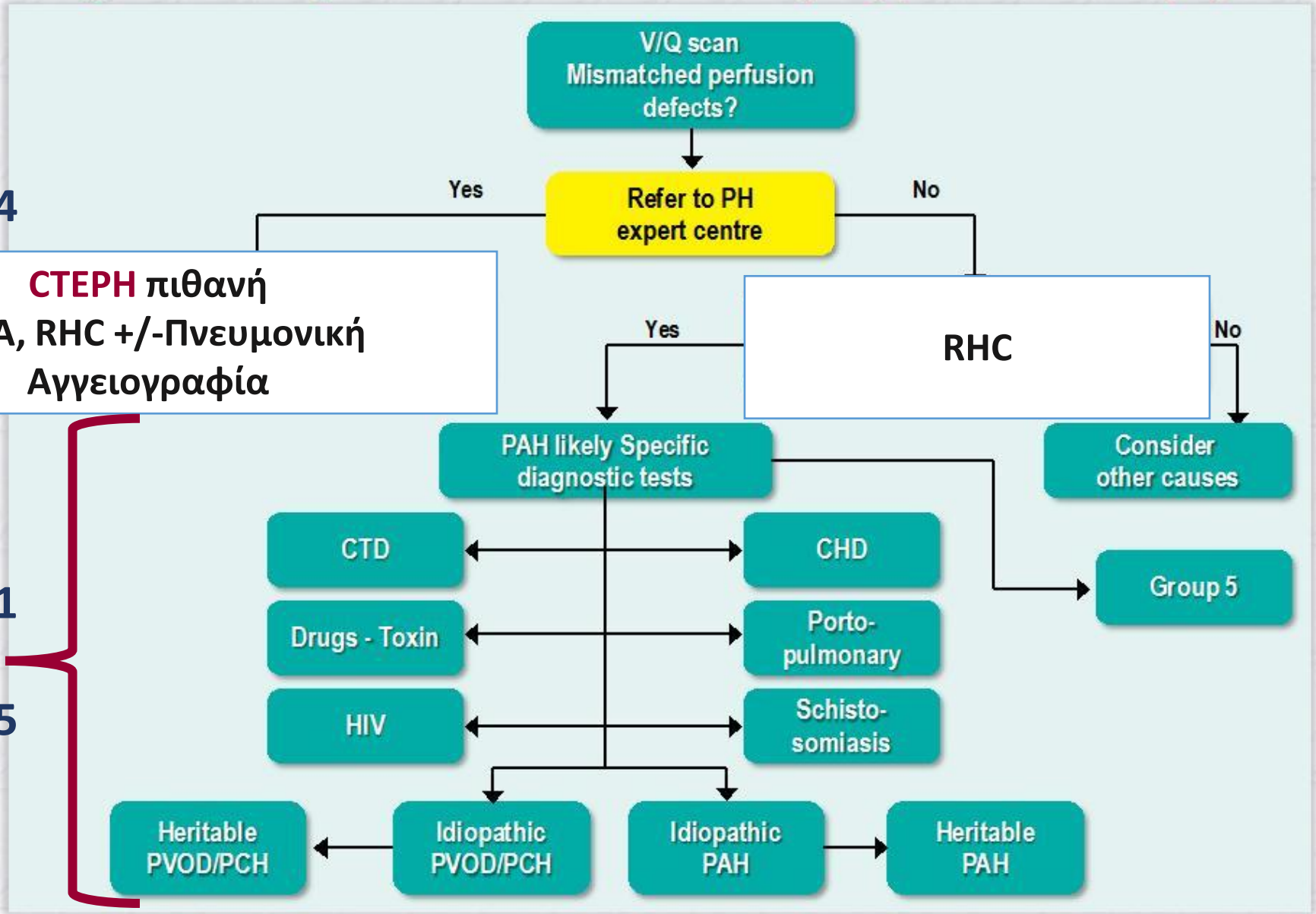
Diagnostic Algorithm for Pulmonary Hypertension (2)

Κατηγορία 4

CTEPH πιθανή
CTPA, RHC +/-Πνευμονική Αγγειογραφία

Κατηγορία 1

Κατηγορία 5



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5. Εκτίμηση κινδύνου

για θάνατο σε 1 έτος

5.Εκτίμηση κινδύνου

Table 13 Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

φ.ε

WHO-FC

6MWT

CPET

BNP

ECHO, MRI

RHC

VALLERIE V. MCLAUGHLIN 00:10:51

WSPH

Simplified Risk stratification in PAH

Prognostic Criteria		Low risk variables	Intermediate risk variables	High risk variables
A.	WHO functional class	I, II	III	IV
B.	6MWD	> 440 m	165–440 m	< 165 m
C.	NT-proBNP/BNP plasma levels OR RAP	BNP < 50 ng/l NTproBNP < 300 ng/ml OR RAP < 8 mmHg	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l OR RAP 8–14 mmHg	BNP > 300 ng/l NT-proBNP > 1400 ng/l OR RAP > 14 mmHg
D.	CI OR SvO2	CI ≥ 2.5 l/min/m² OR SvO_2 > 65%	CI 2.0–2.4 l/min/m² OR SvO_2 60–65%	CI < 2.0 l/min/m² OR SvO_2 < 60%

Simplified Risk stratification in PAH

Low risk	Intermediate risk	High risk
At least 3 low risk criteria and no high risk criteria	Definitions of low or high risk not fulfilled	At least 2 high risk criteria including CI or SvO_2

Scores εκτίμησης κινδύνου

TABLE 1

Summary of four registries assessing risk scores

	REVEAL [17–19]	Swedish PAH Register [6]	COMPERA [7]	French Pulmonary Hypertension Network [8]#
Required variables n	12–14	8	8	4
Patients at baseline n	2716	530	1588	1017
Patients at follow-up n	2529	383	1094	1017
Associated PAH included	Yes	Yes	Yes	No
Definition of low risk	≤6 REVEAL score	<1.5 average score	<1.5 average score	3–4 out of 4 low-risk criteria
1-year mortality by risk group (low/intermediate/high) %	≤2.6/7.0/≥10.7	1.0/7.0/26.0	2.8/9.9/21.2	1.0/NA/13.0–30.0

6. Η μεριά του κλινικού

Η μεριά του πνευμονολόγου
2ον - Διερεύνηση

Διερεύνηση ΠΥ σε ασθενή με Γνωστό Αναπνευστικό Νόσημα

Υποψία	Ενίσχυση	Επιβεβαίωση
Συμπτώματα και σημεία Δύσπνοια δυσανάλογη, ↑P2, ΗΚΓ,BNP-nT proBNP		
PFT's DLCO		
6MWT ↓απόσταση, σημαντικός αποκορεσμός, Borg↑	**ECHO** **TRV max, PASP** **RV δυσλειτουργία**	**RHC** **Παραπομπή**
CT Έκταση νόσου/Αυξημένη PA P/A>1		
CPET		

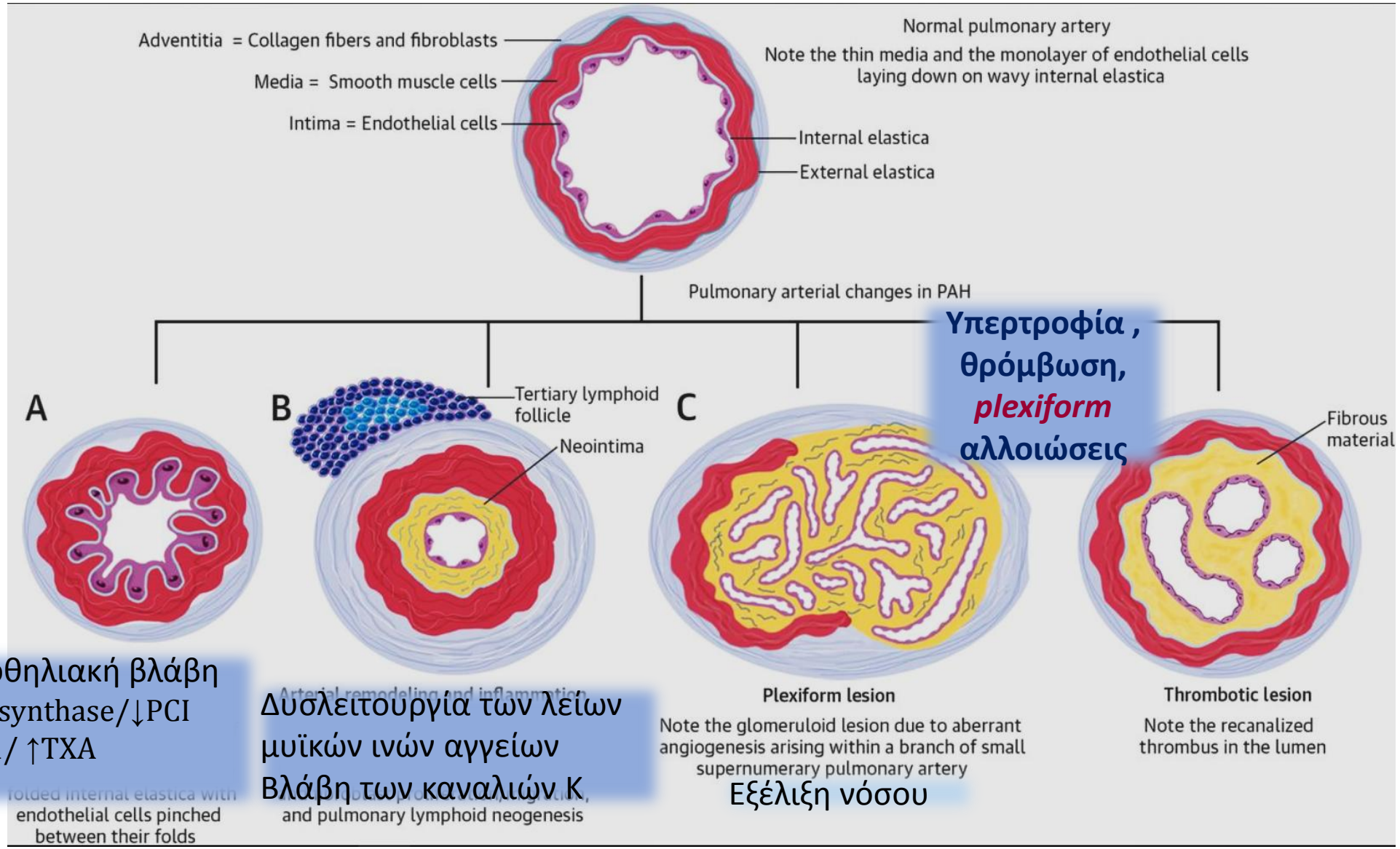
Steven Nathan

Η μεριά του κλινικού 1ον –Υποψία

Διερεύνηση	
Ανεξήγητη δύσπνοια κόπωσης	iPAH
Δύσπνοια σε ασθενή με νόσο του συνδετικού ιστού	CTD-PAH
Εμμένουσα δύσπνοια σε ασθενή με ΠΕ	CTEPH
Δυσανάλογη Δύσπνοια	CPFE, COPD, ILDs, ΣΑΥΥ

7. Θεραπεία

ΠΑΥ -Νόσος υπερπλασίας και απόφραξης

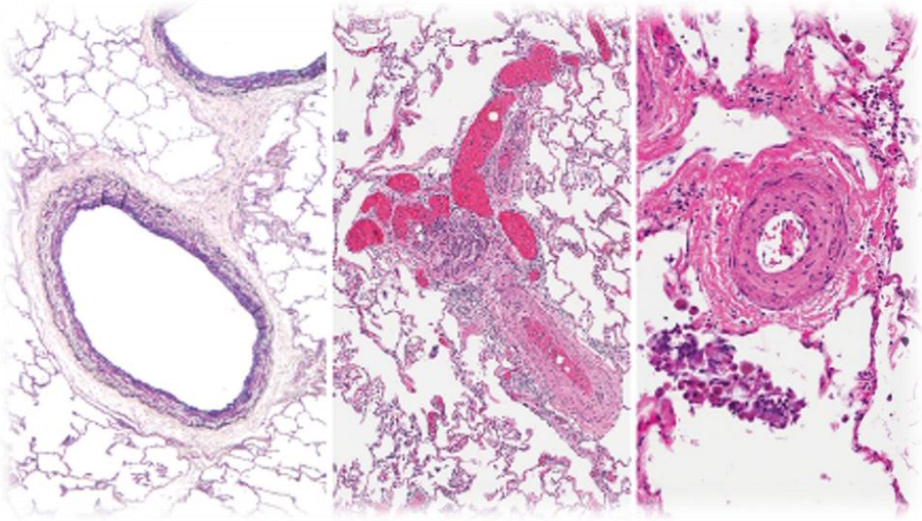


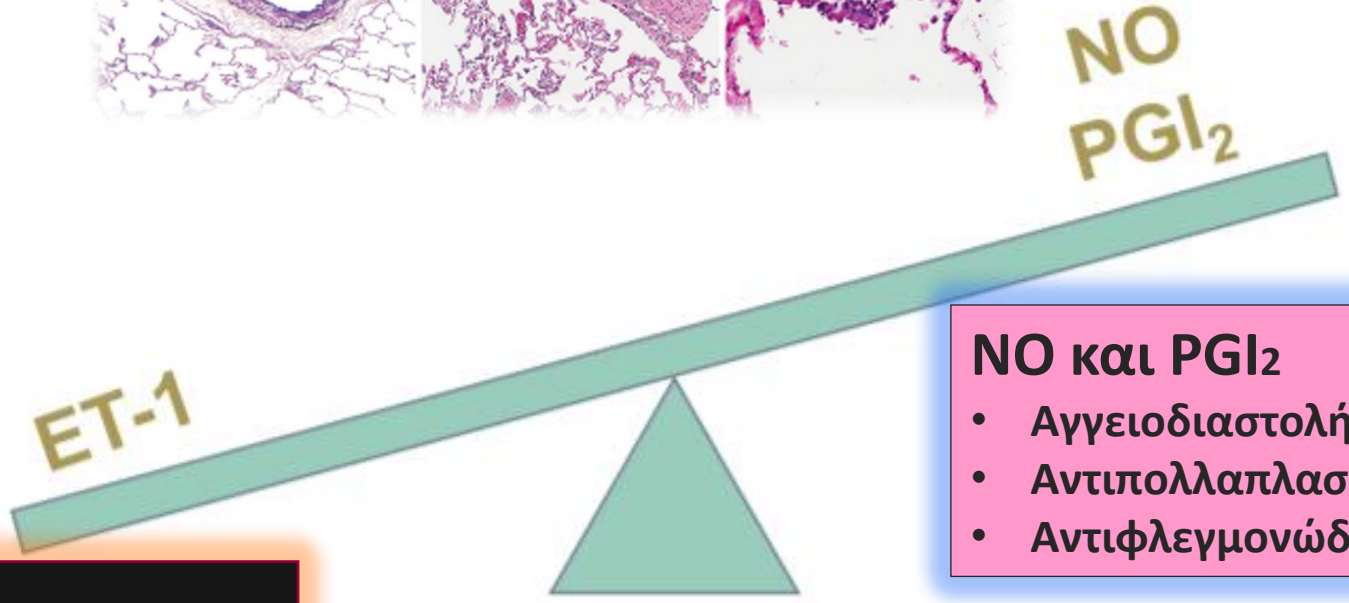
Ενδοθηλιακή βλάβη
↓NO synthase/↓PCI
↑ET1/ ↑TXA

Δυσλειτουργία των λείων μυϊκών ινών αγγείων
Βλάβη των καναλιών Κ

Υπερτροφία , θρόμβωση, *plexiform* αλλοιώσεις

Εξέλιξη νόσου

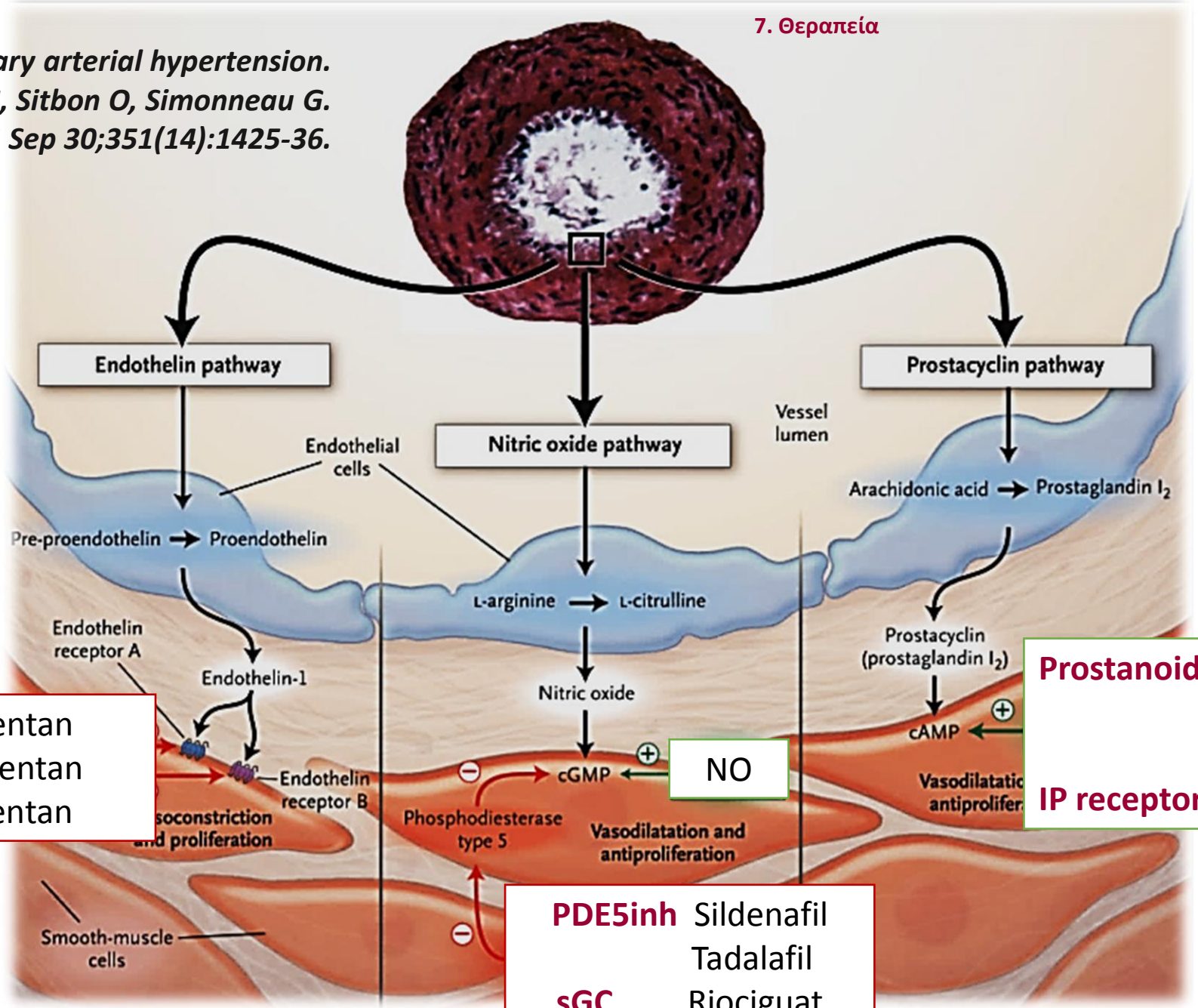




ET-1
- Αγγειοσύσπαση
- Κυτταρικό πολλαπλασιασμό/Υπετροφία

NO και PGI_2
- Αγγειοδιαστολή
- Αντιπολλαπλασιαστική δράση
- Αντιφλεγμονώδη δράση

Treatment of pulmonary arterial hypertension.
Humbert M, Sitbon O, Simonneau G.
N Engl J Med. 2004 Sep 30;351(14):1425-36.

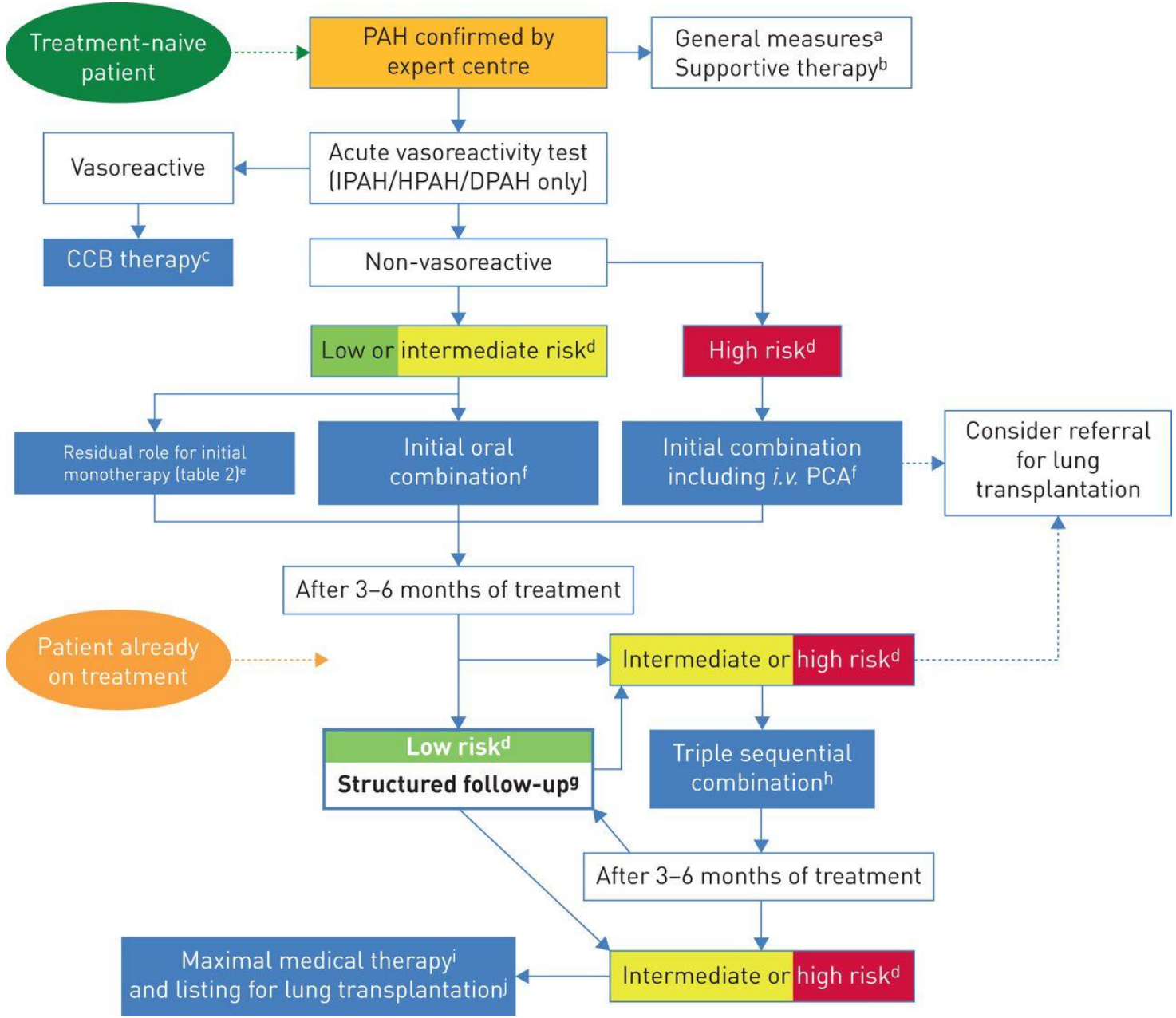


ERAs Bosentan
Ambrisentan
Macitentan

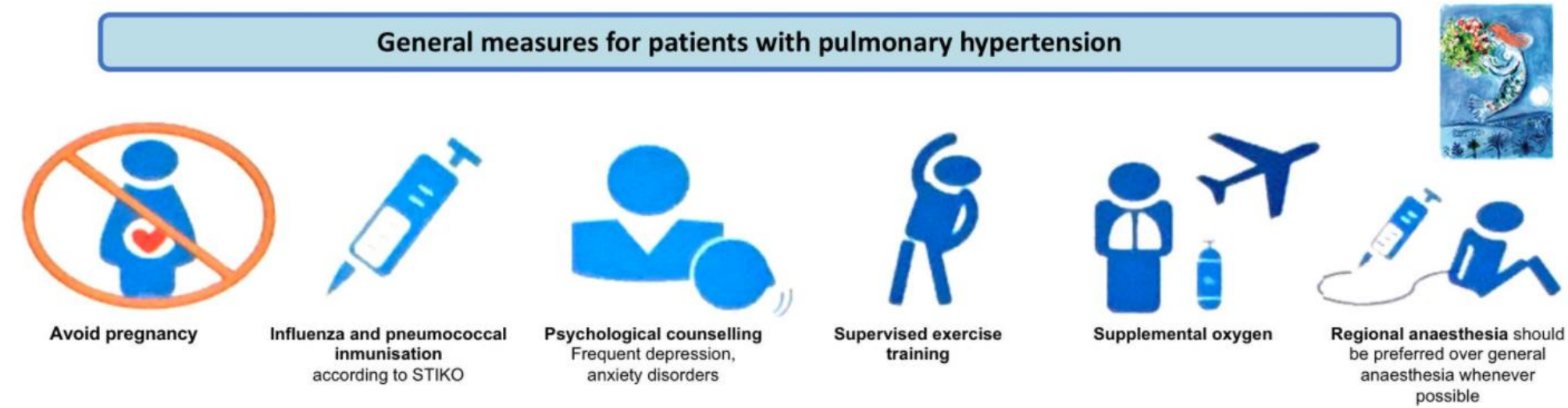
NO

PDE5inh Sildenafil
Tadalafil
sGC Riociguat

Prostanoids: Epoprostenol iv
Iloprost inh
Treprostinil iv, sc, inh,
IP receptor agonist: Selexipag p.os.


Treatment-naive patient
PAH confirmed by expert centre
General measures[a]
Supportive therapy[b]
Acute vasoreactivity test (IPAH/HPAH/DPAH only)
Vasoreactive
CCB therapy[c]
Non-vasoreactive
Low or intermediate risk[d]
High risk[d]
Residual role for initial monotherapy (table 2)[e]
Initial oral combination[f]
Initial combination including i.v. PCA[f]
Consider referral for lung transplantation
After 3–6 months of treatment
Patient already on treatment
Intermediate or high risk[d]
Low risk[d]
Structured follow-up[g]
Triple sequential combination[h]
After 3–6 months of treatment
Intermediate or high risk[d]
Maximal medical therapy[i] and listing for lung transplantation[j]

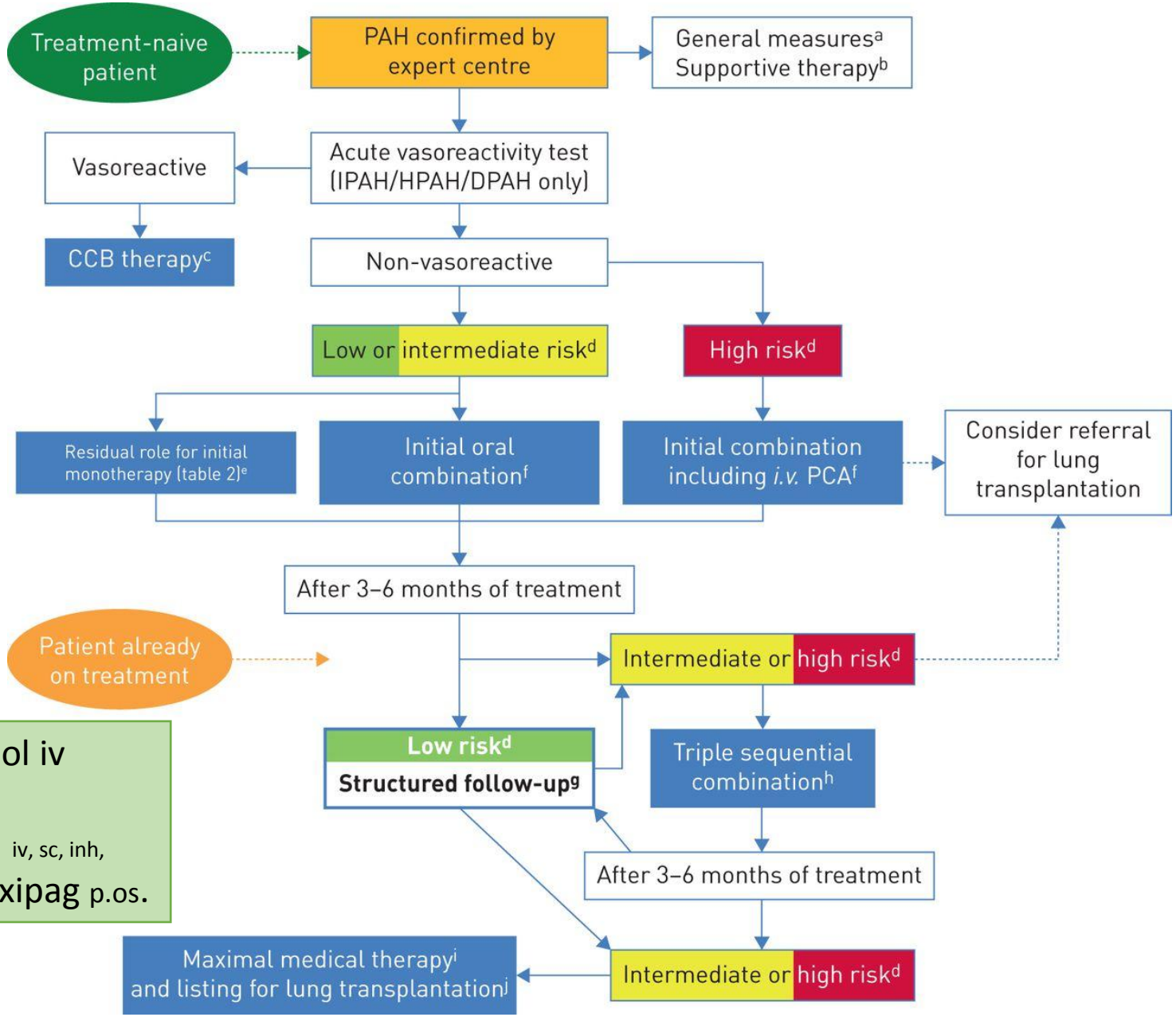
7. Θεραπεία


General measures for patients with pulmonary hypertension
Avoid pregnancy
Influenza and pneumococcal inmunisation according to STIKO
Psychological counselling Frequent depression, anxiety disorders
Supervised exercise training
Supplemental oxygen
Regional anaesthesia should be preferred over general anaesthesia whenever possible
Supportive therapy
Diuretic administration loop diuretics, aldosterone antagonists
Long-term oxygen therapy Saturation <90%, (PaO_2 <60 mm Hg)
Anticoagulation CTEPH Not routinely recommended in PAH
Iron deficiency Correction
ACE Inhibitors, AT_1-antagonists, β-blockers, ivabradine only if specifically indicated
Treatment of arrhythmias Electrical cardioversion / ablation for atrial fibrillation

ERAs Bosentan
Ambrisentan
Macitentan

PDE5inh Sildenafil
Tadalafil
sGC Riociguat

Prostanoids: Epoprostenol iv
Iloprost inh
Treprostinil iv, sc, inh,
IP receptor agonist: Selexipag p.os.



Μελλοντικοί θεραπευτικοί στόχοι

Vascular stiffness	Can activate the YAP/TAZ co-transcription factors, leading to further ECM remodelling and modulation of metabolic pathways		
Endothelial-to-mesenchymal transition	Can be induced by haemodynamic changes associated with PAH TGF-β signalling and HMGA1 may play a role in EndMT EndMT cells can migrate, remodel the ECM and have increased apoptosis resistance		
Pericyte-mediated vascular remodelling	Increased pericyte density in distal pulmonary arteries has been reported in PAH FGF-2 and IL-6 can stimulate pericyte migration and proliferation TGF-β can promote the differentiation of pericytes into SMCs		
TGF-β signalling	Loss of function heterozygous *BMPR2* mutations have been reported ir PAH In the absence of a mutation, BMPR-II expression is frequently reduced in PAH Suppression of BMPR-II signalling leads to increased proliferation and decreased apoptosis in vascular cells Inflammatory mediators, *e.g.* TNF-α, may play a role in PAH pathogenesis in the context of *BMPR2* mutations		
PDGF and FGF signalling	Over-expression of PDGF and FGF has been reported in PAH and may be involved in abnormal proliferation and migration of SMCs, as wel as endothelial dysfunction		
Inflammation and immunity	Inflammatory mediators and cell infiltrates are frequently observed in PAH Vascular cells can respond to inflammatory stimuli by enhanced proliferation and migration and reduced apoptosis		
Resting membrane potential	Loss-of-function *KCNK3* mutations have been reported in PAH May contribute to pulmonary vasoconstriction and pulmonary vascular remodelling Expression of the Kv1.5 channel is also reduced in human and experimental PAH		
Oestrogen signalling	E2 metabolites can exert both detrimental and protective effects in PAH E2 may directly protect against the development of PH in animal models		
Iron homeostasis	Iron deficiency may play a role in pulmonary vascular remodelling	Iron replacement	[76–81]

targets

TABLE 2 Additional pathogenic pathways and potential therapeutic targets in pulmonary arterial hypertension (PAH)

Pathway	Role in PAH	Potential therapeutic targets	Refs
Transcription factors	FoxO1, a member of the Forkhead box O (FoxO) family of transcription factors that are key regulators of cellular proliferation, is downregulated in pulmonary vessels/PASMCs of human/experimental PH lungs Activation of the prosurvival transcription factors STAT3, NFAT, and HIF-1α has been demonstrated in experimental models of PAH	FoxO1 STAT3/PIM1 NFAT, HIF-1α	[28, 82, 83]
NOTCH3-HES5 signalling	*NOTCH3* is overexpressed in small PASMCs in human PH There is evidence for a link between NOTCH3 receptor signalling through HES5 and SMC proliferation in the development of PAH	NOTCH3-HES5 pathway	[84]
Epigenetic mechanisms	Methylation-induced downregulation of SOD2 in PASMCs may create a metabolic state that favours proliferation and suppresses apoptosis Aberrant expression of HDACs and BRD4 (a transcriptional regulator that recognises acetylated lysine residues) is consistent with altered epigenetic mechanisms in PAH Studies have shown that miRNAs (small RNA molecules that negatively regulate expression of target genes) are dysregulated in patients with PAH	SOD2 HDACs BRD4 miRNAs	[85–88]
DNA damage/ PARP-1 signalling pathway	Activation of PARP-1 (a DNA repair enzyme) may lead to subsequent activation of transcription factors (NFAT, HIF-1α) that are implicated in PAH Inflammation induces DNA damage in PASMCs (levels of baseline and mutagen-induced DNA damage are intrinsically higher in PAH cells), which may lead to activation of PARP-1 in PAH	DNA damage/PARP-1 signalling pathway	[82, 89]
VEGFR signalling	VEGF plasma levels are elevated in patients with severe PAH, and expression of VEGF and VEGFR2 is robust in complex vascular lesions of PAH lungs Role of VEGF in mechanisms of PAH development is not clear	VEGFR signalling	[90]

NAZZARENO GALIÈ

Potential role of initial monotherapy -1

- I/H/D PAH patients responders to acute vasoreactivity tests and with near-normalization of symptoms, exercise capacity, PAP and PVR on highest tolerated doses of CCBs
- Long-term treated historical PAH patients with monotherapy (> 5-10 years) stable with low risk profile
- PAH Patients > 75 yo with multiple risk factors for heart failure with preserved left ventricular ejection fraction (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity)
- PAH patients with suspicion or high probability of PVOD/PCH

NAZZARENO GALIÈ

00:07:19

Potential role of initial monotherapy -2

- Patients with PAH associated with HIV or portal hypertension or uncorrected CHD as they were not included in RCTs of initial combination therapy
- PAH patients with very mild disease (e.g. WHO FC I, PVR < 4 WU, mPAP < 30 mmHg, normal RV at echocardiography)
- Combination therapy unavailable or contraindicated (e.g. severe liver disease)

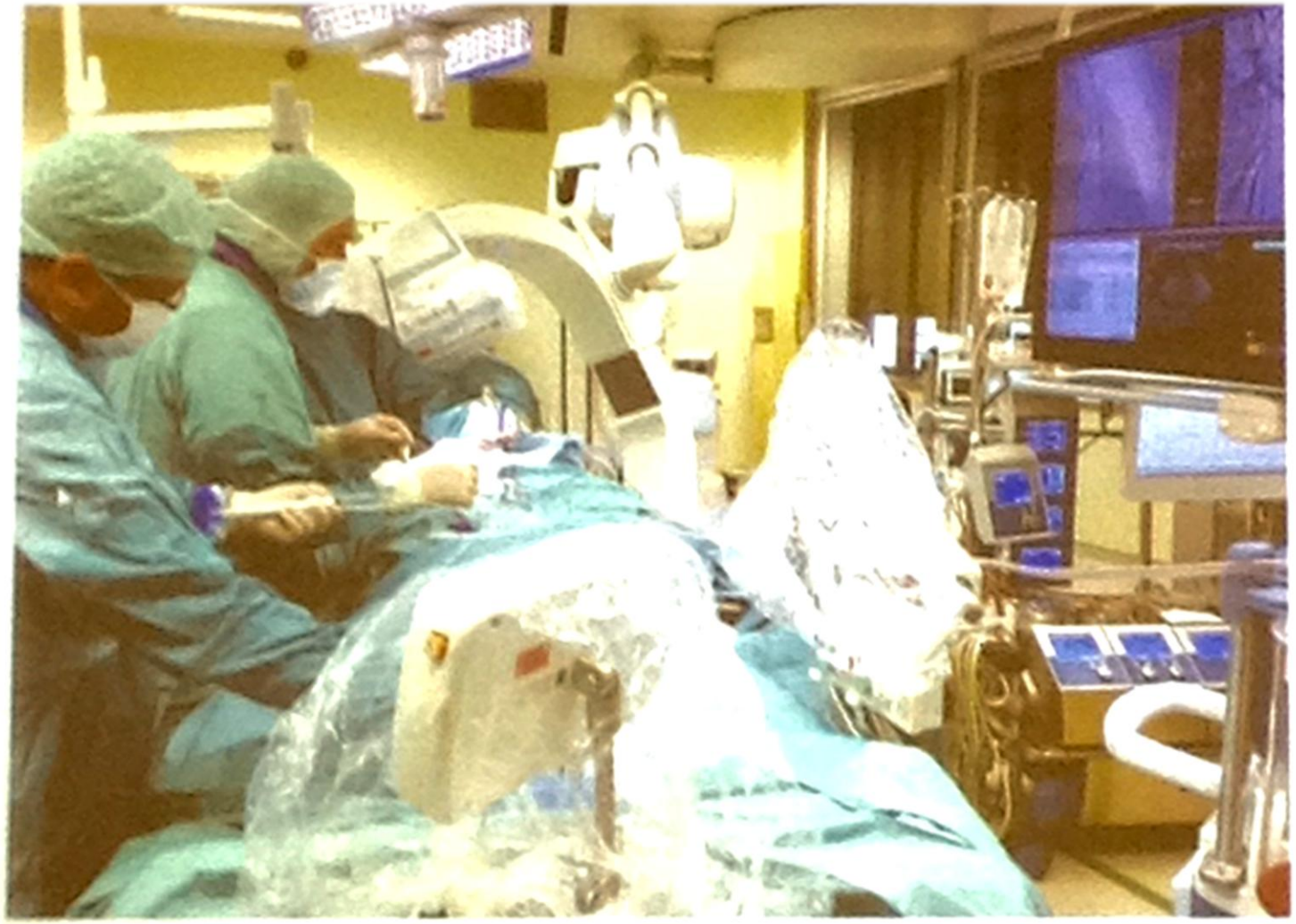
Μονοθεραπεία όταν

TABLE 2

Potential role for initial monotherapy in specific pulmonary arterial hypertension (PAH) subsets

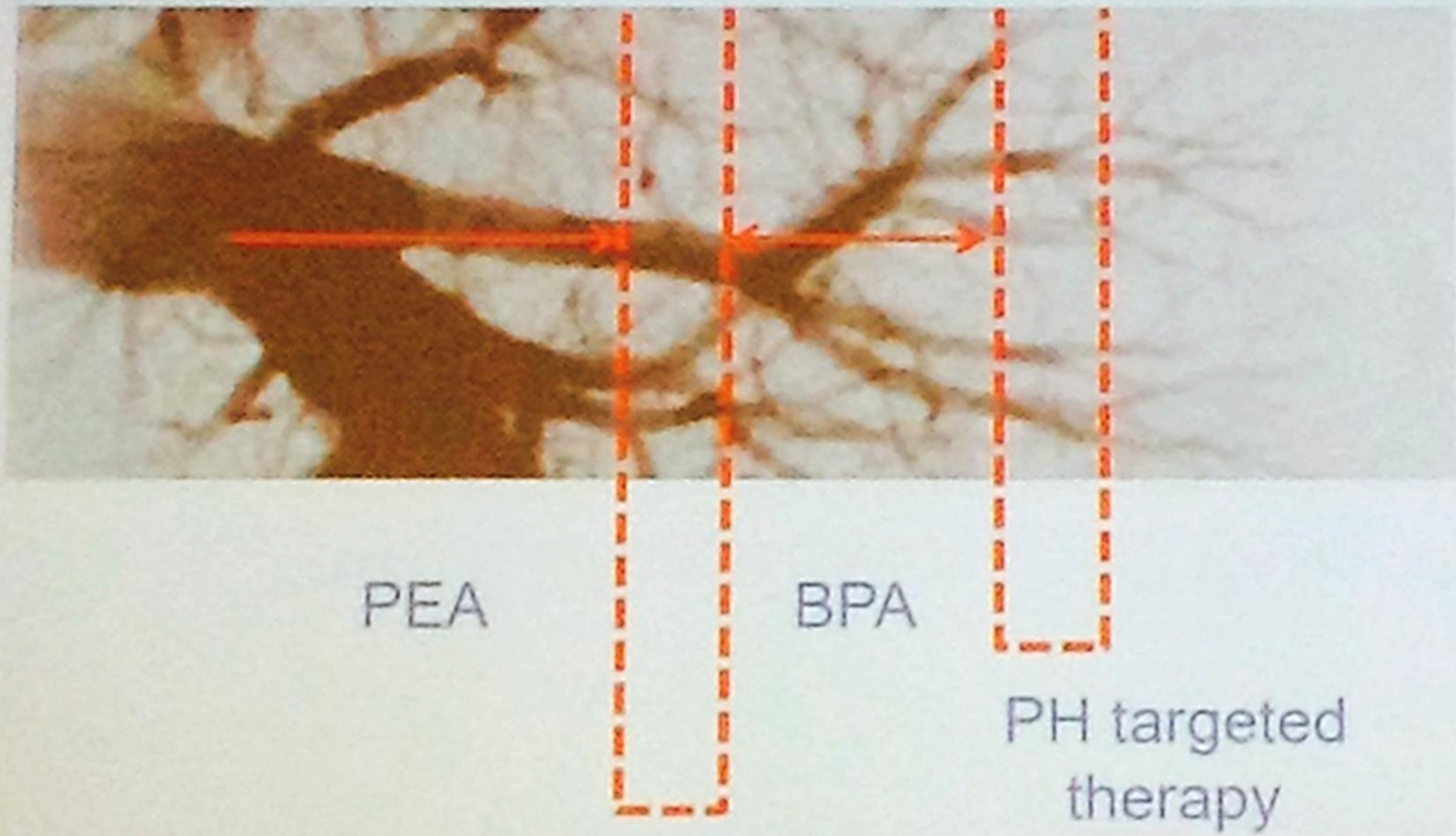
IPAH, HPAH and drug-induced PAH patient responders to acute vasoreactivity tests and with WHO FC I/II and sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only
Long-term-treated historical PAH patients with monotherapy (>5–10 years) stable with low-risk profile
IPAH patients >75 years old with multiple risk factors for heart failure with preserved LVEF (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity)
PAH patients with suspicion or high probability of pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis
Patients with PAH associated with HIV infection or portal hypertension or uncorrected congenital heart disease, as they were not included in RCTs of initial combination therapy
PAH patients with very mild disease (*e.g.* WHO FC I, PVR 3–4 WU, mPAP <30 mmHg, normal right ventricle at echocardiography)
Combination therapy unavailable or contraindicated (*e.g.* severe liver disease)

CTEPH-GROUP 4



Localization of PA obstructions is critical for therapeutic decisions (Germany 2017)

and these are dependent on CTEPH center experience with surgery, BPA, and medical treatment



Ομιλία Dr Mayer 2017 Bologna

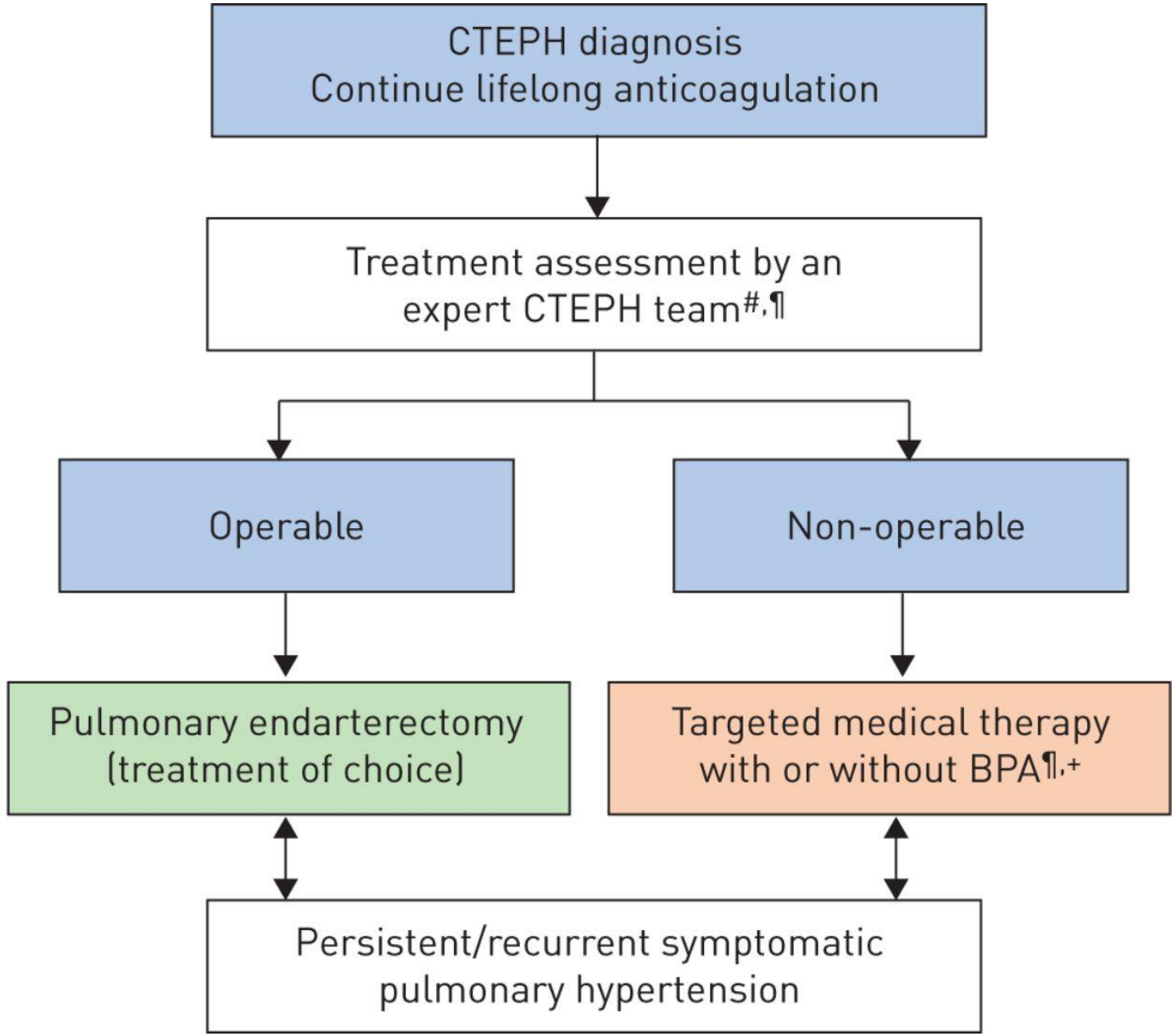
Combination of treatment modalities

There are many „hybrid" options in CTEPH

- PEA +/- medical treatment
- BPA +/- medical treatment
- Hybrid PEA/BPA vs staged PEA/BPA or BPA/PEA?
- Combination medical CTEPH therapy?

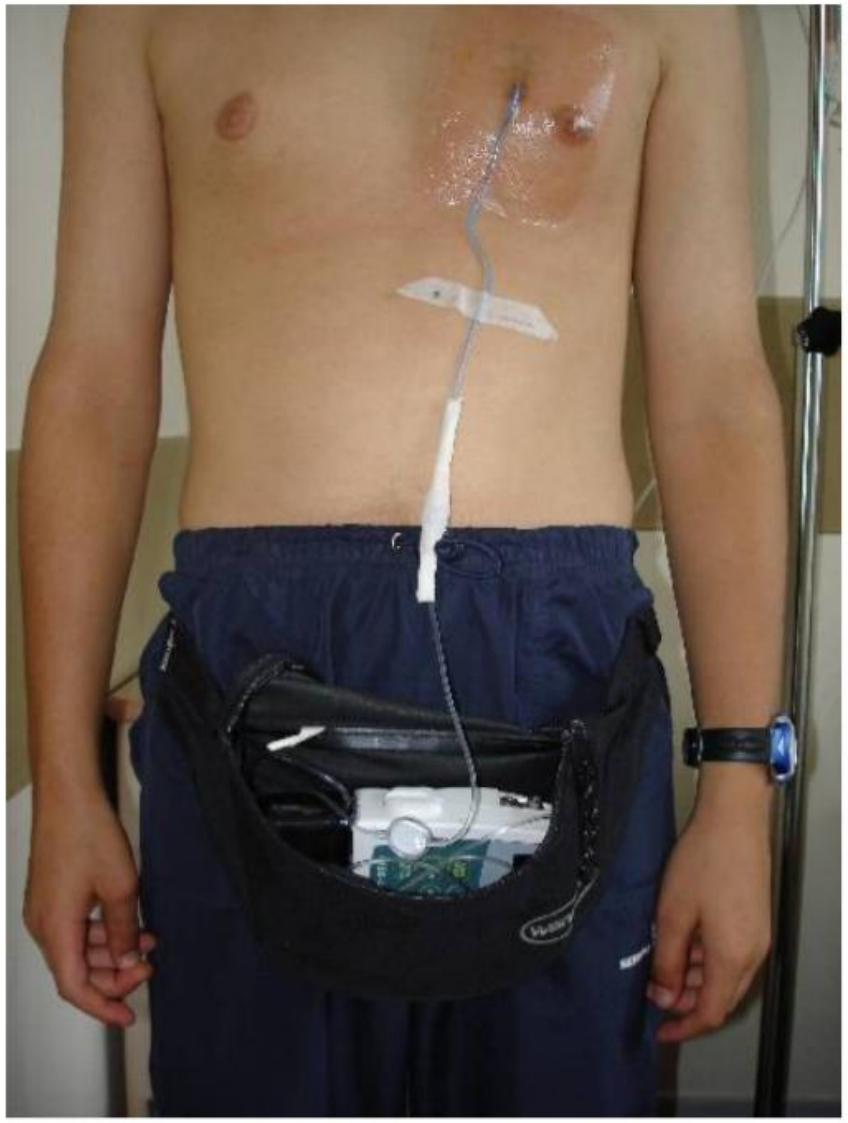
Θεραπεία

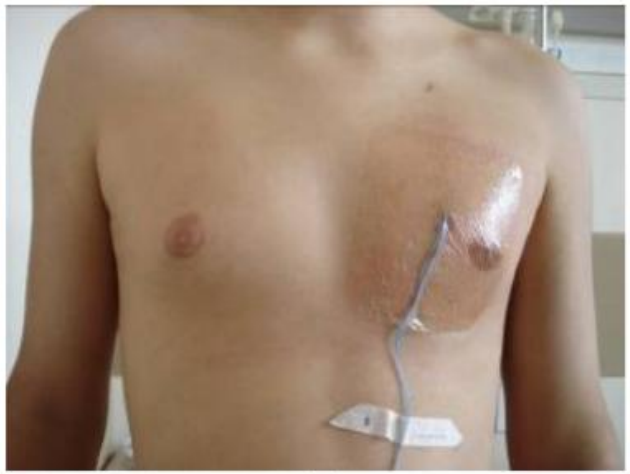
Ομιλία Dr Mayer 2017 Bologna


CTEPH diagnosis
Continue lifelong anticoagulation
Treatment assessment by an expert CTEPH team#,¶
Operable
Non-operable
Pulmonary endarterectomy (treatment of choice)
Targeted medical therapy with or without BPA¶,+
Persistent/recurrent symptomatic pulmonary hypertension

Διεπιστημονική ομάδα (Καρδιολόγοι, Πνευμονολόγοι κλπ) νοσηλευτής εξειδικευμένος, σύστημα υποστήριξης –ψυχολόγο, κοινωνικό λειτουργό και on call υποστήριξη

I.V. Εποπροστενόλη





ΔΙΠΥ ΠΓΝ ‘ΑΤΤΙΚΟΝ’

WHY IS THIS PLANT STILL BEING WATERED?

A PILL (there are now many) IS TOO EASY TO GIVE

IT'S EASY TO JUST FOLLOW THE INSTRUCTIONS, BUT TREATING TOO LONG WITHOUT RECOGNIZING FAILURE IS DANGEROUS

IRREPLACEABLE TIME IS LOST BEFORE ESCALATING THERAPY

NEED EXPERIENCED FOLLOW UP

Take home messages

1. **mPAP= PAWP+ CO x PVR**
2. **PH-PAH → PAH: αρτηριοπάθεια πνευμονικών αγγείων (↑PVR)**
3. **1ο βήμα να το υποψιαστώ:**
   - **Αδιευκρίνιστη δύσπνοια,**
   - **Δυσανάλογη του υποκείμενου αναπνευστικού νοσήματος,**
   - **Εμμένουσα μετά από ΠΕ,**
   - **High risk πληθυσμοί (CTD)**
4. **Screening tool το διαθωρακικό υπερηχοκαρδιογράφημα**
   1. **TRVmax και έμμεσους δείκτες (PA, RV, IVC-RA)**
5. **RHC πάντα**
6. **Ειδική θεραπεία κατηγορίες 1 και 4 και κατά περίπτωση σε άλλες κατηγορίες (2,3,5)**

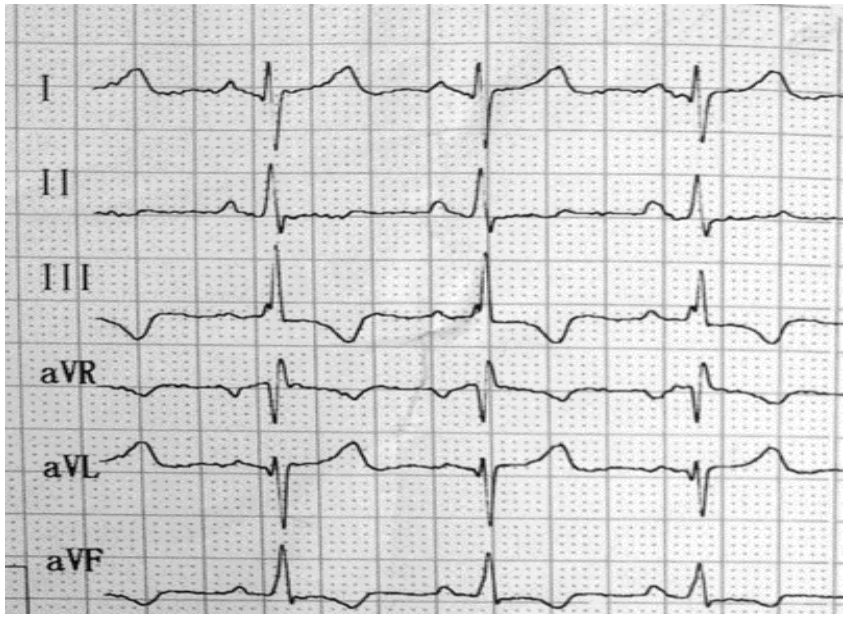
Καλά Χριστούγεννα

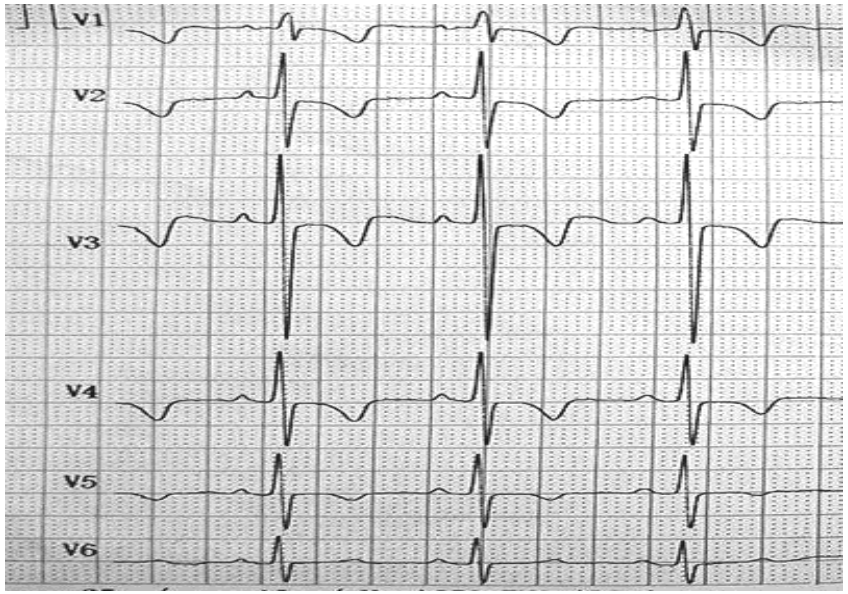
Ευχαριστώ

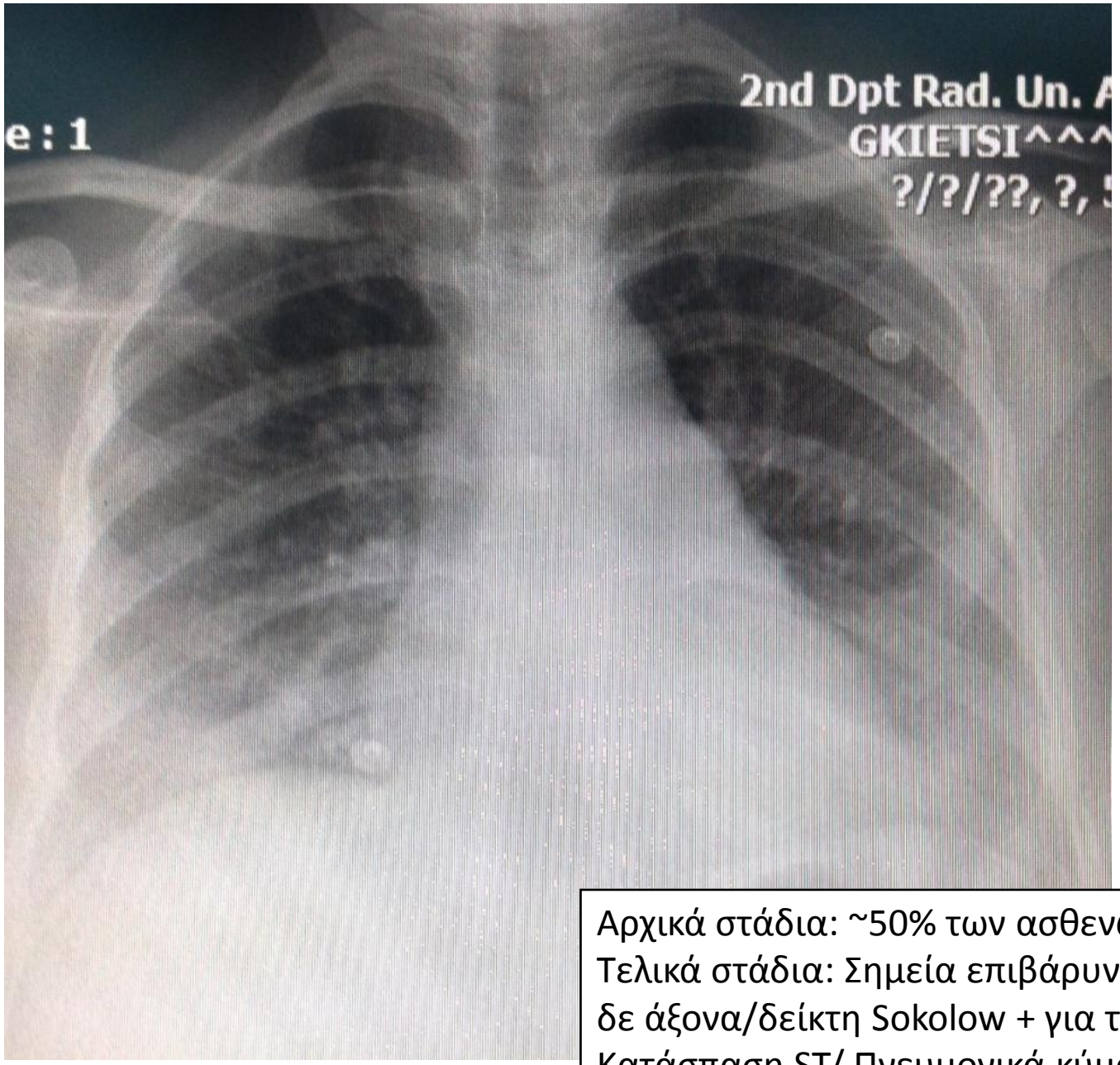
♀ 31y, μη καπνίστρια,
μητέρα ενός αγοριού 7ετών

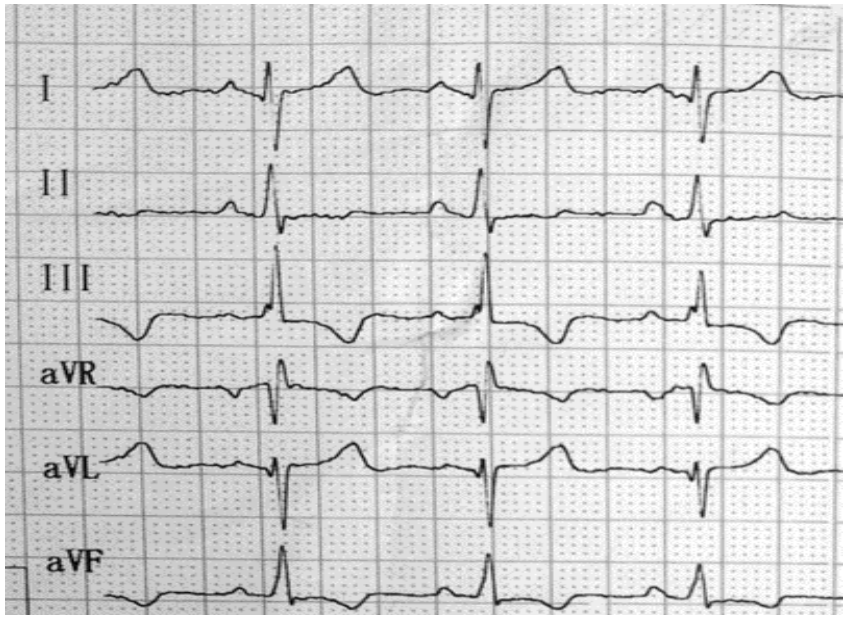
8 Νοε 2015
ΤΕΠ ΠΓΝ «ΑΤΤΙΚΟΝ» για προσυγκοπτικό επεισόδιο
Δύσπνοια επιδεινούμενη

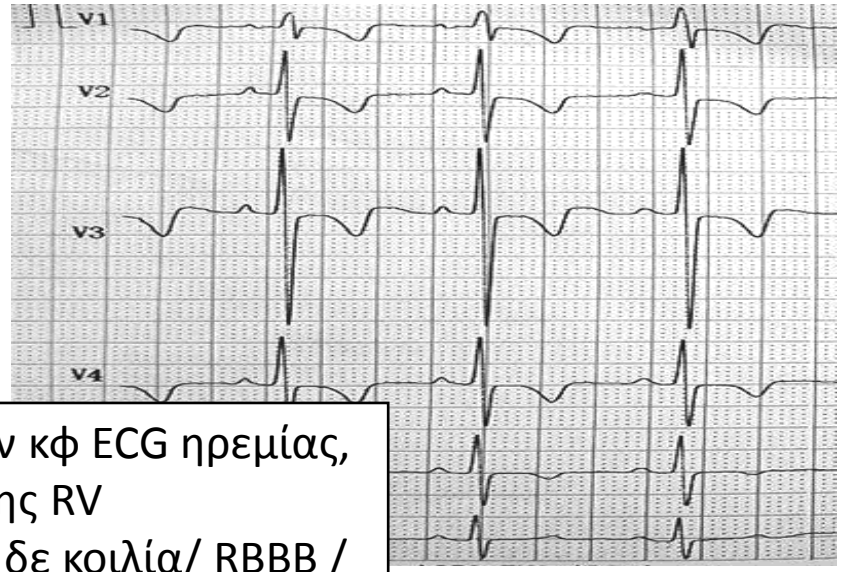
ΑΑ
Σκλήρυνση κατά πλάκας (2009)/ INF-b (2010)











Αρχικά στάδια: ~50% των ασθενών κφ ECG ηρεμίας,
Τελικά στάδια: Σημεία επιβάρυνσης RV
δε άξονα/δείκτη Sokolow + για τη δε κοιλία/ RBBB /
Κατάσπαση ST/ Πνευμονικά κύματα P

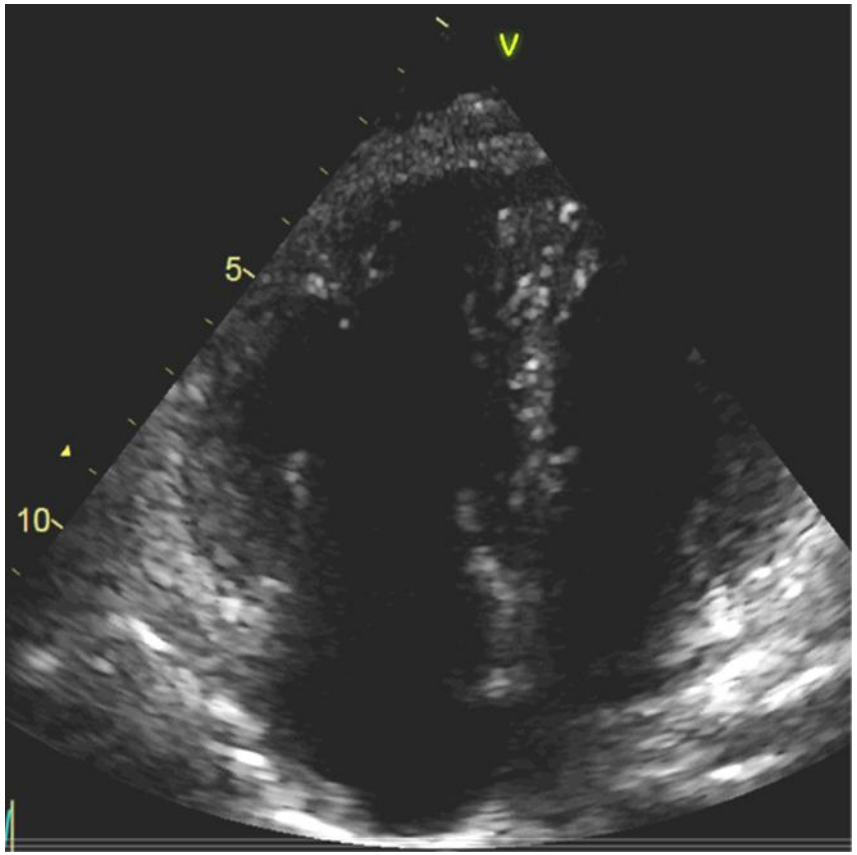
Echocardiography

TRVmax	4,8	m/s
RVSP	95	mmHg
TAPSE	16	mm

Διάταση RV

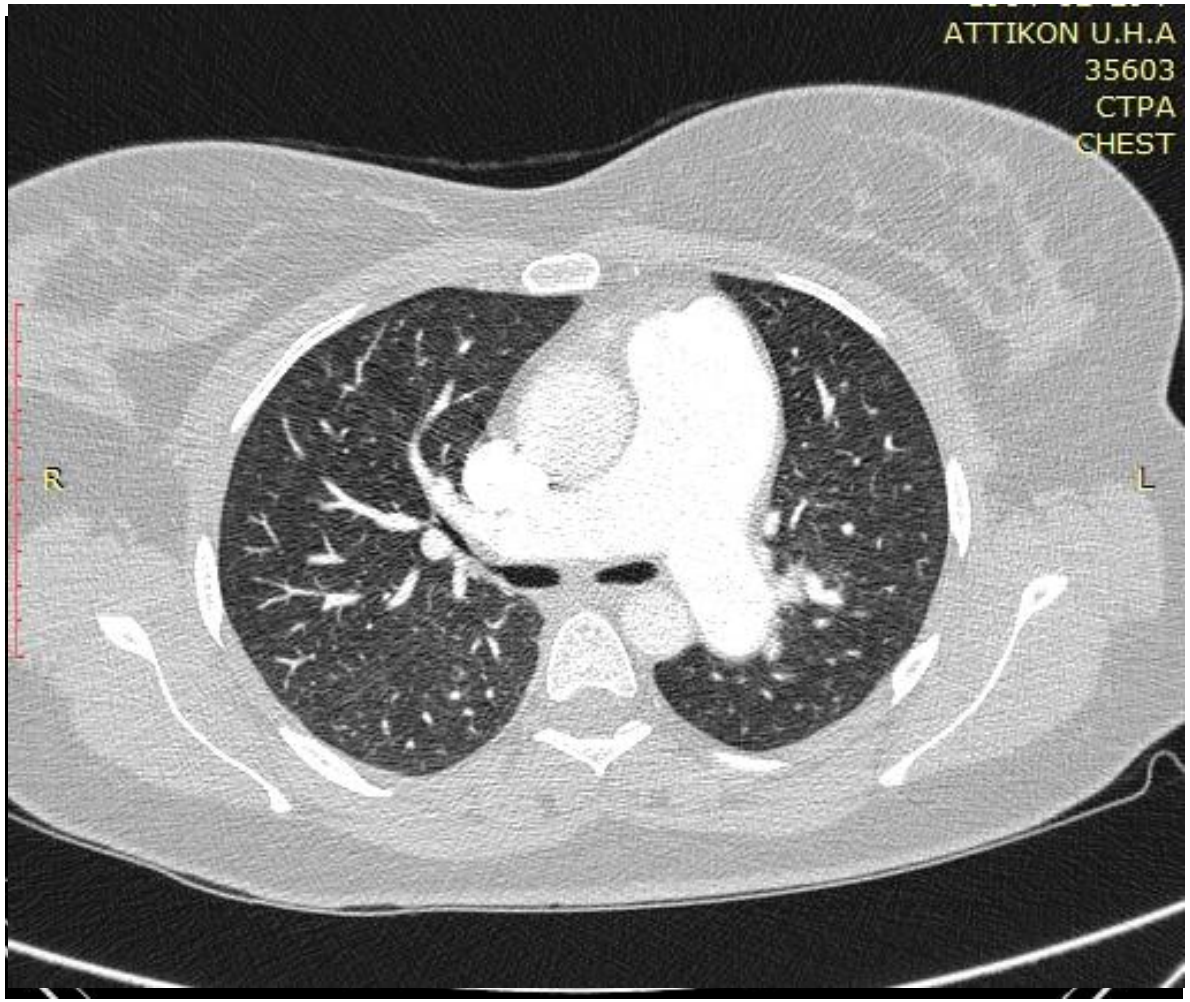
Με διάχυτη υποκινησία

D-shape LV



Διερεύνηση

PFT's εφο
DLCO 72 %
pro BNP 182 pg/ml



Χωρίς ιδιαίτερα ευρήματα από:
Q scanning πνευμόνων
Απλό εργαστηριακό ανοσολογικό, θυρεοειδικό
HIV (-)

Διερεύνηση

RHC 1

RHC -1		Results
RAP	(mmHg)	5
PAP	(mmHg)	74/42/53
PAWP	(mmHg)	10
CO	(l/min)	3.3
CI	(l/min/m²)	1.9
PVR	(Wood Units)	13
SvO2	(%)	78

Test αγγειοδραστικότητας (-)
(iv epoprostenol- 12ng/kg/min)

Clinical classification of Pulmonary Hypertension (ESC/ERS guidelines 2015)

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

Table 7 Updated risk level of drugs and toxins known to induce pulmonary arterial hypertension

Definite	Likely	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex • Selective serotonin reuptake inhibitors[a]	• Amphetamines • Dasatinib • L-tryptophan • Methamphetamines	• Cocaine • Phenylpropanolamine • St John's Wort • Amphetamine-like drugs • Interferon α and β • Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[b]

[a]Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors.
[b]Alkylating agents are possible causes of pulmonary veno-occlusive disease.

PH guidelines 2015

Θεραπεία

Measure/ treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C	247
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C	-
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C	246
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C	198, 245
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C	-
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C	-

1. Διακοπή
Interferone-b

Αντικατάσταση με γκλατιραμέρη(copaxone)

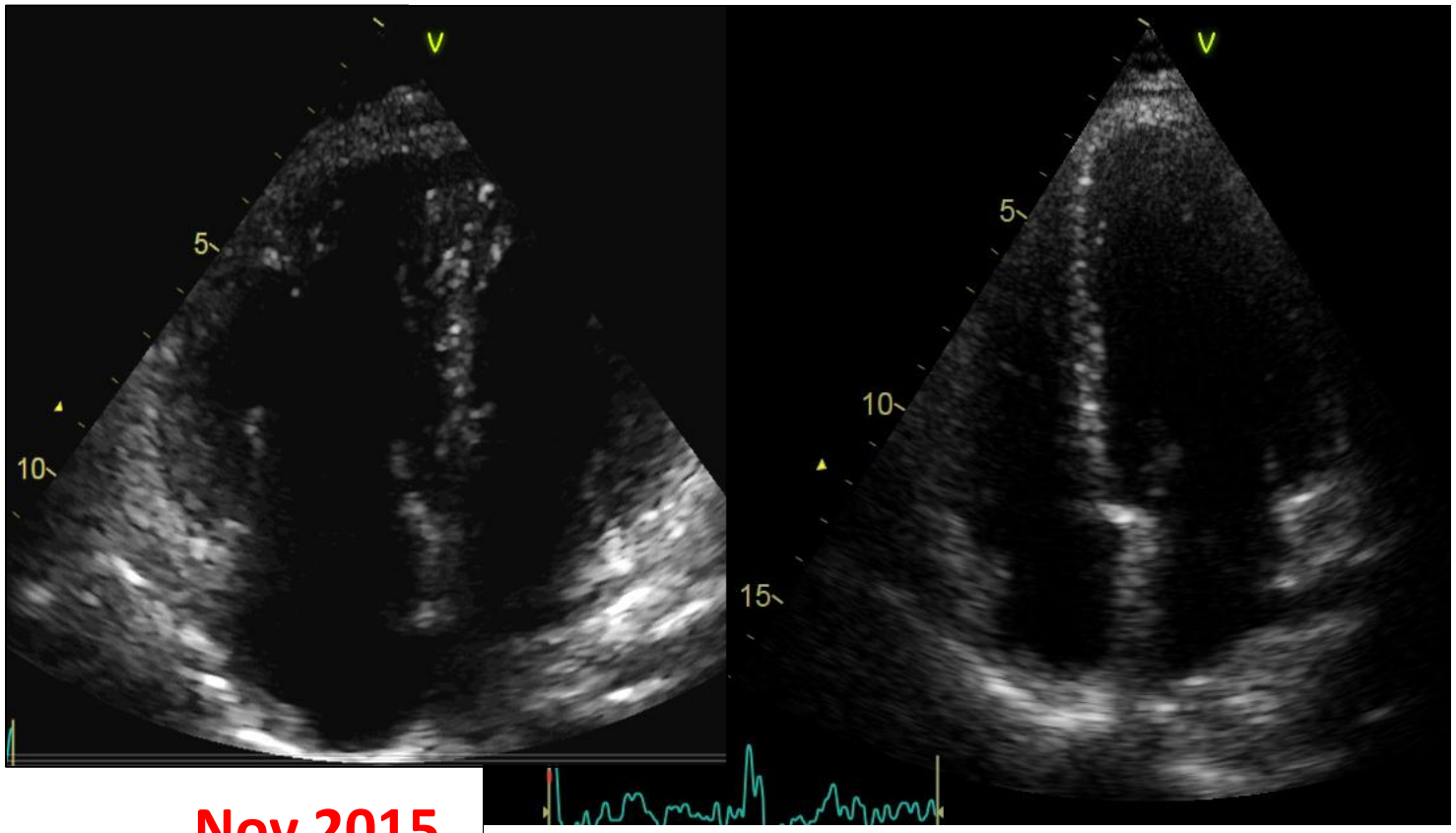
2. 3m
Ambrisentan 10mg
+
Tadalafil 40mg

Recommendations for *efficacy* of initial drug combination therapy for PAH (group 1) according to WHO FC

Παρακολούθηση- Follow up

PARAMETERS		Nov 2015	Sep 2016	Feb 2017
NYHA		III	II	II early
6MWT		312	510	536
nT-pro BNP	(pg/ml)	184		32
TTECHO				
TRVmax	(m/s)	4.9	3.6	2.8
RVSP	(mmHg)	95	60	35-40
TAPSE	(mm)	16	21	20
RHC				
RAP	(mmHg)	5	6	
PAP (S/D/m)	(mmHg)	74/42/53	49/21/30	
PAWP	(mmHg)	10	7	
CO	(l/min)	3.3	6.5	
CI	(l/min/m²)	1.9	3.8	
PVR	WU	13 →	3.5	
SVO2	(%)	78	82	

Παρακολούθηση- Follow up

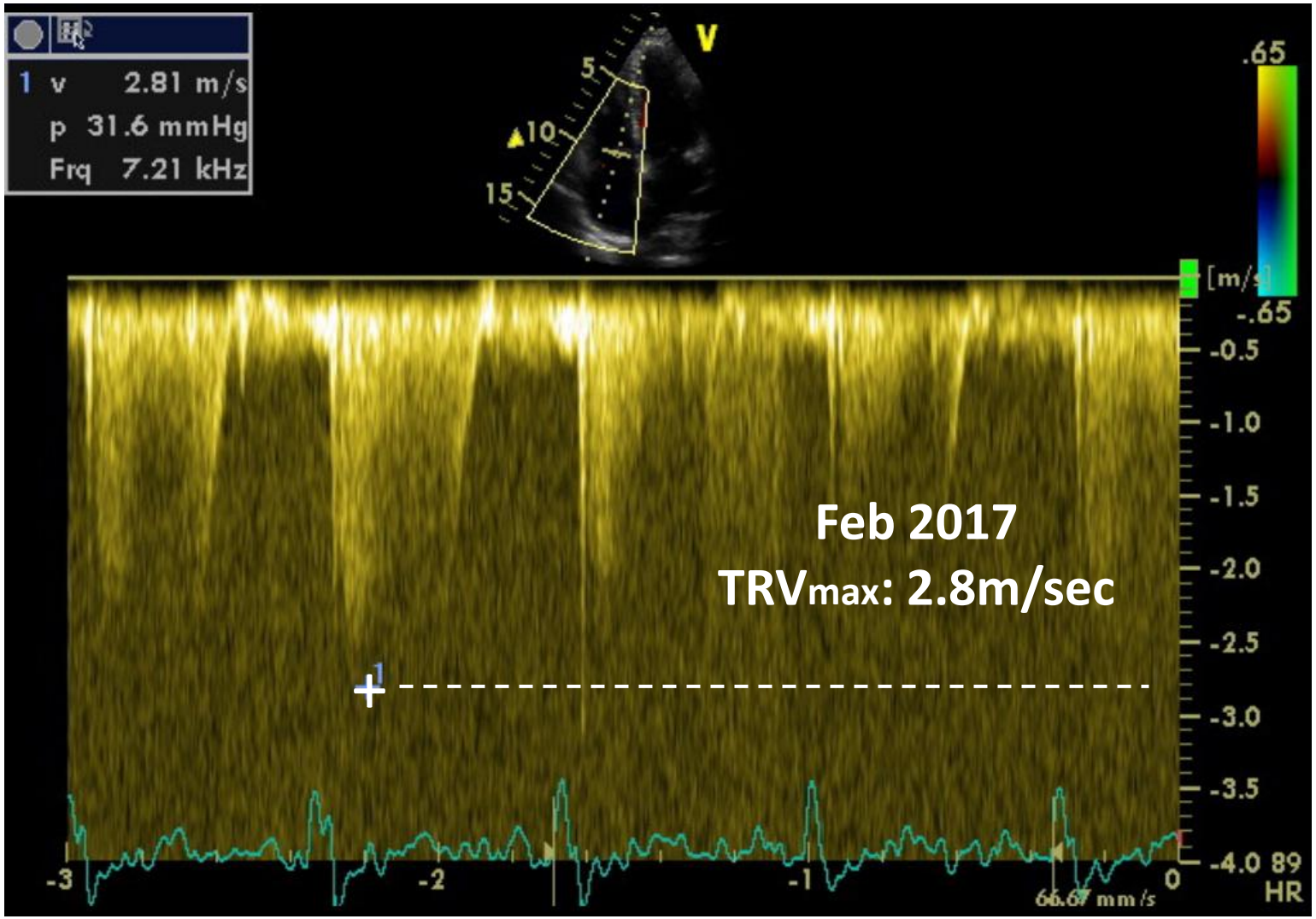


Nov 2015

Feb 2017

BYLYRE13FEB24.wmv

Παρακολούθηση- Follow up



Risk assessment 2

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent *	Absent	Present
Progression of symptoms	No *	Slow	Rapid
Syncope	No *	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II *	III	IV
6MWD	>440 m *	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l * NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 * No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 * SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%