Πνευμονική υπέρταση: Νεότερα Δεδομένα για τη διάγνωση και Διαγνωστικά εργαλεία

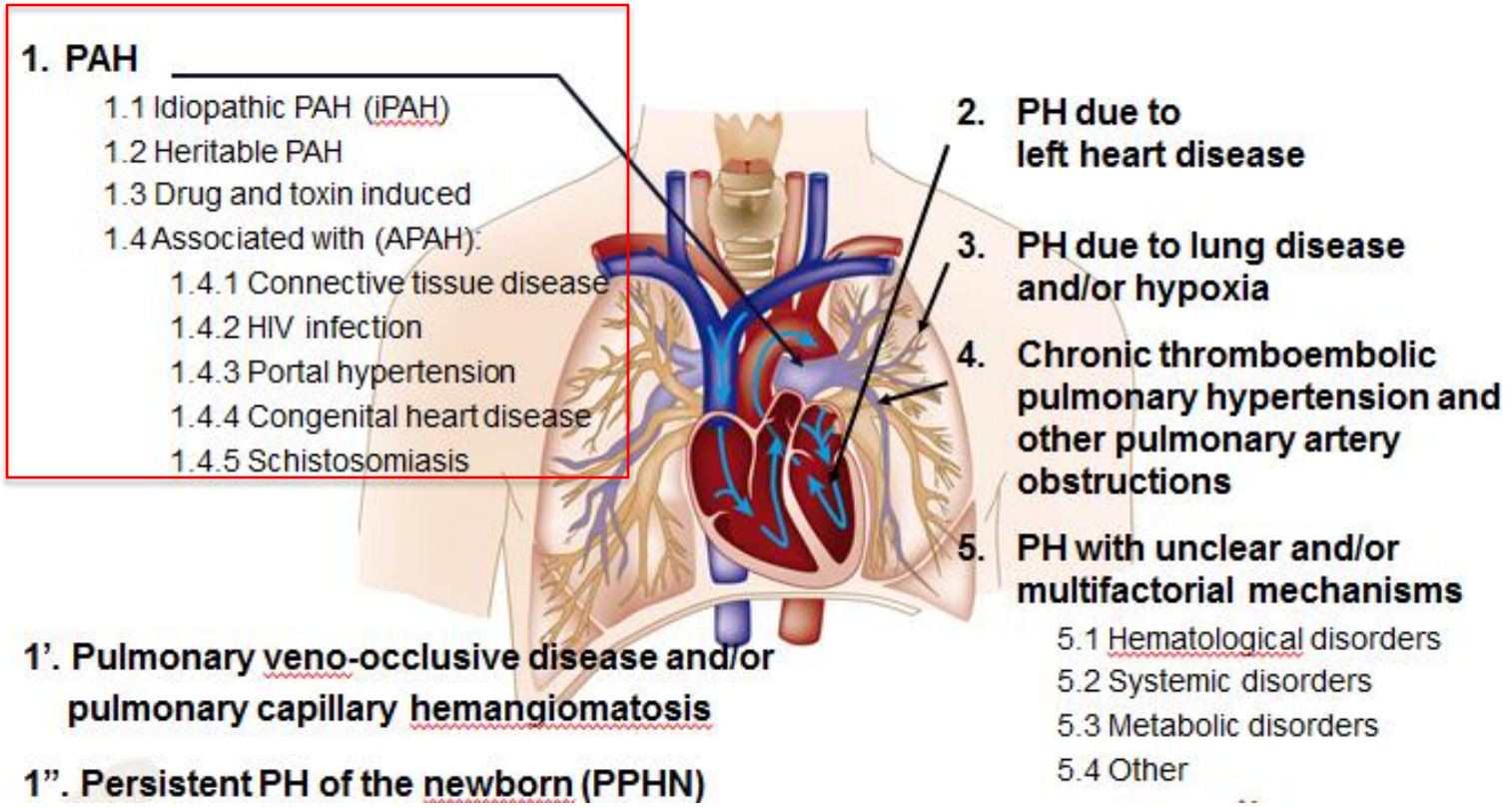
Γεωργία Γ. Πίτσιου
Αναπληρώτρια Καθηγήτρια Πνευμονολογίας
Κλινική Αναπνευστικής Ανεπάρκειας ΑΠΘ
Γ.Ν.Θ. "Γ.Παπανικολάου"

Conflicts of interest

The speaker has received

Honoraria and/or research grants from Actelion, Bayer, ELPEN, Galenica, GSK, Pfizer and MSD.

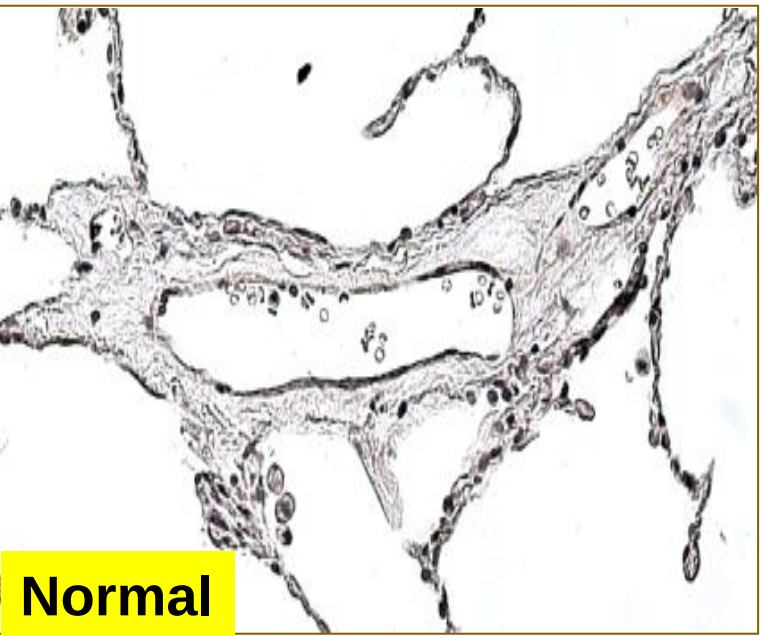
Classification of PH in five groups (ESC/ERS 2015)

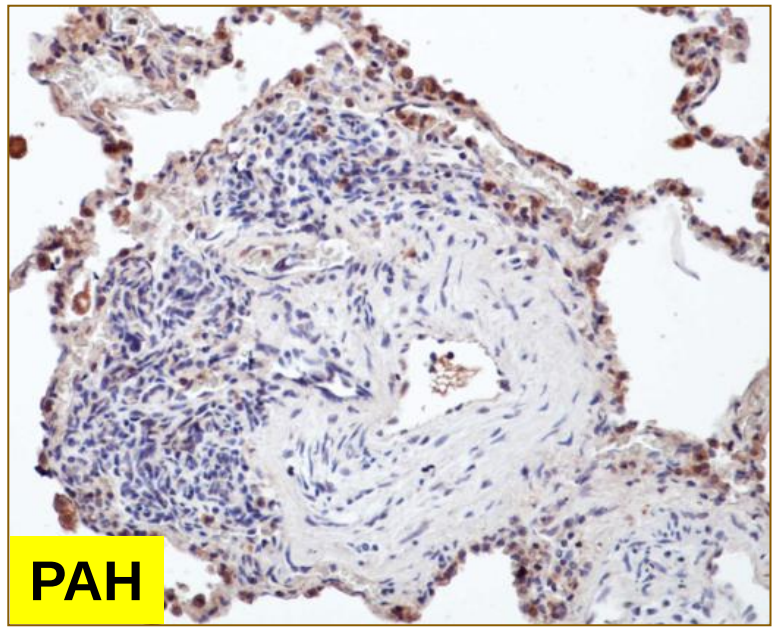


Galiè N, et al Eur Heart J 2016

Pulmonary Arterial Hypertension : a severe pulmonary vascular disease

- ***Definition*** **: chronic precapillary pulmonary hypertension**
- ***Cause*** **: progressive structural remodeling of the small pulmonary arteries**
- ***Consequence*** **: right heart failure and death**





Delay in diagnosis of PAH has not substantially changed over the two decades

Clinical Review & Education

JAMA Cardiology | Review

Diagnosis, Treatment, and Clinical Management of Pulmonary Arterial Hypertension in the Contemporary Era
A Review

Bradley A. Maron, MD; Nazzareno Galiè, MD

IMPORTANCE Pulmonary arterial hypertension (PAH) is characterized by severe remodeling of the distal pulmonary arteries, increased pulmonary vascular resistance, and right ventricular dysfunction that promotes heart failure. Once regarded as largely untreatable, evidence-based decision making now guides clinical management of PAH and improves outcomes. However, misconceptions regarding the approach to PAH in the modern era are common and associated with substandard clinical care.

OBSERVATIONS The clinical profile of PAH has changed substantially since its original description. Patients are older at diagnosis than previously reported; disease severity appears greater in men compared with women; and patients with PAH in association with connective tissue disease are identified as a particularly high-risk subgroup. Risk stratification scales for PAH are now available at point of care, which inform treatment goals, including a 6-minute walk distance of greater than 440 m, peak volume of oxygen consumption of greater than 15 mL/min/kg, right atrial area of less than 18 cm^2, cardiac index of greater than 2.5 L/min/m^2, and absent or low symptom burden with routine physical activity. At present, 14 therapies targeting 6 PAH-specific molecular intermediaries are used clinically. Recent landmark trial data have demonstrated the critical importance of initial combination therapy in treatment-naive patients. These findings underscore a global shift in PAH that couples early disease detection with aggressive pharmacotherapy. Indeed, recent longitudinal data from patients receiving combination therapy show that the 3-year survival rate in PAH may be as high as 84% compared with 48% from the original National Institutes of Health registry on idiopathic PAH (1980-1985). Despite these gains, incomplete clinical evaluation and misdiagnosis by referring clinicians is common and associated with inappropriate therapy.

CONCLUSIONS AND RELEVANCE Compared with the original clinical experience, PAH has evolved into a contemporary and treatable disease characterized by improved survival and a high standard for defining therapeutic success. However, underawareness among clinicians regarding the importance of early and accurate PAH diagnosis persists and is a potentially reversible cause of adverse outcome in this disease.

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Published online November 16, 2016.

Author Audio Interview
Related article
Supplemental content

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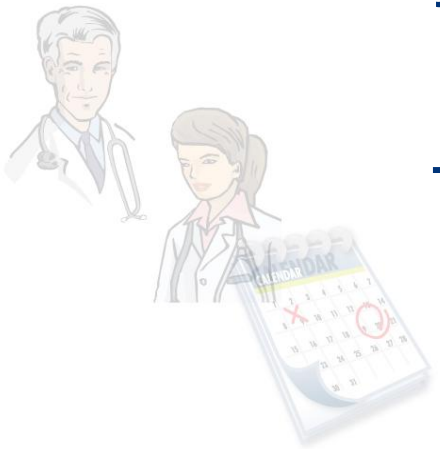
Corresponding Author: Bradley A. Maron, MD, Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 77 Avenue Louis Pasteur, New Research Bldg, Room 0630-O, Boston, MA 02115 (bmaron@partners.org).

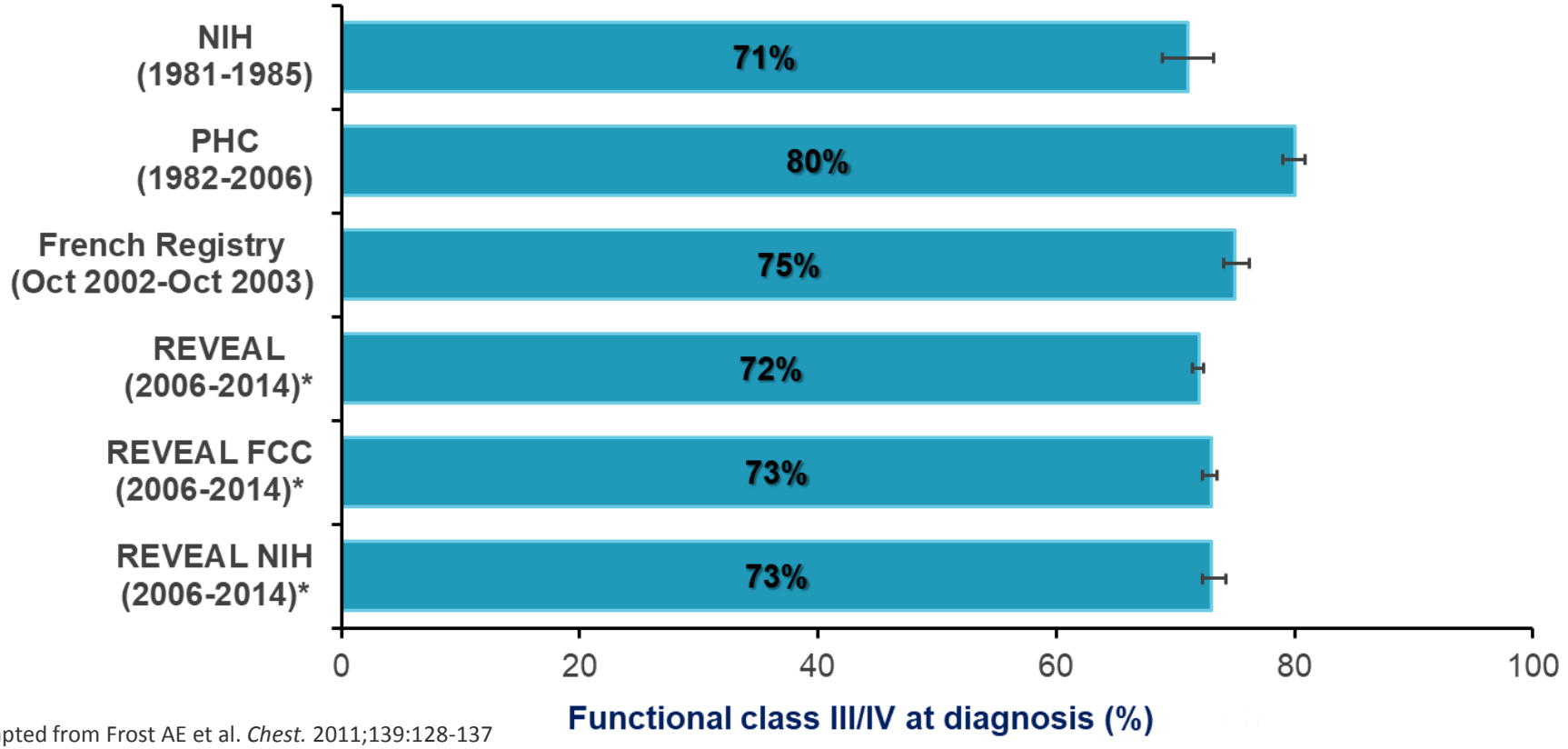


Delay from onset of symptoms to diagnosis

Two years on average

Delayed diagnosis of pulmonary hypertension is common and reported in as many as 85% of at-risk patients.

Registry data suggest PAH is often advanced when diagnosed



Adapted from Frost AE et al. *Chest.* 2011;139:128-137

*REVEAL enrollment was completed in December 2009, with all patients followed for 5 years.
REVEAL was funded and sponsored by Actelion Pharmaceuticals US, Inc.
NIH: National Institutes of Health; PAH: pulmonary arterial hypertension; PHC: Pulmonary Hypertension Connection; REVEAL: Registry to EValuate Early And Long-term PAH Disease Management; REVEAL FCCRegistry to EValuate Early And Long-term PAH Disease Manage

PAH diagnosis is typically delayed and has a negative impact on patients' long-term outcomes

Delays in diagnosis of over 1 year have been reported in almost half of PAH patients

- non specific symptoms
- low level of suspicion in everyday clinical practice

- Delays in diagnosis adversely affect long term outcomes and can result in patients feeling distressed and frustrated

Table 2 Time to diagnosis after experiencing symptoms

	Proportion of patients, n (%)					
	< 3 months	3–6 months	6–12 months	1–2 years	2–3 years	3+ years
Time between noticing symptoms and going to see a doctor (n = 542)	161 (30)	128 (24)	97 (18)	68 (13)	29 (5)	59 (11)
Time between seeing general practitioner with symptoms and referral to hospital (n = 378)	139 (37)	87 (23)	58 (15)	40 (11)	18 (5)	35 (9)
Time before referral from local hospital to specialist pulmonary hypertension centre (n = 426[a])	160 (38)	90 (21)	65 (15)	37 (9)	20 (5)	29 (7)
Time from first noticing symptoms to diagnosis with pulmonary hypertension (n = 545)	78 (14)	99 (18)	107 (20)	85 (16)	65 (12)	111 (20)

[a]Of these patients 25 (6%) were not referred

Armstrong I et al. BMC Pulm Med 2019

The disease is characterized by a pre- symptomatic phase

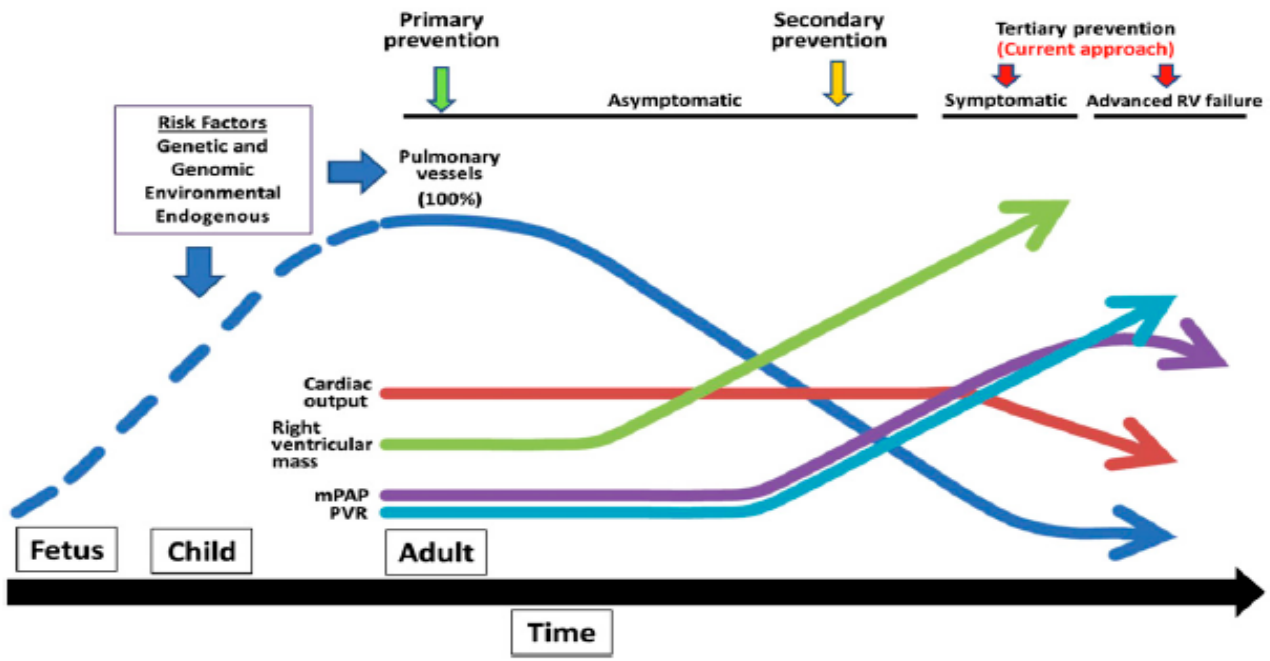
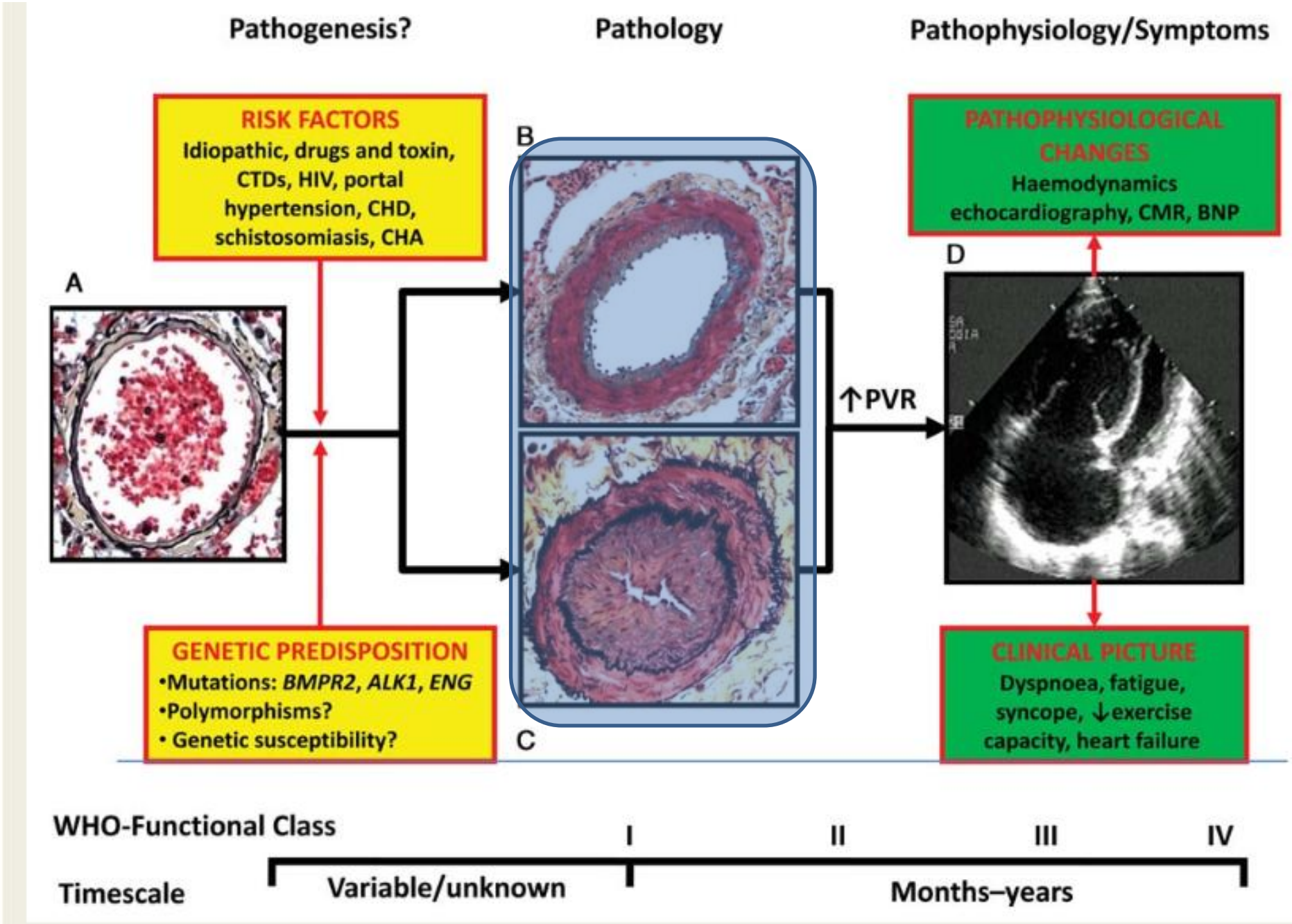


Figure 1. Due to the tremendous reserve of the pulmonary vasculature, resting pulmonary arterial hypertension (PAH) and symptoms occur long after the initial inciting events trigger pulmonary vascular dysfunction (PVD). Multiple known risk factors exist that can prompt the loss of normal pulmonary vessel function *in utero* and beyond. Risk factors are variable, including: (*1*) genetic (e.g., bone morphogenetic protein receptor type 2 [*BMPR2*] gene mutations and sickle cell lung disease); (*2*) environmental (e.g., dietary stimulants); and (*3*) endogenous (e.g., premature lung disease and portal hypertension). Resting pulmonary hypertension (PH) only occurs after an enormous proportion of the pulmonary vascular bed is lost, causing a rise in mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR). By the time a diagnosis of PH is made, PVD is far advanced. Ultimately, advanced right ventricular (RV) failure will occur. Primary prevention efforts must focus upon the detection and prevention of PVD, before the onset of PH.

Ann Am Thorac Soc Vol 11, Supplement 3, pp S178–S185, Apr 2014

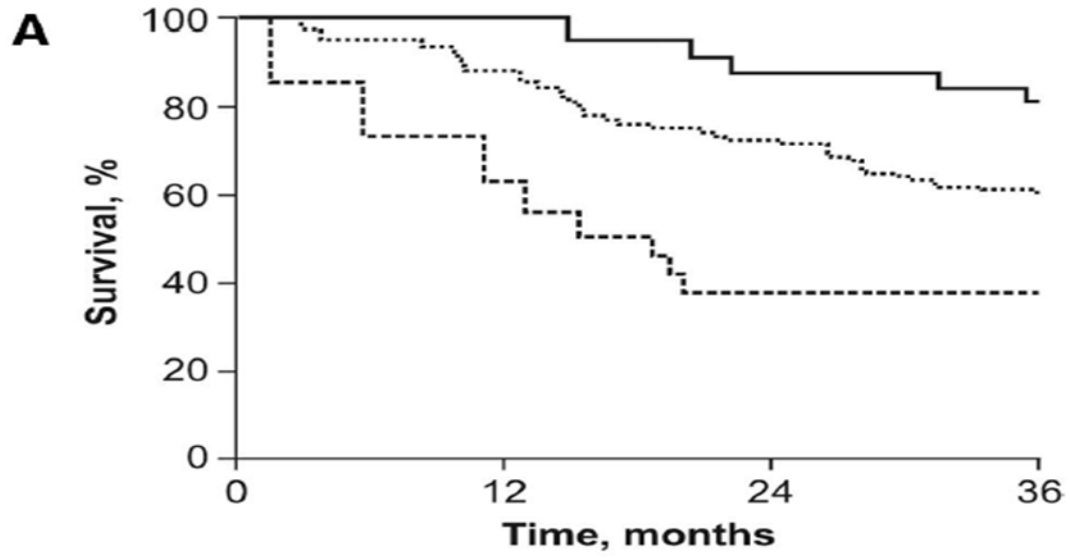
DOI: 10.1513/AnnalsATS.201312-443LD



Galie N et al. Eur Heart j 2010

Why is early treatment needed?

Survival depends on NYHA FC at diagnosis



PAH patients in (WHO-FC) I/II had significantly better long-term survival than those patients in WHO-FC III/IV

A, Kaplan-Meier estimates of survival among the combined population of patients with idiopathic, familial, and anorexigen-associated PAH stratified according to baseline NYHA FC.

Humbert M et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010

Phenotyping PH

Registries: The Changing Phenotype of PAH

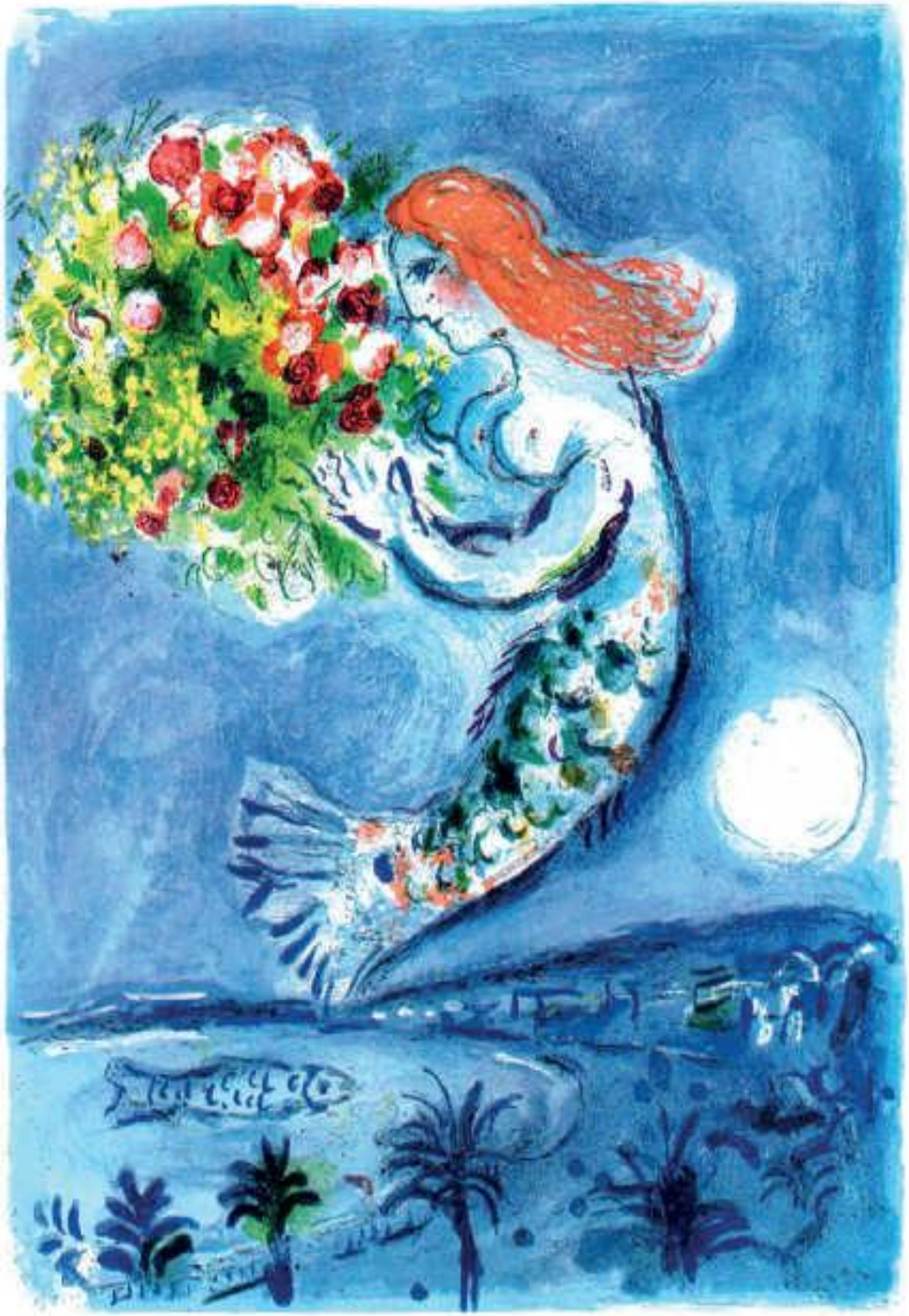
- Elderly patients, mean age at diagnosis 50-65 years
- Comorbidities
- Female predominance is quite variable

Table 1 General Information of PAH Registries From Different Countries and Time Periods

Registry (Ref. #)	Study Cohort	Study Design and Time Period	No. of Centers	No. of Patients	Incidence/Prevalence	Predominant Etiologies of PAH
U.S. NIH (17,18)	IPAH	Prospective, 1981–1985	32	187	NA	NA
U.S. PHC (19)	Group 1 PH, age >18 yrs	Retrospective, 1982–2004; prospective, 2004–2006	3	578	NA	IPAH, 48%; CTD-PAH, 30%; CHD-PAH, 11%
Scottish-SMR (20)	Group 1 PH (IPAH, CHD-PAH, and CTD-PAH), age 16–65 yrs	Retrospective, 1986–2001	NA	374	PAH, 7.6/26 cases/MAI; IPAH, 2.6/9 cases/MAI	IPAH, 47%; CTD-PAH, 30%; CHD-PAH, 23%
French (9,21,22)	Group 1 PH, age >18 yrs	Prospective, 2002–2003	17	674	PAH, 2.4/15 cases/MAI; IPAH, 1.0/5.9 cases/MAI	IPAH, 39%; CTD-PAH, 15% (SSc, 76%); CHD-PAH, 11%
Chinese (23)	IPAH and HPAH	Prospective, 1999–2004	1	72	NA	NA
U.S. REVEAL (8,24–33)	Group 1 PH	Prospective, 2006–2009	55	3,515 (age >3 months)	PAH, 2.0/10.6 cases/MAI IPAH, 0.9 cases/MAI	IPAH, 46%; CTD-PAH, 25% (SSc, 62%); CHD-PAH, 10%
Spanish (34)	Group 1 PH and CTEPH, age >14 yrs	Retrospective, 1998–2006; prospective, 2007–2008	31	PAH, 866; CTEPH, 162	PAH, 3.2/16 cases/MAI; IPAH, 1.2/4.6 cases/MAI	IPAH, 30%; CTD-PAH, 15% (SSc 61%); CHD-PAH, 16%
UK (6,35)	IPAH, HPAH, and anorexigen-associated PAH	Prospective, 2001–2009	8	482	1.1/6.6 cases/MI	NA
New Chinese Registry (36,37)	Group 1 PH, age >18 yrs	Prospective, 2008–2011	9	956	NA	CHD-PAH, 43%; IPAH, 35%; CTD-PAH, 19% (SLE, 51%; SSc, 9%)
Mayo (38)	Group 1 PH	Prospective, 1995–2004	1	484	NA	IPAH, HPAH 56%; CTD-PAH, 24%, other, 20%
Compera (39)	IPAH, age >18 yrs	Prospective, 2007–2011	28	587	NA	IPAH, 100%

CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; MAI = million adult inhabitants; MI = million inhabitants; NA = not available; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PHC = pulmonary hypertension connection; SMR = Scottish morbidity record; SSc = systemic sclerosis.

McGoon et al. JACC 2013



6TH

WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

Nice
February 27-28 / March 1, 2018

Redefining PH and pre-capillary PH

Nice proceedings 2018

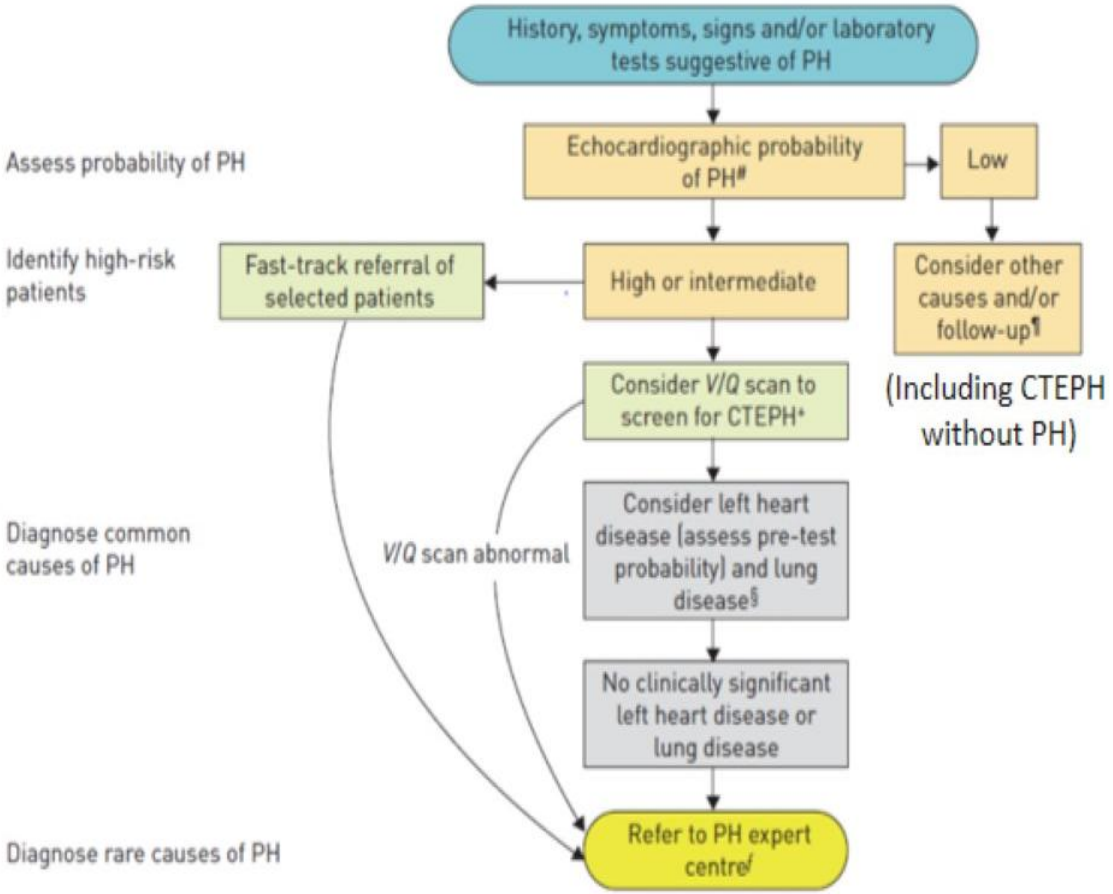
TABLE 1 Haemodynamic definitions of pulmonary hypertension (PH)

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

Effort to identify early Pulmonary Vascular Disease (PVD)

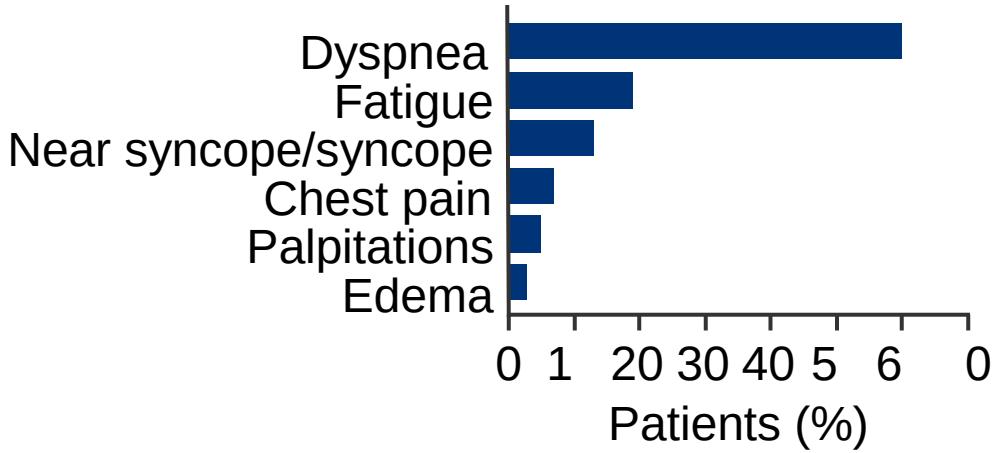
Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2018

Algorithm for Diagnosing PH



TTE remains the most important non-invasive screening tool and RHC remains mandatory to establish the diagnosis

The symptoms are non-specific, leading to a great delay in diagnosis



Median Time From Symptom Onset to Diagnosis

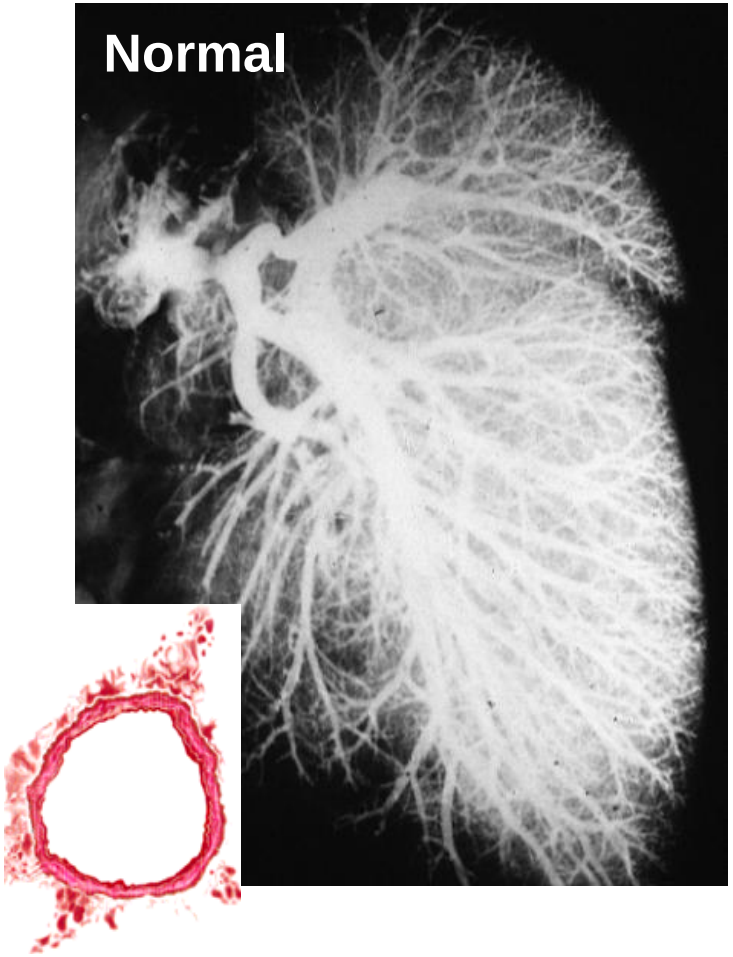
NIH Registry (1981 to 1985)	**1.3 years**
REVEAL Registry (2006 to 2007)	**1.1 years**

Rich A et al. *Ann Intern Med*. 1987;107:216-223.
Badesch DB et al. *Chest.* 2010;137:376-387.

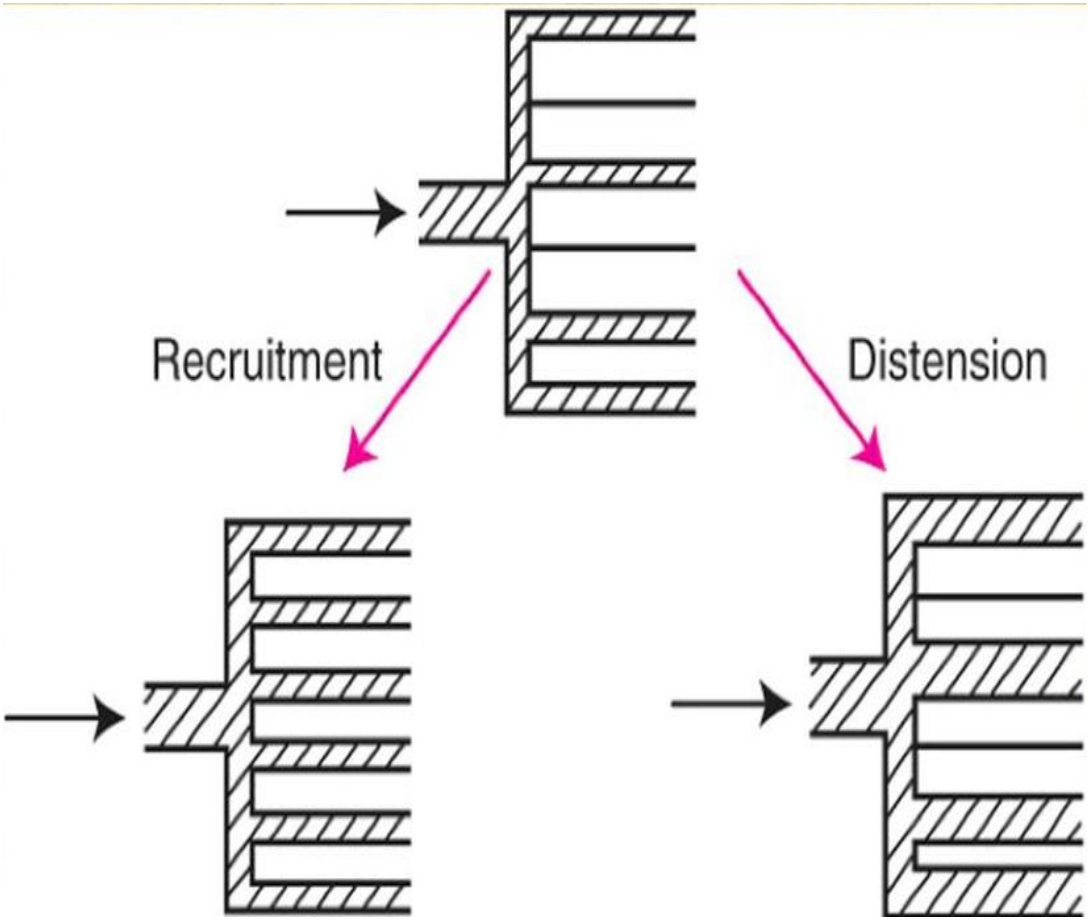
Pulmonary arterial hypertension (PAH)

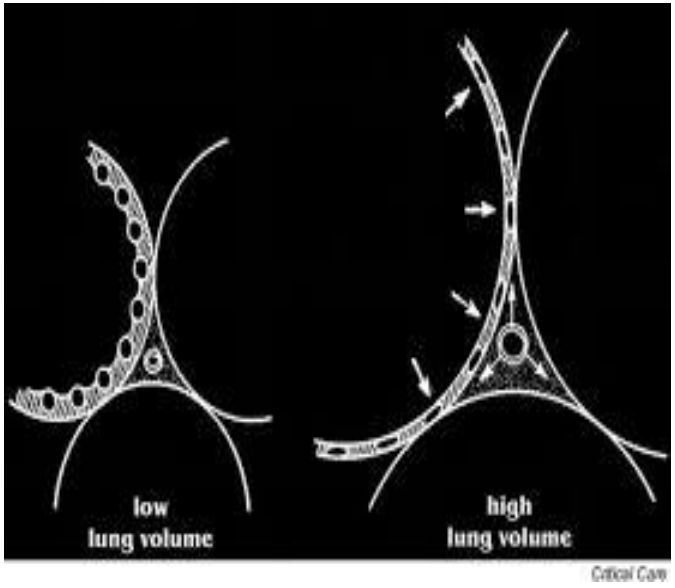
Pathophysiology

Increased resistance (impedance) to flow



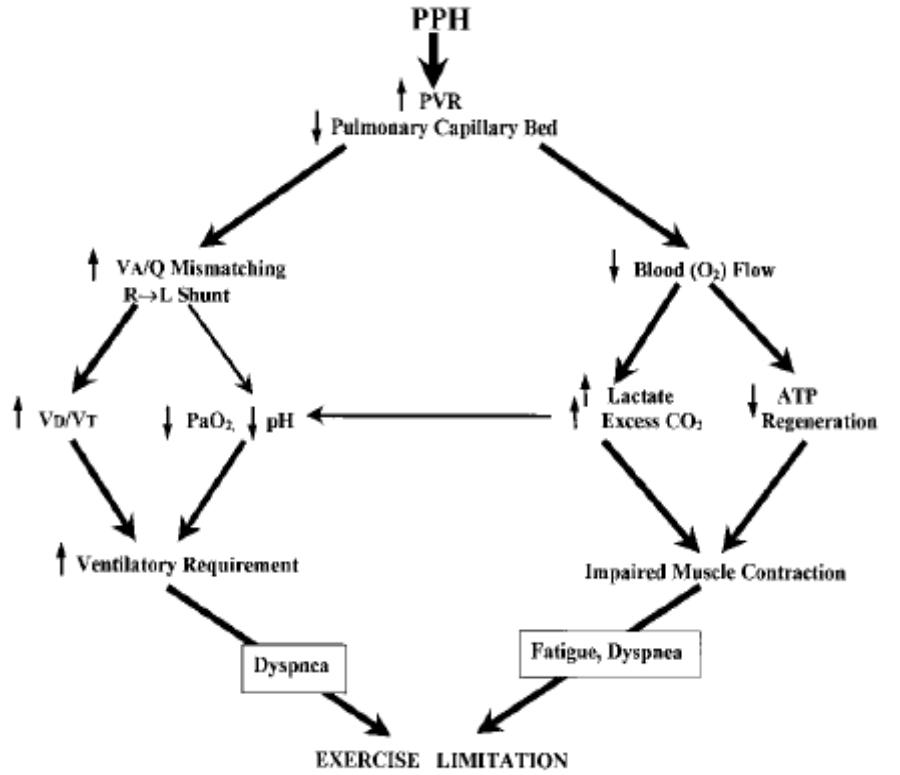
Capillary recruitment and Vascular distention





During exercise a healthy subject can increase cardiac output 4-5 times while MPAP increases 2-3 times normal - almost doubles the resting lung capillary blood volume

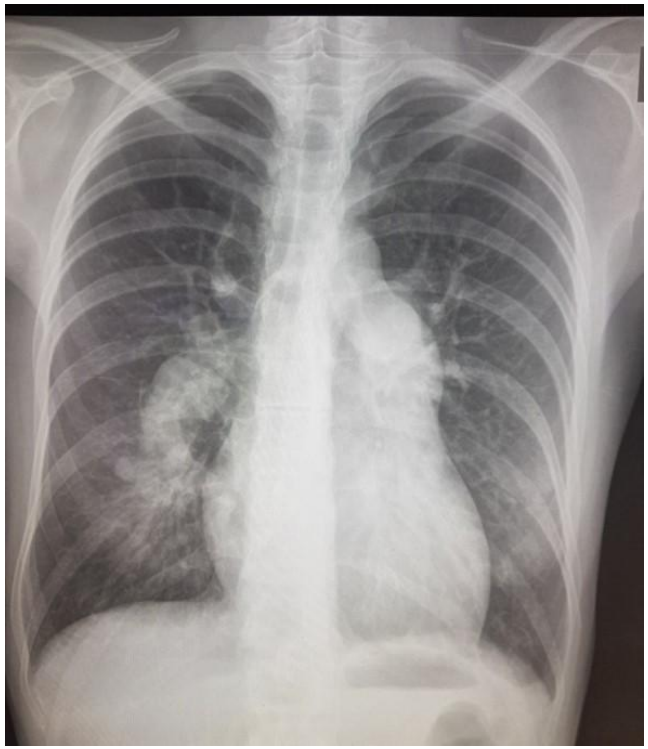
Exercise pathophysiology in PAH



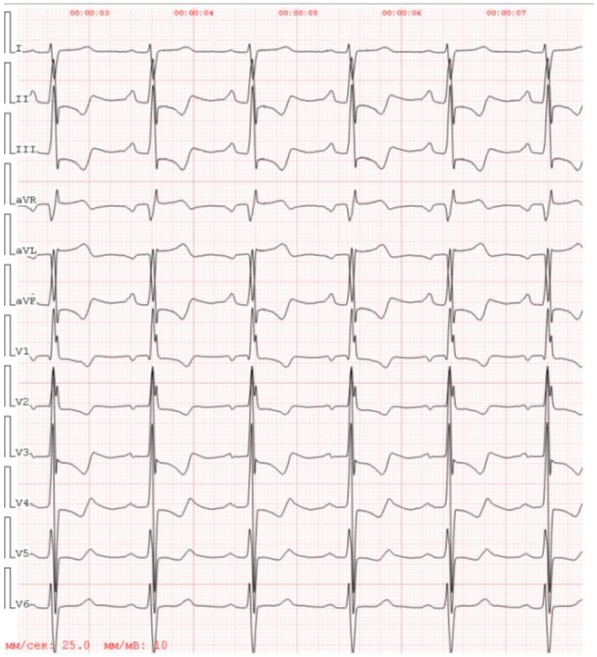
- Inefficient pulmonary vascular bed recruitment:

  increase of “functional” dead space ventilation (VD/Vt)
- Failure of cardiac output to increase: inadequate oxygen transport, lactic acidosis
- Hypoxemia
- Respiratory muscle impairment

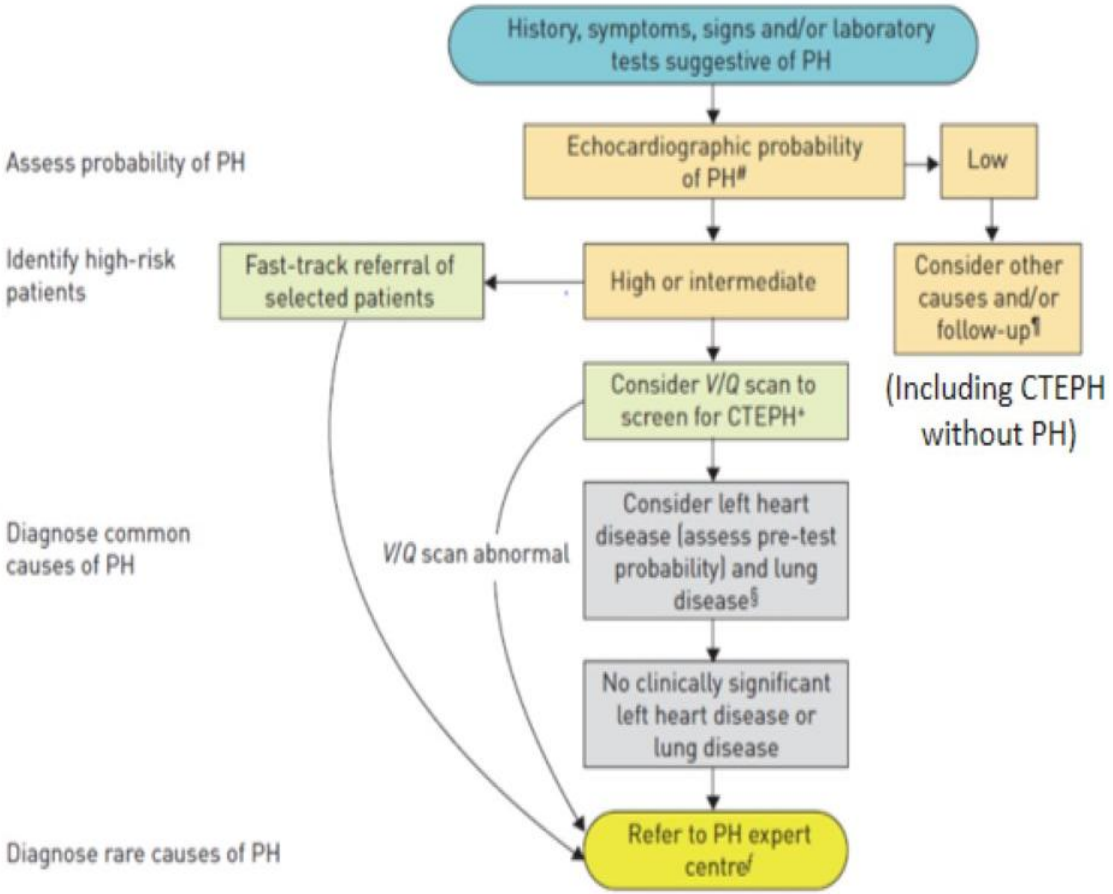
Sun XG et al.Circulation 2001, Paolillo et al. Eur J Prev Cardiol 2011



- 42-year-old woman with dyspnea, fatigue, palpitations
- Diagnosed with “depression”…



Algorithm for Diagnosing PH



TTE remains the most important non-invasive screening tool and RHC remains mandatory to establish the diagnosis

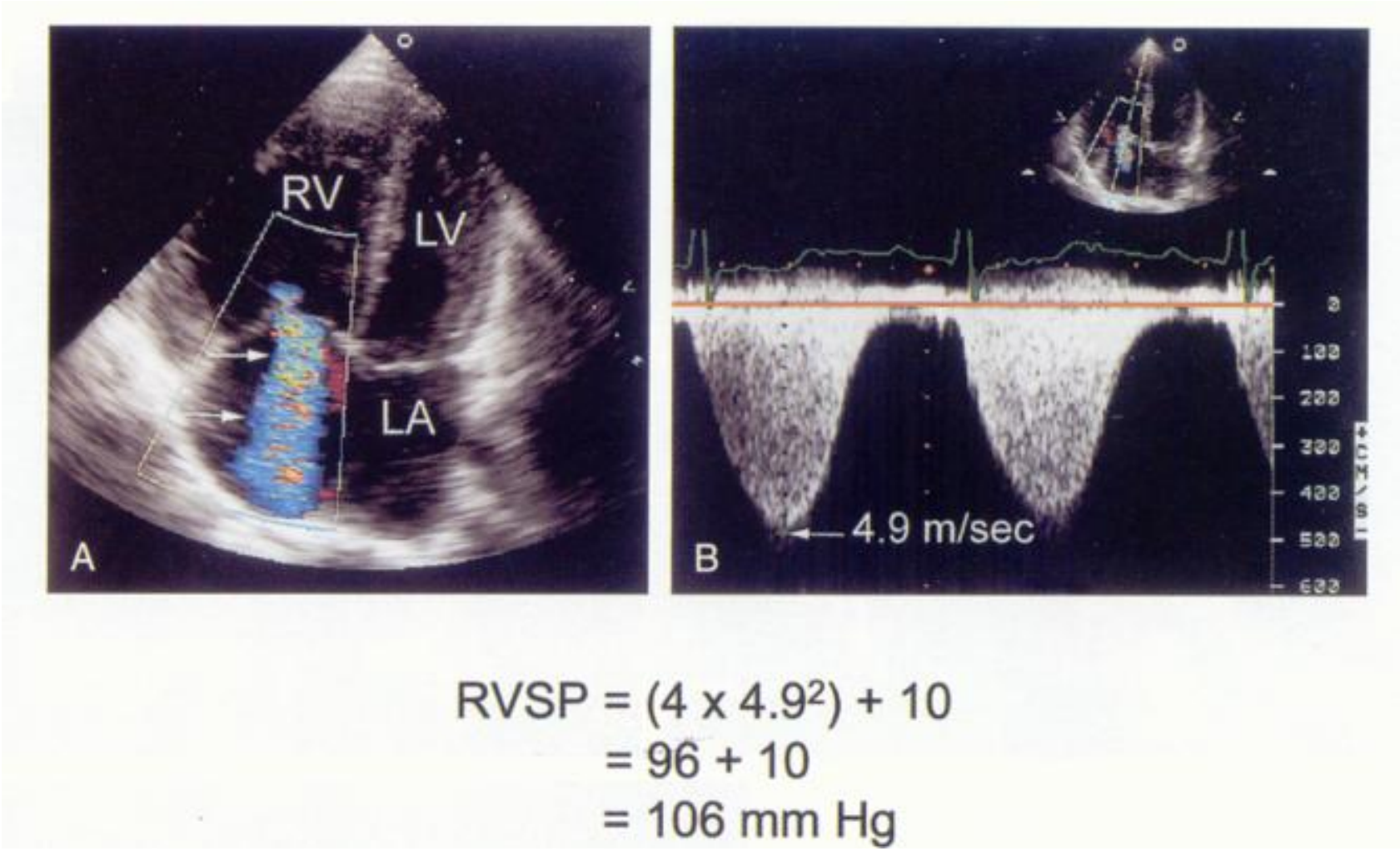
Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension according with PTRV & additional signs

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs"[a]	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	

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow 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	

EUROPEAN SOCIETY OF CARDIOLOGY

Συνεχές Doppler δια της τριγλώχινας για την εκτίμηση της συστολικής πίεσης της δεξιάς κοιλίας



$$RVSP = (4 \times 4.9^2) + 10$$
$$= 96 + 10$$
$$= 106 \text{ mm Hg}$$

$RVSP = 4xVmax^2 + RAP$

Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension according with PTRV & additional signs

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	PA diameter >25 mm.	

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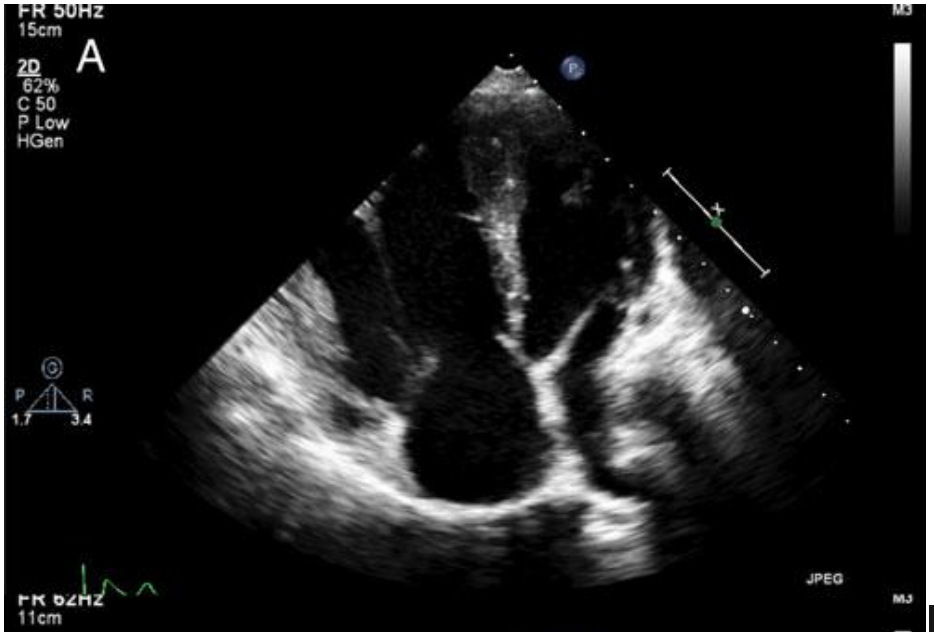
/ESC2015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15cm
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C 50
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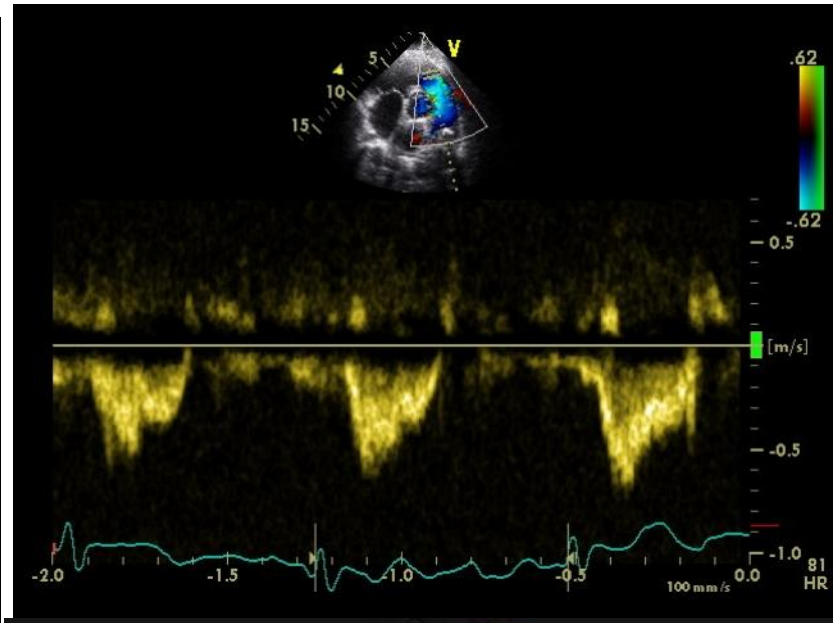
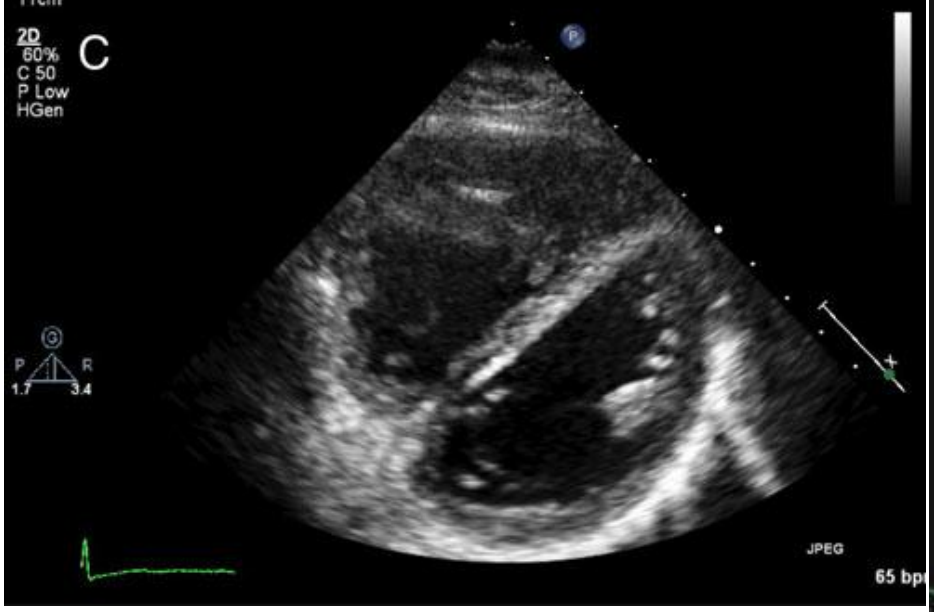
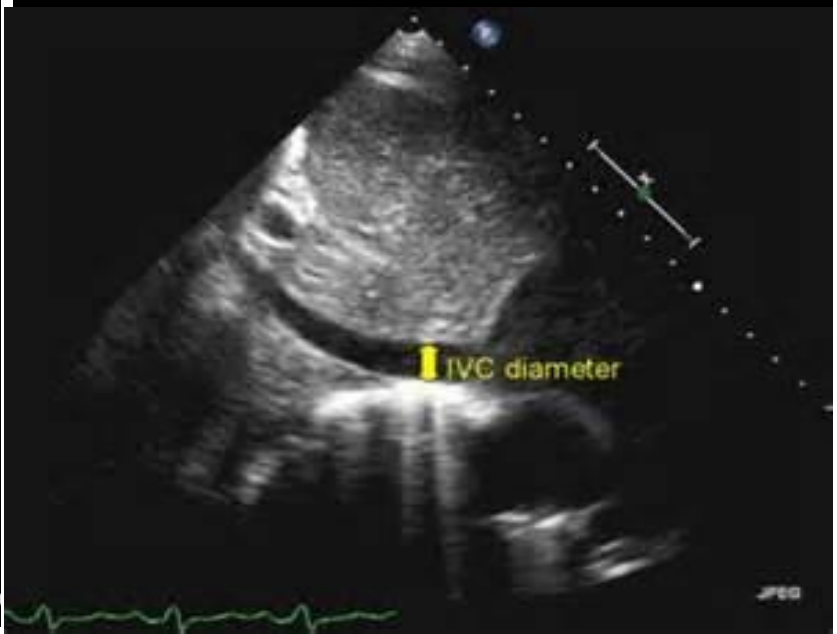
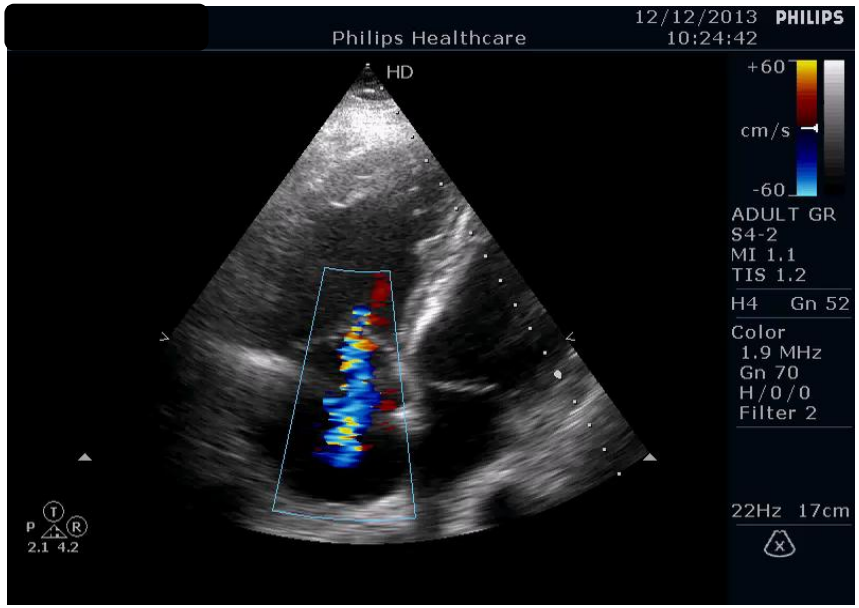
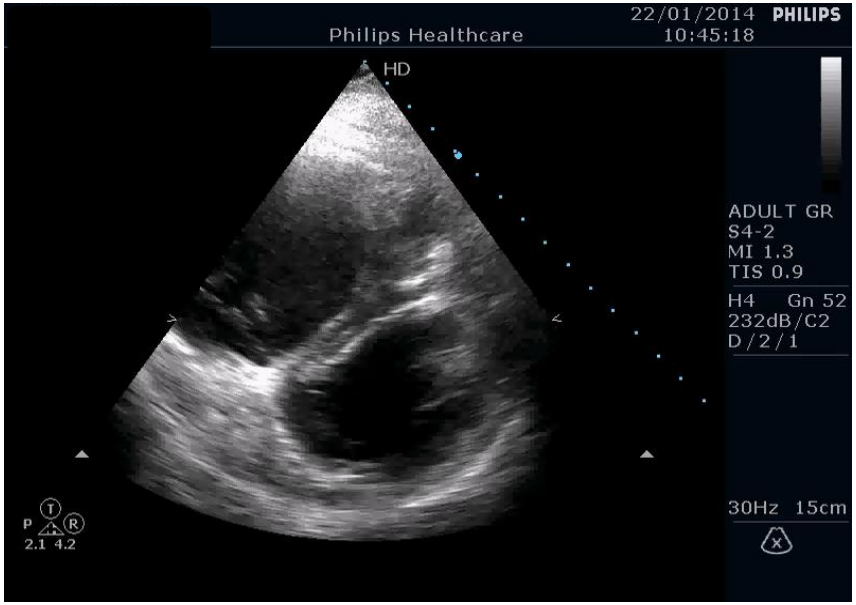

.62
-.62
0.5
[m/s]
-0.5
-1.0
-2.0
-1.5
-1.0
-0.5
0.0
100 mm/s
81
HR


11cm
2D
60%
C 50
P Low
HGen
C
JPEG
65 bp

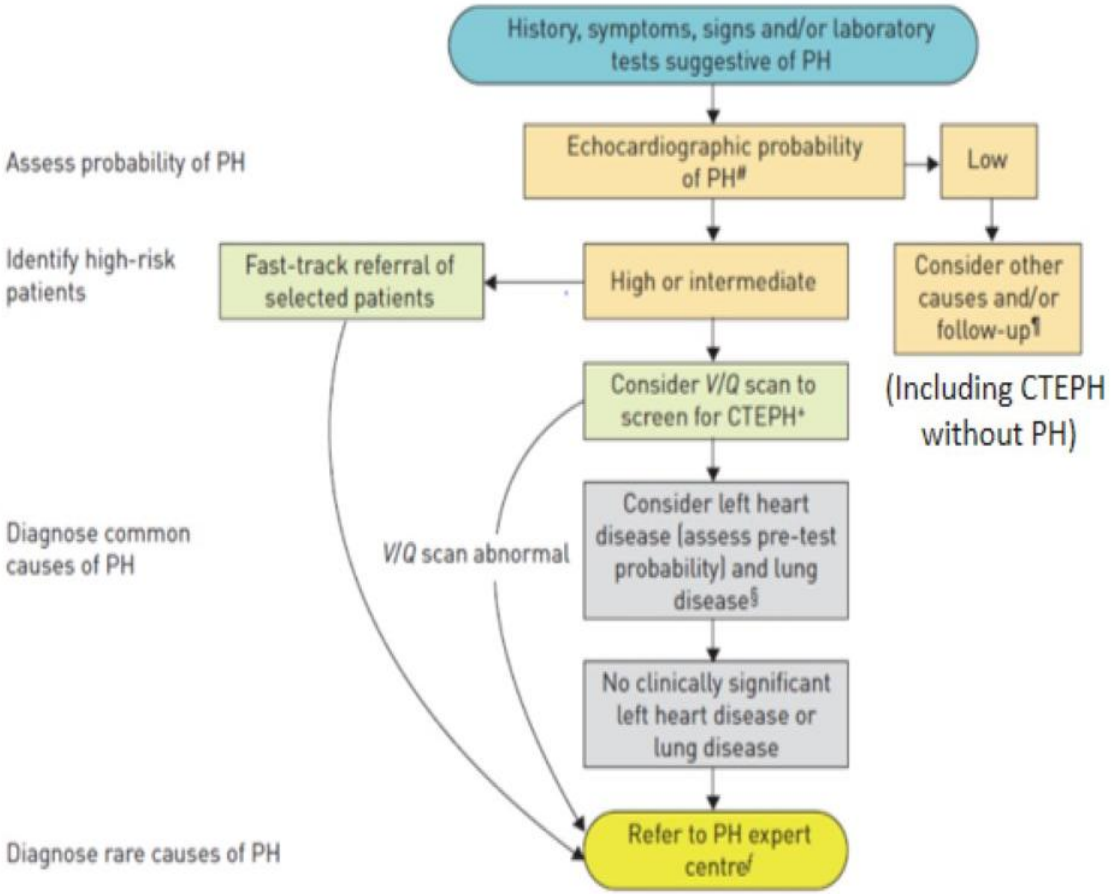

IVC diameter





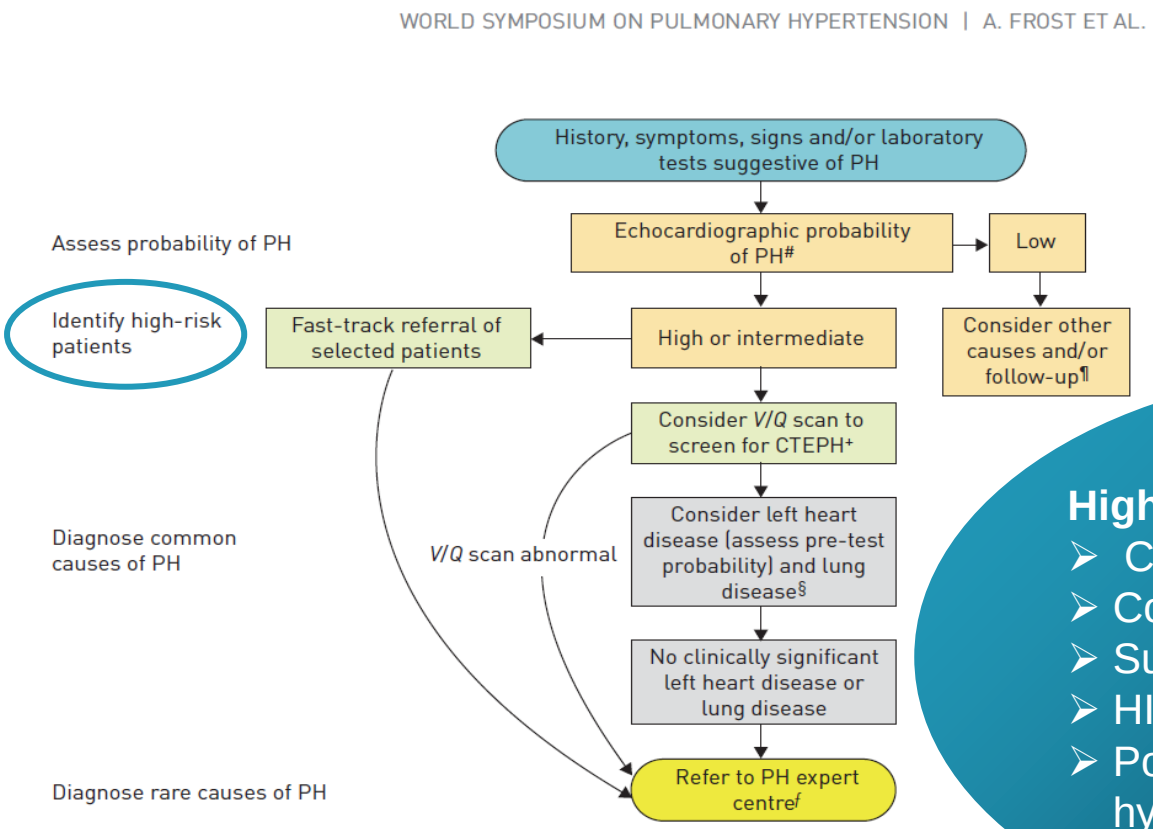
- Γυναίκα 42 ετών
- Ιστορικό ΣΣ από το 1985
- Ιστορικό δακτυλικών ελκών (Ilomedin, Adalat, τρέχουσα αγωγή Bosentan 125mg x2), χρόνιας οισοφαγίτιδα (2005), περικαρδίτιδα, θρόμβωση ιγνυακής αρτηρίας (2008)
- Παραπέμπεται από ρευματολογική κλινική: δύσπνοια στην ελάχιστη προσπάθεια
- Raynaud (+) , σκληρό οίδημα άνω-κάτω άκρων, αρχόμενη μικροστομία και περιστοματική ρυτίδωση, τρίζοντες βάσεων άμφω

Algorithm for Diagnosing PH



TTE remains the most important non-invasive screening tool and RHC remains mandatory to establish the diagnosis

Recent Nice proceedings emphasize on the need to identify high risk populations



High risk patients:

- Congenital heart disease
- Connective Tissue Disease
- Suggestive family history
- HIV and
- Portopulmonary hypertension(POPH)

Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. Eur Respir J 2018

Systemic Sclerosis-associated PAH

Risk factors

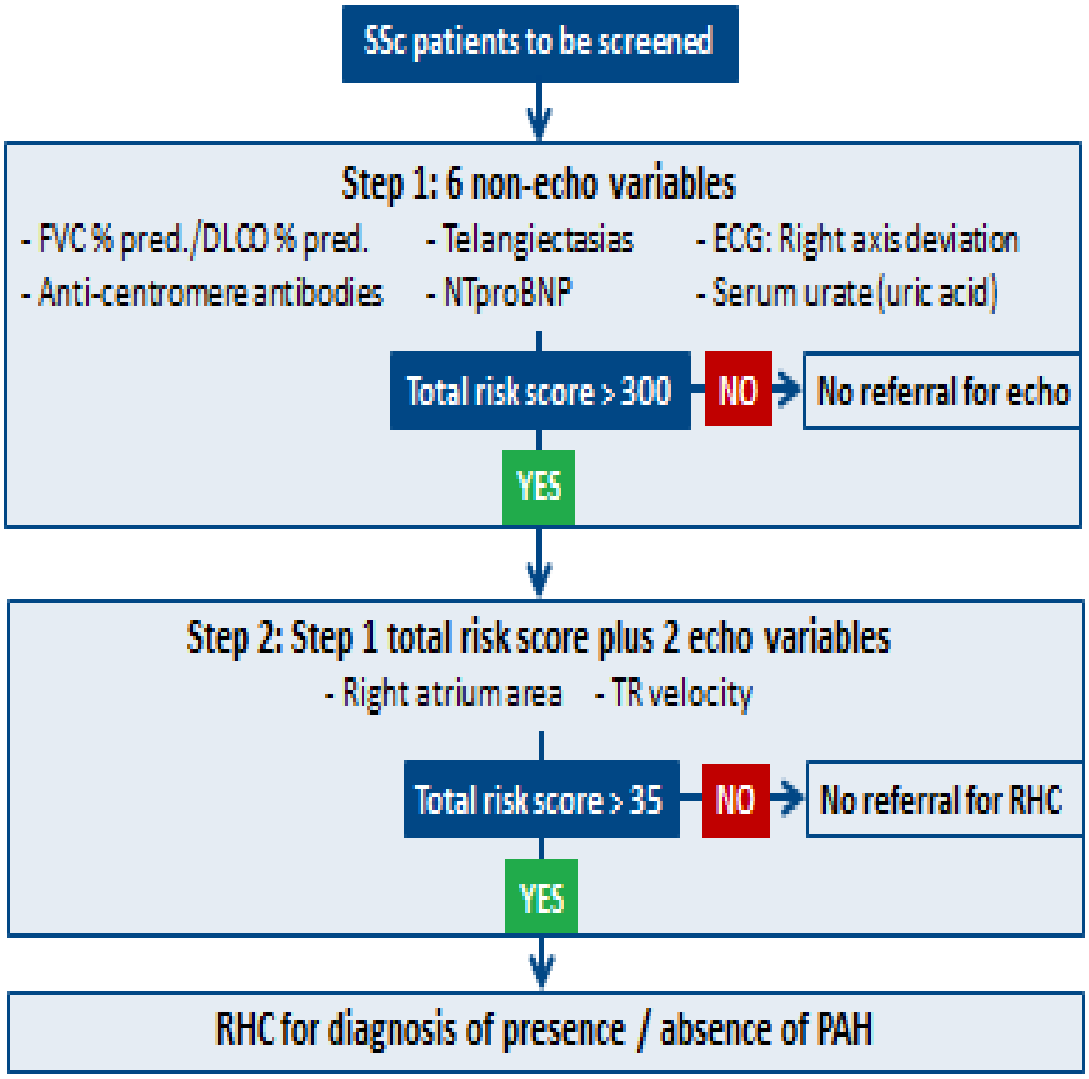
- Limited scleroderma

  13-25% of pts with PAH present diffuse skin involvement
- Disease duration>10 years
- Late age of onset of SSc
- Raynaud's phenomenon (duration or severity)
- Reduction of diffusing capacity

  DLco<60% (annual reduction>10-15%) or FVC%/DLco%>1.6 or decrease of DLco/VA together with increase of NT-proBNP levels
- Autoantibodies anti-Th/To, anticentromere

Le Pavec et al. ARRCCM 2010,
Mathai et al. Exp Rev Respir Med 2011

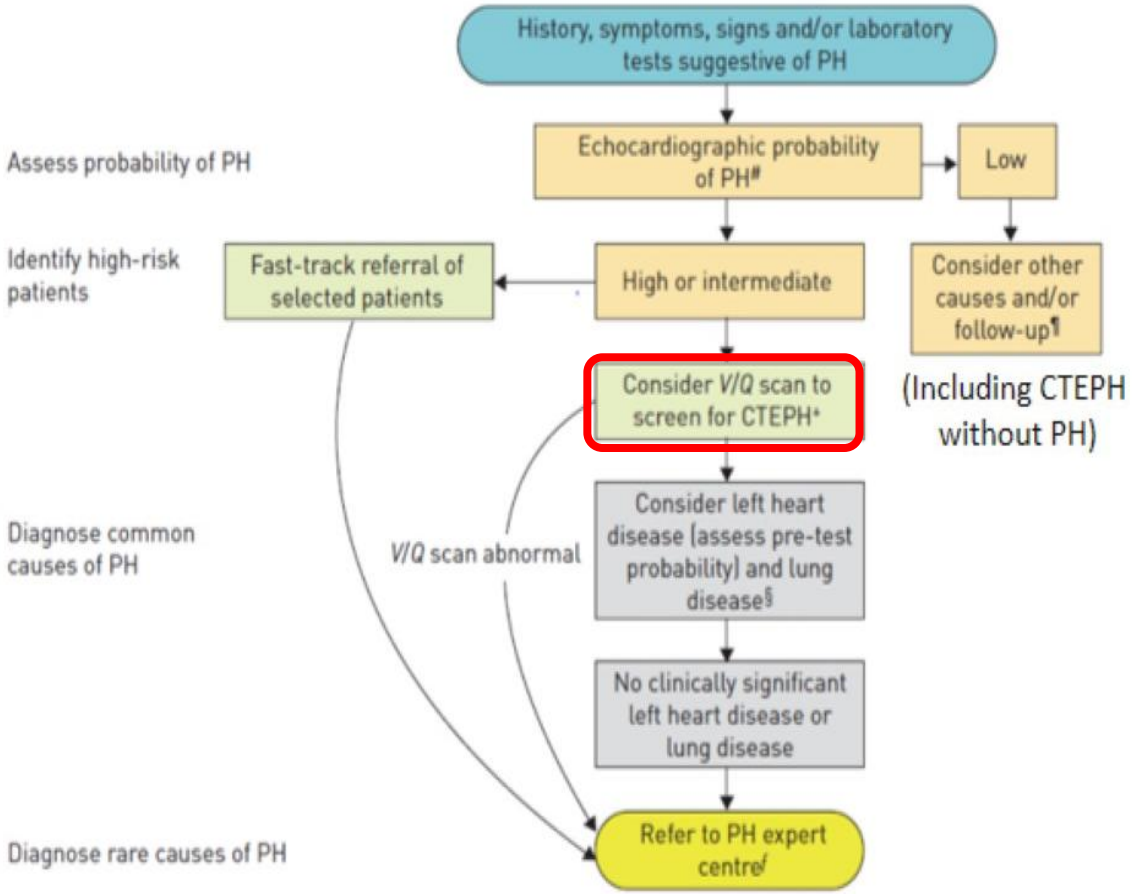
DETECT Risk Calculator in SSc patients



Population: SSc patients with >3years disease duration and a DLCO< 60%predicted

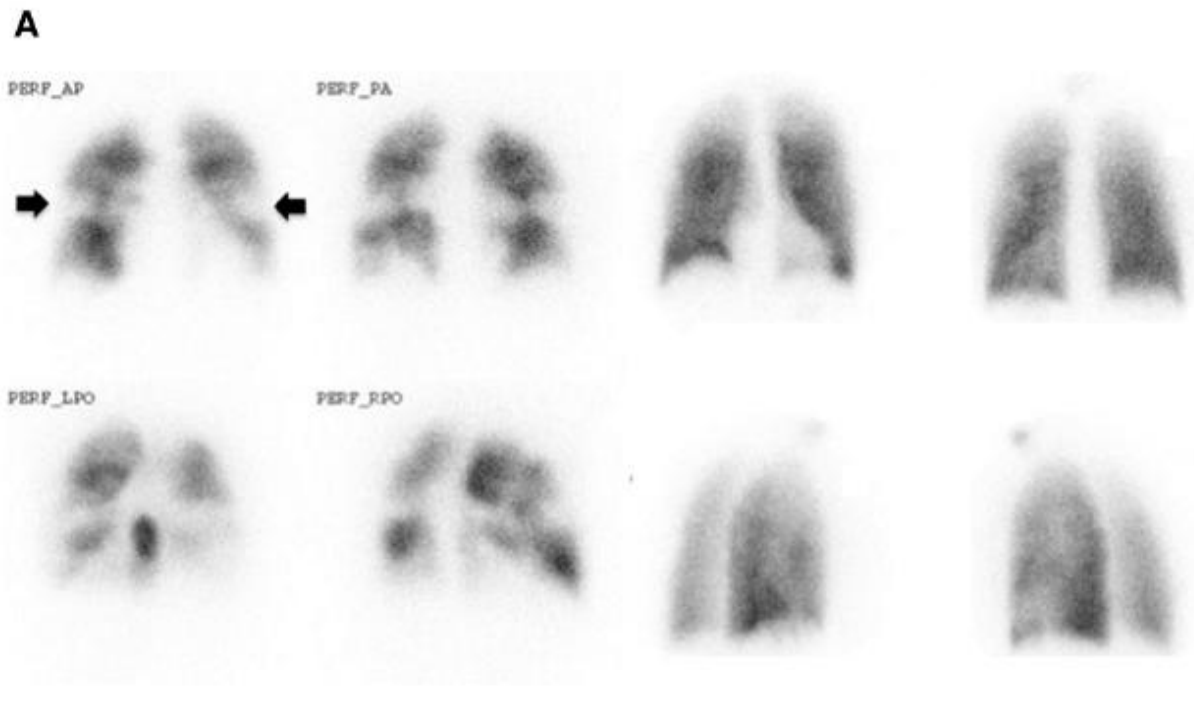
Coghlan et al. *Ann Rheum Dis* 2014

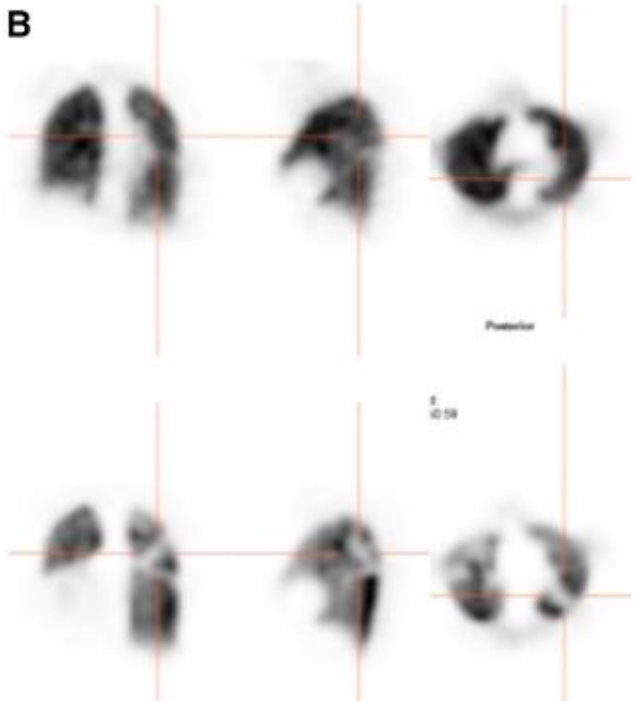
Algorithm for Diagnosing PH



TTE remains the most important non-invasive screening tool and RHC remains mandatory to establish the diagnosis

TYPICAL V/Q SCAN –PLANAR VS SPECT





Gopalan D et al. Annals ATS 2016

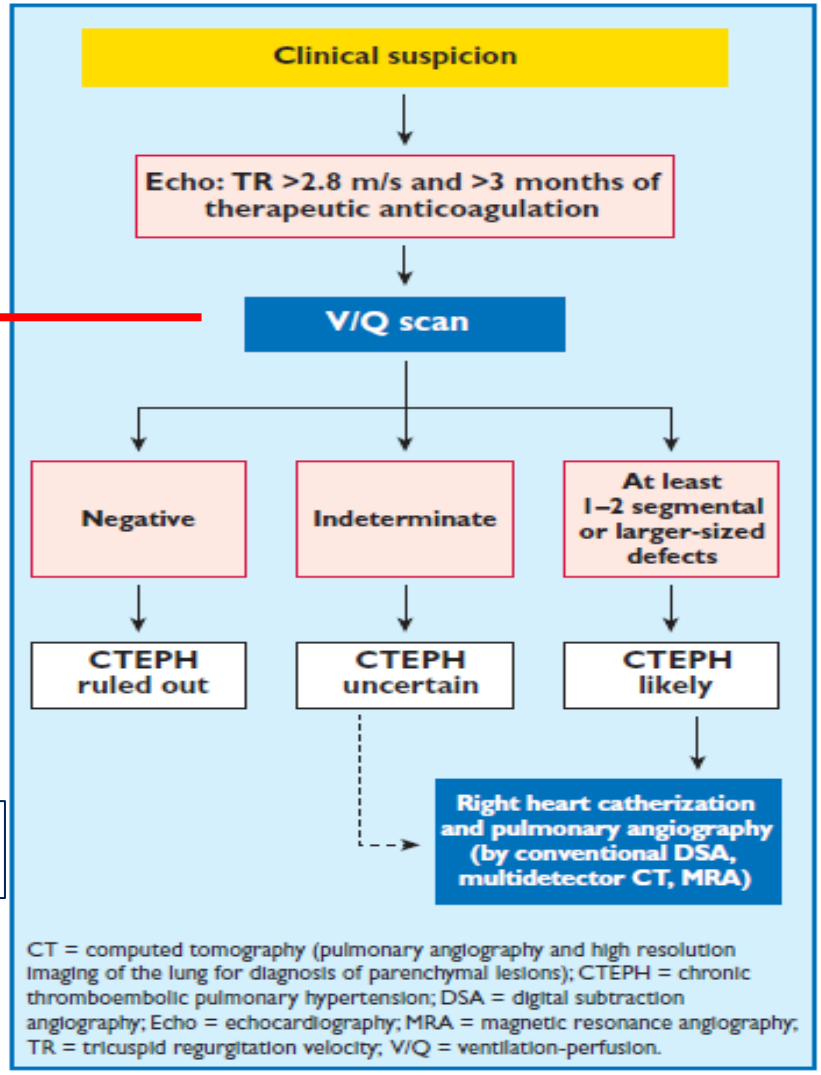
ESC 2015 guidelines

Summary of Performance Indicators for V/Q Scintigraphy and CTPA

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.

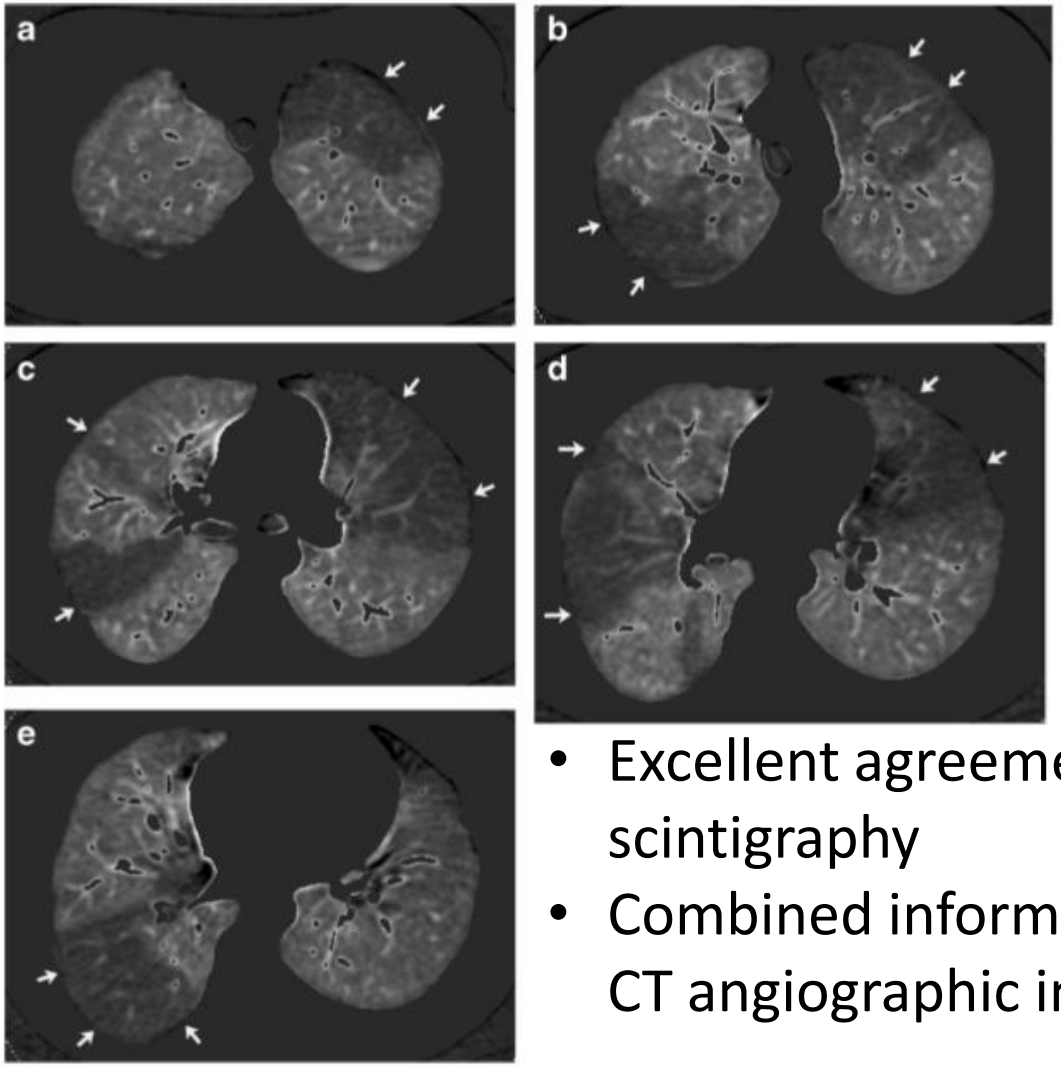
Place of dual-energy CTPA vs V/Q scan?



CT = computed tomography (pulmonary angiography and high resolution imaging of the lung for diagnosis of parenchymal lesions); CTEPH = chronic thromboembolic pulmonary hypertension; DSA = digital subtraction angiography; Echo = echocardiography; MRA = magnetic resonance angiography; TR = tricuspid regurgitation velocity; V/Q = ventilation-perfusion.

Tanariu et al. J Nucl Med 2007,
Galie N et al. Eur Heart J 2016

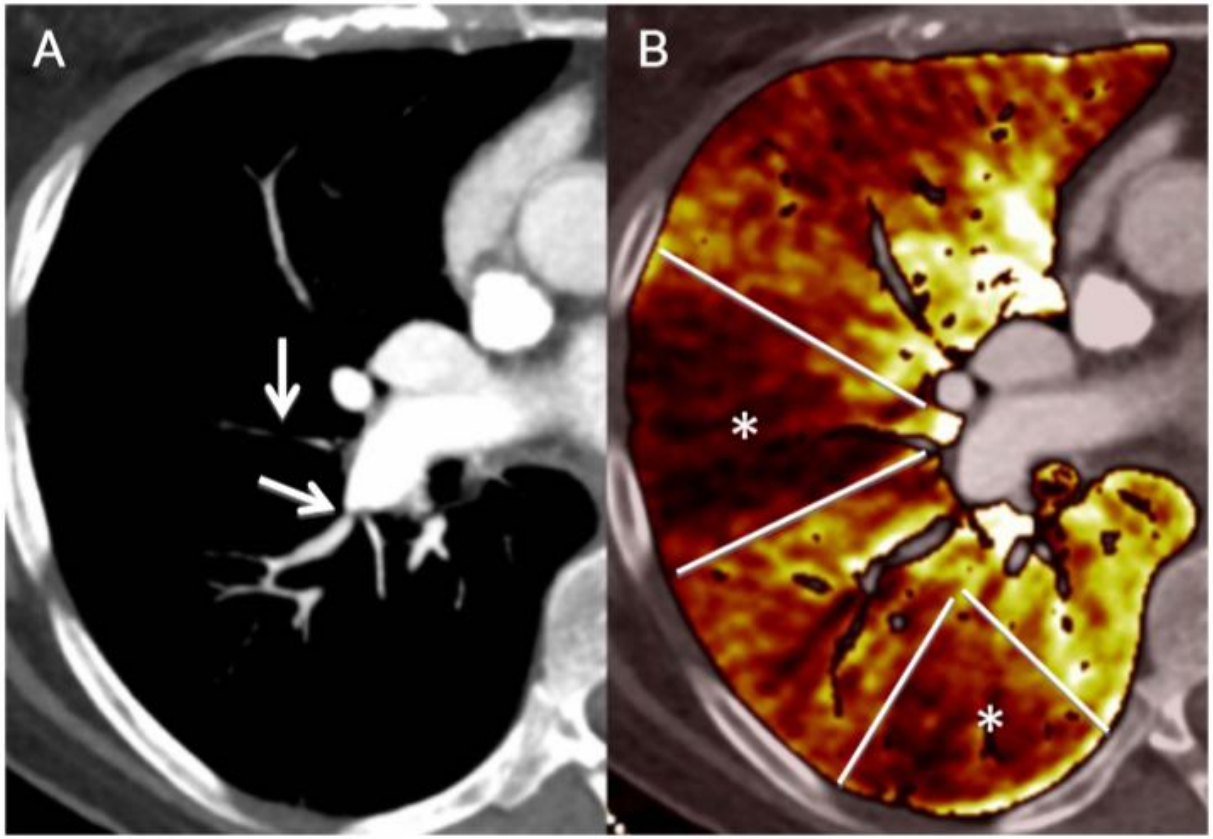
Dual-energy CT vs V/Q in diagnosing CTEPH



- Excellent agreement between CT perfusion and scintigraphy
- Combined information from DECT perfusion and CT angiographic images

Macy M et al. Eur Radiol 2018,
Machida H et al. Radiographics 2016

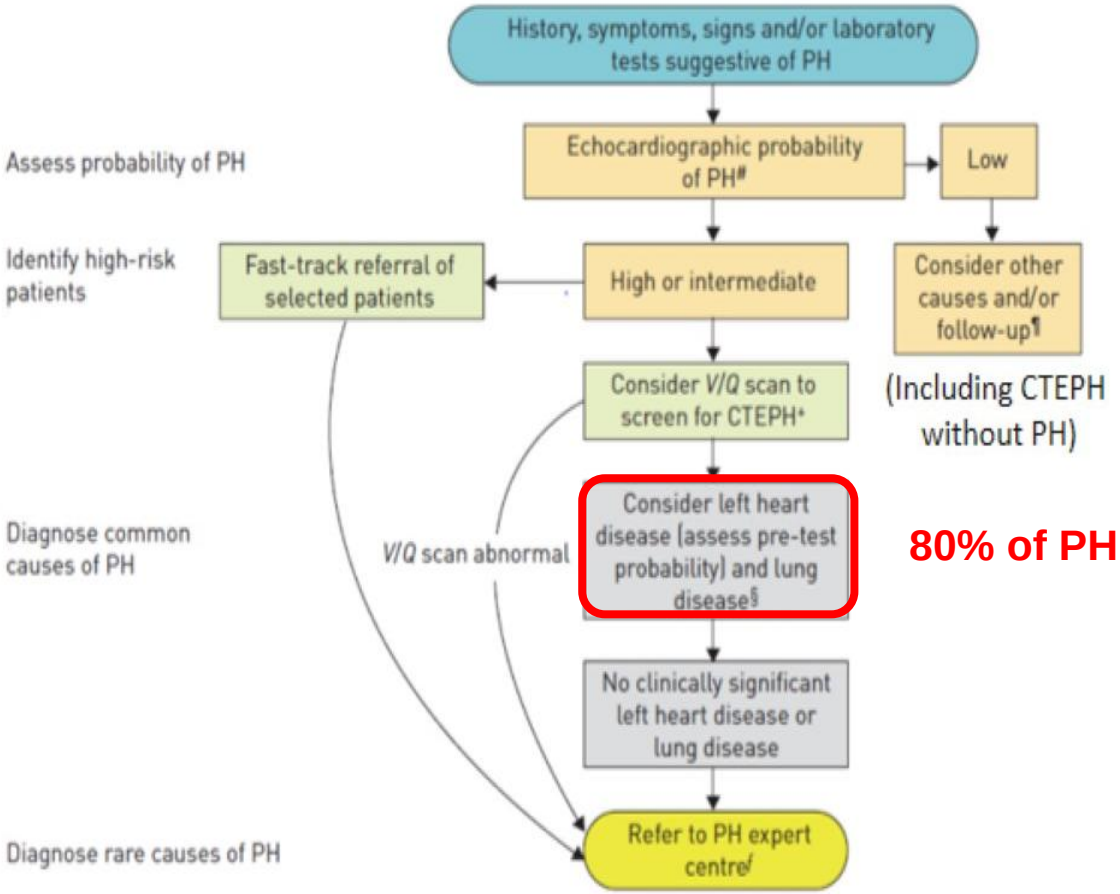
Dual-energy CT in diagnosing CTEPH



- Dual-Energy CT offers the advantage of combining morphological images with functional consequences of segmental perfusion defects seen on perfusion map during the same acquisition.

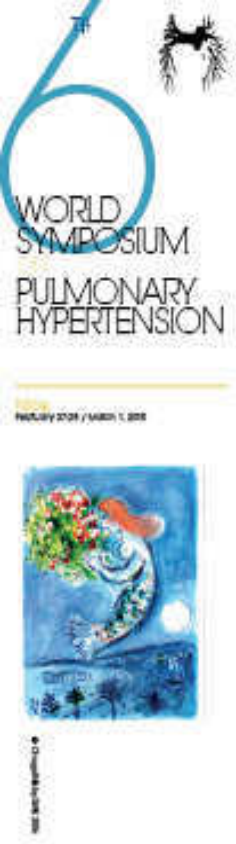
Kharat A et al. Thromb Res 2018

Algorithm for Diagnosing PH



80% of PH cases

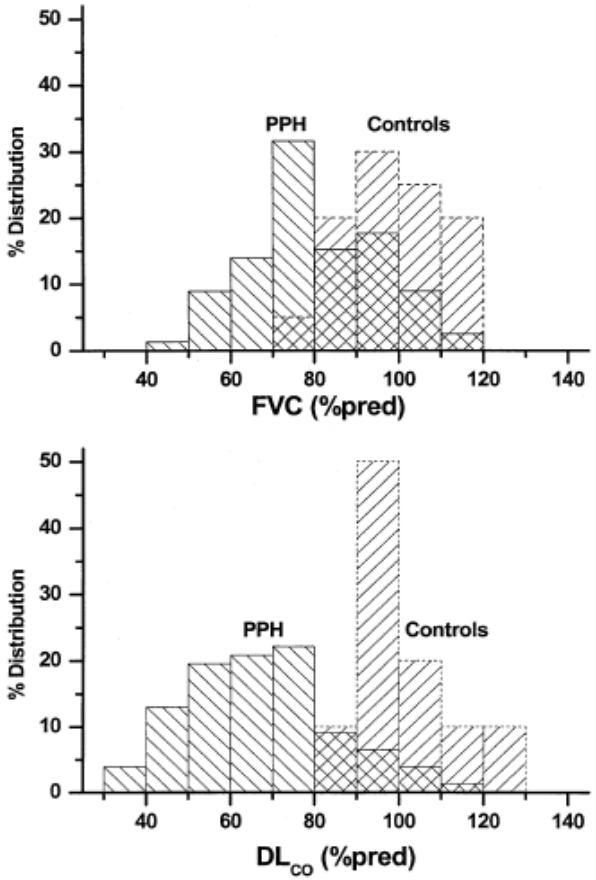
TTE remains the most important non-invasive screening tool and RHC remains mandatory to establish the diagnosis



Multimodality investigation for the differential diagnosis of PH

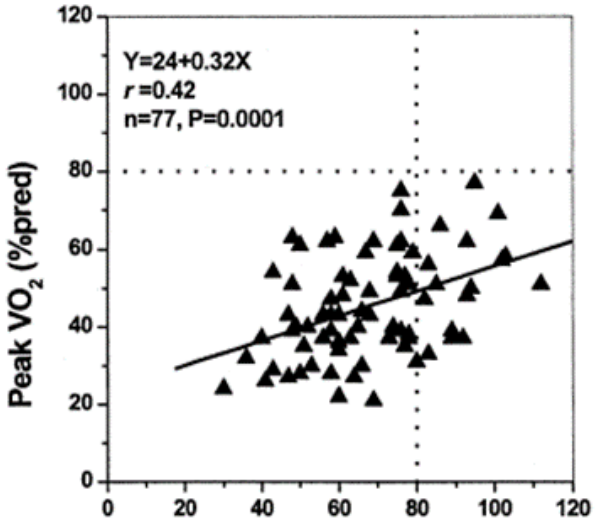
	Investigation	Possible findings related to PH classification
Cardiac	ECG	RV hypertrophy, RA enlargement, LV hypertrophy, myocardial ischaemia
	ECHO/Cardiac MRI	LA dilatation, LV disease, valvular heart disease, congenital defects, pericardiac effusion, RV strain
Respiratory	Pulmonary function tests/DLco	Obstructive and/or restrictive lung function, impaired gas diffusion
	Arterial blood gases	Hypoxia, hyper-/hypocapnia
	Overnight oximetry	Nocturnal desaturation
Blood	PAH serology	Connective tissue diseases, HIV, liver disease
	Genetics	BMPR2, EIF2AK4 in PVOD/PCA
Exercise	Cardiopulmonary exercise test	Patterns of gas exchange which describe different pathophysiology

Pulmonary function in primary pulmonary hypertension



- 79 pts with IPAH
- In 3/4 of IPAH pts, the DLco values were below 80% pred (68±17% pred)
- Mild to moderate restriction

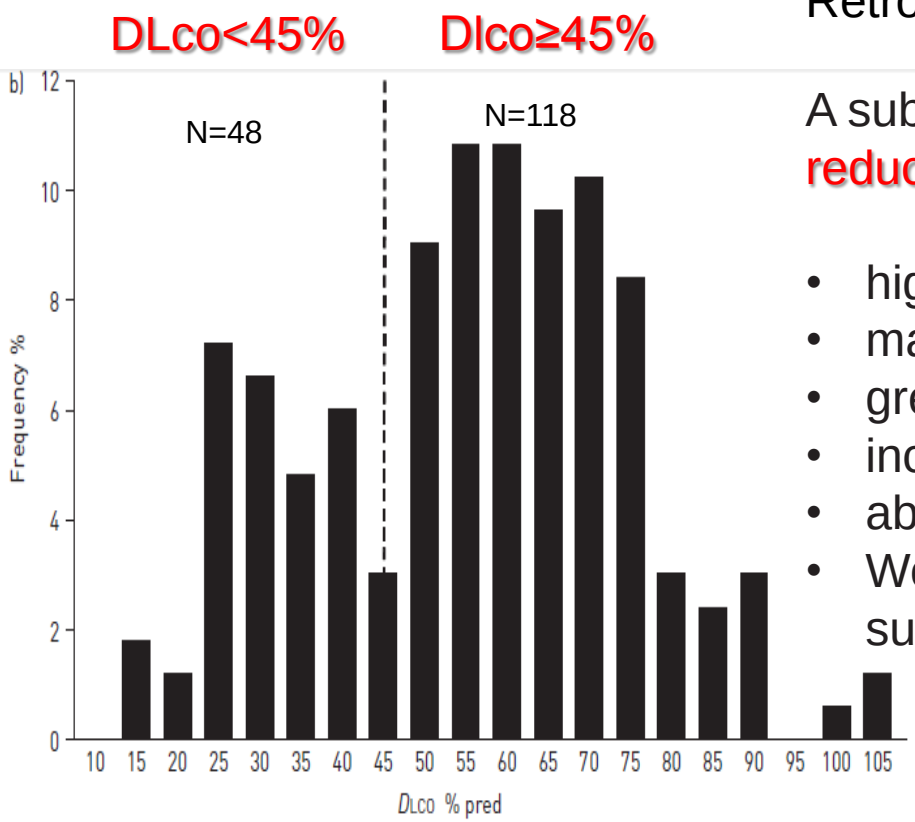
- Low DLco in PAH: Reduction of pulmonary alveolar capillary bed



- Correlation of DLco vs peak O_2 uptake

Sun XG et al. JACC 2003

The distribution of DLco in IPAH



Retrospective, 166 IPAH patients

A subgroup of IPAH patients with a **severely reduced DLco** has a distinct clinical profile:

- higher age
- male sex
- greater tobacco exposure,
- increased prevalence of coronary disease
- abnormalities on chest CT scan
- Worse exercise performance and worse survival

Trip P et al. ERJ 2013

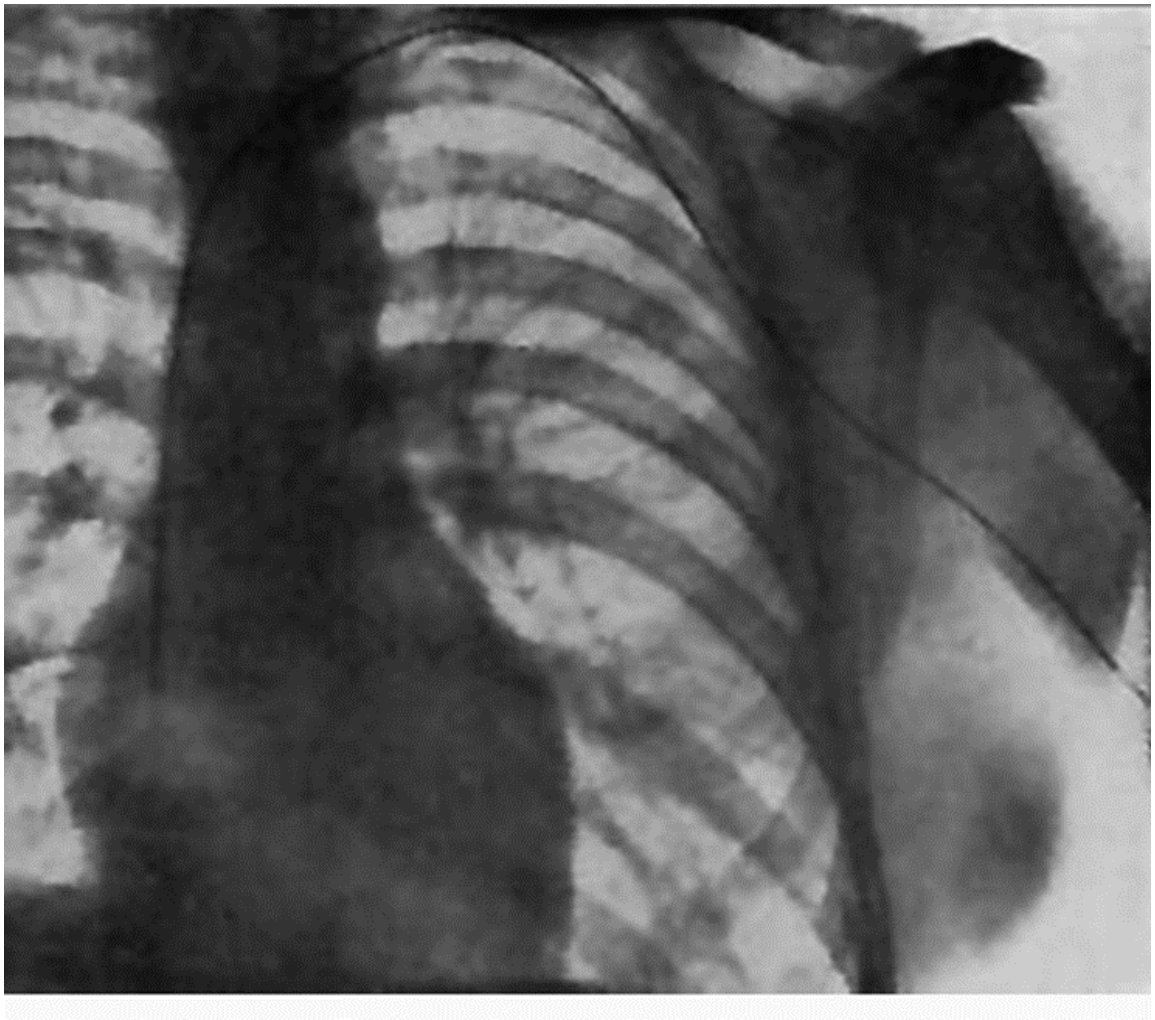
More on idiopathic pulmonary arterial hypertension with a low diffusing capacity

Smoking-related pulmonary vasculopathy

The first right heart catheterization

1929

Werner Forssmann
(1904-1979)



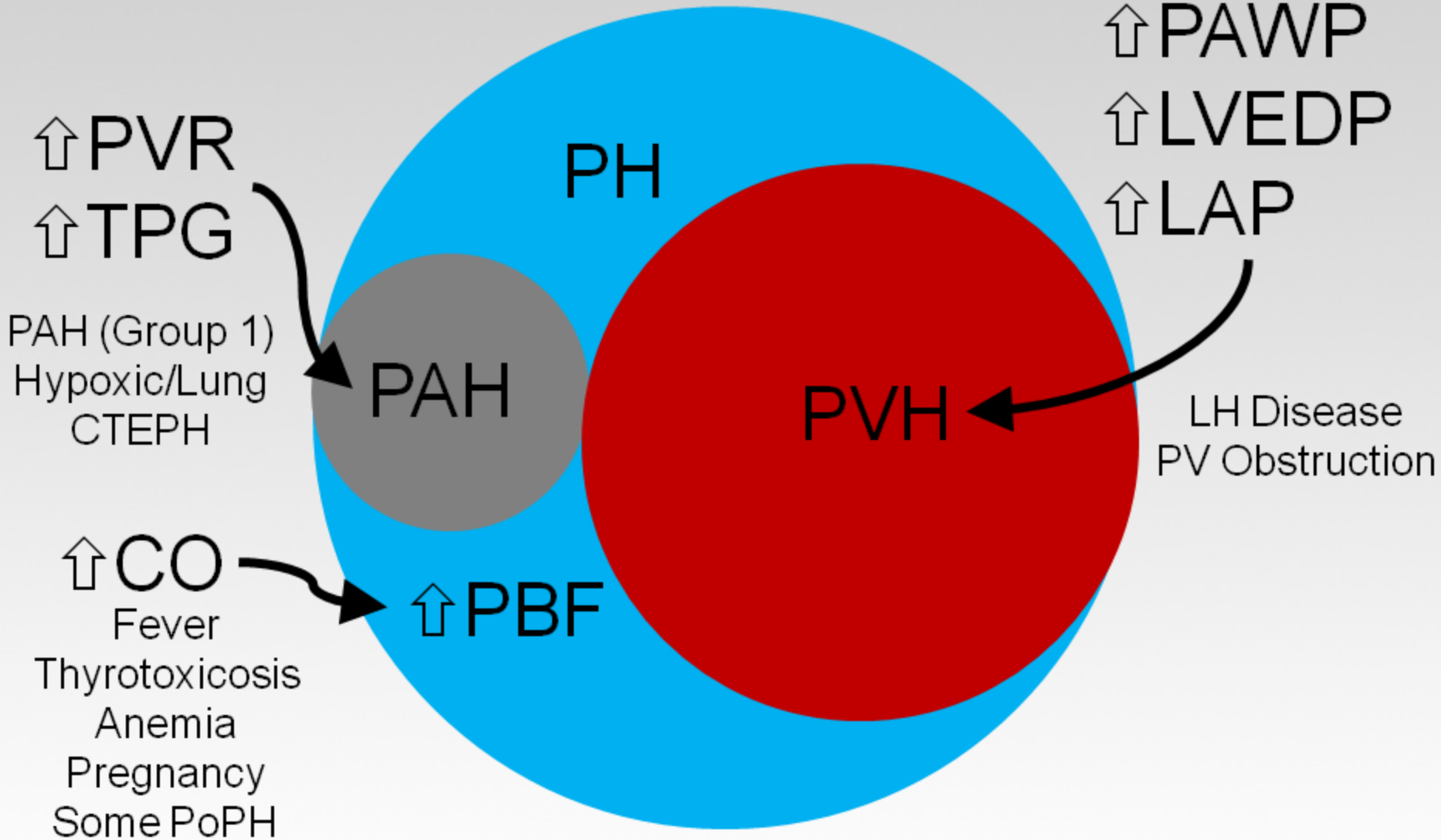
Recommendations for right heart catheterization and vasoreactivity testing in PH

Recommendations	Class[a]	Level[b]	Ref.[c]
RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (group 1) and to support treatment decisions	I	C	
In patients with PH, it is recommended to perform RHC in expert centres (see section 12) as it is technically demanding and may be associated with serious complications	I	B	69
RHC should be considered in pulmonary arterial hypertension (group 1) to assess the treatment effect of drugs (Table 16)	IIa	C	

Recommendations	Class[a]	Level[b]	Ref.[c]
Vasoreactivity testing is indicated only in expert centres	I	C	69
Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a CCB	I	C	84,85
A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥10 mmHg to reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged cardiac output	I	C	85,86
Nitric oxide is recommended for performing vasoreactivity testing	I	C	85,86
Intravenous epoprostenol is recommended for performing vasoreactivity testing as an alternative	I	C	85,86
Adenosine should be considered for performing vasoreactivity testing as an alternative	IIa	C	87,88
Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative	IIb	C	89,90
The use of oral or intravenous CCBs in acute vasoreactivity testing is not recommended	III	C	
Vasoreactivity testing to detect patients who can be safely treated with high doses of a CCB is not recommended in patients with PAH other than IPAH, HPAH and PAH associated with drugs use and is not recommended in PH groups 2, 3, 4 and 5	III	C	

Galiè N. et al Eur Heart J 2015, Eur Respir J, 2015

Importance of Right Heart Catheterization

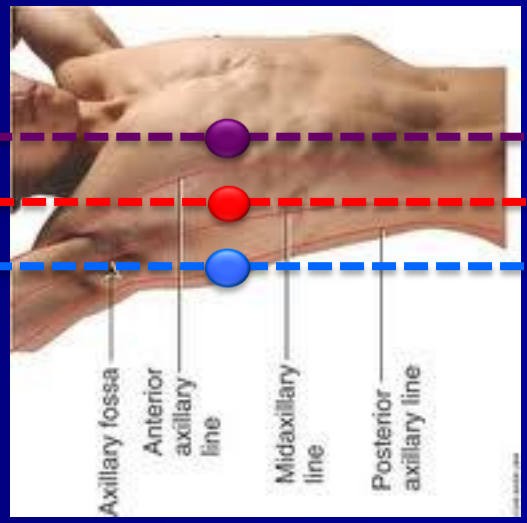


CO = carbon monoxide; LAP = left atrial pressure; LH = left heart; PAWP = pulmonary artery wedge pressure; PBF = pulmonary blood flow; PoPH = portopulmonary hypertension; PVH = pulmonary venous hypertension

Where is the ideal zero point?

1 mmHg = 13 mmH_2O = 1.3 cmH_2O

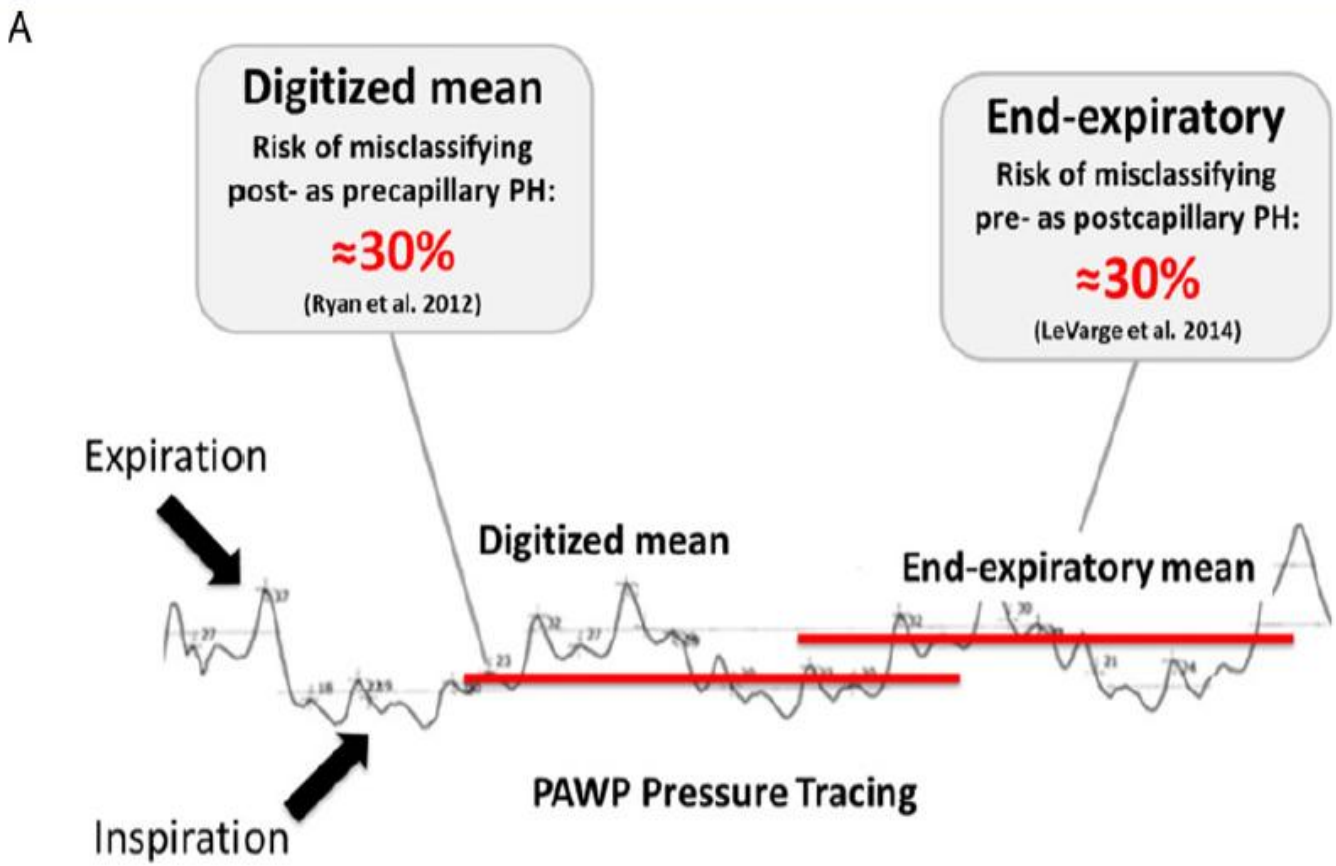
- **-10 mmHg** = -13 cmH_2O
- **+10 mmHg** = +13 cmH_2O



Ideal zero line

mid-thoracic level

Right heart catheterization:
The dilemma of PAWP measurements



Potential misclassifications between pre- and post-capillary pulmonary hypertension depending on the method of PAWP reading

S. Rosenkranz et al. Eur Heart J 2015

Risk Assessment in PAH

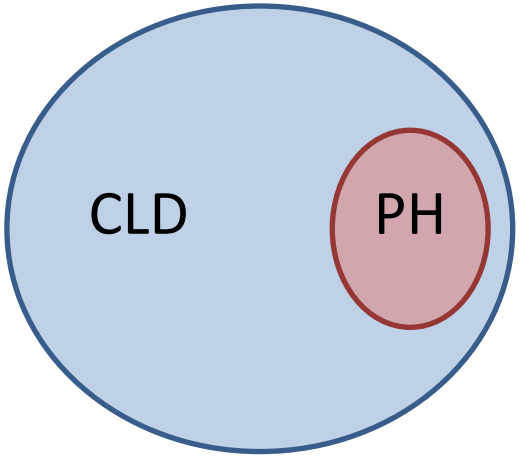
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 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 %

[a]Most of the proposed variables and cut-off values are based on expert opinion.
[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity.

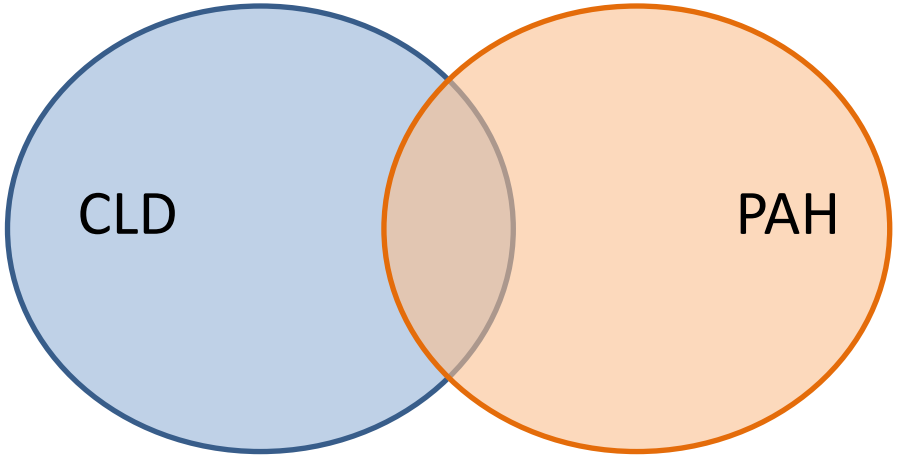
Galié N, et al. *Eur Heart J.* 2015;46:903-975.

PH in chronic lung diseases (CLD)

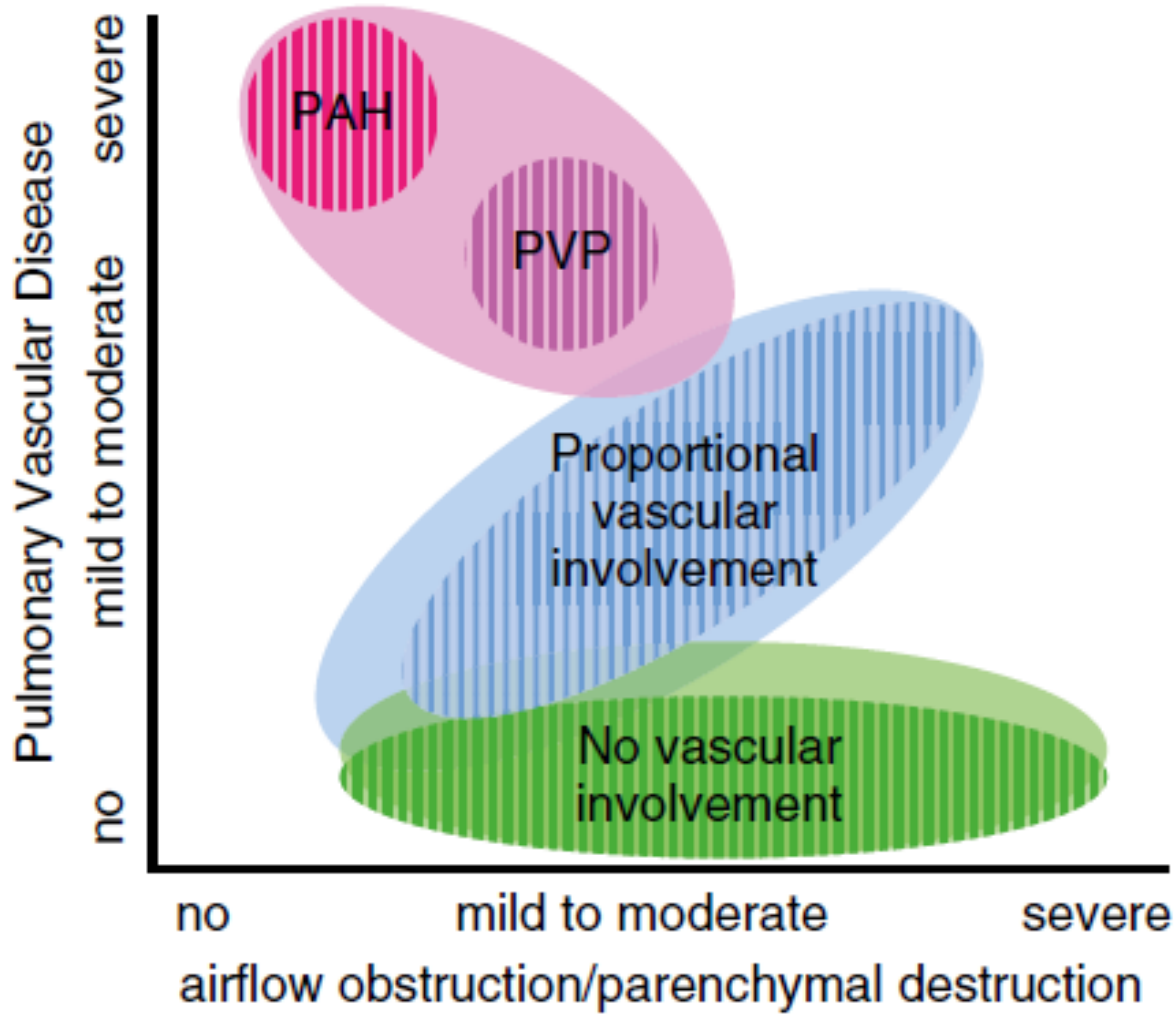
PH due to Chronic Lung Disese



Chronic Lung Disease & PAH coexist

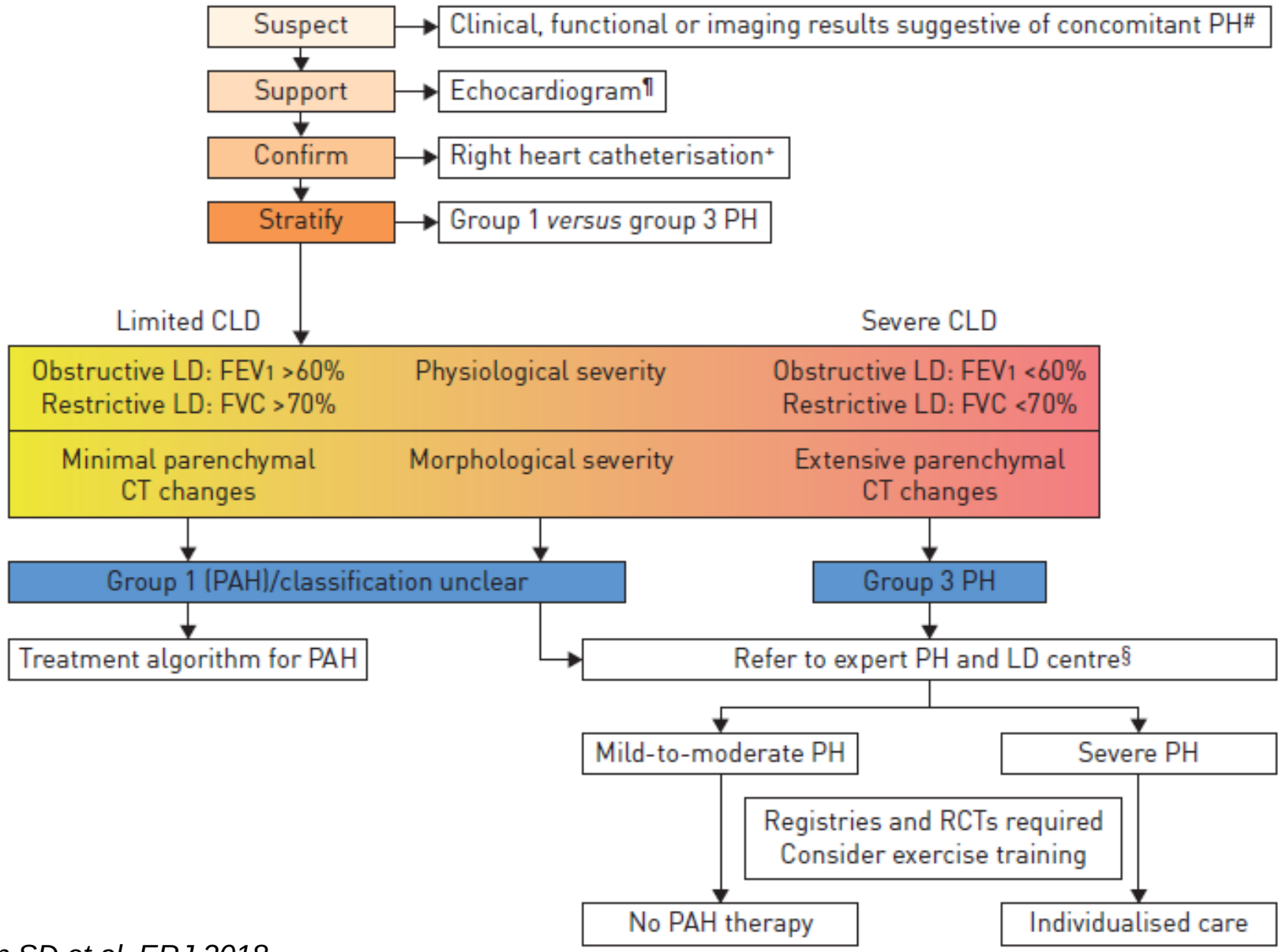


PH in CLD: Is There a Pulmonary Vascular Phenotype- PVP?



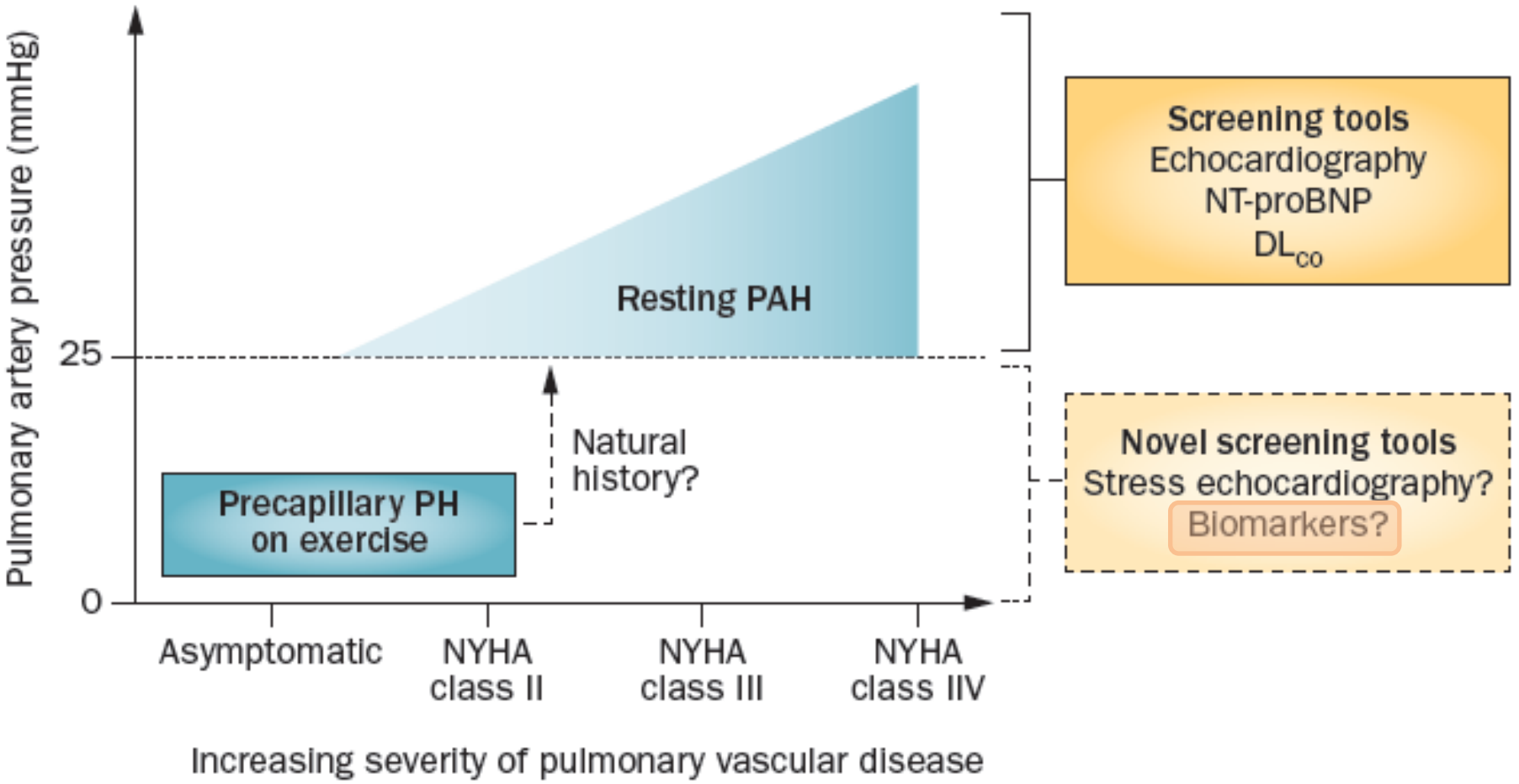
Kovacs G et al. AJRCCM 2018

Evaluation of PH in chronic lung disease



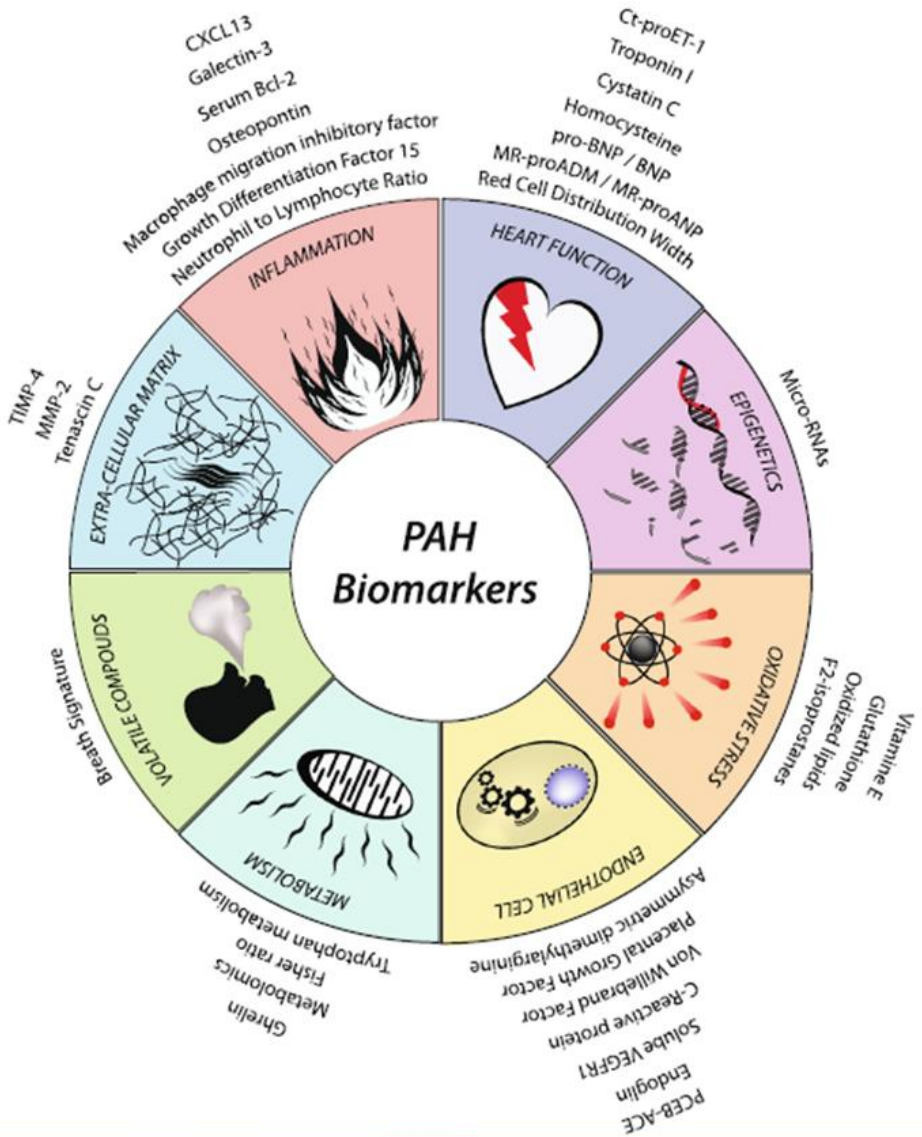
Nathan SD et al. ERJ 2018

Screening-Early diagnosis



Humbert et al, Circulation. 2014;130:2189-2208

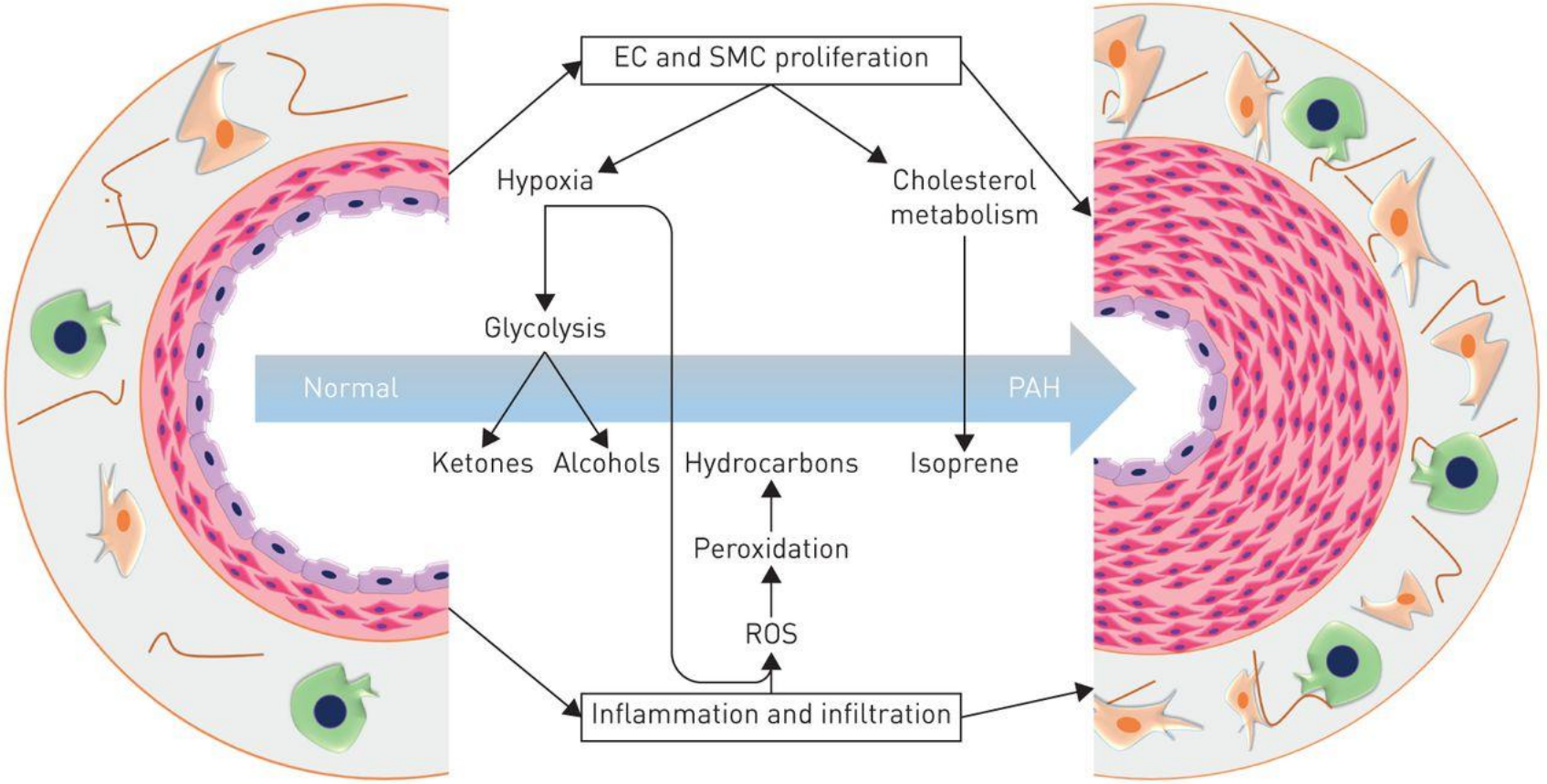
Screening: Biomarkers in PAH

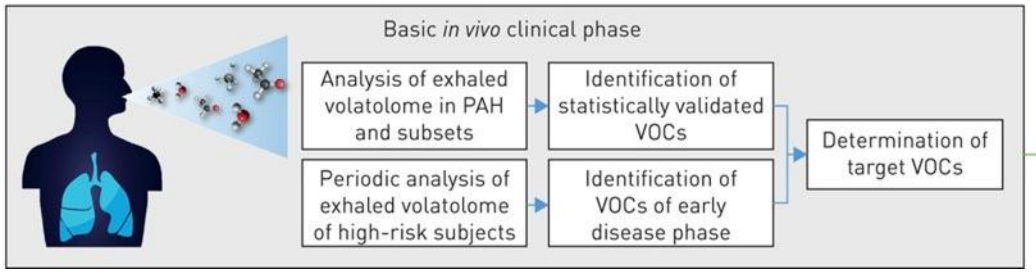


- Predictive biomarkers
- Prognostic biomarkers

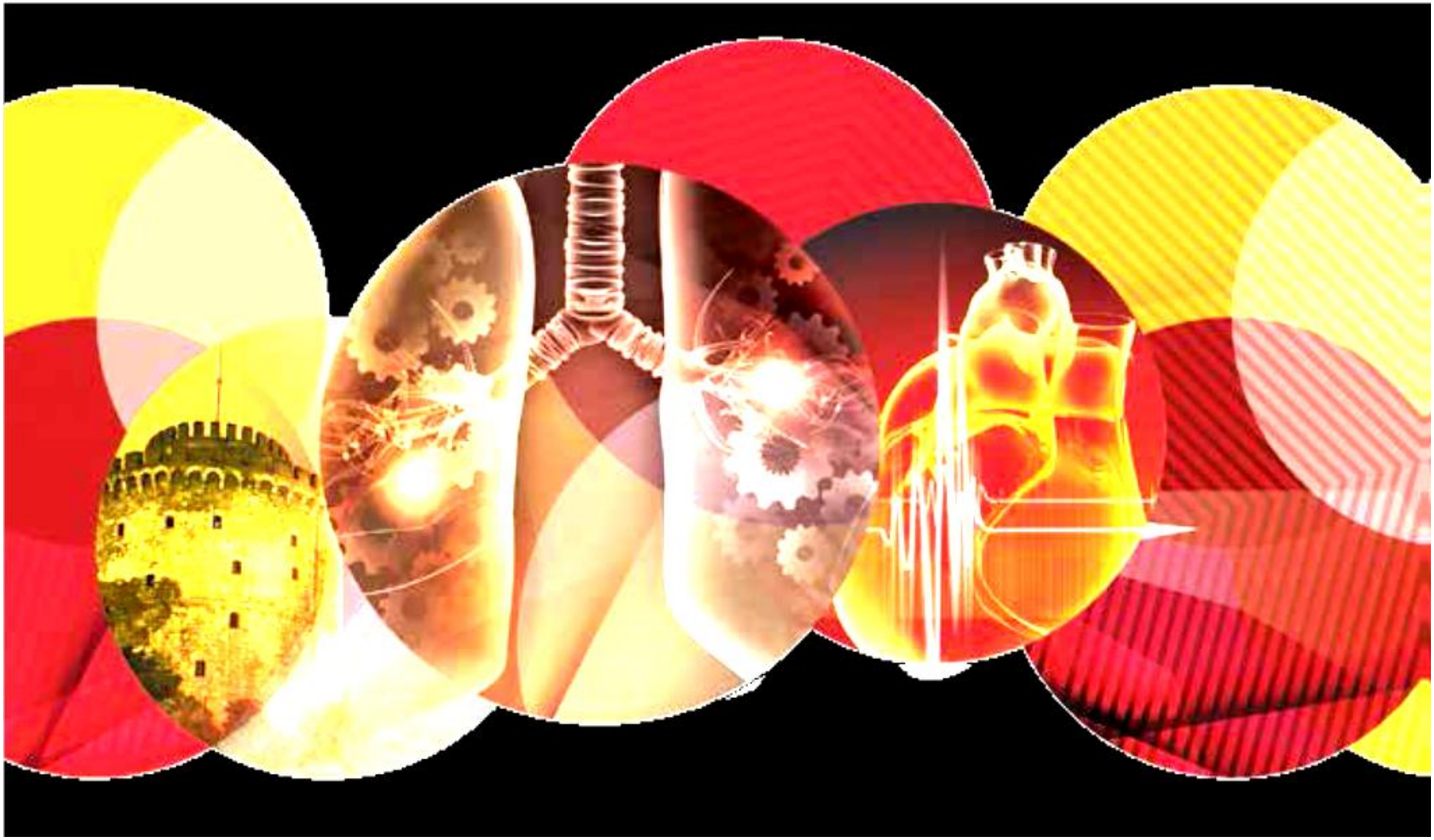
Anwar et al. Respiratory Research (2016) 17:88

Hypothetical schema of possible sources of volatile organic compounds at the level of a remodelled artery in pulmonary arterial hypertension (PAH).



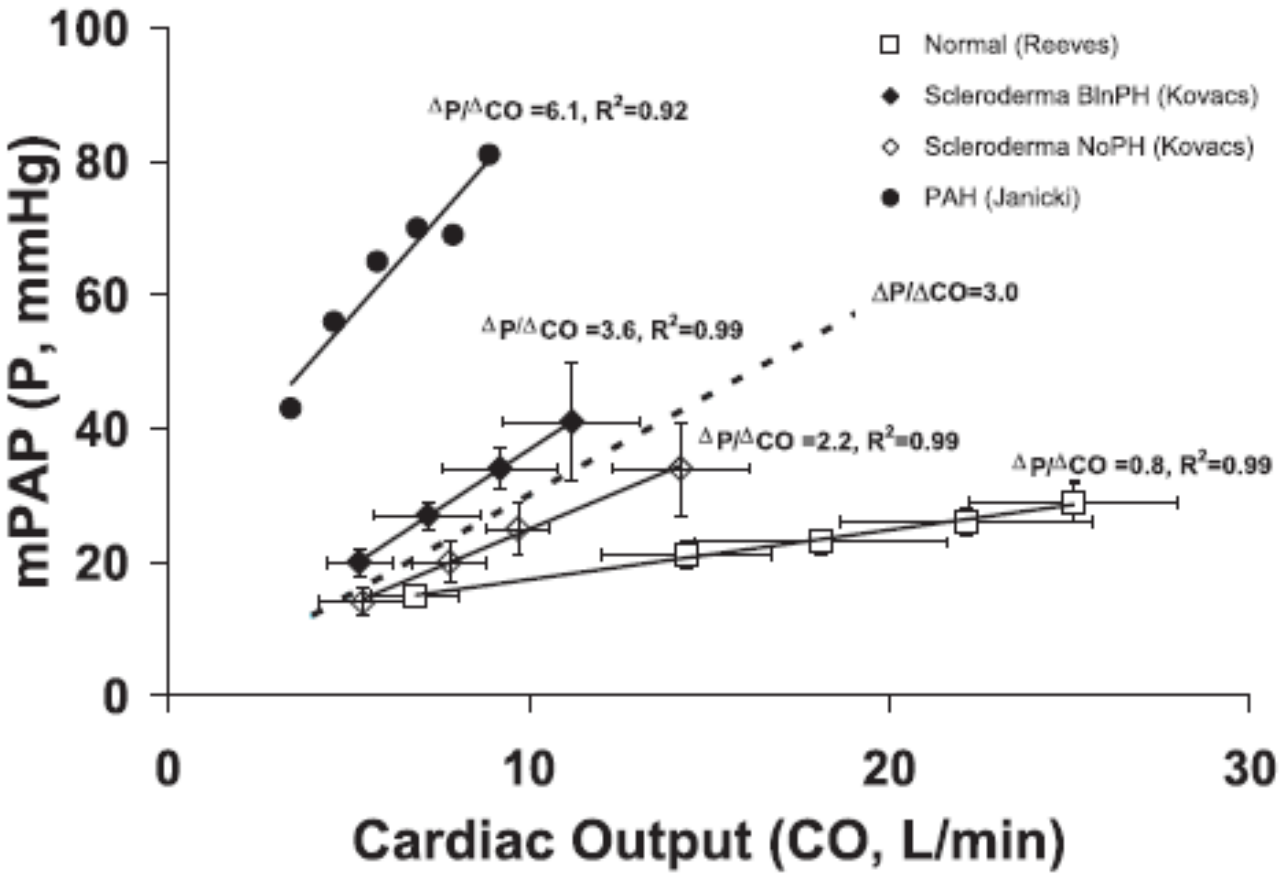


Morad K. Nakhleh et al. Eur Respir J 2017;49:1601897



Thank you!

The mPAP-CO slope represents an abnormal pulmonary vascular response to exercise and may be indicative of early pulmonary vasculopathy



Lewis GD et al. Circulation 2013