Διαγνωστικά εργαλεία στην Πνευμονική Υπέρταση

Ηρακλής Τσαγκάρης

Αναπληρωτής Καθηγητής Εντατικής Θεραπείας

Αττικό Νοσοκομείο

Δήλωση συμφερόντων

Καμία για τη συγκεκριμένη ομιλία

Algorithm for the diagnosis of pulmonary hypertension (PH)

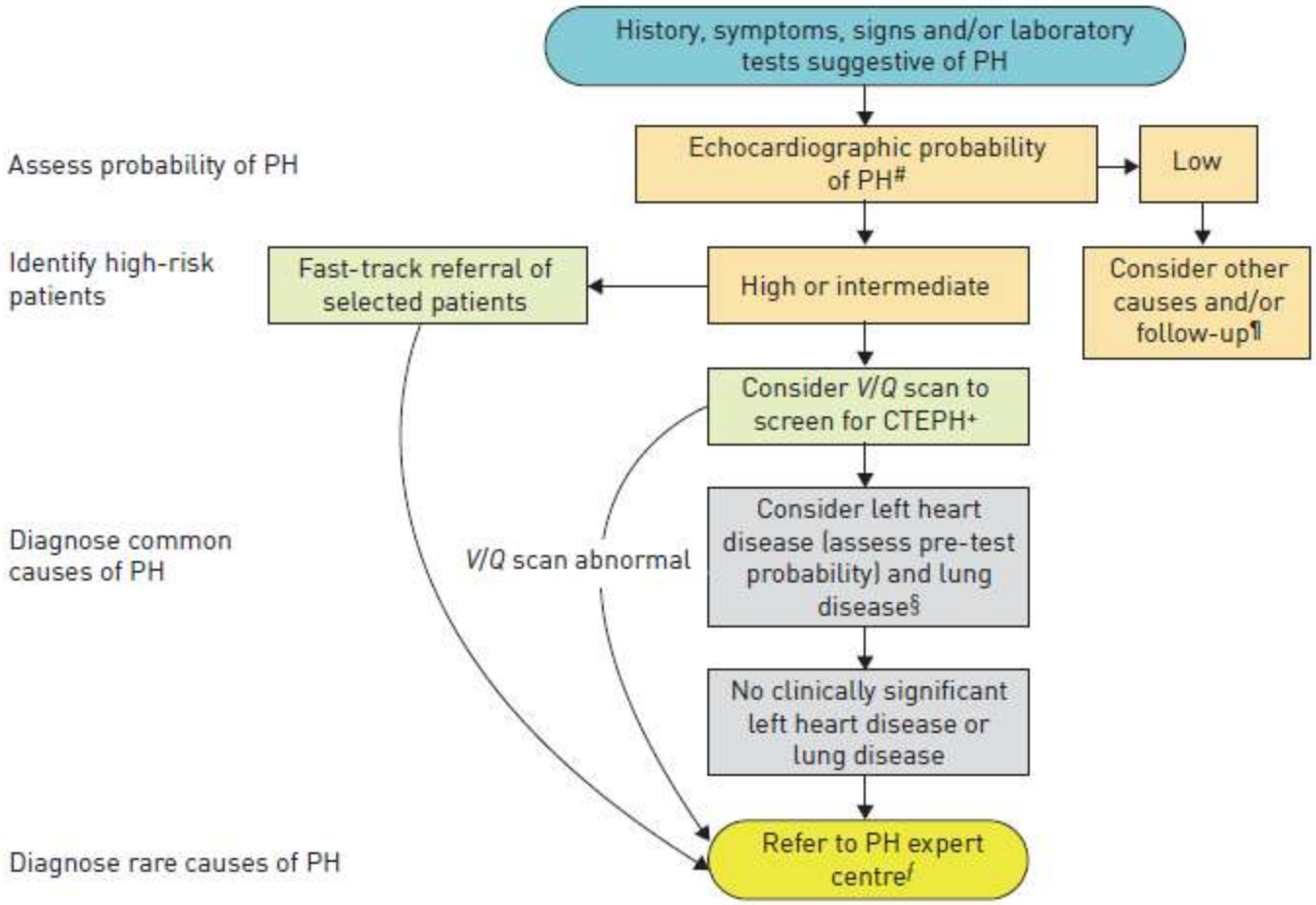
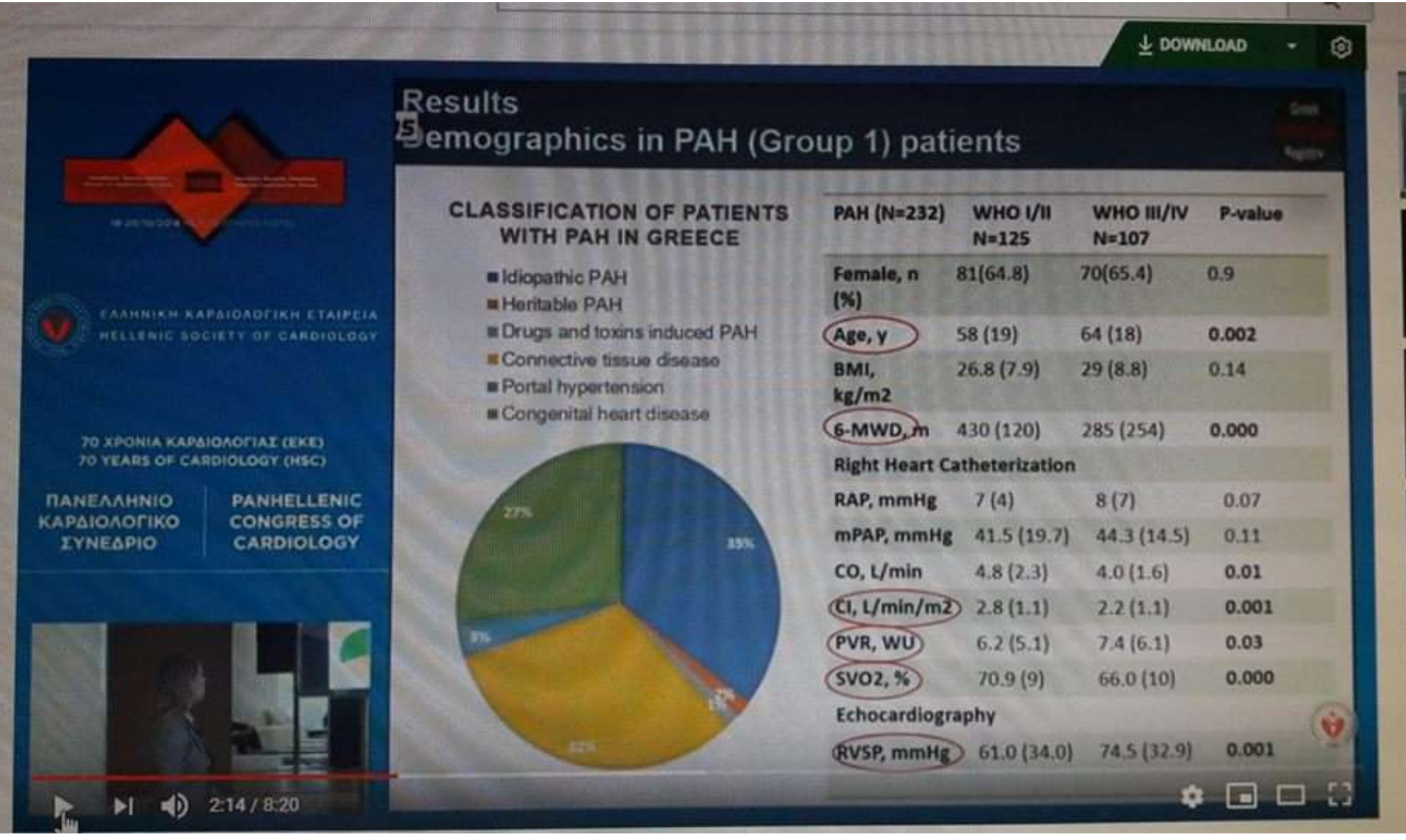


Table 14 Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension

	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[f]	+[e]	+[e]

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%

NYHA III/IV 46% vs 75% (all 4 major registries)



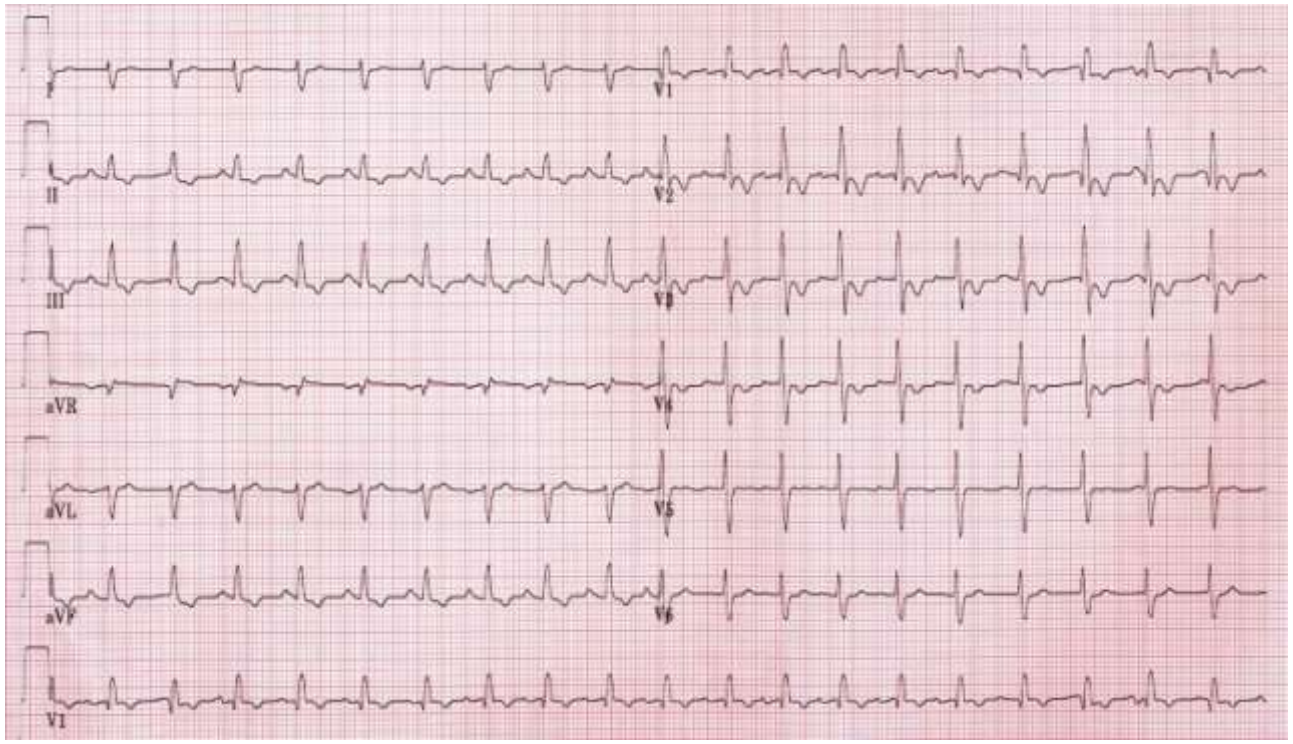
PAH (N=232)	WHO I/II N=125	WHO III/IV N=107	P-value
Female, n (%)	81(64.8)	70(65.4)	0.9
Age, y	58 (19)	64 (18)	0.002
BMI, kg/m2	26.8 (7.9)	29 (8.8)	0.14
6-MWD, m	430 (120)	285 (254)	0.000
Right Heart Catheterization			
RAP, mmHg	7 (4)	8 (7)	0.07
mPAP, mmHg	41.5 (19.7)	44.3 (14.5)	0.11
CO, L/min	4.8 (2.3)	4.0 (1.6)	0.01
CI, L/min/m2	2.8 (1.1)	2.2 (1.1)	0.001
PVR, WU	6.2 (5.1)	7.4 (6.1)	0.03
SVO2, %	70.9 (9)	66.0 (10)	0.000
Echocardiography			
RVSP, mmHg	61.0 (34.0)	74.5 (32.9)	0.001

ECG

Often misinterpreted

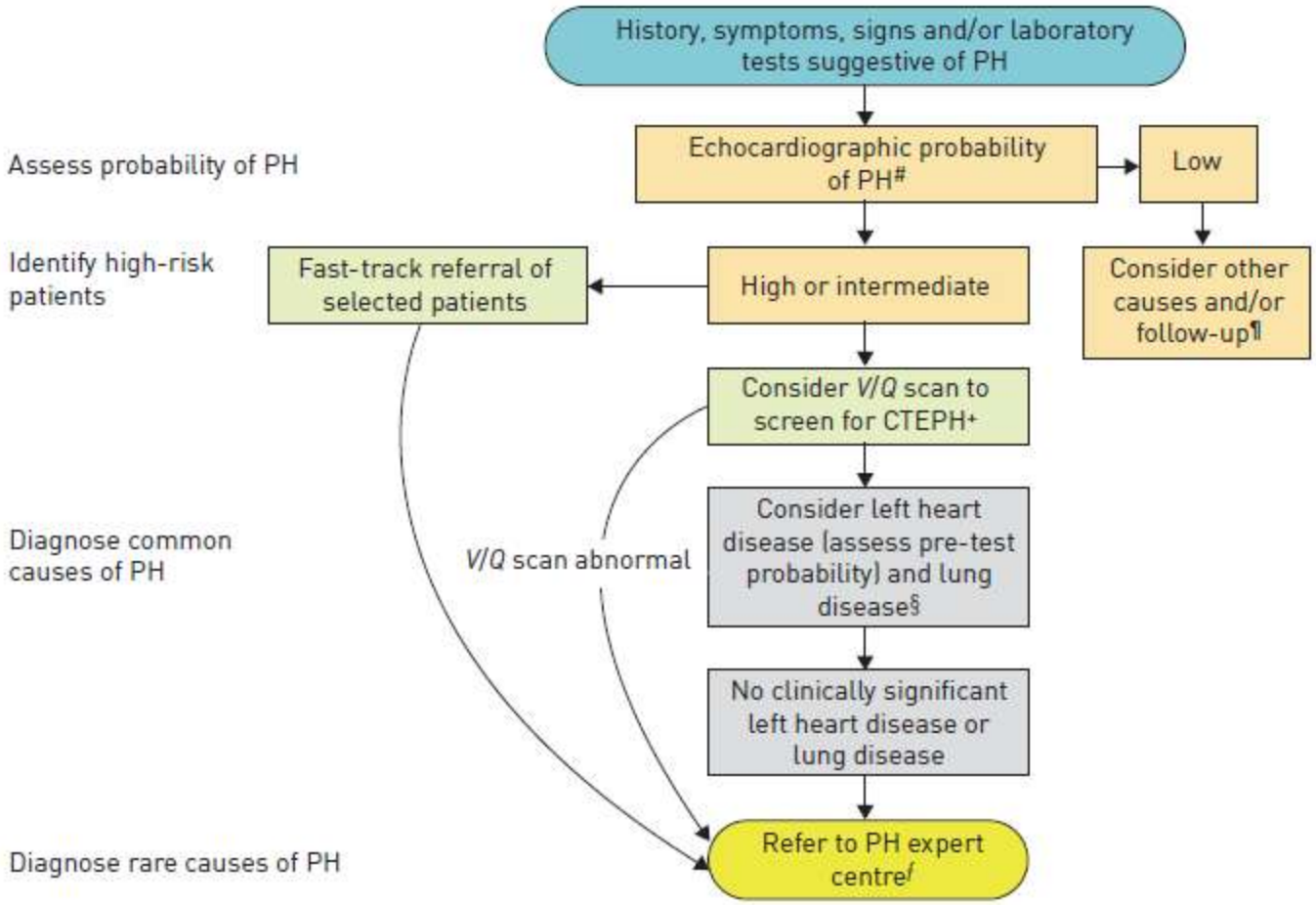
Normal in one third of the patients

Does not parallel hemodynamics

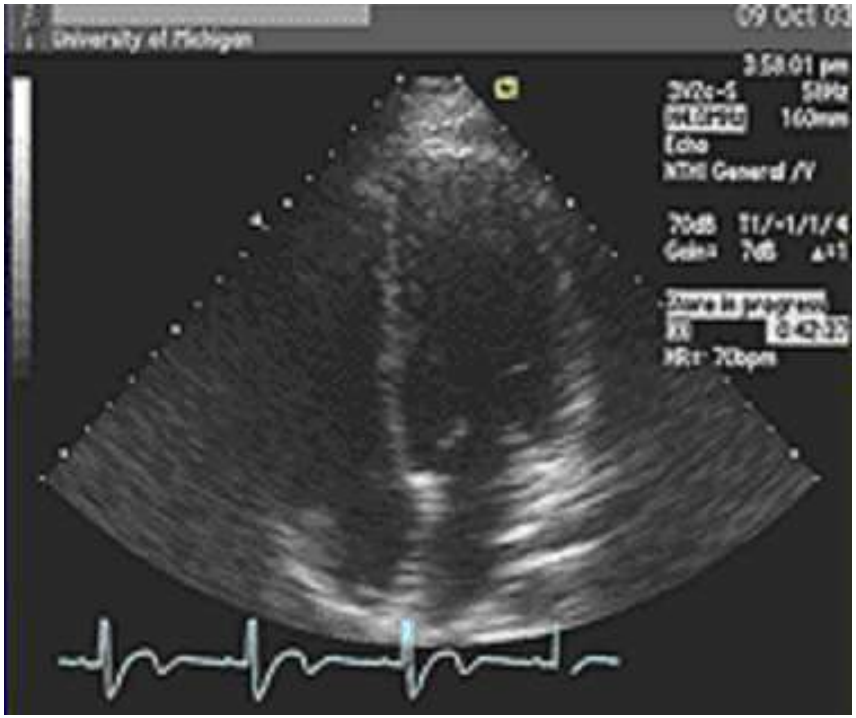


With permission of Prof. Ewert

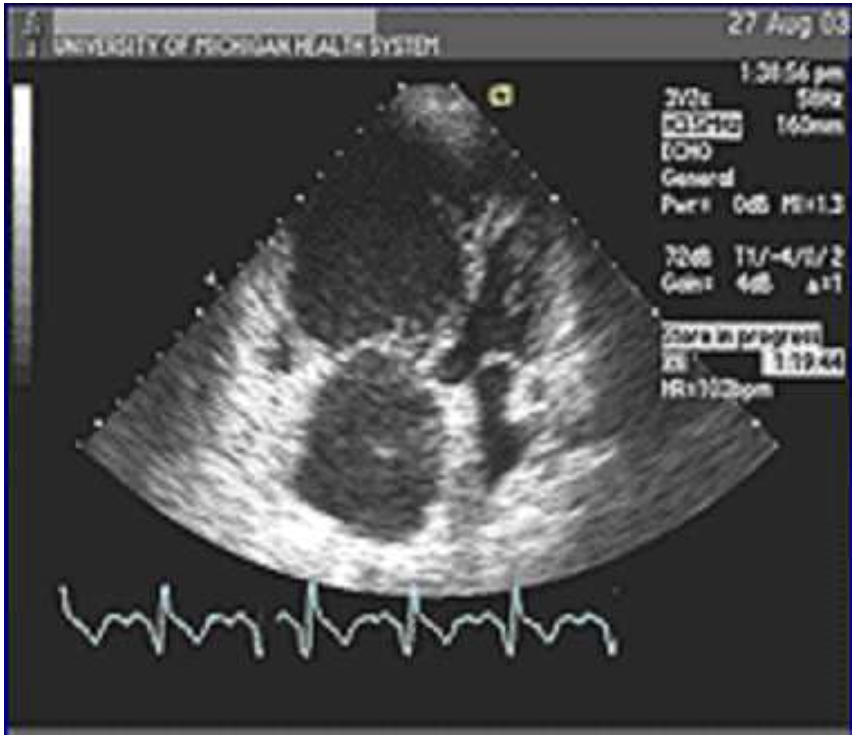
Algorithm for the diagnosis of pulmonary hypertension (PH)



Apical 4-chamber

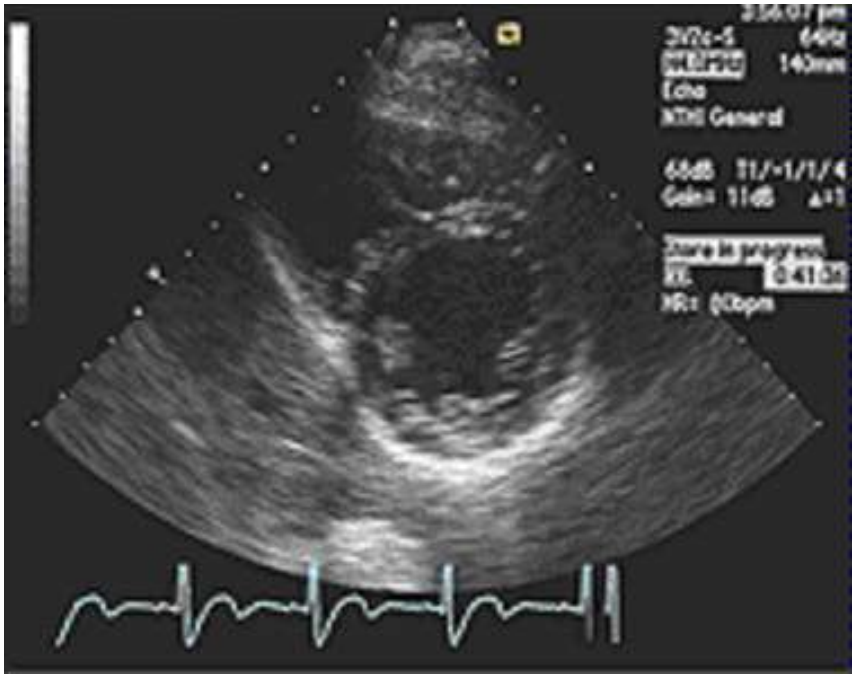


Normal

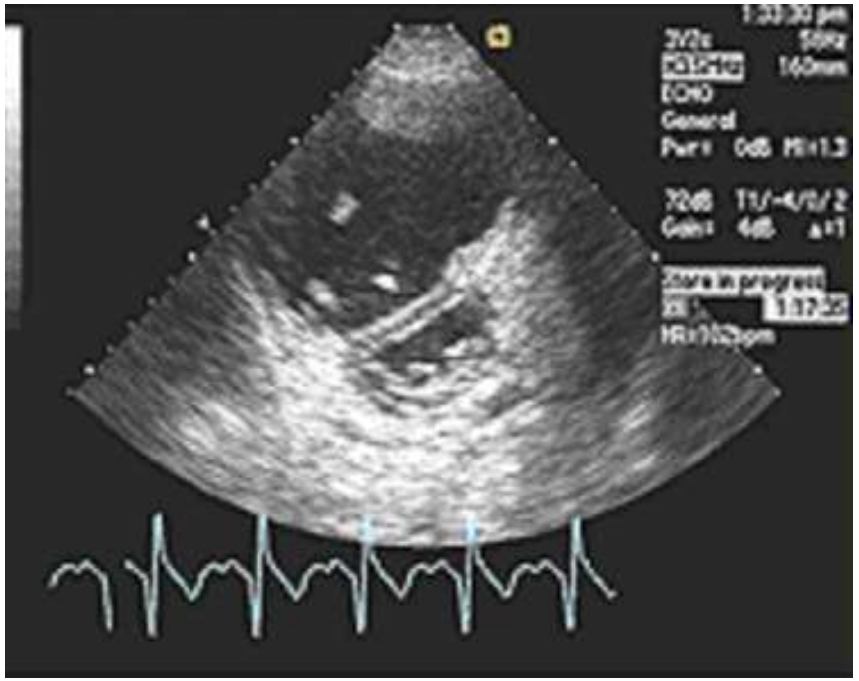


PAH

Parasternal short axis

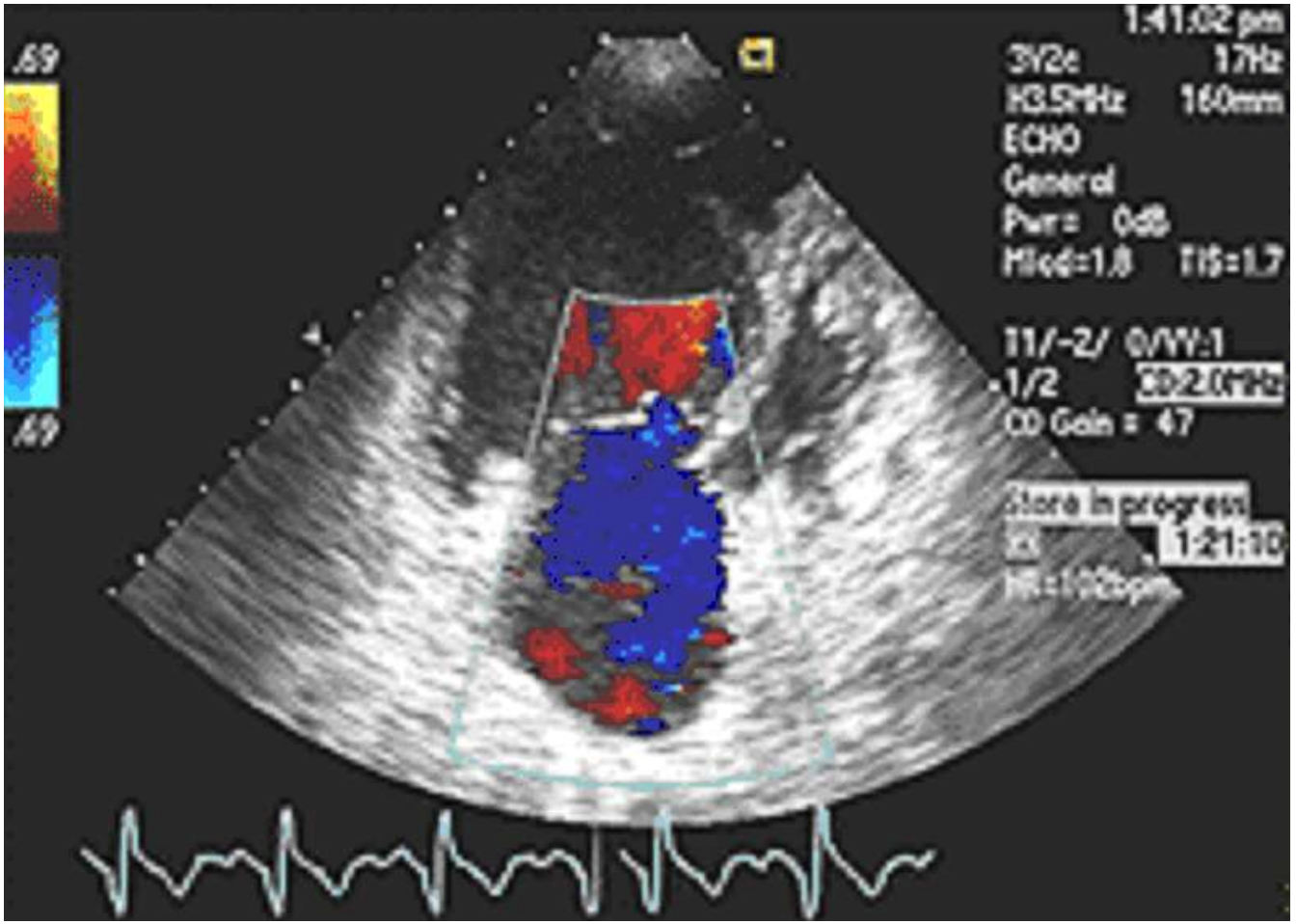


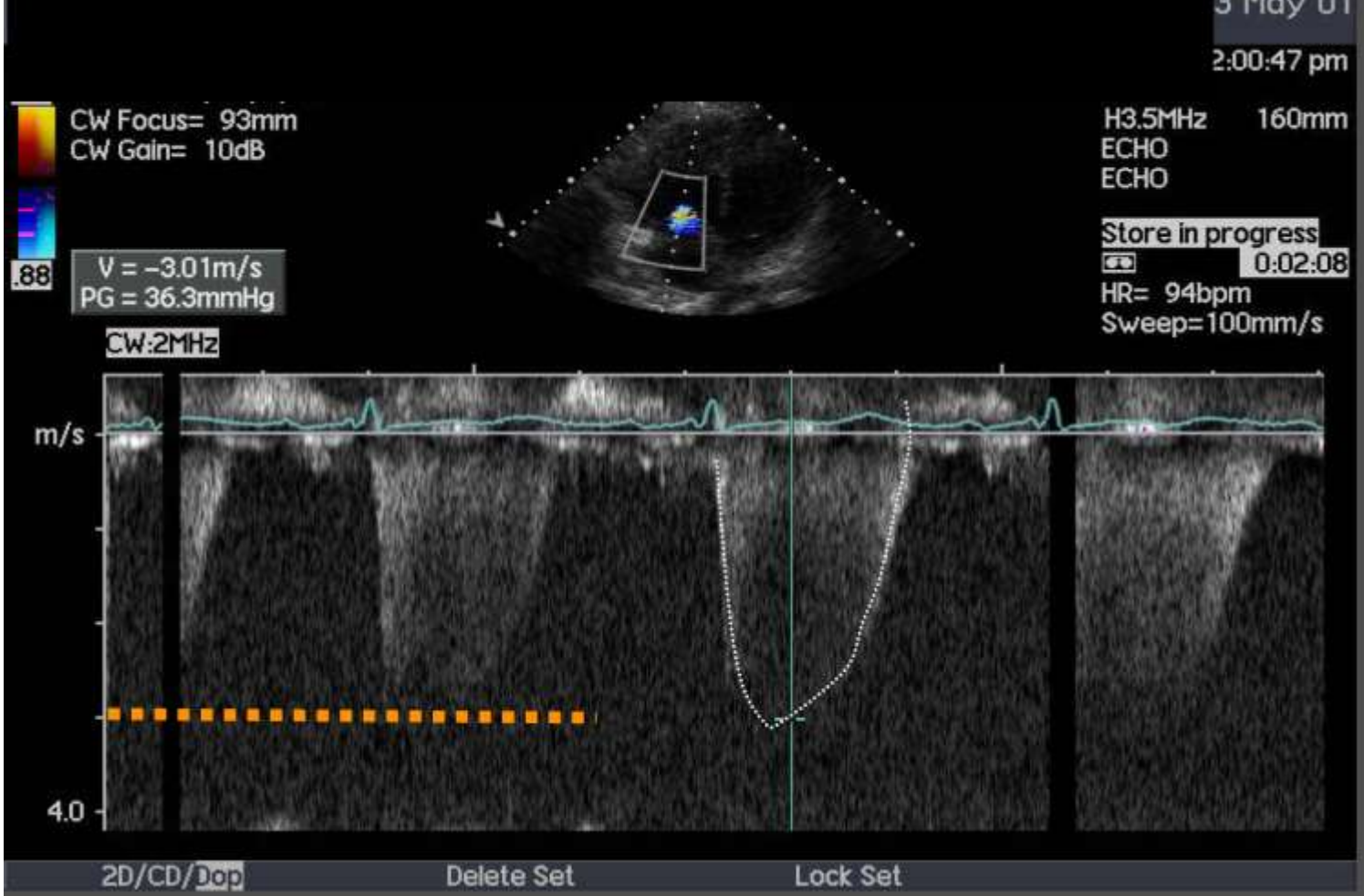
Normal



PAH

Tricuspid Regurgitation





Tricuspid insufficiency Vmax

TI Pressure Gradient = 4 $Vmax^2$

PASP = 4 x $Vmax^2$ + RAP*(est)*

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	

Echocardiographic probability of pulmonary hypertension (PH) in symptomatic patients with a suspicion of PH

Peak tricuspid regurgitation velocity $m \cdot s^{-1}$	Presence of other echocardiographic "PH signs"#	Echocardiographic probability of PH
≤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	

Echocardiographic signs suggesting pulmonary hypertension (PH) used to assess the probability of PH in addition to tricuspid regurgitation velocity measurement

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and right atrium
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 ms and/or mid-systolic 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 $m \cdot s^{-1}$	Right atrial area (end-systole) >18 cm^2
	Pulmonary artery diameter >25 mm	

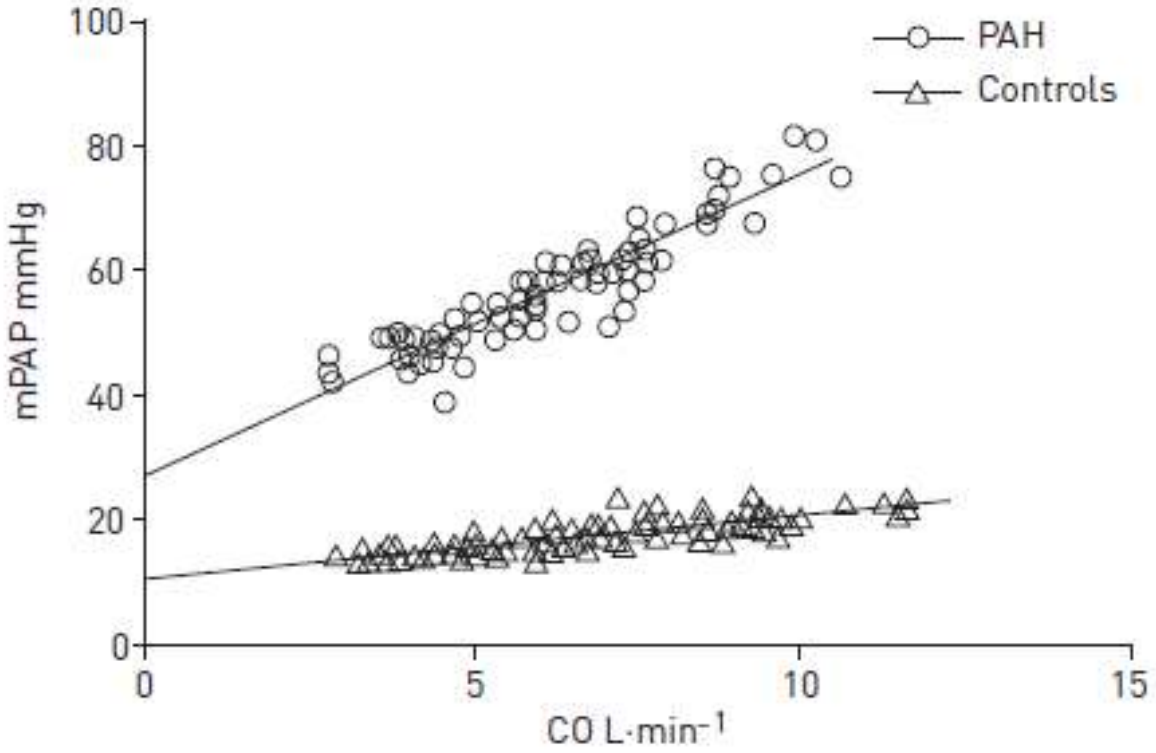
Diagnostic management (2015…)

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[d]	Class[a]	Level[b]	With risk factors or associated conditions for PAH or CTEPH[c]	Class[a]	Level[b]
Low	Alternative diagnosis should be considered	IIa	C	Echo follow-up should be considered	IIa	C
Intermediate	Alternative diagnosis, echo follow-up, should be considered	IIa	C	Further assessment of PH including RHC should be considered[e]	IIa	B
	Further investigation of PH may be considered[e]	IIb				
High	Further investigation of PH (including RHC[e]) is recommended	I	C	Further investigation of PH[e] including RHC is recommended	I	C

“Unmasking” PVD

- A rise in resting PH pressure is a late event in the natural history of PVDs, because of microvascular “reserves”.
- PAP rises only when ⩾50% of the microcirculation has been lost and much effort has been directed towards detecting PVD at an earlier (and potentially more treatable) stage.
- Intuitively by increasing CO to demonstrate increased resistance is a logical idea.
- PH patients first develop symptoms on exercise.

The slope of the mean pulmonary arterial pressure (mPAP)–cardiac output (CO) relationship is different in normal control versus pulmonary arterial hypertension (PAH) subjects



Lau EMT, et al. Dobutamine stress echocardiography for the assessment of pressure-flow relationships of the pulmonary circulation. Chest 2014; 146: 959–966.

A Clinical and Echocardiographic Score to Identify Pulmonary Hypertension Due to HFpEF

EMMANUELLE BERTHELOT, MD,[1] DAVID MONTANI, MD, PhD,[2,3,4] VINCENT ALGALARRONDO, MD, PhD,[2,5] CÉLINE DREYFUSS, MD,[1] RAED RIFAI, MD,[1] ANOUAR BENMALEK, PhD,[6] XAVIER JAIS, MD,[2,3,4] AMIR BOUCHACHI, MD,[1] LAURENT SAVALE, MD,[2,3,4] GERALD SIMONNEAU, MD,[2,3,4] DENIS CHEMLA, MD, PhD,[1,7] MARC HUMBERT, MD, PhD,[2,3,4] OLIVIER SITBON, MD, PhD,[2,3,4] AND PATRICK ASSAYAG, MD, PhD[1,2]

Table 2. Logistic Regression to Predict PH-HFpEF

	Multivariate Analysis		
	OR	95%CI	*P*
Diabetes mellitus	8.85	2.00–39.12	.004
Atrial fibrillation	26.1	1.31–520.1	.033
LV mass index	2.076	1.46–2.96	<.001
Left atrial area	14.29	3.61–56.53	<.001
RV end-diastolic area	0.84	0.76–0.93	.001

Chest computed tomography (CT)

- Chest computed tomography (CT) demonstrating right ventricular dilation, right atrial dilation, enlarged main pulmonary artery (diameter ⩾29 mm) or a main pulmonary artery/ascending aorta diameter ratio ⩾1 is suggestive of PH.
- High-resolution non-contrast examination can identify parenchymal lung disease and discriminate between PH lung disease and PAH (group 3 versus group 1).

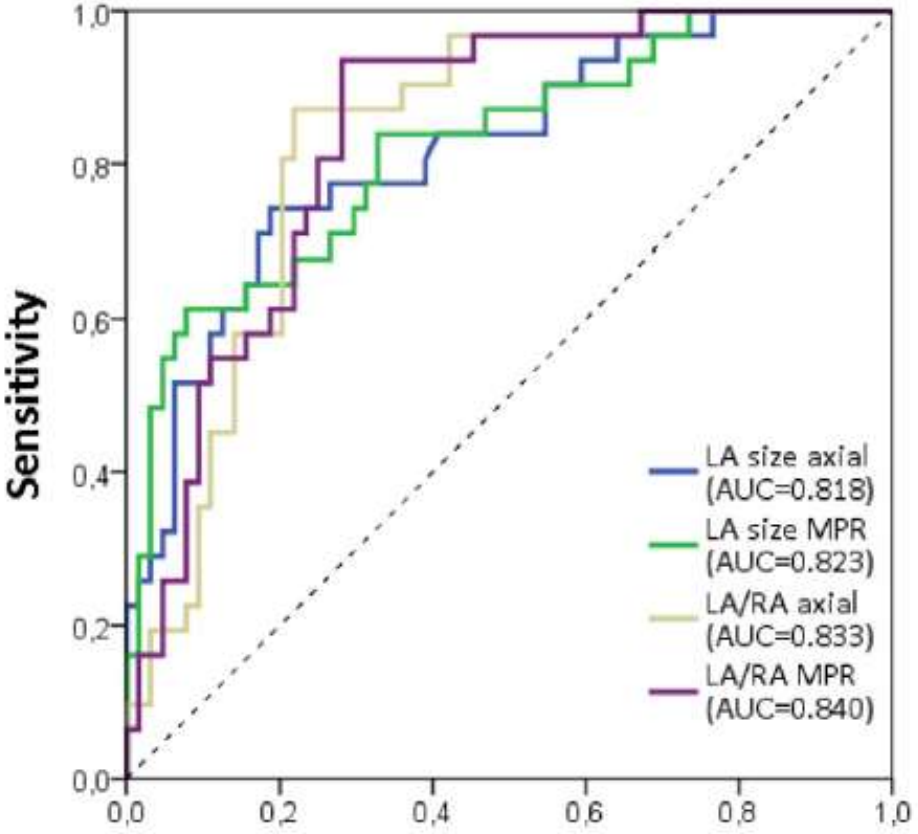
Shen Y, Wan C, Tian P, et al. CT-Base pulmonary artery measurement in the detection of pulmonary hypertension: a meta-analysis and systematic review. Medicine 2014; 93: e256–e264.

PAH or HEFpEF?

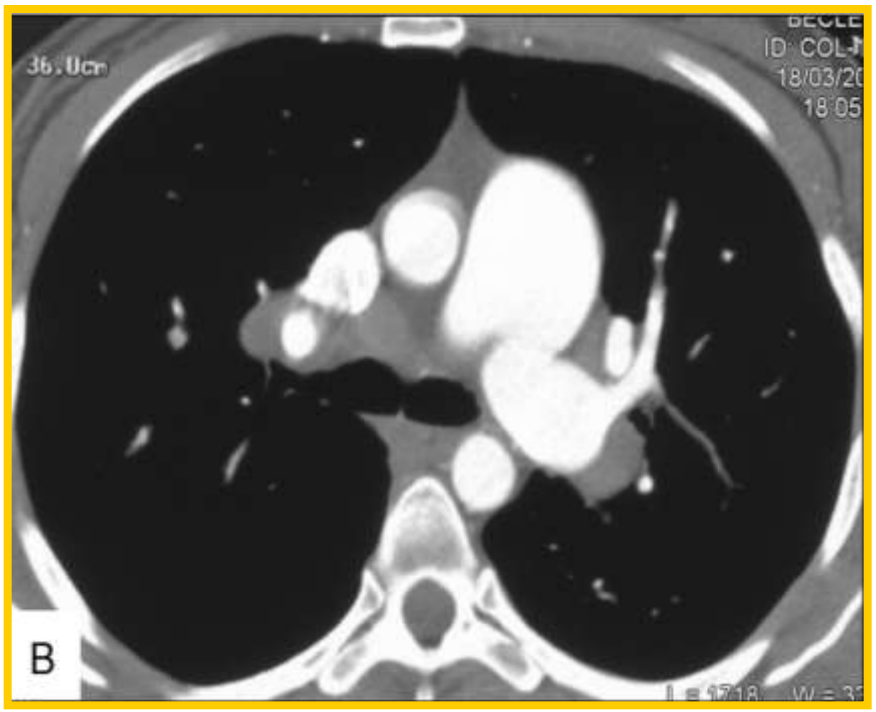
CTA-derived left to right atrial size ratio distinguishes between pulmonary hypertension due to heart failure and idiopathic pulmonary arterial hypertension

Anna E. Huis in 't Veld [a,1], Alexander G. Van Vliet [a,1], Onno A. Spruijt [a,1], M. Louis Handoko [b,1], J. Tim Marcus [a,1], Anton Vonk Noordegraaf [a,1], Harm-Jan Bogaard [a,*,1]

International Journal of Cardiology 223 (2016) 723–728

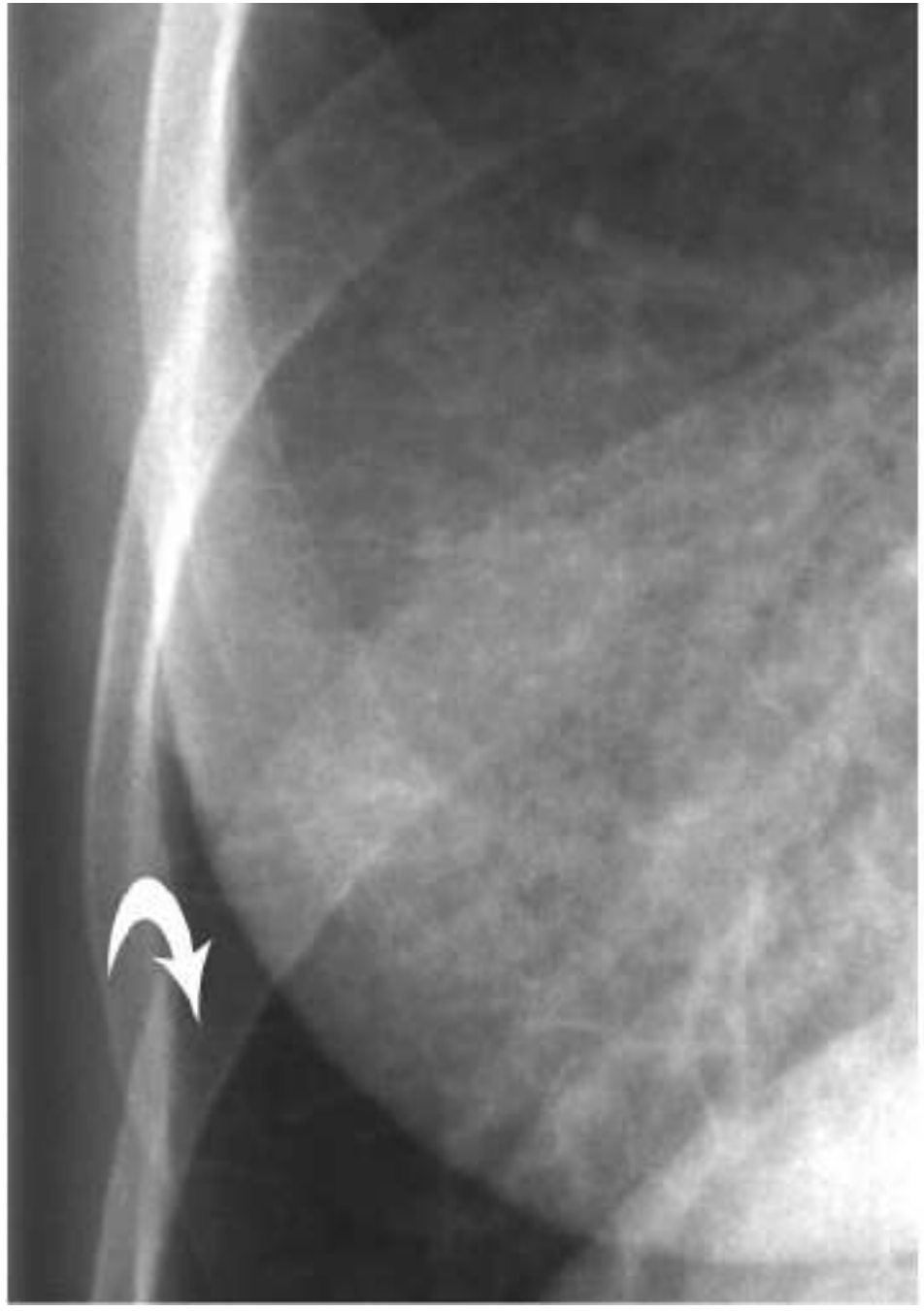


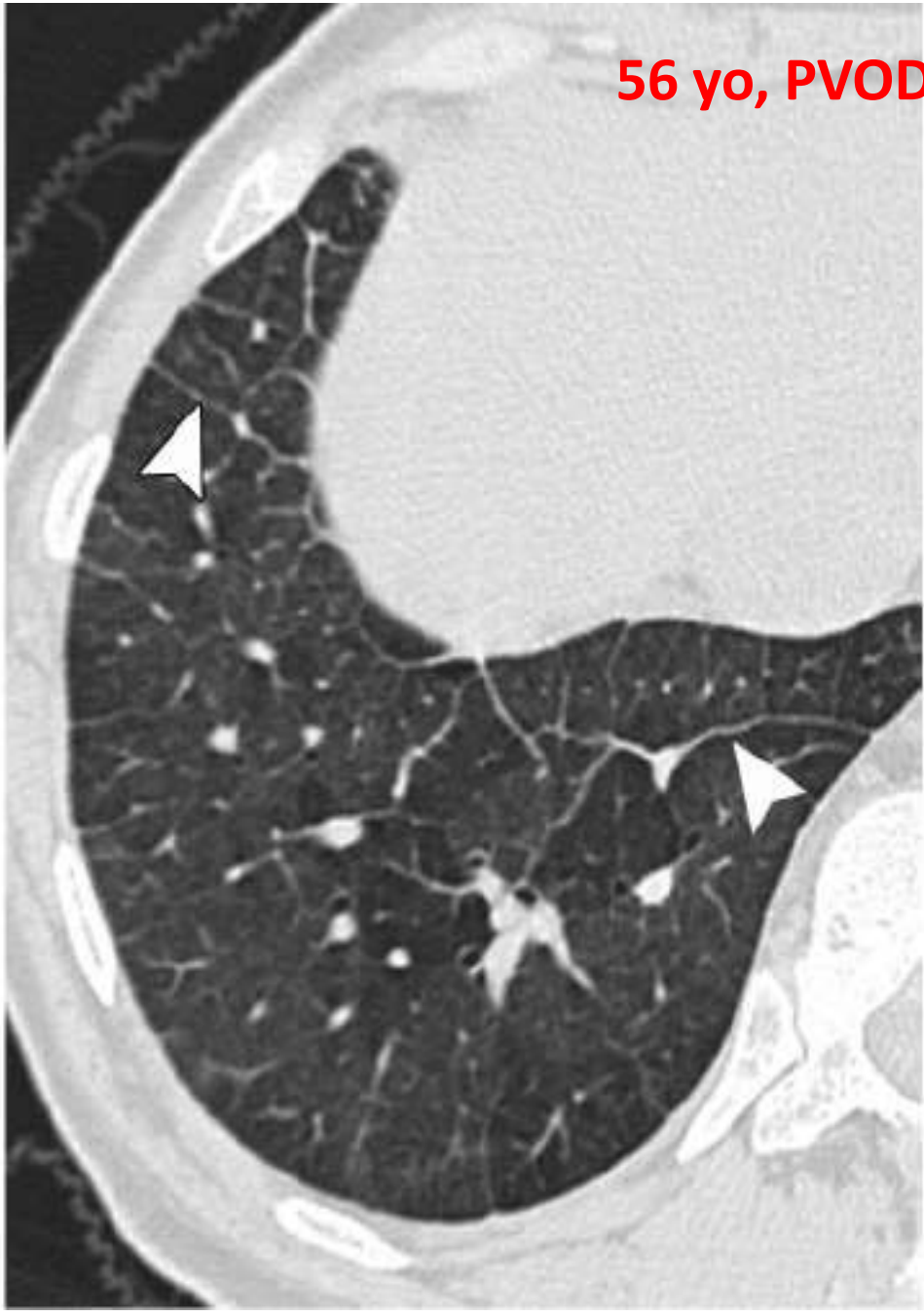
Pulmonary Veno-Occlusive Disease



- ✓ Septal lines
- ✓ Ground glass opacities
- ✓ Mediastinal lymphadenopathy
- ✓ 100% spec, 66% sens

Resten et al. AJR 2004;183:65-70




56 yo, PVOD

Subclinical right ventricular dysfunction-MRI

- Parametric mapping

A meta-analysis of Ventricular Mass Index revealed a positive likelihood ratio of 5, indicating a modest ability to differentiate PH patients from healthy controls.

Late gadolinium enhancement

T1 mapping: a non-invasive technique for extracellular volume

- Right ventricular strain

Magnetic resonance strain indices are similar to echocardiographic indices, but longitudinal and circumferential strain measurements are more reliable.

- Pulmonary artery four-dimensional flow imaging

Data extraction is complex and clinical trials are necessary to explore the benefits of four-dimensional flow magnetic resonance over standard practices.

Novel diagnostic modalities

Innovative imaging

- V/Q single photon emission CT
- Dual-energy CT: pulmonary perfusion
- Three-dimensional dynamic contrast-enhanced magnetic resonance: lung perfusion
- Functional magnetic resonance imaging: ventilation

Pulmonary Function Tests

- LFTs should include total lung capacity and diffusing capacity of the lung for carbon monoxide (DLCO).
- In most patients with PAH there is a mild restrictive component.
- Marked reduction in DLCO (<60% of predicted) or severe exertional hypoxaemia can indicate pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis.

Hadinnapola C, Bleda M, Haimel M, et al. Phenotypic characterization of EIF2AK4 mutation carrier in a large cohort of patients diagnosed clinically with pulmonary arterial hypertension. Circulation 2017; 136: 2022–2033.

Cardiopulmonary exercise testing

- Cardiopulmonary exercise testing (CPET) for diagnostic purposes can be done non-invasively or with haemodynamic testing.
- CPET can quantify the degree of relative hypoperfusion of the lung and the systemic circulation that occurs during exercise in patients with PH, and can grade the severity of exercise limitation and assess responses to therapy.

Berry NC, et al. Protocol for exercise hemodynamic assessment: performing an invasive cardiopulmonary exercise test in clinical practice. Pulm Cir 2015; 5: 610–618.

Cardiopulmonary exercise testing

- Accurate utilisation of CPET requires performance by a competent facility and interpretation by a clinician with expertise in gas exchange in conjunction with the pt's history, physical and laboratory findings.
- CPET is useful for determining the nature of the exercise limitation in patients with unexplained dyspnoea, but should not be used as the sole screening tool for asymptomatic subjects at risk for developing PAH; CPET can help evaluate cardiopulmonary limitations and assess pulmonary vascular involvement in these patients; emerging evidence suggests that CPET may be useful for evaluating symptomatic patients at high risk for developing PAH.

Cardiopulmonary exercise testing

- Abnormalities in effort-independent ratio of minute ventilation to carbon dioxide production ($\dot{V}'E/\dot{V}'CO_2$) and end-tidal carbon dioxide tension ($PETCO_2$) obtained during CPET have been used to estimate the likelihood of PH (lower peak oxygen uptake ($\dot{V}'O_2$) and/or higher $\dot{V}'E/\dot{V}'CO_2$ signifying an increasing likelihood of pulmonary vascular disease).

Genetics

- Counselling offered by French PH referral centres have identified PAH mutations in 16.9% of presumed sporadic PAH patients, in 89% of patients with a family history and in asymptomatic first-degree relatives of mutation carriers pre-emptively screened.
- Longevity data indicates a lifelong risk of developing disease in 14% of male and 42% of female carriers, prompting the recommendation for annual echocardiography in asymptomatic carriers.

Biomarkers

- Natriuretic peptides
- Numerous potential biomarkers (e.g. asymmetric dimethylarginine, cystatin C, volatile exhaled gases, exhaled nitric oxide (NO) fraction (FENO) and NOx derivates) have been associated with endothelial cell dysfunction, inflammation, epigenetics, cardiac function, oxidative stress, metabolism, extracellular matrix and exhaled breath condensate; **while novel, these have not yet demonstrated sensitivity and specificity for diagnosis, risk assessment or management of PH.**

Right Heart Cath

- RHC is a technically demanding procedure that requires meticulous attention to detail to obtain clinically useful information.
- To obtain high-quality results and to be of low risk to patients, the procedure should be limited to expert centres.

ESC/ERS guidelines 2015

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Complications of Right Heart Catheterization Procedures in Patients With Pulmonary Hypertension in Experienced Centers

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Research Article

Pulmonary Circulation

Safety of right heart catheterization for pulmonary hypertension in very elderly patients

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Abstract

Right heart catheterization (RHC) is the reference test in diagnosing pulmonary hypertension (PH). The increasing age of patients at the time of diagnosis raises the issue of the morbidity of this invasive test in elderly individuals. We hypothesized that the morbidity associated with RHC would be increased in elderly patients and highlight differences in hemodynamic characteristics compared to younger patients. A retrospective study was conducted in a regional referral center for PH. Data for all consecutive RHCs performed during the study period were analyzed. Over a five-year period, 1060 RHCs were performed. Of the patients, 228 (21.5%) were aged $\geq$75 years and 832 (78.5%) were aged <75 years. Duration of the procedure and site of puncture did not differ according to age group (all $P > 0.05$). Nine procedures (0.9%) led to complications: three (1.3%) in patients aged >75 years and six (0.7%) in younger patients aged ($P = 0.5$). Eight were local vascular injuries, directly related to a femoral vein puncture ($P < 0.001$). Pulmonary arterial pressure and cardiac output were lower in patients aged >75 years than in younger patients ($P = 0.001$). RHC may be performed regardless of patient age. The rate of RHC complications is not increased in individuals aged >75 years. As most complications were related to femoral vein puncture, this route should be avoided whenever possible.

Keywords

hemodynamics, morbidity, pulmonary hypertension

Date received: 15 June 2018; accepted: 17 August 2018

Pulmonary Circulation 2018; 8(4) 1–4

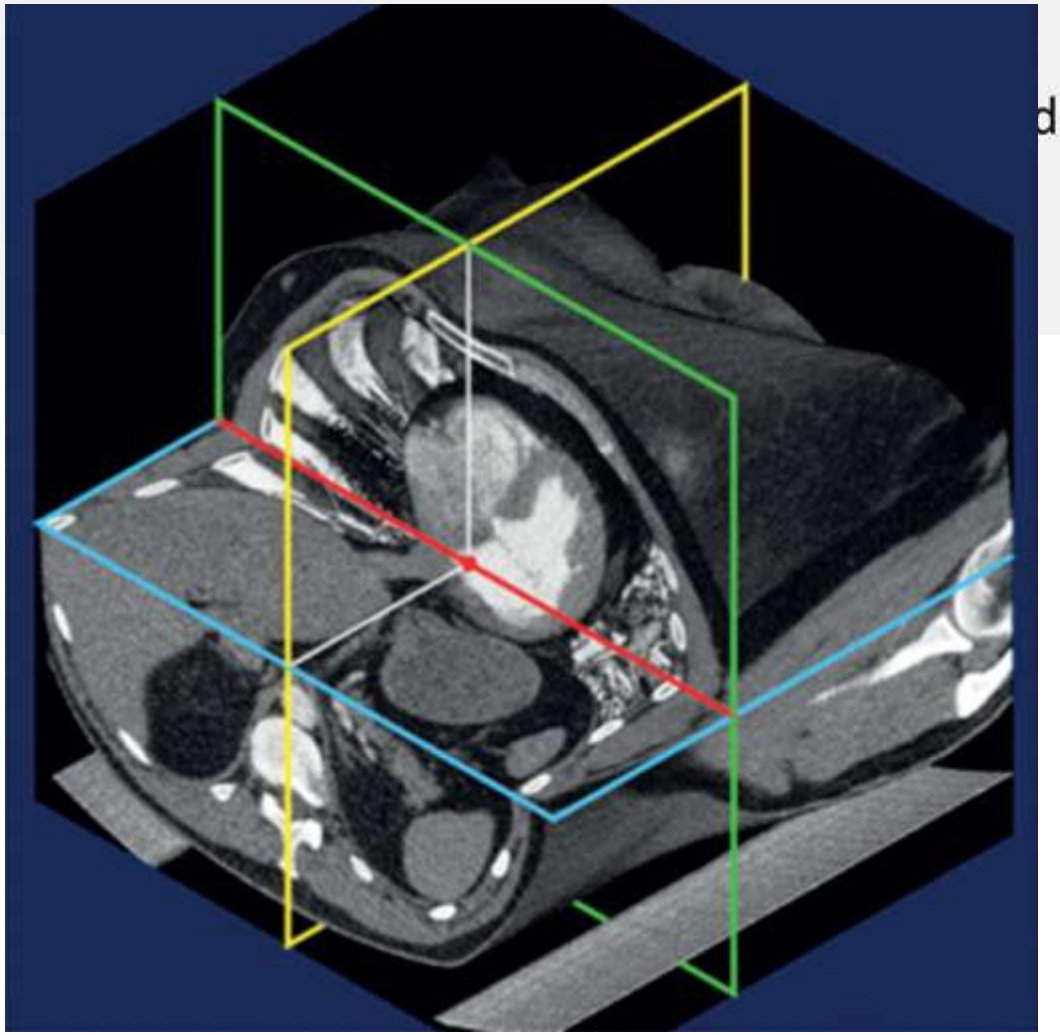
Table 10 **Recommendations for right heart catheterization in pulmonary hypertension**

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	
RHC is recommended in patients with congenital cardiac shunts to support decisions on correction (Table 24)	I	C	
RHC is recommended in patients with PH due to left heart disease (group 2) or lung disease (group 3) if organ transplantation is considered	I	C	
When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP	IIa	C	
RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist in the differential diagnosis and support treatment decisions	IIb	C	
RHC is indicated in patients with CTEPH (group 4) to confirm the diagnosis and support treatment decisions	I	C	

Measurement and reading of pressure tracings

- Measurement

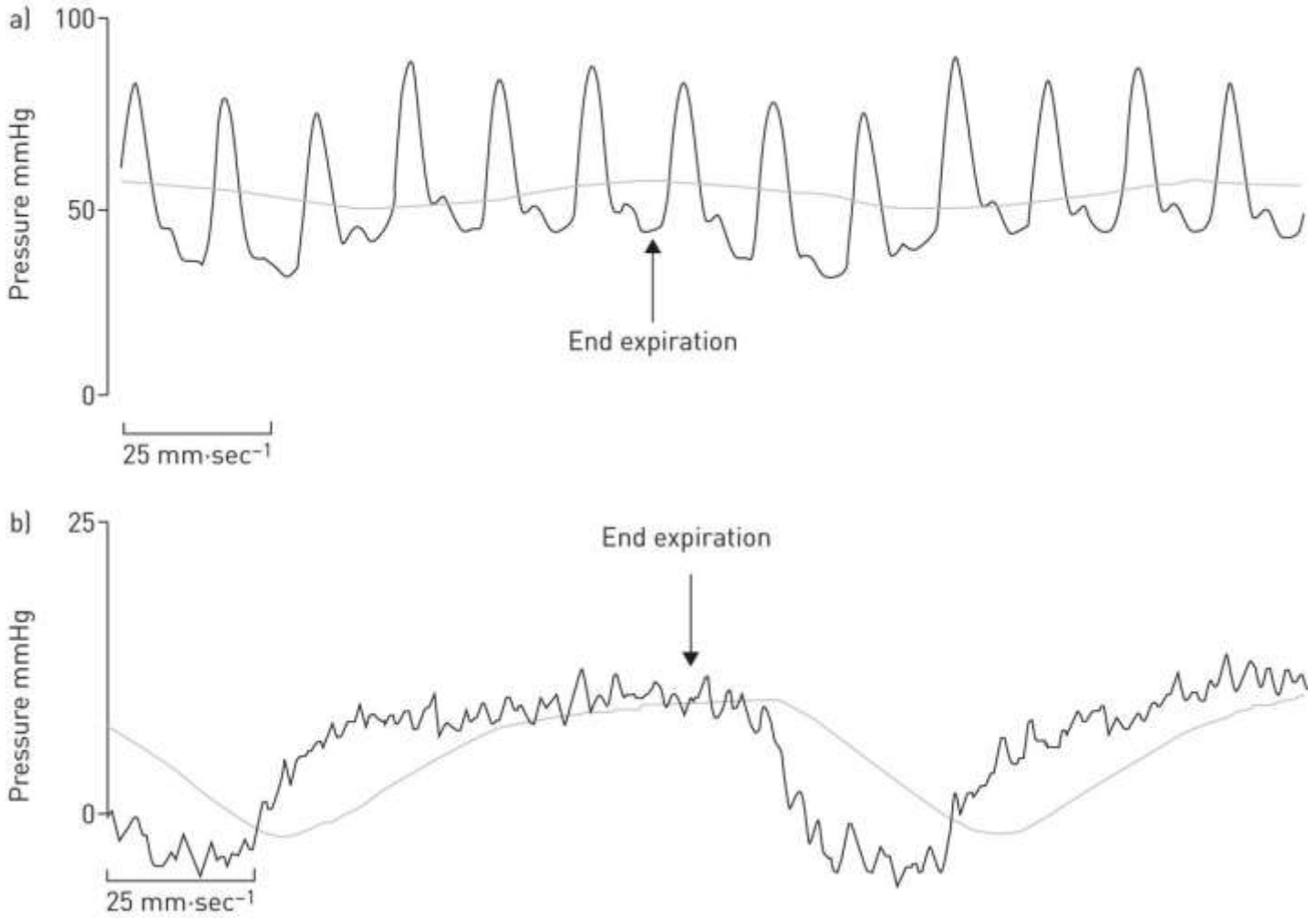
- Zero point
- Point of reading



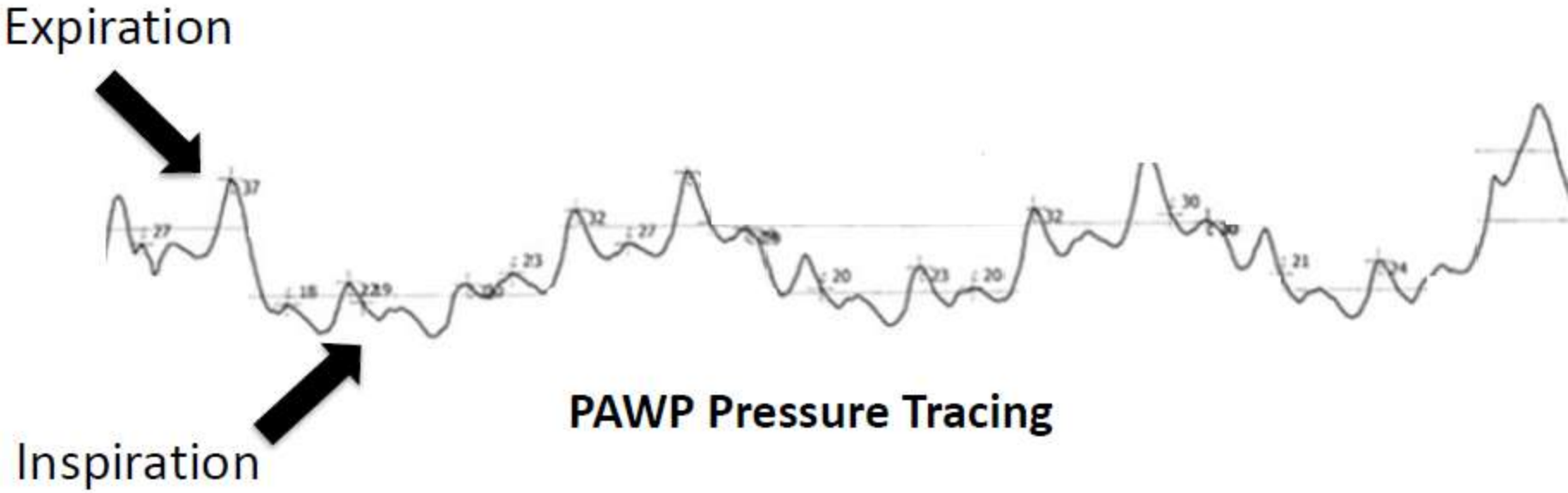
dilated arteries)

Kovacs G, Avian A, Pienn M, et al. Reading pulmonary vascular pressure tracings. How to handle the problems of zero leveling and respiratory swings. Am J Respir Crit Care Med 2014; 190: 252–257.

Representative pressure tracings of a) pulmonary arterial pressure and b) pulmonary arterial wedge pressure (PAWP).



Stephan Rosenkranz, and Ioana R. Preston Eur Respir Rev 2015;24:642-652

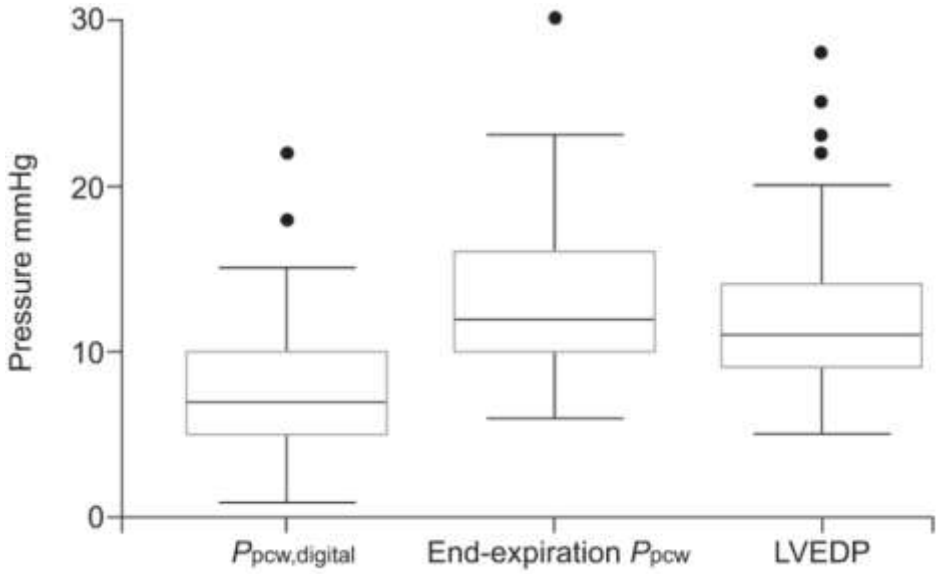

Expiration
Inspiration
PAWP Pressure Tracing

Digitized mean

Risk of misclassifying post- as precapillary PH:

≈30%

(Ryan et al. 2012)

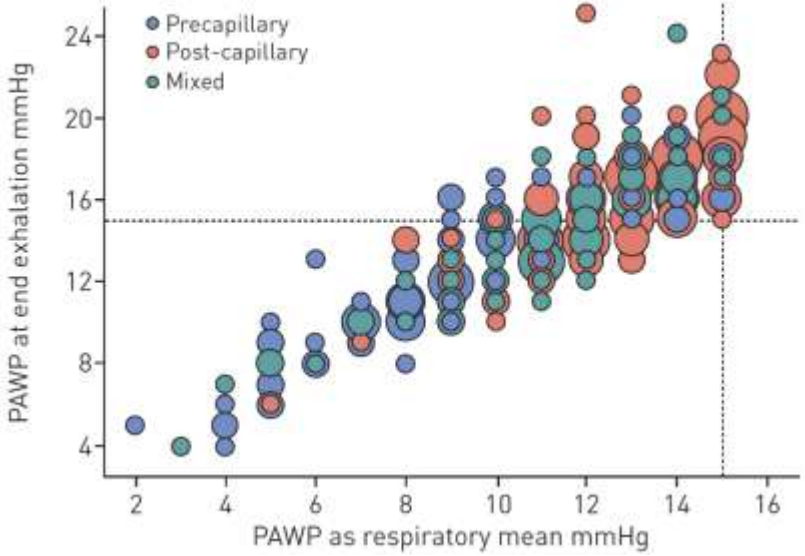


Expiration

Digitized mean

PAWP Pressure Tracing

Inspiration



End-expiratory

Risk of misclassifying pre- as postcapillary PH:

≈30%

(LeVarge et al. 2014)

Expiration

End-expiratory mean

PAWP Pressure Tracing

Inspiration

The limit

- In 1961, a report of the World Health Organization (WHO) Expert Committee on Chronic Cor Pulmonale mentioned clearly that the mean pulmonary arterial pressure (mPAP) does not normally exceed 15 mmHg when the subject is at rest in a lying position, and that the value was little affected by age and never exceeded 20 mmHg.

World Health Organization. Chronic cor pulmonale. Report of an expert committee. World Health Organ Tech Rep Ser 1961; 213: 35.

1st World Symposium on Pulmonary Hypertension

- PH has been defined as mPAP ⩾25 mmHg measured by right heart catheterisation (RHC) in the supine position at rest.
- In Geneva at 1973 it was recognised that this upper limit of normal mPAP of 25 mmHg was somewhat empirical and arbitrarily defined.

Hatano S, Strasser T, eds. Primary Pulmonary Hypertension. Report on a WHO Meeting. Geneva, World Health Organization, 1975.

Definition: mPAP ⩾25

- This definition remained unchanged during the subsequent World Symposiums on Pulmonary Hypertension meetings from 1998 to 2013, at least in part to preclude potential overdiagnosis and overtreatment of PH.

What is actually the upper limit of normal mPAP?

- In 1187 normal subjects from 47 studies mPAP at rest was 14.0±3.3 mmHg; this value was independent of sex and ethnicity, and was only slightly influenced by age and posture.
- Considering this mPAP of 14 mmHg, two standard deviations would suggest mPAP >20 mmHg as above the upper limit of normal (i.e. above the 97.5th percentile).
- This definition is, therefore, no longer arbitrary, but based on a scientific approach.

Kovacs G, et al. Eur Respir J 2009; 34: 888–894

A value of mPAP used in isolation is not accurate enough to characterise a clinical condition

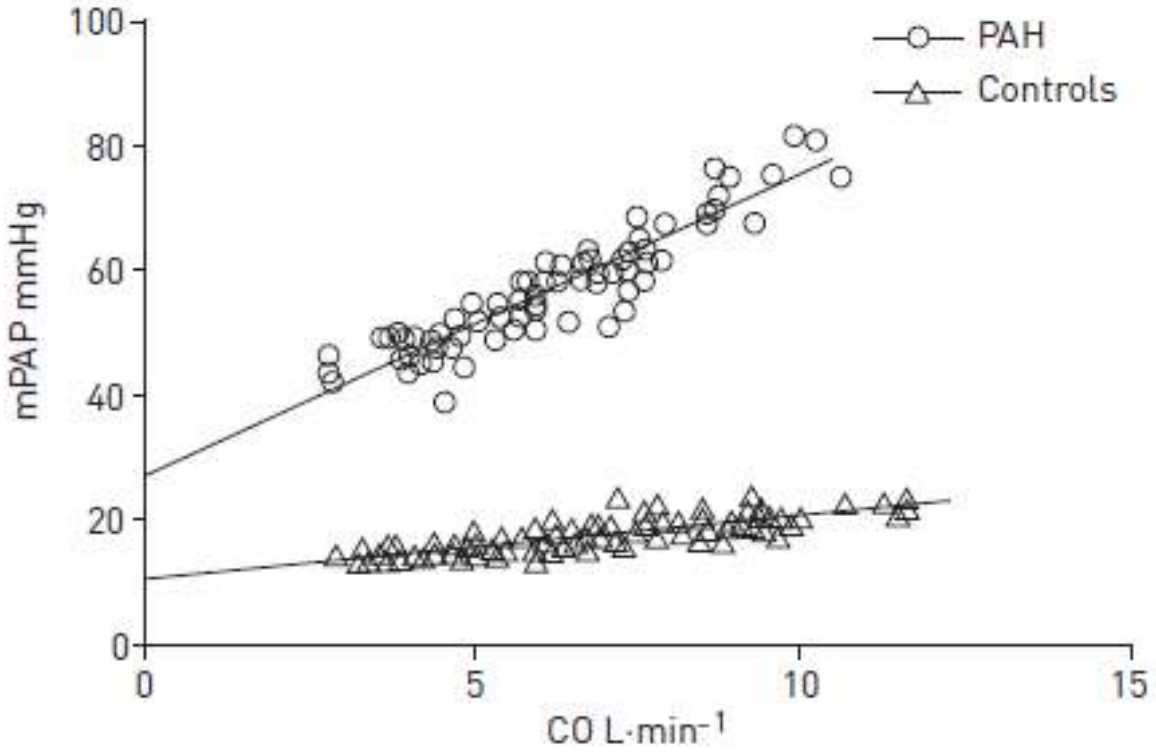
- Whatever the mPAP cut-off value considered for defining PH (⩾25 or >20 mmHg), it is important to emphasise that this value used in isolation cannot characterise a clinical condition and does not define the pathological process per se.

To identify pre-capillary PH suggesting the presence of PVD, an above normal elevation of pulmonary vascular resistance should be included in the definition

- The cut-off value of PVR ⩾3 WU is also quite arbitrary since some recent data suggest that PVR >2 WU could be also considered abnormal*.
- In this sense, the use of a cut-off value of PVR ⩾3 WU is conservative, suggesting the presence of a manifest pre-capillary PH.

*Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013; 62: D42–D50.

The slope of the mean pulmonary arterial pressure (mPAP)–cardiac output (CO) relationship is different in normal control versus pulmonary arterial hypertension (PAH) subjects



Lau EMT, et al. Dobutamine stress echocardiography for the assessment of pressure-flow relationships of the pulmonary circulation. Chest 2014; 146: 959–966.

Dynamic testing for the identification of HF-PH

- Fluid loading

Fluid challenge with 7 ml/kg NS increases PAWP, more in post-capillary PH(+7) than in pre-capillary PH(+3) or no-PH. A cut-off 18 mmHg allows to re-classify 6-8% of pts with pre-capillary PH or normal hemodynamics at baseline.

D'Alto, Chest, 2016

Exercise-induced PH (EIPH)

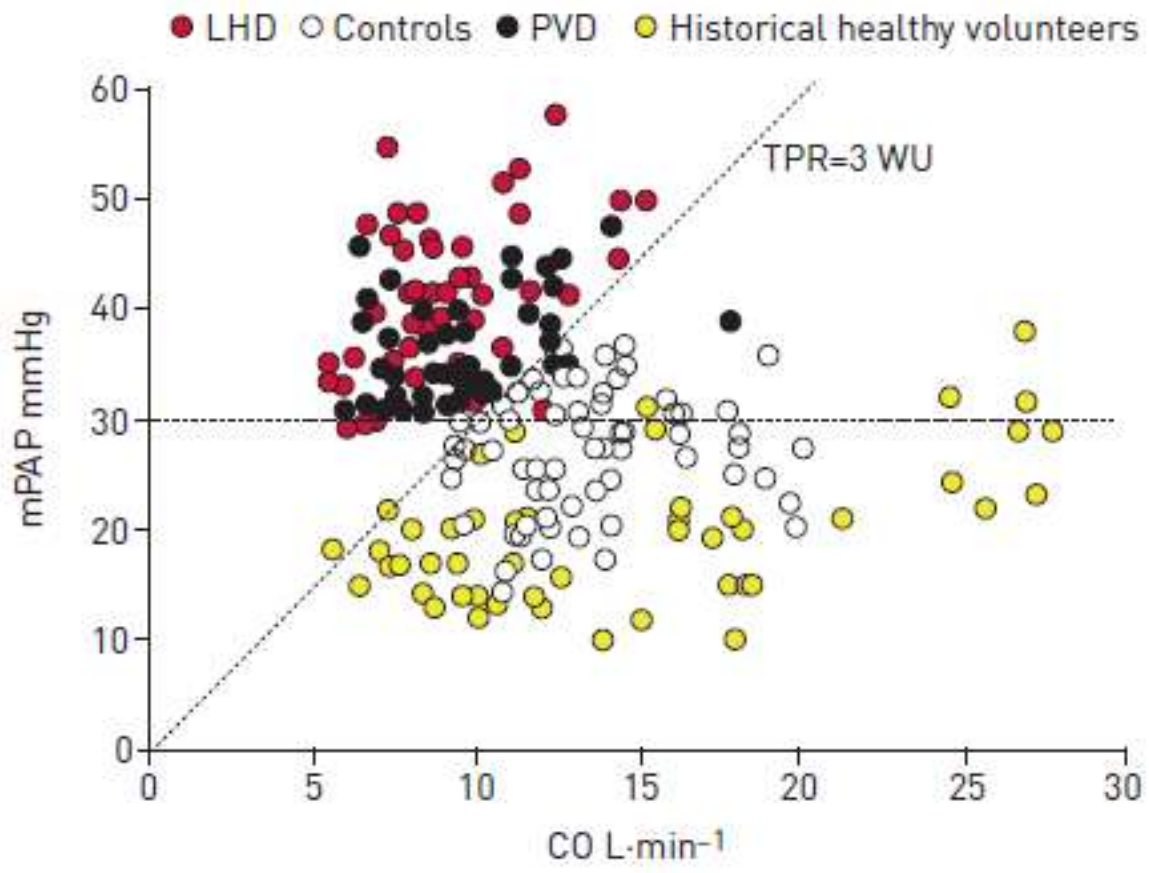
- mPAP >30 mmHg at a CO >10 L/min, or
- maximum total VR >3 WU,

measured either invasively or noninvasively

- *The limits of normal of exercise PAWP or VEDP have not yet been defined with certainty*

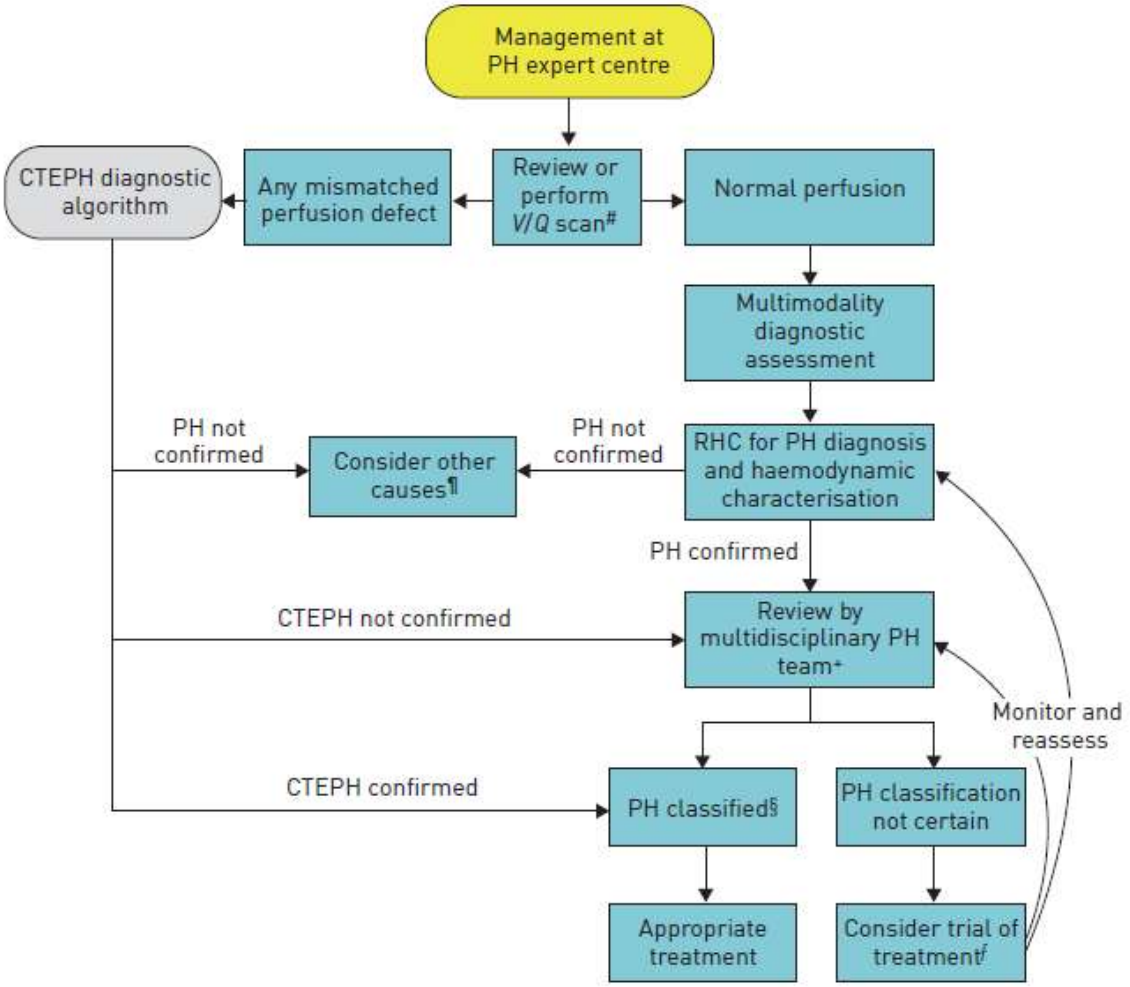
Naeije, Progr Card Dis, 2016

The slope of the mean pulmonary arterial pressure (mPAP)–cardiac output (CO) relationship is different in normal control versus pulmonary arterial hypertension (PAH) subjects



Herve P, Lau EM, Sitbon O, et al. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J 2015; 46:728–737.1

Algorithm for the diagnosis of pulmonary hypertension (PH)



Research Article

Pulmonary Circulation

Changes in hemodynamic classification over time are common in systemic sclerosis-associated pulmonary hypertension: insights from the PHAROS cohort

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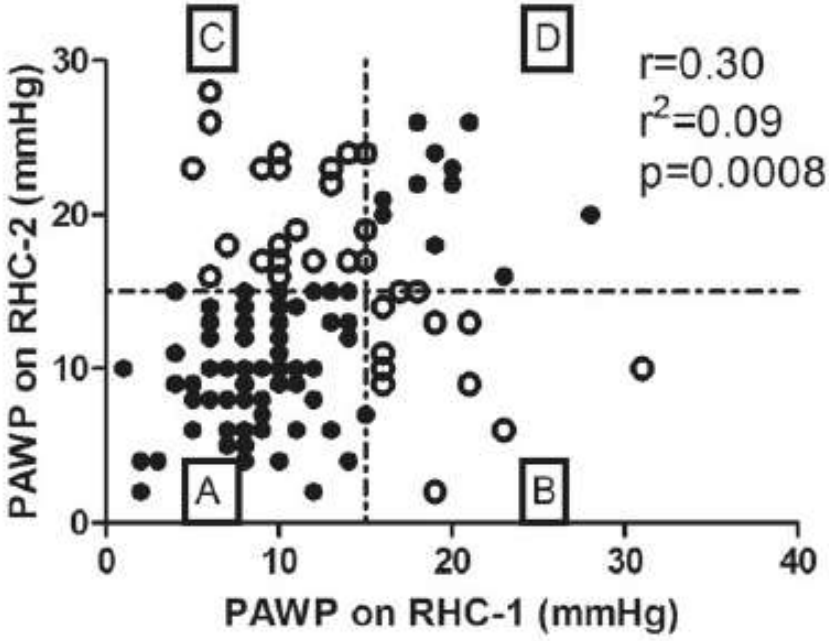

30%

36/120

1.4 yr

Thank you for your attention