INSTITUTE OF MOLECULAR BIOMEDICINE

Cor pulmonale

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www.imbm.sk

Introduction

2,71828182845904523536028747135 2

e

Leonhard Euler (1707-1783)

Introduction

Ulf von Euler (1905-1983)

Nobel prize in 1970

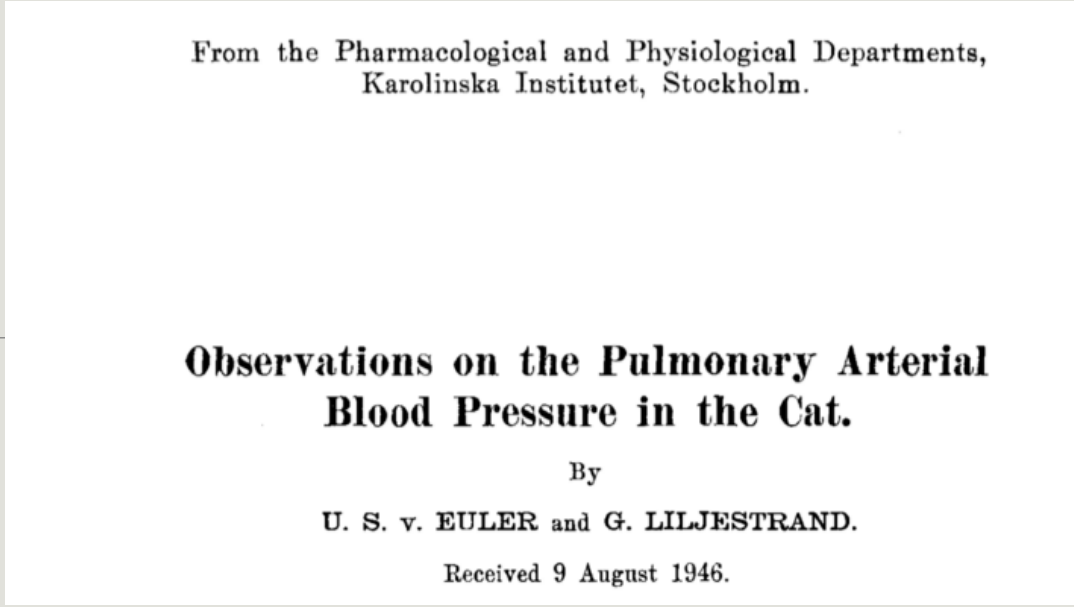
neurotransmitters

Göran Liljestrand (1886-1968)

Karolinska Institute

Introduction

Euler–Liljestrand mechanism



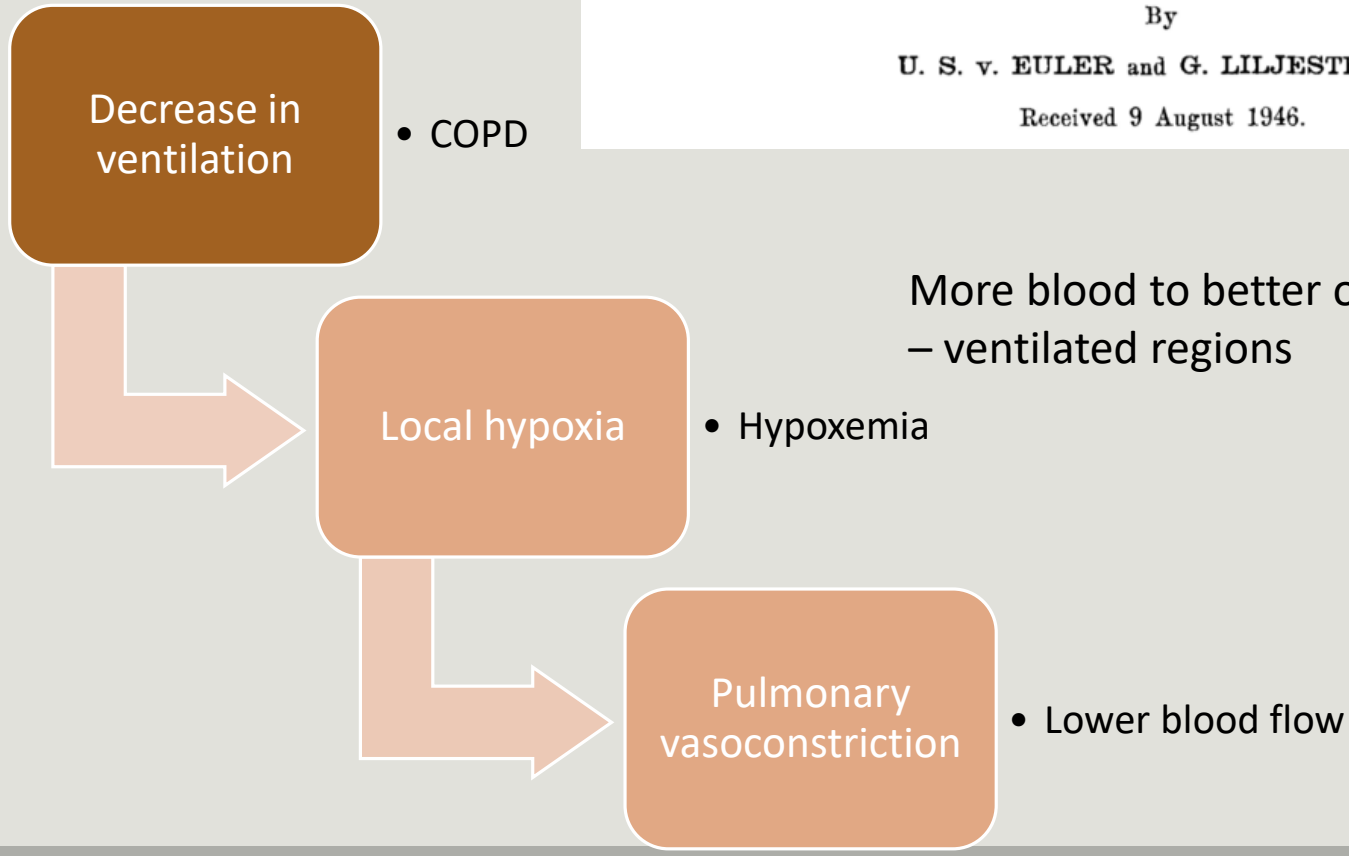
From the Pharmacological and Physiological Departments,
Karolinska Institutet, Stockholm.

Observations on the Pulmonary Arterial Blood Pressure in the Cat.

By

U. S. v. EULER and G. LILJESTRAND.

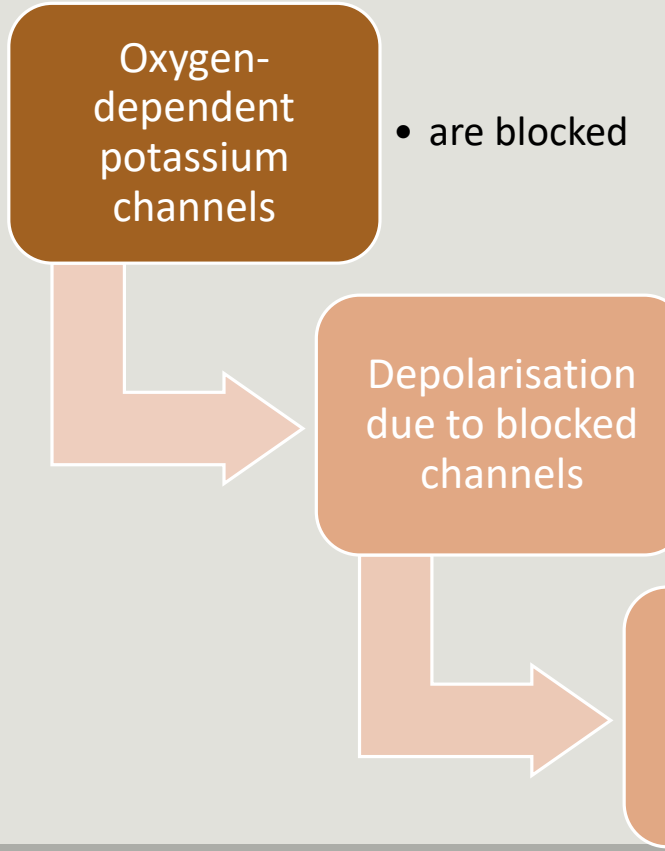
Received 9 August 1946.



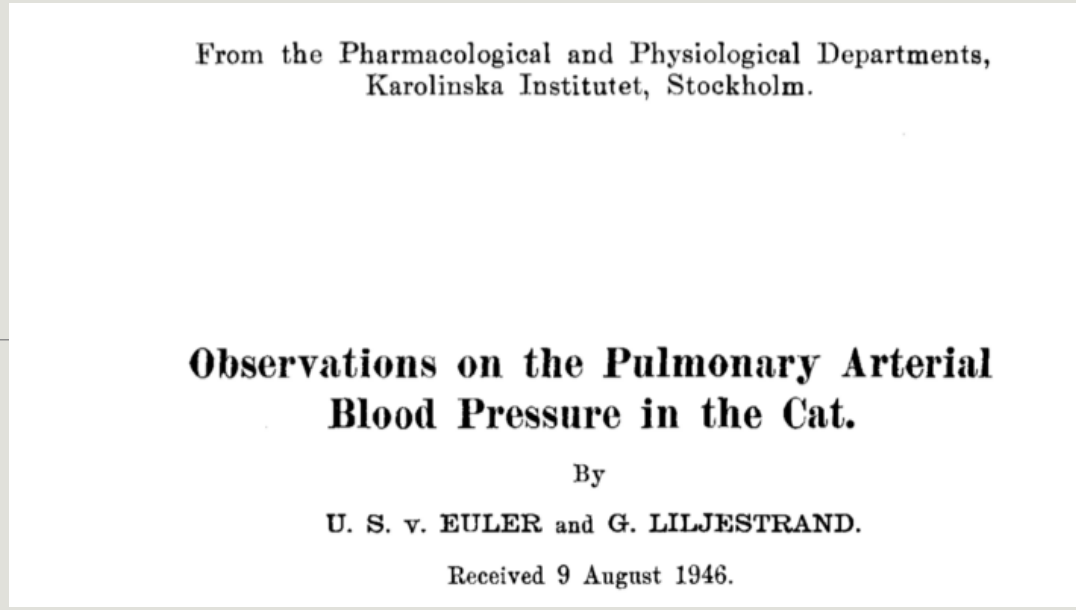
More blood to better oxygenated – ventilated regions

Introduction

Euler–Liljestrand mechanism



More blood to better oxygenated – ventilated regions



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Pulmonary arterial pressure

Pulmonary circulation vs systemic circulation

Lungs are the only organ to receive the entire cardiac output

Same volume of blood, but much lower arterial pressure

Why?

Large cross-sectional area of pulmonary capillaries

Pulmonary arterial pressure

Systolic PAP
- 18-25 mm Hg

Mean PAP
- 12-16 mm Hg

Pulmonary venous pressure
- 6-10 mm Hg

PAP = (Pulmonary flow x pulmonary vascular resistance) + PVP

Pulmonary hypertension

Mean pulmonary pressure at rest > 25 mm Hg

WHO classification

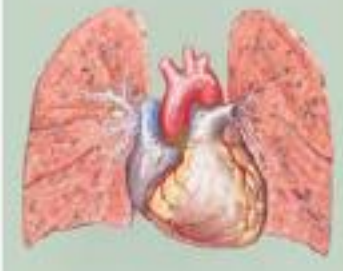
- 5 groups

Main cause – COPD

Pulmonary hypertension

WHO Classification System of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)

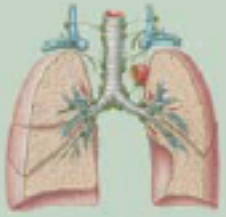


- Idiopathic pulmonary arterial hypertension
- Heritable
- Drug- and toxin-induced
- Persistent PH of newborn
- Associated with:
  - –connective tissue disease
  - –HIV infection
  - –portal hypertension
  - –coronary heart disease
  - –schistosomiasis
  - –chronic hemolytic anemia

1A. Pulmonary venoocclusive disease and pulmonary capillary hemangiomatosis

Pulmonary hypertension

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



- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Developmental abnormalities

Pulmonary hypertension

SWOT analysis

- Strenghts
- Weaknesses
- Opportunities
- Threats

Causes of pulmonary hypertension

- Arterial hypertension
- Venous hypertension (left heart)
- Obstructive lung disease – hypoxemia
- Thromboembolism

Pulmonary Artery Hypertension

Idiopathic pulmonary hypertension
Familial pulmonary hypertension

- Collagen vascular disease
- Congenital systemic-to-pulmonary shunts
- Hepatic portal vein hypertension
- HIV infection
- Drugs and toxins
- Others

Associated with venous or capillary involvement

- Pulmonary veno-occlusive disease
- Pulmonary capillary hemangiomatosis

Pulmonary Venous Hypertension

Left atrial, left ventricular, aortic valve, and mitral valve disease
Cor triatriatum
Left atrial myxoma

Pulmonary Hypertension associated with Hypoxemia

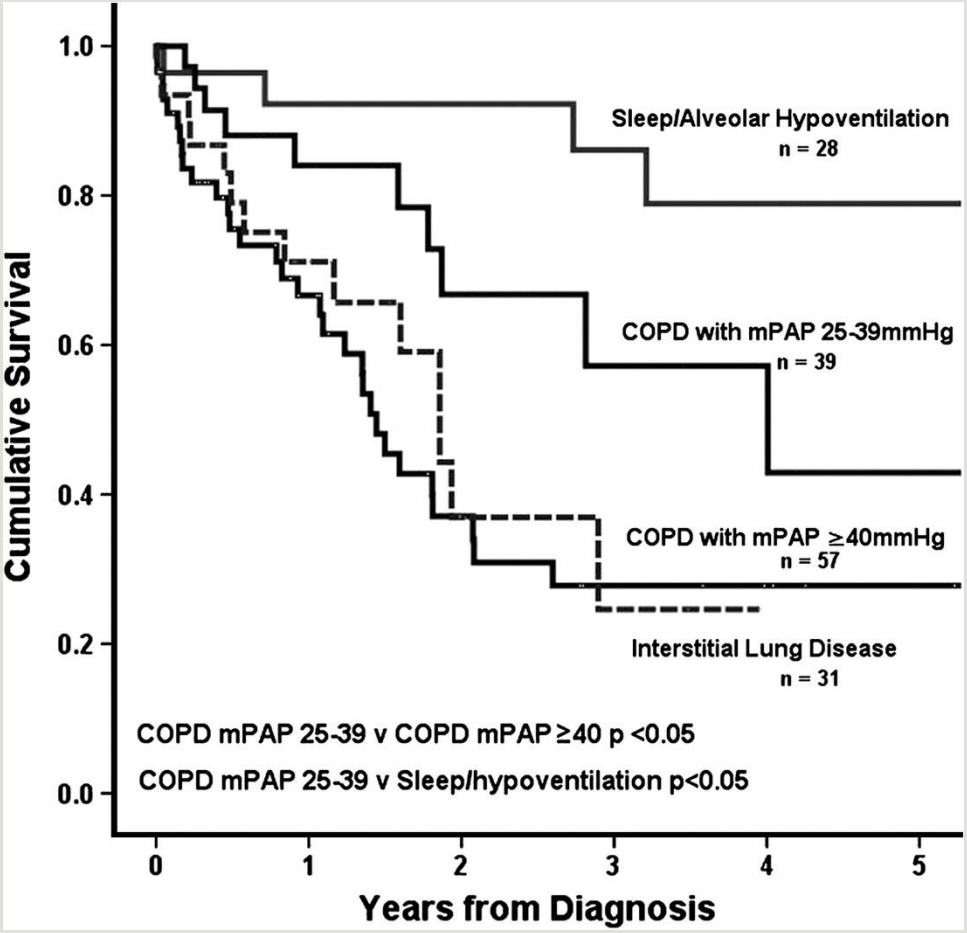
Chronic obstructive lung disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude

Pulmonary Arterial Hypertension due to Chronic Thrombotic or Embolic Disease

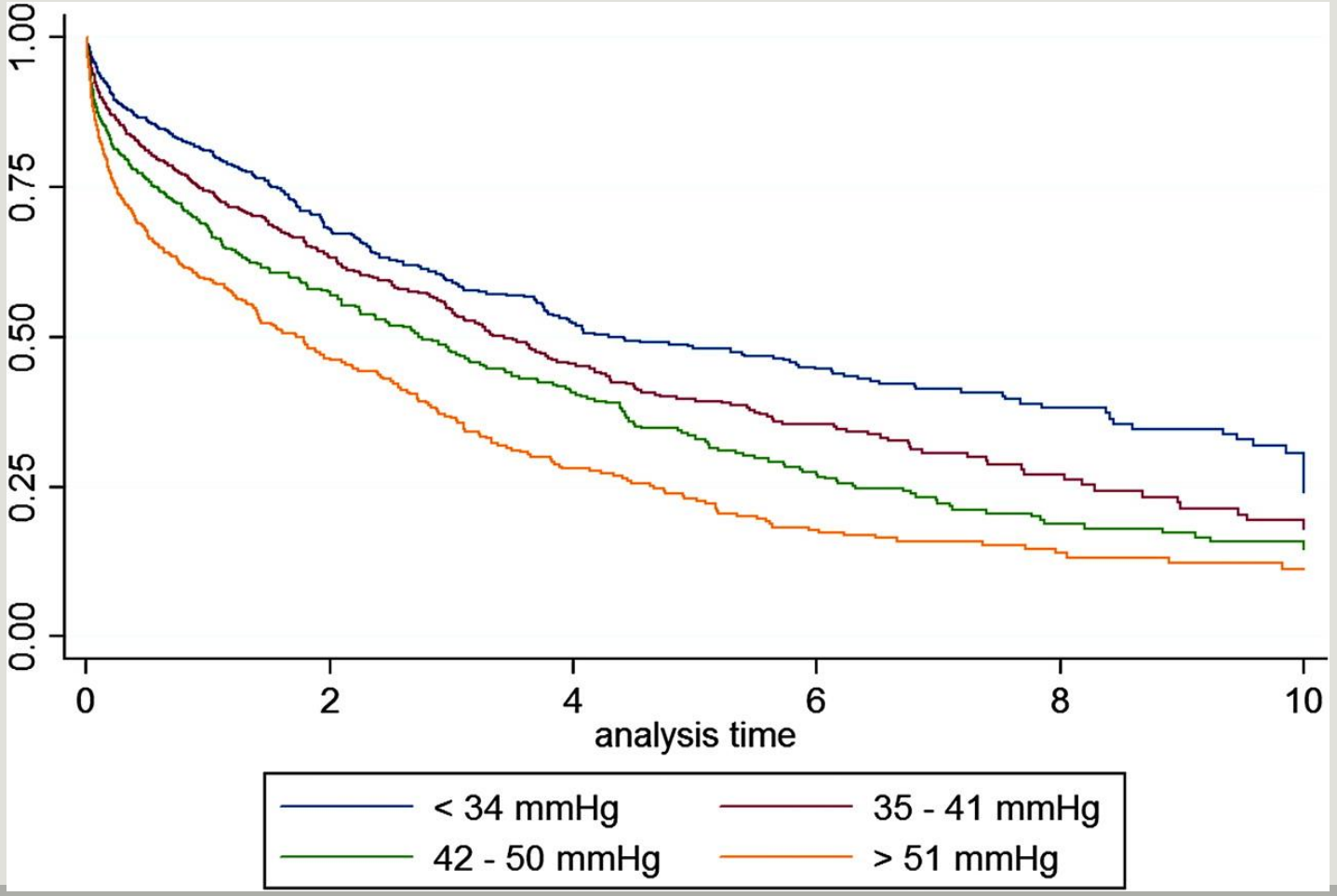
Miscellaneous

- Sarcoidosis
- Compression of pulmonary vessels
- Sickle cell disease
- Others

Survival


Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Years from Diagnosis
Sleep/Alveolar Hypoventilation
n = 28
COPD with mPAP 25-39mmHg
n = 39
COPD with mPAP ≥40mmHg
n = 57
Interstitial Lung Disease
n = 31
COPD mPAP 25-39 v COPD mPAP ≥40 p <0.05
COPD mPAP 25-39 v Sleep/hypoventilation p<0.05

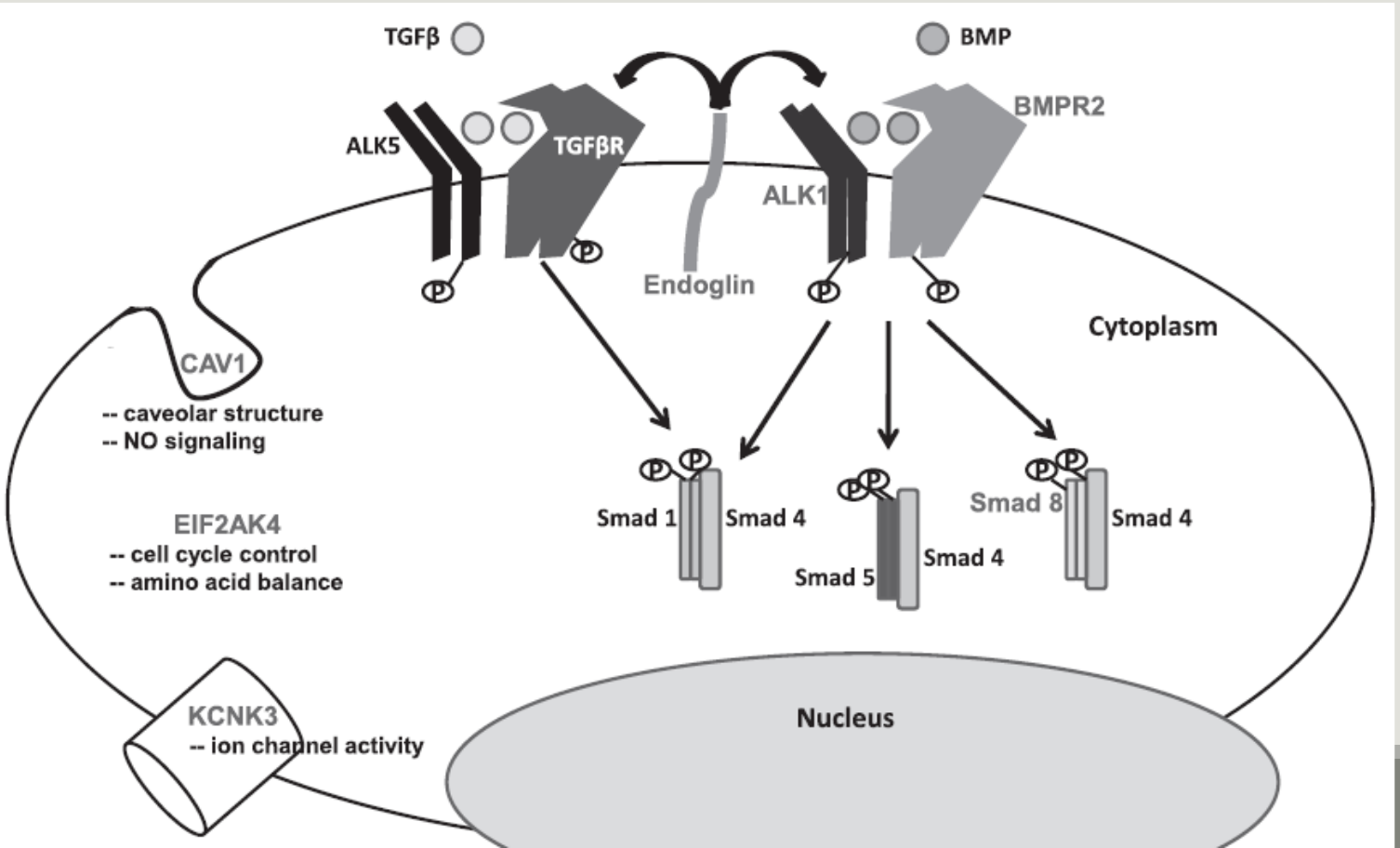
Survival


1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
analysis time
< 34 mmHg
35 - 41 mmHg
42 - 50 mmHg
> 51 mmHg

Pulmonary arterial hypertension (PAH)

Idiopathic (1/1 000 000/year) and heritable – familial

- Bone morphogenic protein receptor 2 (BMPR2)



nature genetics

Genome-wide association analysis identifies a susceptibility locus for pulmonary arterial hypertension

Marine Germain[1,2], Mélanie Eyries[2–4], David Montani[5–7], Odette Poirier[2,3], Barb
Florence Coulet[4], Soph
Anton Vonk-Noordegr
Anne-Marie Dupuy[16],
Marion Delcroix[21,22], E
Erika Berman-Rosenzv
Marc Humbert[5–7] & Fl

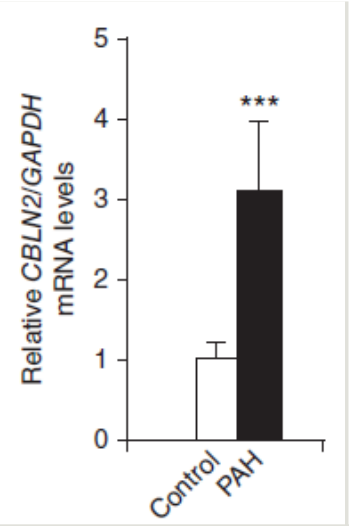
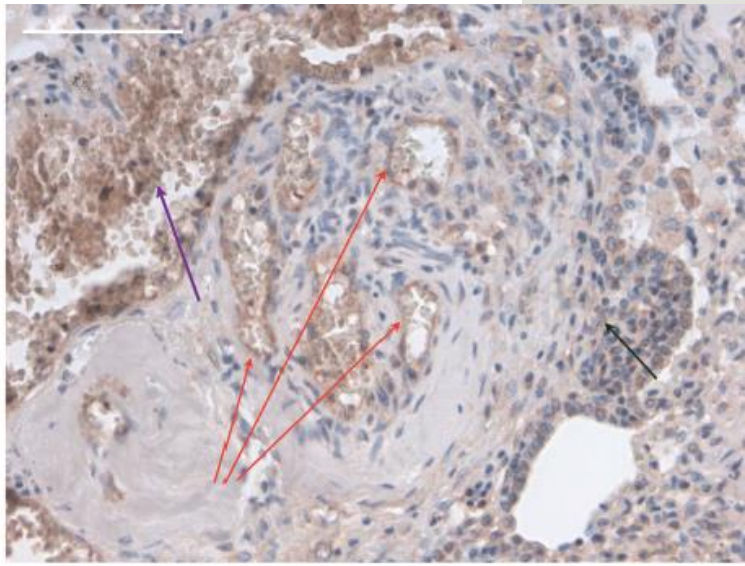
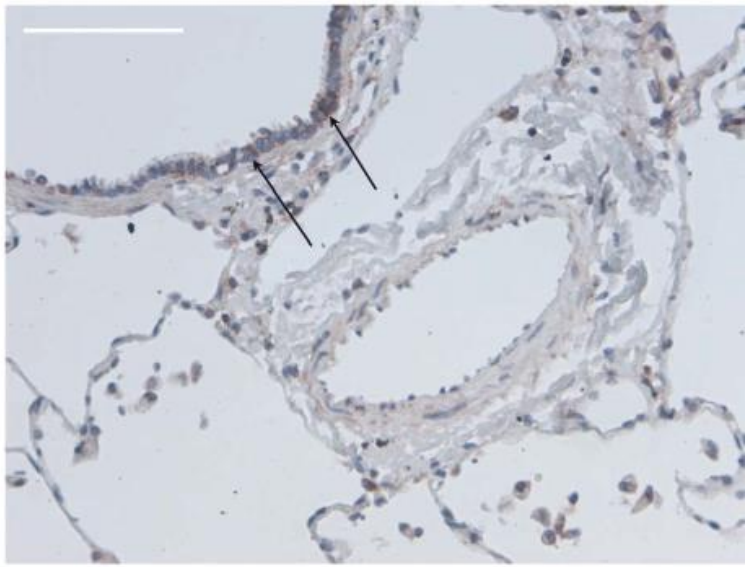


Table 1 Association of *CBLN2* rs2217 familial PAH in two independent case-

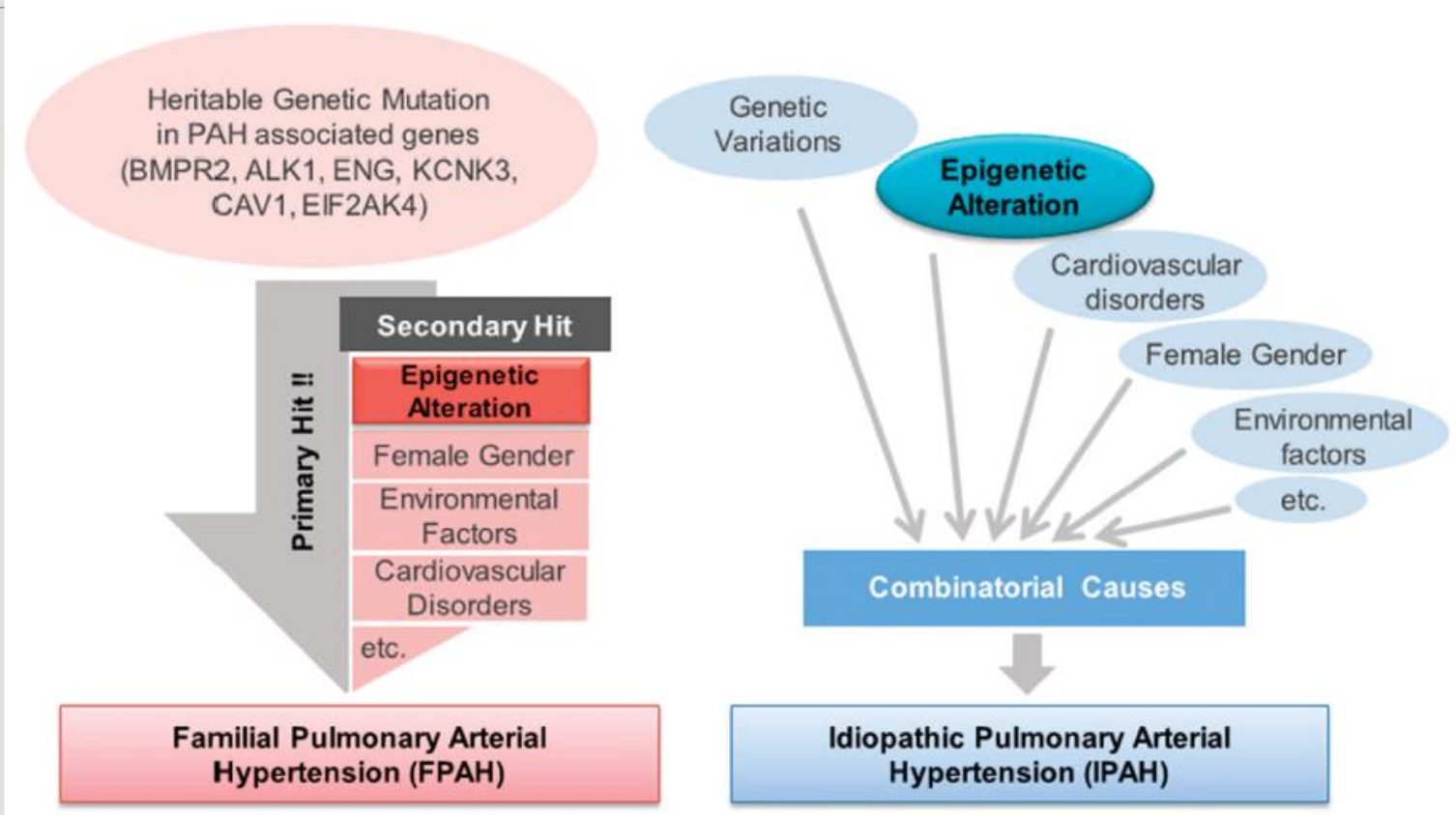
	Discovery		Replic
	Controls	Cases	Controls
rs2217560	*n* = 1,068	*n* = 340	*n* = 456
AA	925 (87%)	262 (77%)	400 (88%)
AG	136 (13%)	72 (21%)	52 (11%)
GG	7 (<1%)	6 (2%)	4 (1%)
MAF (G)	0.070	0.123	0.066
P[a]	1.56×10^{-5}		1.63 ×
Allelic OR[b]	1.87 (1.41–2.48)		2.16 (1.5





CBLN2 (Cerebellin 2 Precursor)

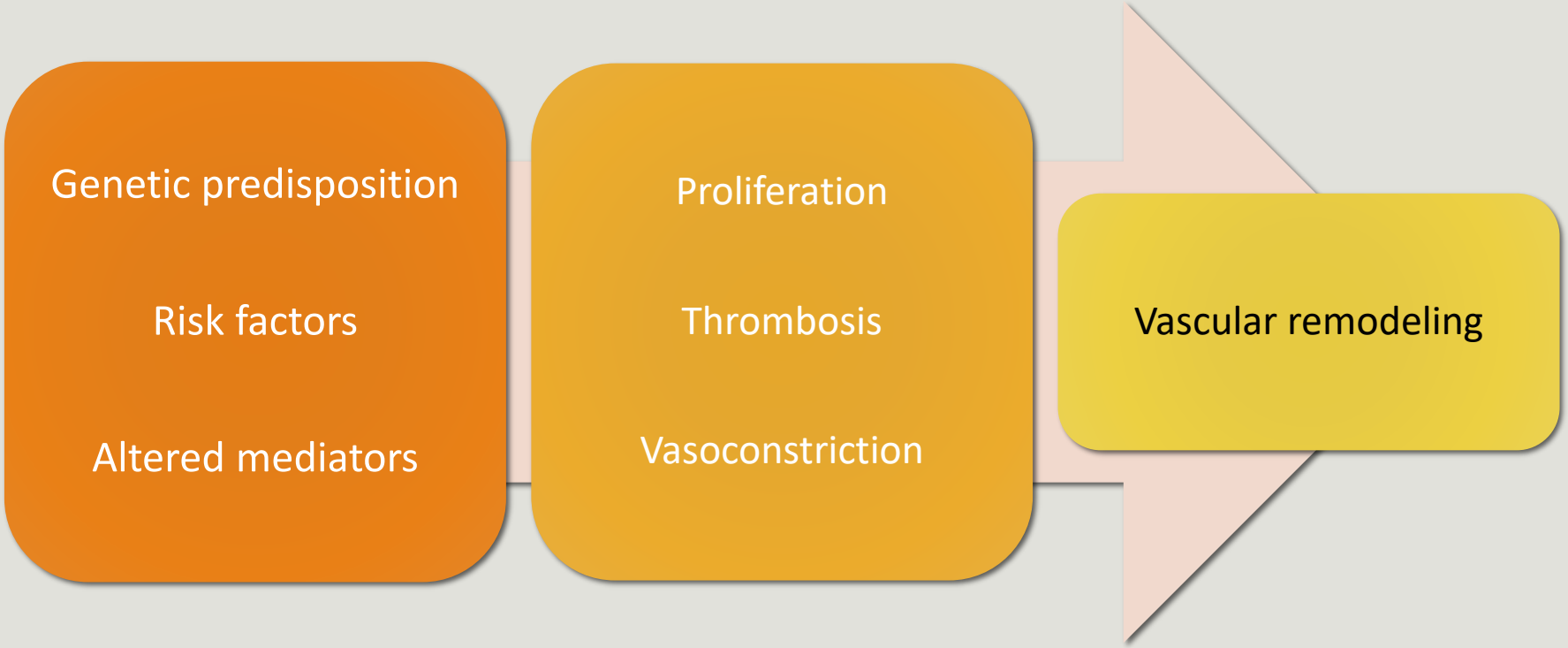
Pulmonary arterial hypertension (PAH)



Issue One: 50% chance a parent with a *BMPR2* mutation will pass that mutation to her child.

Issue Two: 20% chance a person with a *BMPR2* mutation will develop PAH in their lifetime

Pulmonary arterial hypertension (PAH)



Pathogenesis – PAH

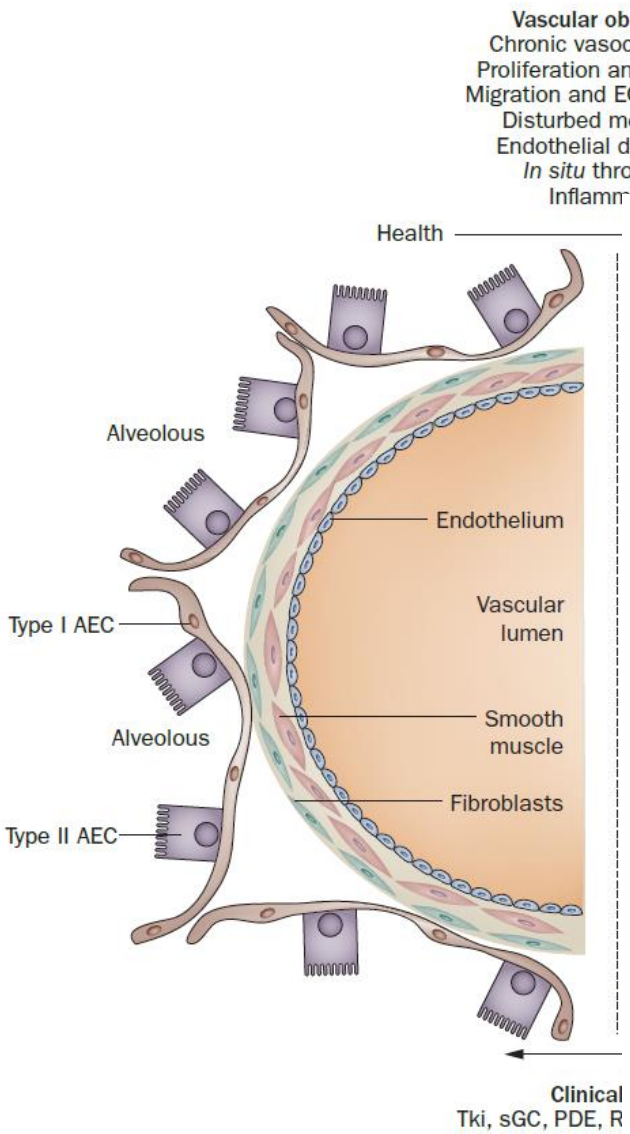
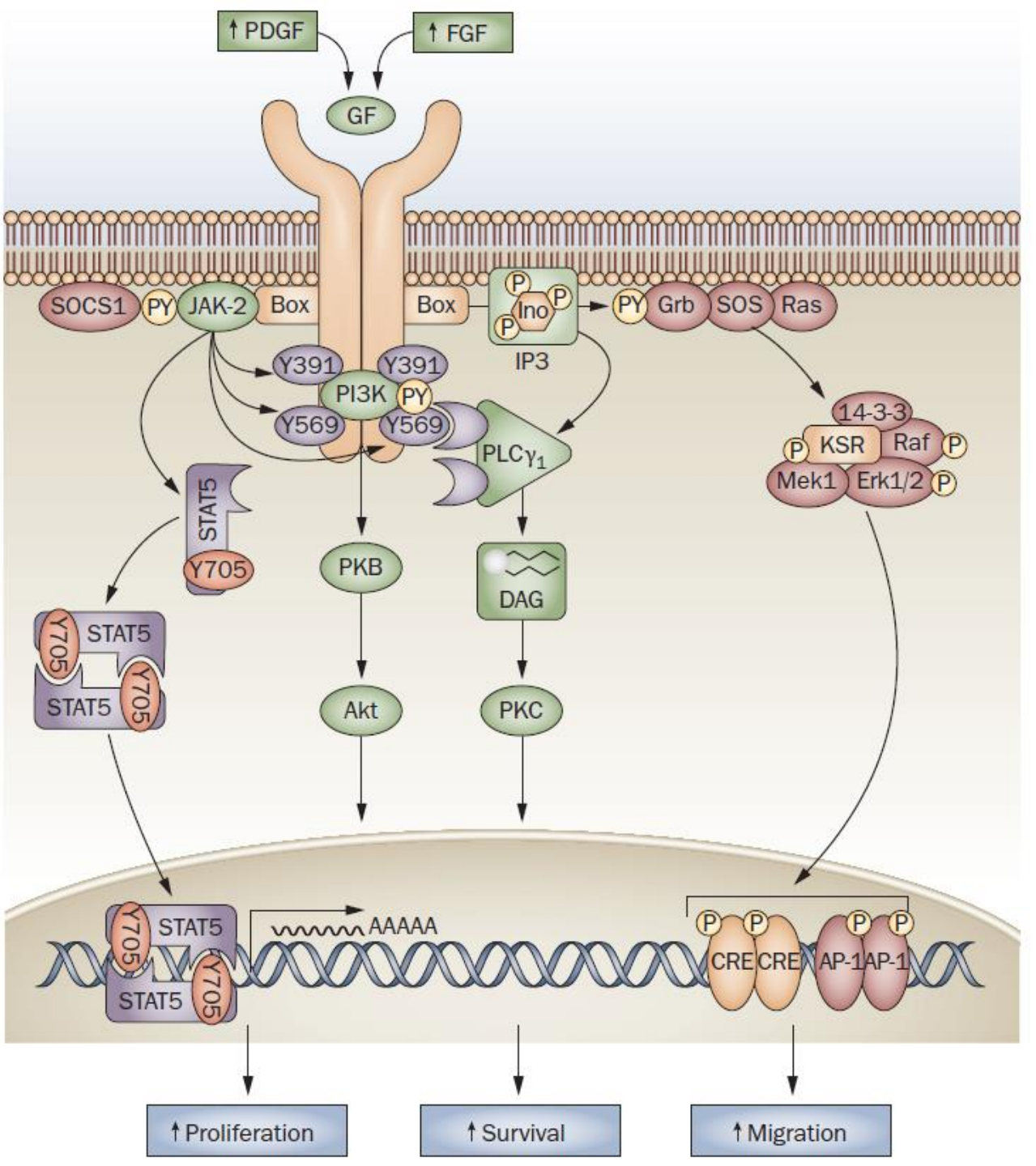
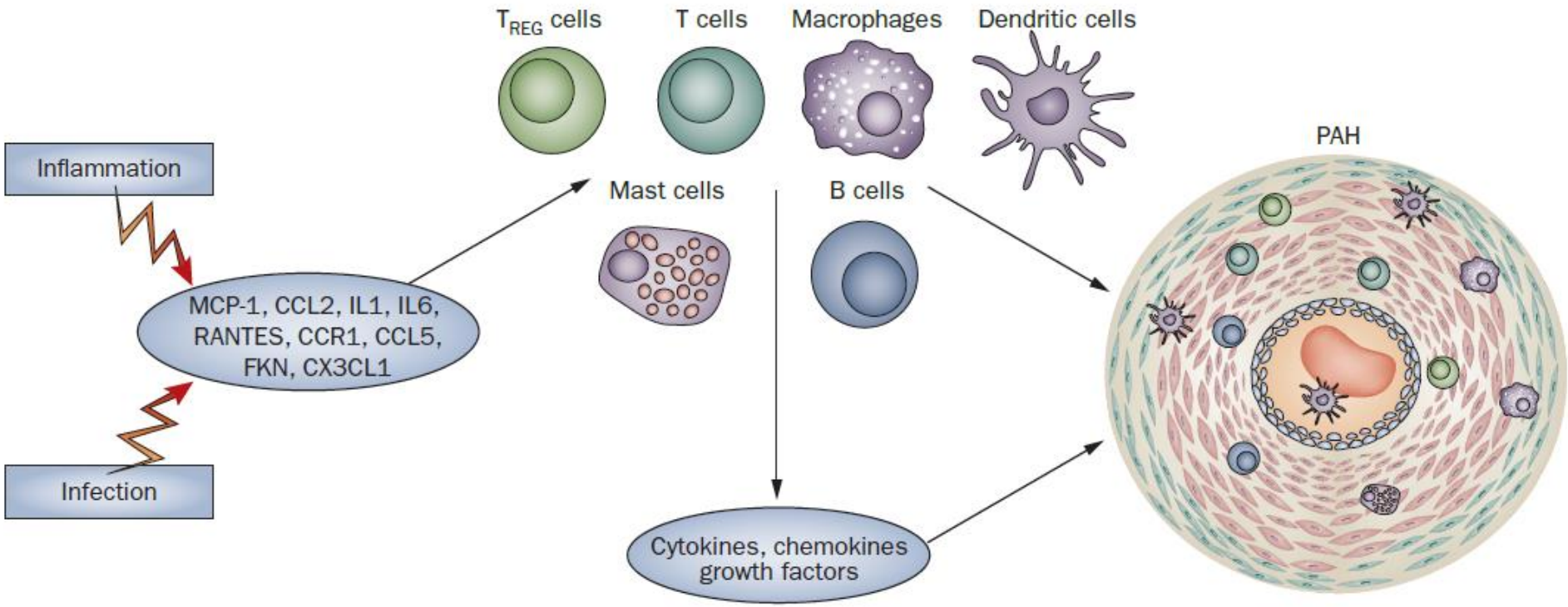


Figure 1 | Vascular remodeling in pulmonary arterial hypertension. Putative therapeutic targets are indicated. Abbreviations: 5-HT, 5-hydroxytryptamin; K- and Ca-channels, potassium and calcium channels; AEC, alveolar epithelial cells; BMP, bone morphogenetic protein; cGMP, cyclic guanosine monophosphate; ECM, extracellular matrix; EGF, epidermal growth factor; EPC, endothelial progenitor cells; HIF, hypoxia inducible factor; MMPs, matrix metalloproteinases; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; PDE, phosphodiesterase; PDGF, platelet-derived growth factor; PGI_2, prostaglandin I_2; Rho-Ki, Rho kinases; ROS, reactive oxygen species; sGC, soluble guanylate cyclase; TGF, transforming growth factor-β; TK, tyrosine kinase; TKi, tyrosine kinase inhibitor; TRPC, transient receptor potential cation channels; VEGF, vascular endothelial growth factor.

Mo AH


↑ PDGF
↑ FGF
GF
SOCS1
PY
JAK-2
Box
Box
P
Ino
P
P
IP3
PY
Grb
SOS
Ras
Y391
Y391
PI3K
PY
Y569
Y569
PLCγ1
14-3-3
P
KSR
Raf
P
Mek1
Erk1/2
P
STAT5
Y705
PKB
DAG
STAT5
Y705
STAT5
Y705
Akt
PKC
STAT5
Y705
STAT5
Y705
AAAAA
P
P
P
P
CRE
CRE
AP-1
AP-1
↑ Proliferation
↑ Survival
↑ Migration

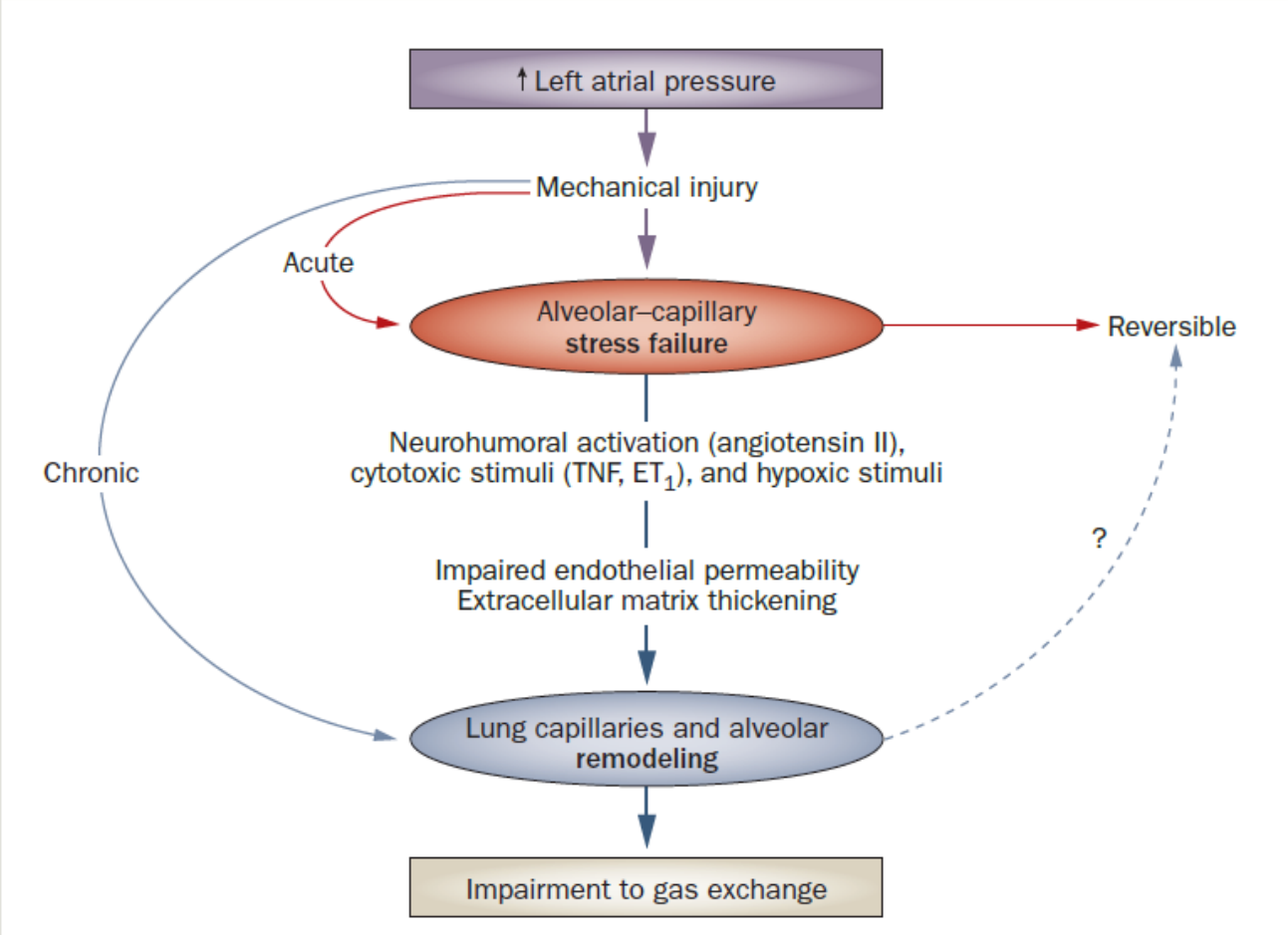
Where do the cytokines come from?



Key points

- Pulmonary hypertension is a progressive disease of various origins, which has a poor prognosis and affects, in its different forms, more than 100 million people worldwide
- Pulmonary arterial hypertension (PAH) is now considered to be a vasculopathy in which structural changes driven by excessive vascular cell growth and inflammation have a major role
- A number of proproliferative signaling pathways involving growth factors, cytokines, metabolic signaling, and elastases and proteases have been identified in the pathophysiology of PAH
- Clinical studies with tyrosine kinase inhibitors, serotonin antagonists, and soluble guanylate cyclase stimulators are underway in patients with PAH
- The benefits of progenitor cells for vascular repair in PAH are under active investigation
- The right ventricular response to increased pressure load is recognized as critical to survival in patients with PAH, and strategies for preserving myocardial function are increasingly attracting interest

PH due to left heart disease

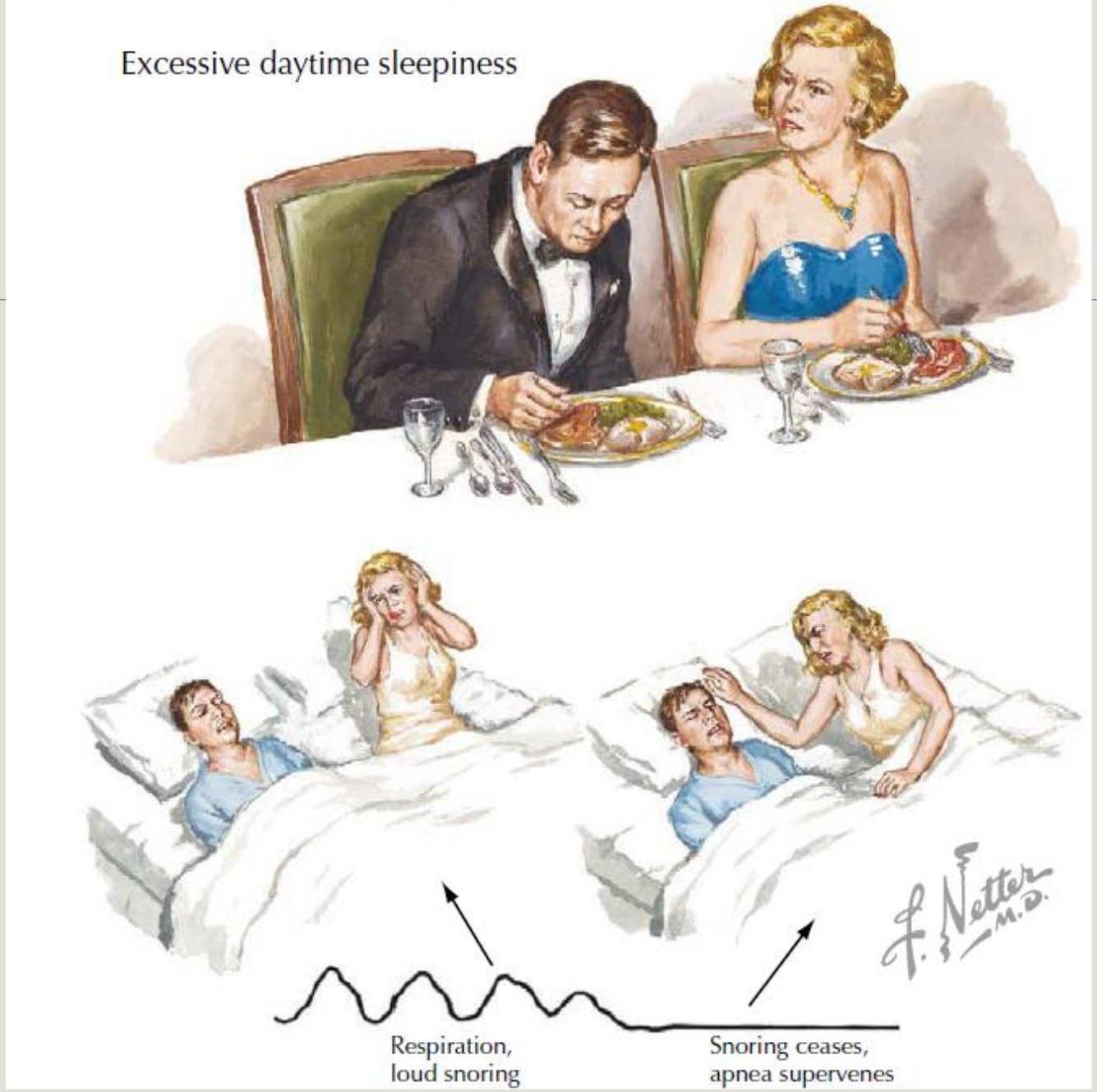


PH due to hypoxia

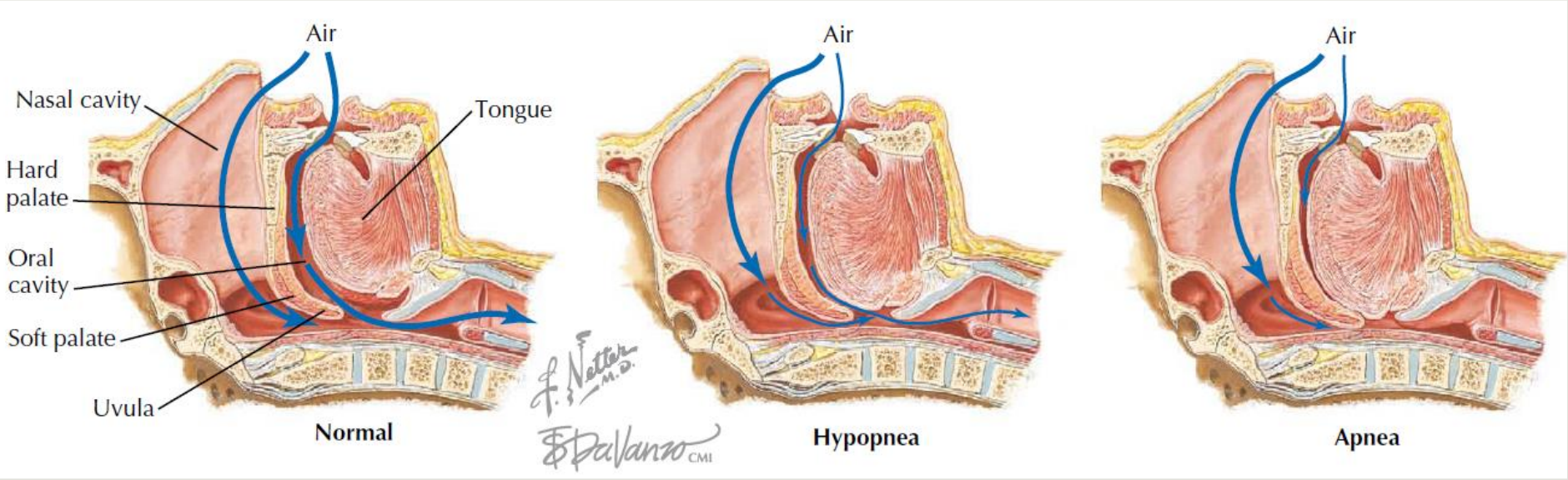
COPD

Interstitial lung diseases

Sleep-disordered breathing


Excessive daytime sleepiness
F. Netter M.D.
Respiration, loud snoring
Snoring ceases, apnea supervenes

Obstructive sleep apnea



Risk factors for obstructive SAS?

- Male gender, age > 65 years, BMI > 30, large adenoids, neck size

Recordings from patient with obstructive sleep apnea

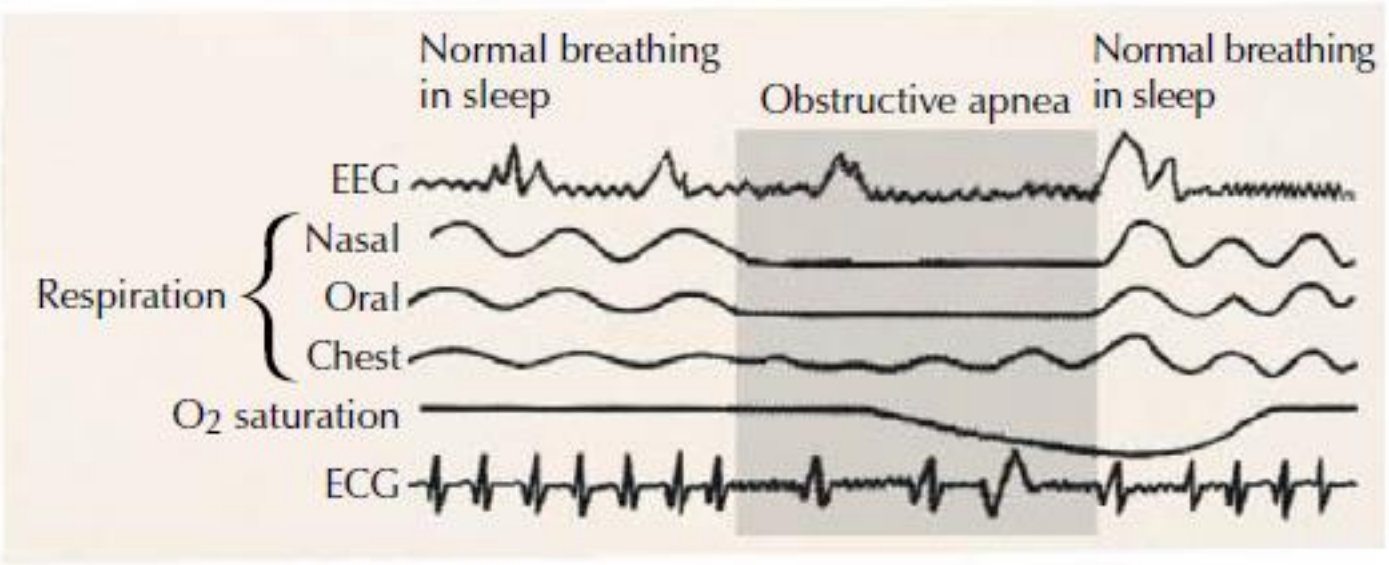
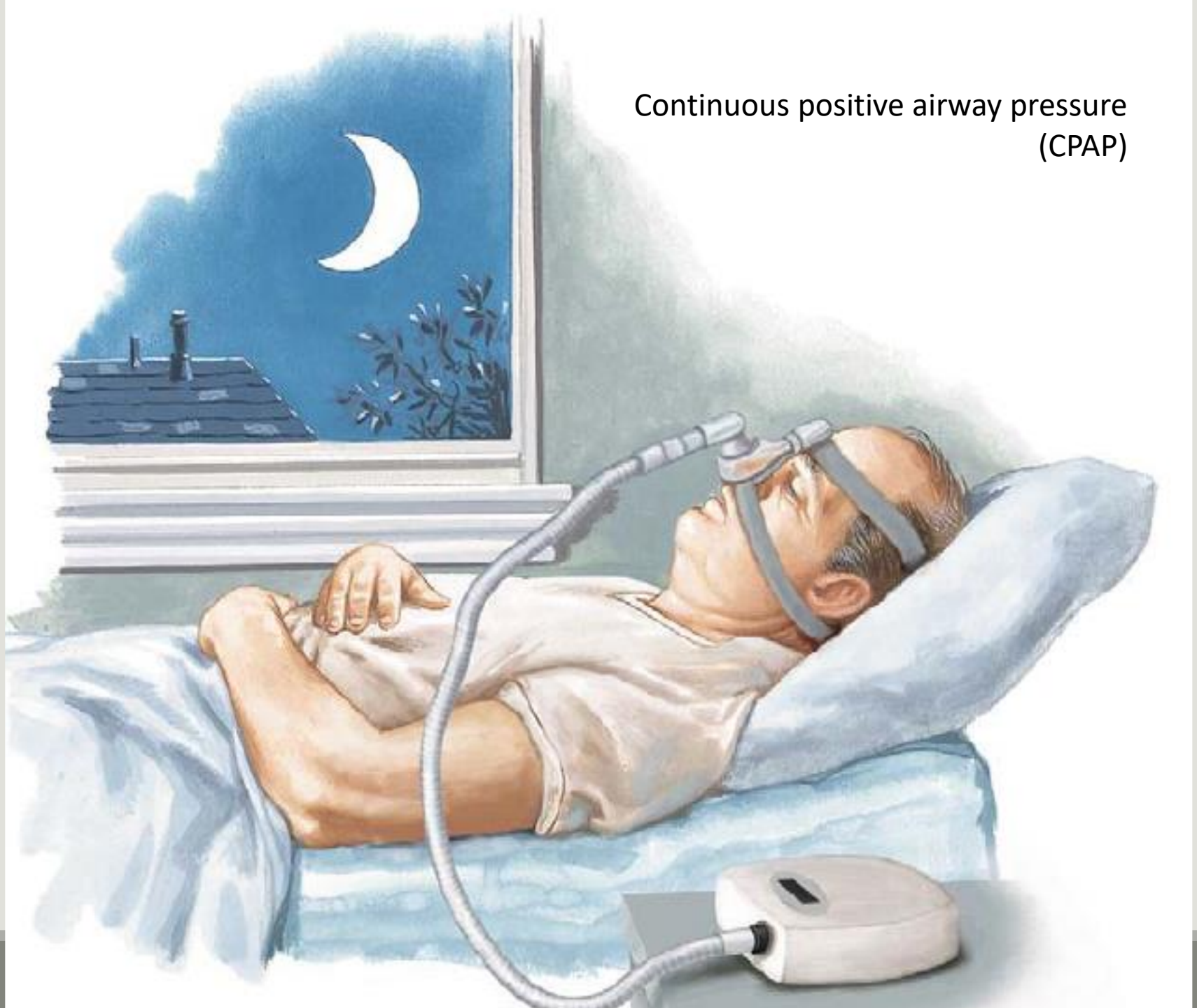


Table 67-1 Apnea Severity

AHI	Apnea Severity
0–5	Normal
5–15	Mild
15–29	Moderate
≥30	Severe

AHI, apnea-hypopnea index.



Continuous positive airway pressure (CPAP)

Pulmonary hypertension

Risk determinants

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO class	IV
Longer (>400 m)	6 minutes walk test	Shorter (<300 m)
Minimally elevated	BNP	Very elevated
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion, significant RV dysfunction
Normal/near normal RA pressure and CO	Hemodynamics	High RA pressure, low CO

Pulmonary hypertension

Table 2. Functional Classification of Pulmonary Arterial Hypertension.*

Class	Description
Class I	Pulmonary arterial hypertension without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Pulmonary arterial hypertension resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near-syncope.
Class III	Pulmonary arterial hypertension resulting in a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near-syncope.
Class IV	Pulmonary arterial hypertension resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnea, fatigue, or both may be present even at rest, and discomfort is increased by any physical activity.

Diagnostics

Diagnostic Test	Potential Findings
Electrocardiography	P pulmonale (P wave in lead II greater than 3 mV) Right-axis deviation R wave greater than S wave in lead V_1
Chest radiography	Enlarged pulmonary arteries RV enlargement Parenchymal lung disease Skeletal abnormalities
Echocardiography	PAP estimated by TR velocity RV hypertrophy RV enlargement LV function/LA size Valvular disease Imaging to detect ASD or VSD
Pulmonary function testing with ABG	COPD Restrictive lung disease Hypoventilation
Ventilation/perfusion lung scan, CT angiogram (MRI in special cases)	To diagnose or exclude pulmonary embolism
PA angiography	For further evaluation of indeterminate lung scan to exclude thromboembolism
Cardiac catheterization	Pressure determinations at rest and after inhalation of 100% oxygen Pulmonary wedge pressure Response to vasodilators

ABG, arterial blood gas; ASD, atrioventricular septal defect; COPD, chronic obstructive pulmonary disease; CT, computed tomography; PA, pulmonary artery; PAP, pulmonary artery pressure; LA, left atrial; LV, left ventricular; MRI, magnetic resonance imaging; RV, right ventricular; TR, tricuspid regurgitation; VSD, ventricular septal defect.

Diagnostics

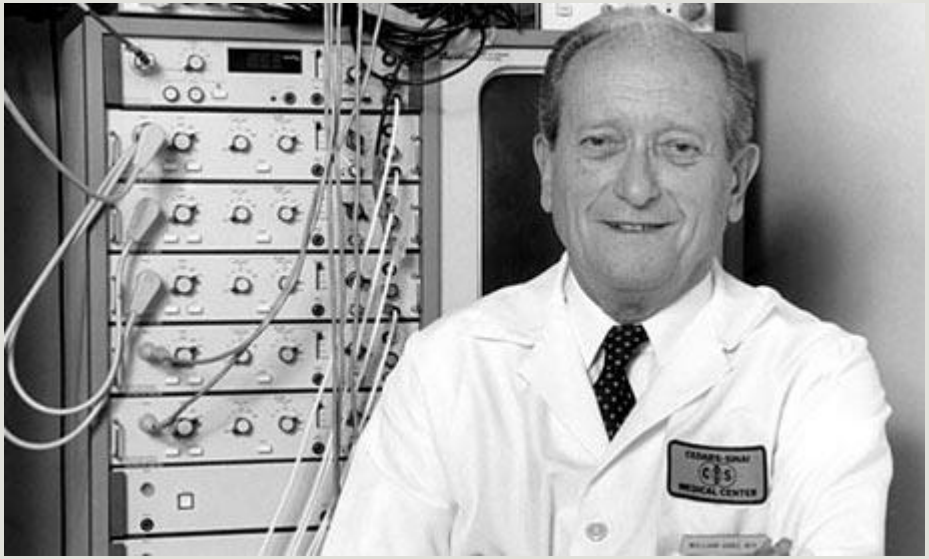
Pulmonary hypertension

- Mean pulmonary arterial pressure > 25 mm Hg at rest

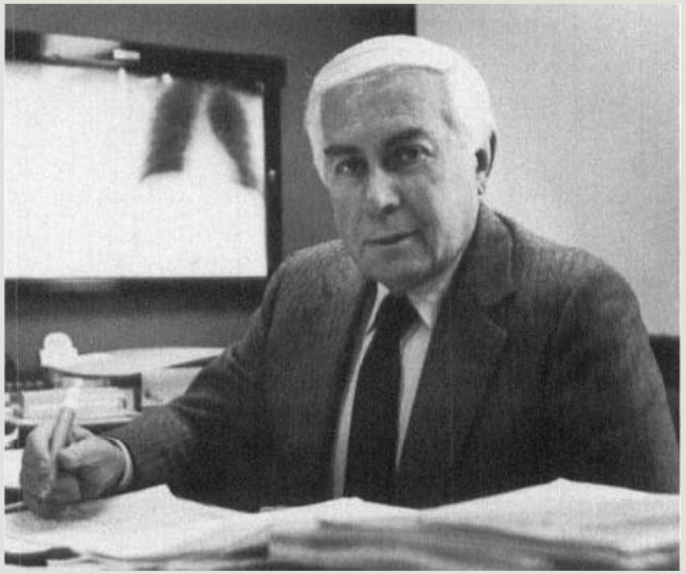
Pulmonary arterial hypertension

- Pulmonary wedge pressure < 15 mm Hg
- Normal left ventricular ejection fraction
- No left-sided valvular disease

Diagnostics



William Ganz (1919-2009)



Jeremy Swan (1922-2005)

CATHETERIZATION OF THE HEART IN MAN WITH USE OF A FLOW-DIRECTED BALLOON-TIPPED CATHETER*

H. J. C. Swan, M.B., Ph.D., F.R.C.P., William Ganz, M.D., C.Sc., James Forrester, M.D., Harold Marcus, M.D., George Diamond, M.D., and David Chonette

Abstract Pressures in the right side of the heart and pulmonary capillary wedge can be obtained by cardiac catheterization without the aid of fluoroscopy. A No. 5 Fr double-lumen catheter with a balloon just proximal to the tip is inserted into the right atrium under pressure monitoring. The balloon is then inflated with 0.8 ml of air. The balloon is carried by blood flow through the right side of the heart into the smaller radicles of the pulmonary artery. In this position when the balloon is inflated wedge pressure is obtained. The average time for passage of the catheter from the right atrium to the pulmonary artery was 35 seconds in the first 100 passages. The frequency of premature beats was minimal, and no other arrhythmias occurred.

THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 27, 1970

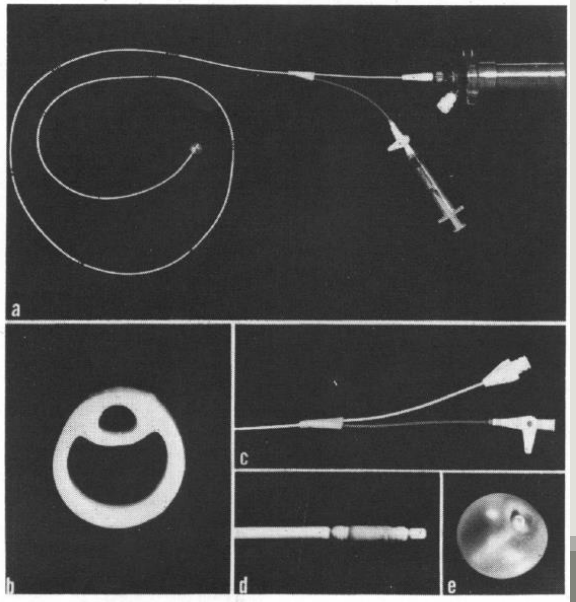
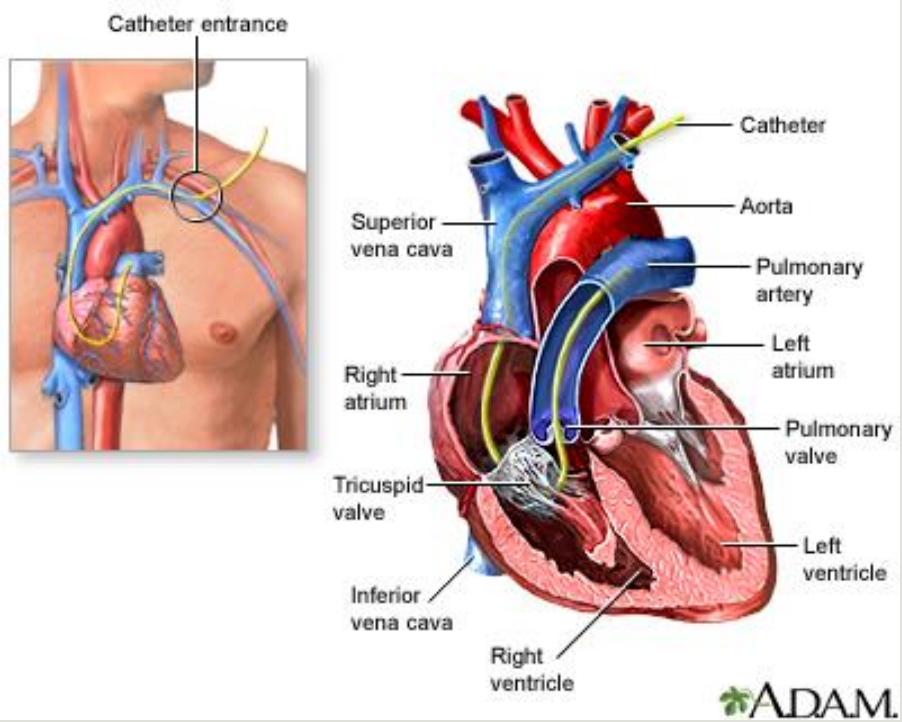


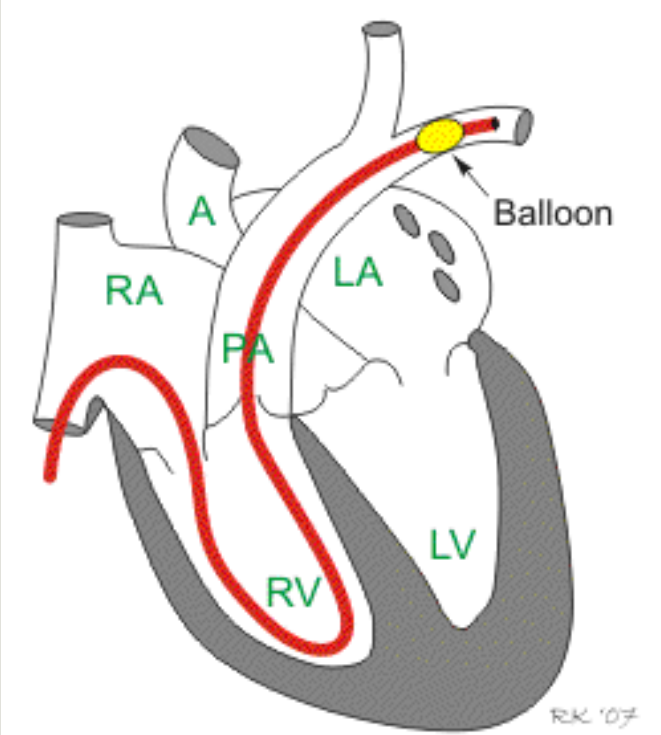
Figure 1. Construction of the Catheter.

Swan-Ganz catheter

Pulmonary artery catheter

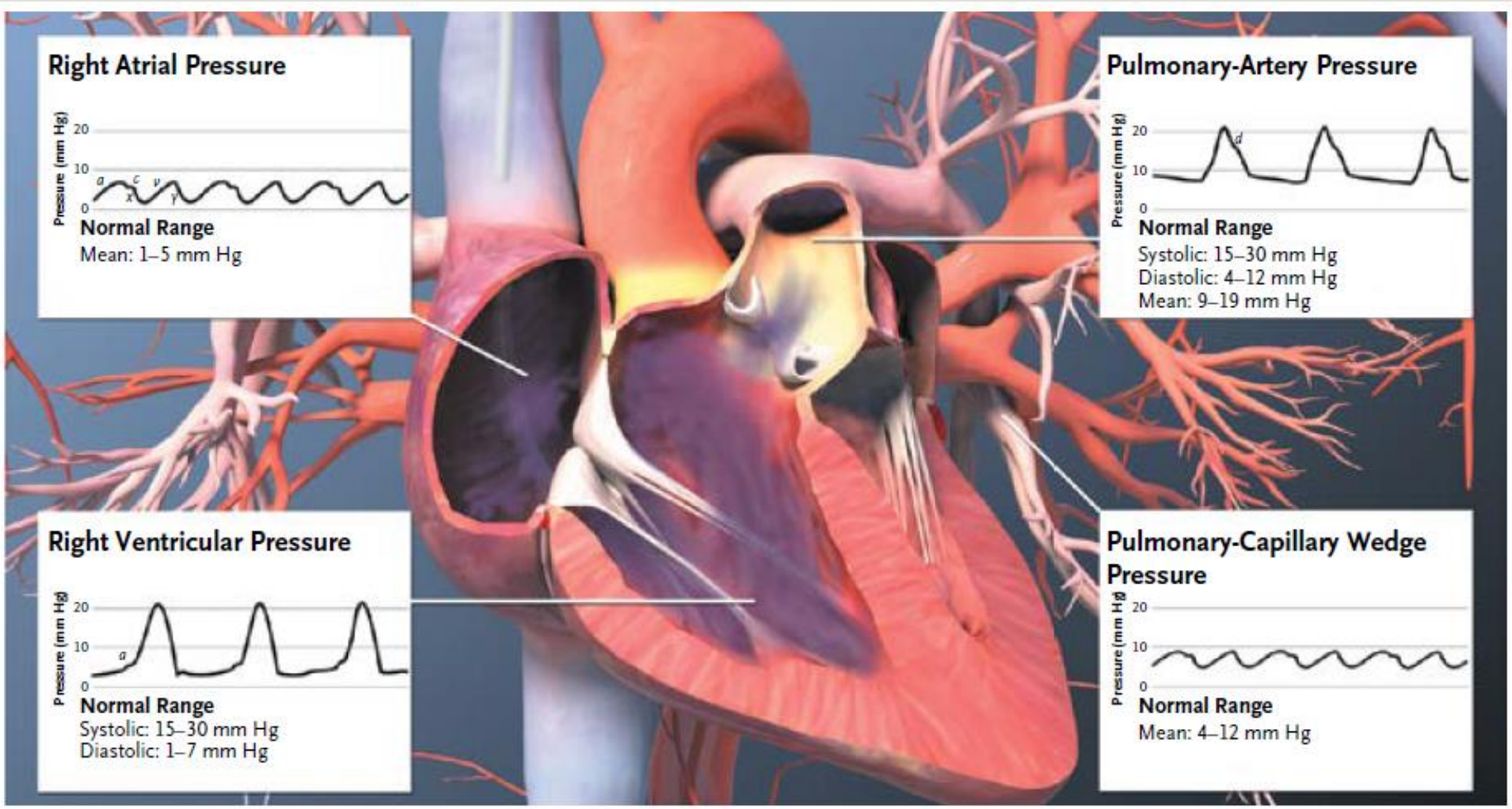
Diagnostics





Balloon-tipped, Swan-Ganz catheter for measuring pulmonary capillary wedge pressure (PCWP).

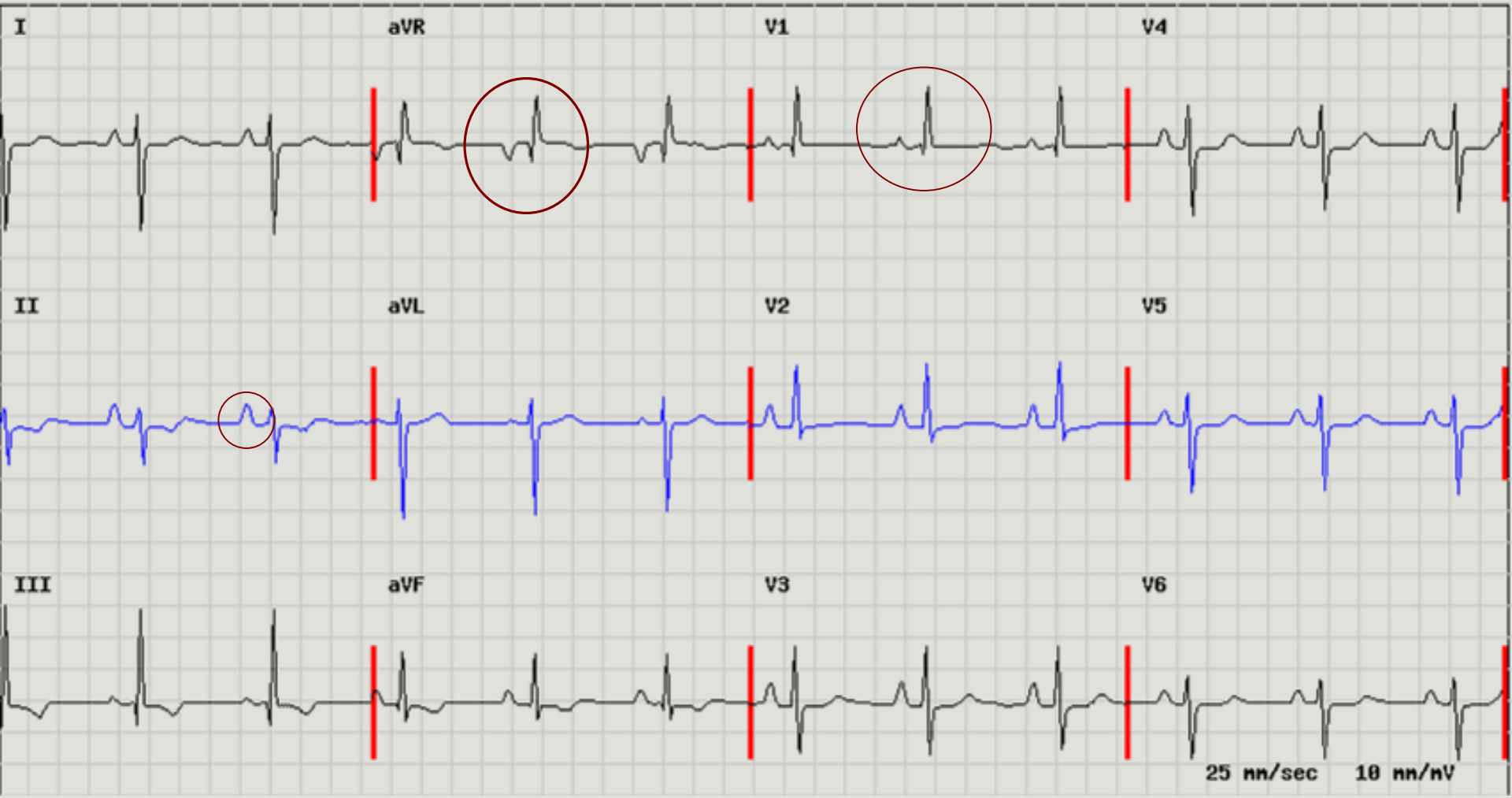
Swan-Ganz catheter



Pivotal tests	Contingent tests	Contribute to assessment of:
History Exam Chest x-ray (CXR) Electrocardiography (ECG)		Index of suspicion of PH
Echocardiogram *Dilation of RV relative to LV and severe septal flattening. Top: Diastole Bottom: Systole*	Transesophageal echocardiogram (TEE) Exercise echo	RVE, RAE, ↑ RSVP, RV Function, Left-sided heart disease VHD, CHD
Ventilation-perfusion scan (VQ scan)	Pulmonary angiography Chest CT angiogram Coagulopathy profile	Chronic PE
Pulmonary function tests (PFTs)	Arterial blood gas test (ABGs)	Ventilatory function Gas exchange
Overnight oximetry	Polysomno-graphy	Sleep disorder
HIV test Antinuclear antibody test (ANA) Liver function tests (LFTs)	Other CTD serologies	HIV infection Scleroderma, SLE, RA Portopul-monary Htn
Functional tests (6MWT, CPET)		Establish baseline prognosis
Right-sided heart catheterization	Vasodilator test Exercise RH cath Volume loading Left-sided heart catheterization	Confirmation of PH Hemodynamic profile Vasodilator response

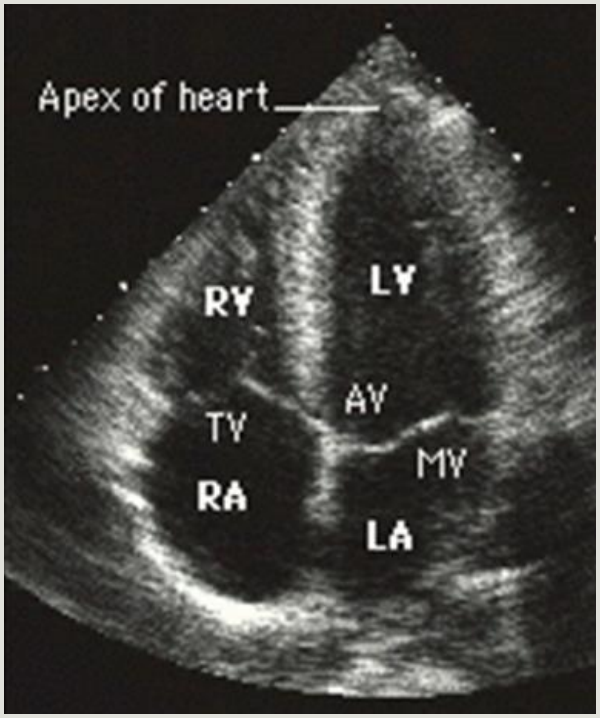
ECG Impression: Normal sinus rhythm, rate 67. Right axis deviation. Right atrial enlargement. RVH with ST-T abnormalities

PR Interval: 189 QT Interval: 413 Axes: P: 40 ST: -56
QRS Duration: 85 QT Interval Corrected: 436 MEAN QRS: 156 T: -32
ECG Severity: - ABNORMAL ECG -

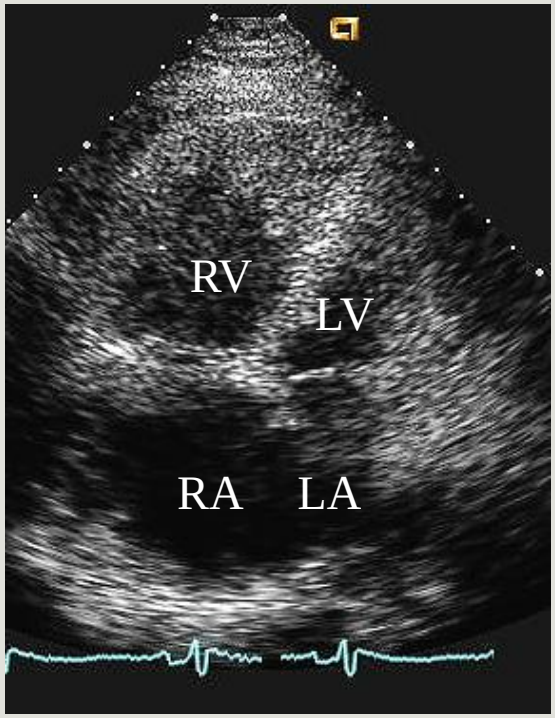


Echocardiography

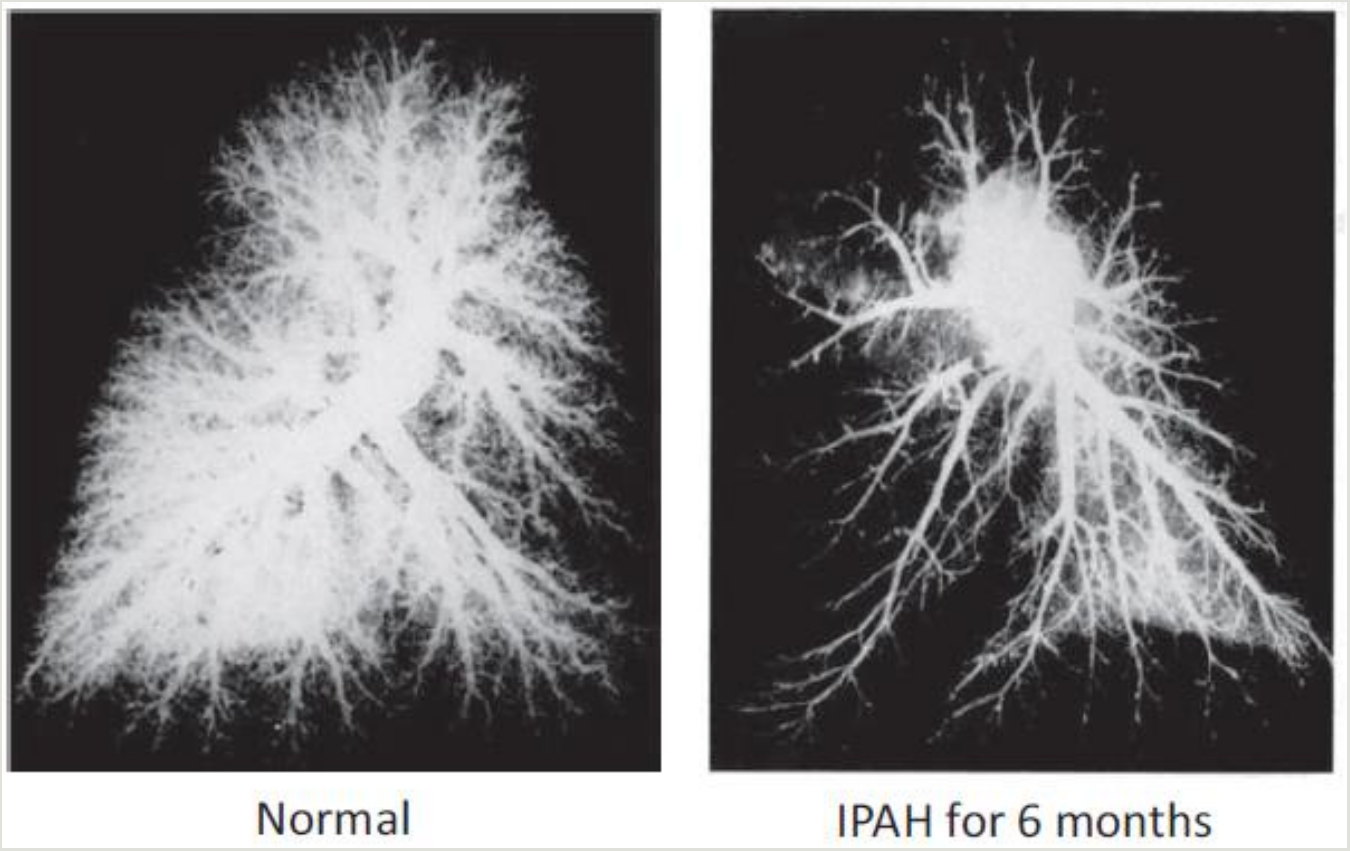
Normal



Pulmonary hypertension



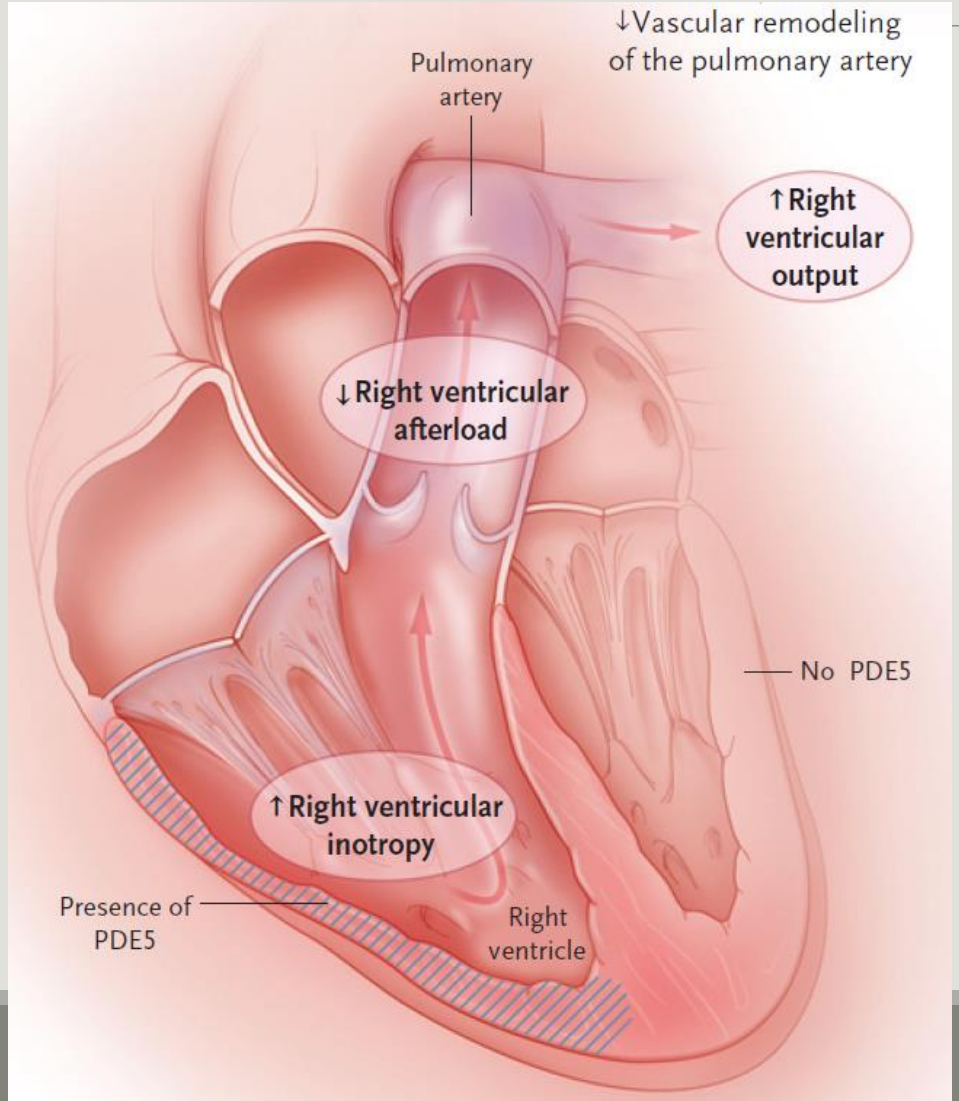
Pulmonary angiography



Normal

IPAH for 6 months

Treatment



Drug and Year Approved	Drug Class	Route of Administration	Doses	Frequency
Epoprostenol (Flolan), 1995	Prostaglandins	IV	Initiate 1–2 ng/kg/min IV and titrate to efficacy and side effects.	Continuous IV
Bosentan (Tracleer), 2001	ERA	PO	62.5 and 125 mg	BID
Treprostinil (Remodulin SC), 2002	Prostaglandins	SC	Initiate 1.25–2.5 ng/kg/min SC; can reduce to 0.625 ng/kg/min if not tolerated.	Continuous SC
Trepostinil (Remodulin IV), 2004	Prostaglandins	IV	Initiate 1.25–2.5 ng/kg/min IV; can reduce to 0.625 ng/kg/min if not tolerated.	Continuous IV
Iloprost (Ventavis), 2004	Prostaglandins	Inhaled	2.5 and 5 µg	6–9 inhalations per day while awake; not more than q2hr
Sildenafil (Revatio), 2005	PDE-5 Inhibitor	PO	20 mg	TID
Ambrisentan (Letairis), 2007	ERA	PO	5 and 10 mg	QD

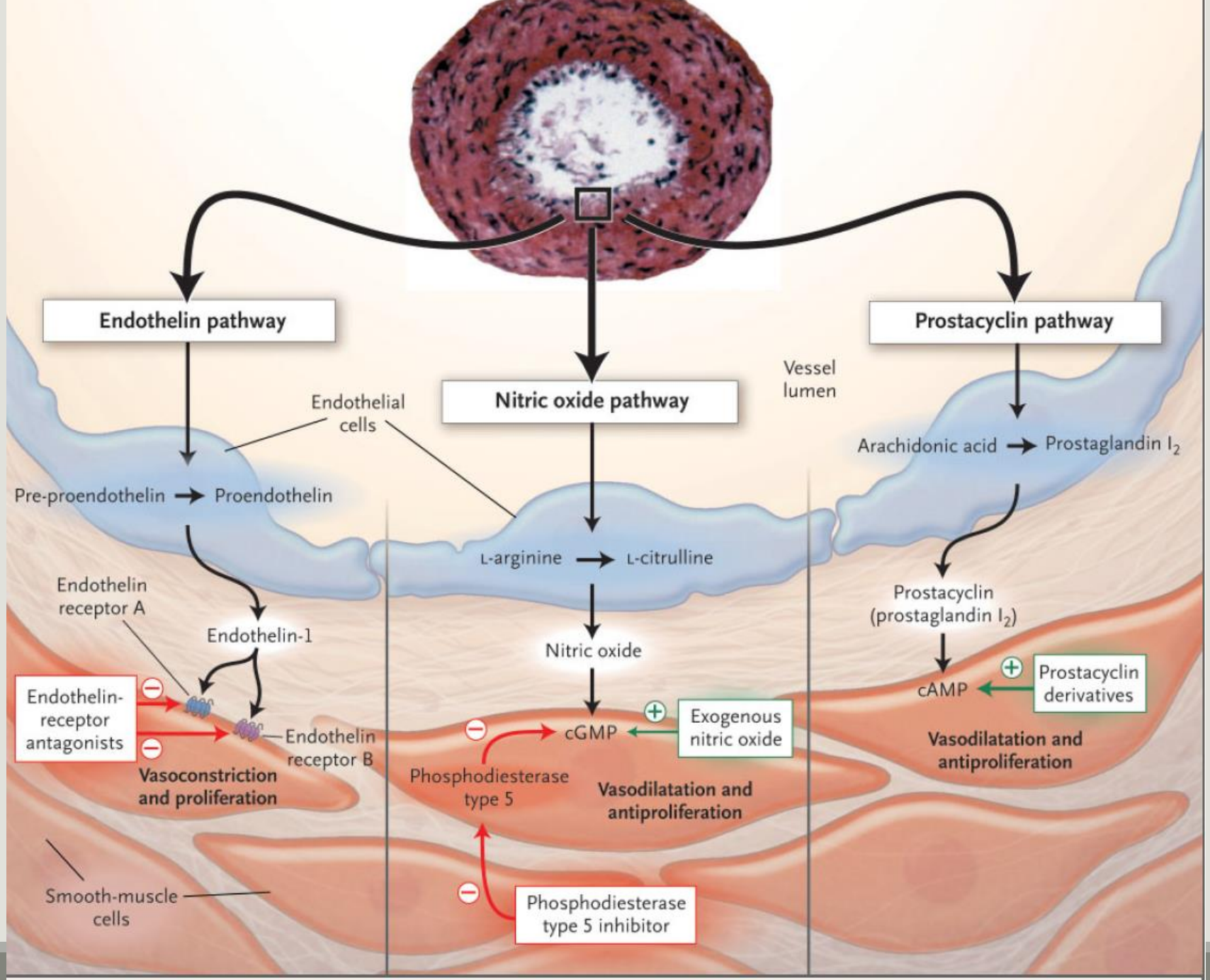
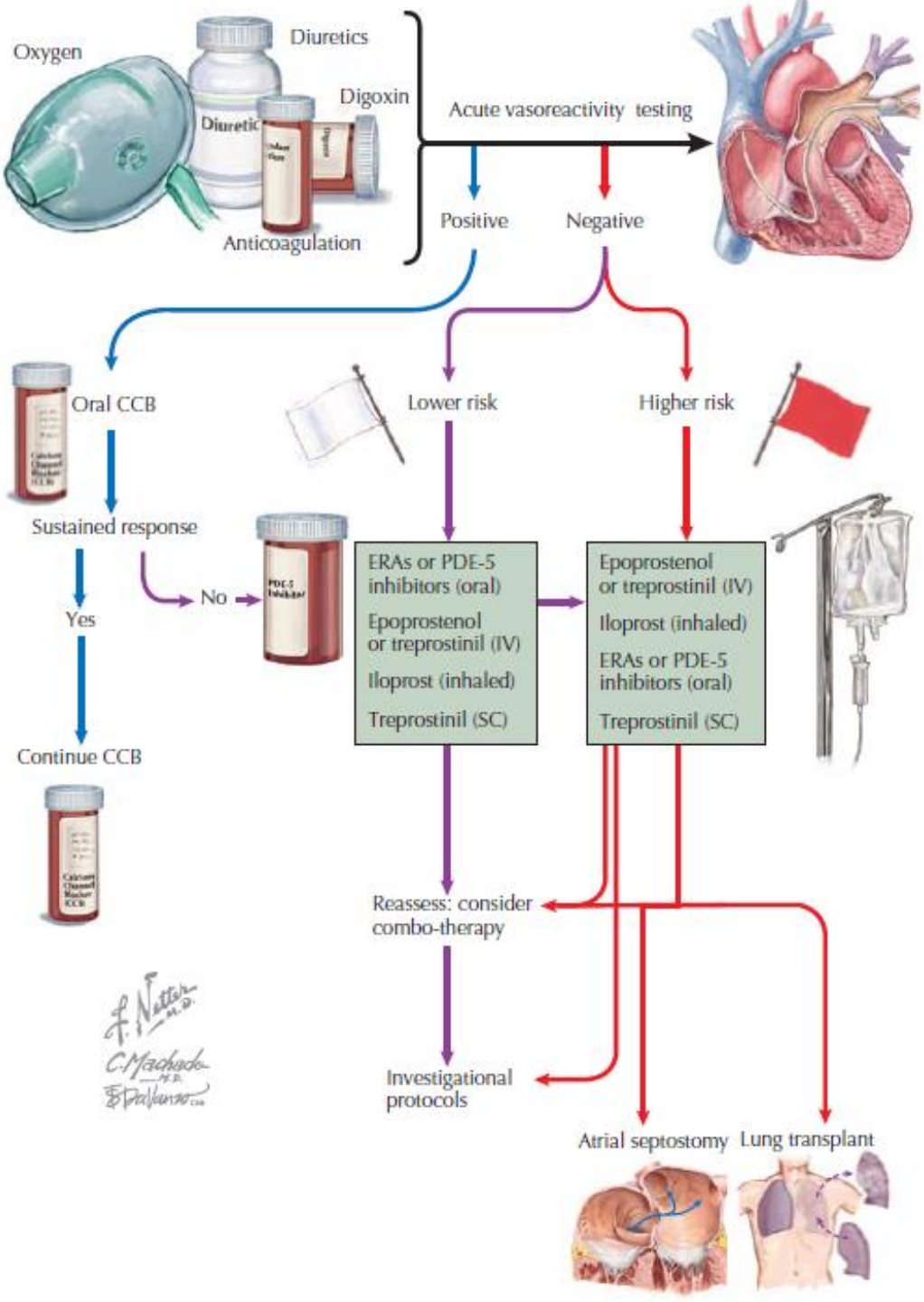
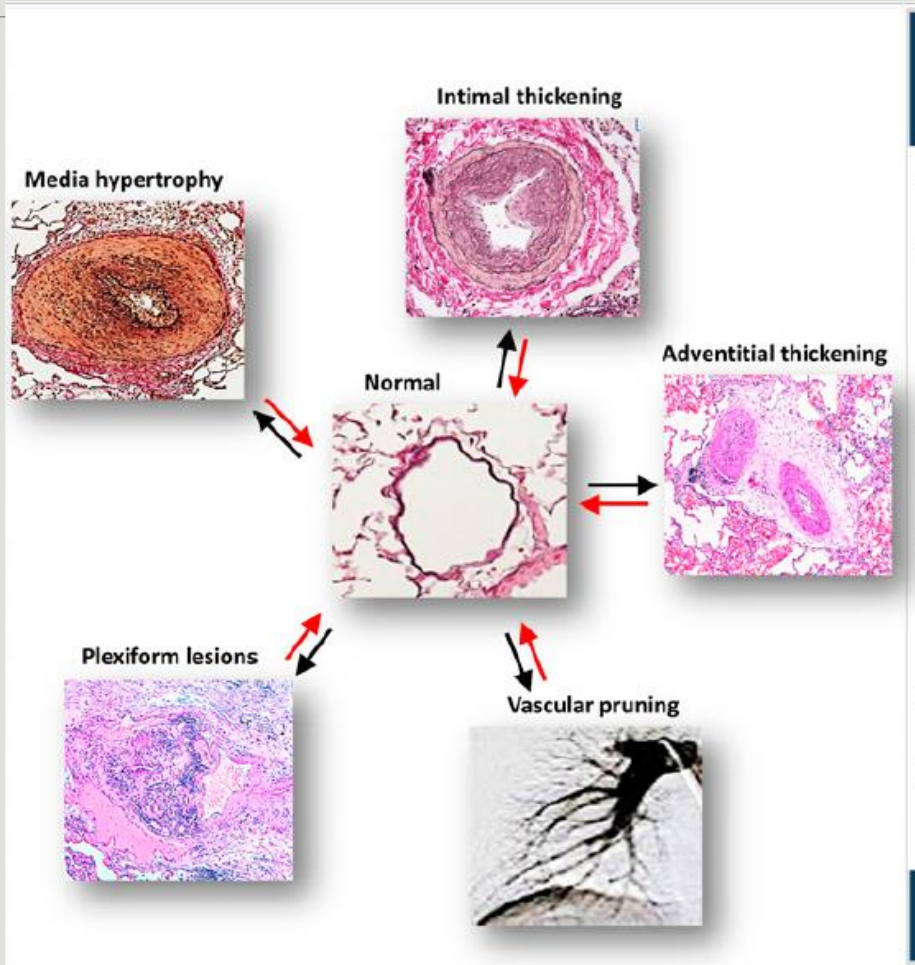


Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.


Oxygen
Diuretics
Digoxin
Diuretic
Anticoagulation
Acute vasoreactivity testing
Positive
Negative
Oral CCB
Lower risk
Higher risk
Sustained response
No
Yes
ERAs or PDE-5 inhibitors (oral)
Epoprostenol or treprostinil (IV)
Iloprost (inhaled)
Treprostinil (SC)
Epoprostenol or treprostinil (IV)
Iloprost (inhaled)
ERAs or PDE-5 inhibitors (oral)
Treprostinil (SC)
Continue CCB
Reassess: consider combo-therapy
Investigational protocols
Atrial septostomy
Lung transplant

Novel therapies for PAH



Reverse remodeling and regenerative strategies – Class I PH

Anti-proliferative strategies
- Tyrosine kinase inhibitors

Transcription factor based therapies
- NFATc inhibitor
- PPARγ agonist
- Notch inhibitor

Anti – inflammatory strategies
- SDF1 blocker
- B cell antagonist

Epigenetic modulation based therapies
- microRNA mimics/ antagomirs
- HDAC inhibitors
- DNMT inhibitor

BMPR2 modulation strategies

Regenerative treatment strategies
- Genetically engineered EPCs
- Genetically engineered MSCs

Guidelines

European Heart Journal (2016) **37**, 67–119
doi:10.1093/eurheartj/ehv317

ESC/ERS GUIDELINES

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

Table 4 Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau *et al.*[5])

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, neurofibromatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Guidelines

Table 3 **Haemodynamic definitions of pulmonary hypertension[a]**

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

Guidelines

1. Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure ≥25 mmHg at rest as assessed by right heart catheterization (Table 3). PH can be found in multiple clinical conditions (Table 4).

Guidelines

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]

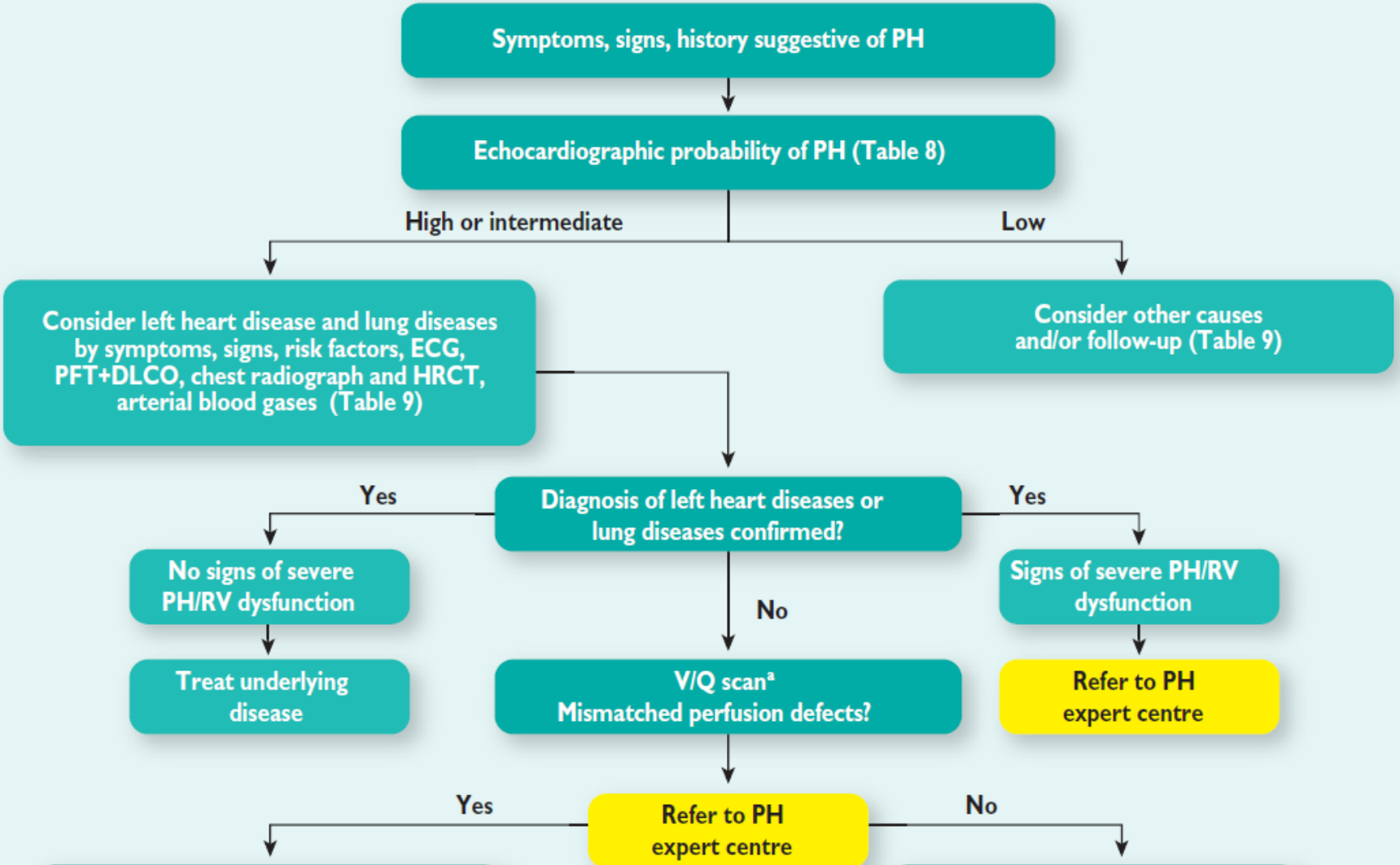
[a]Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors.
[b]Alkylating agents are possible causes of pulmonary veno-occlusive disease.

Guidelines

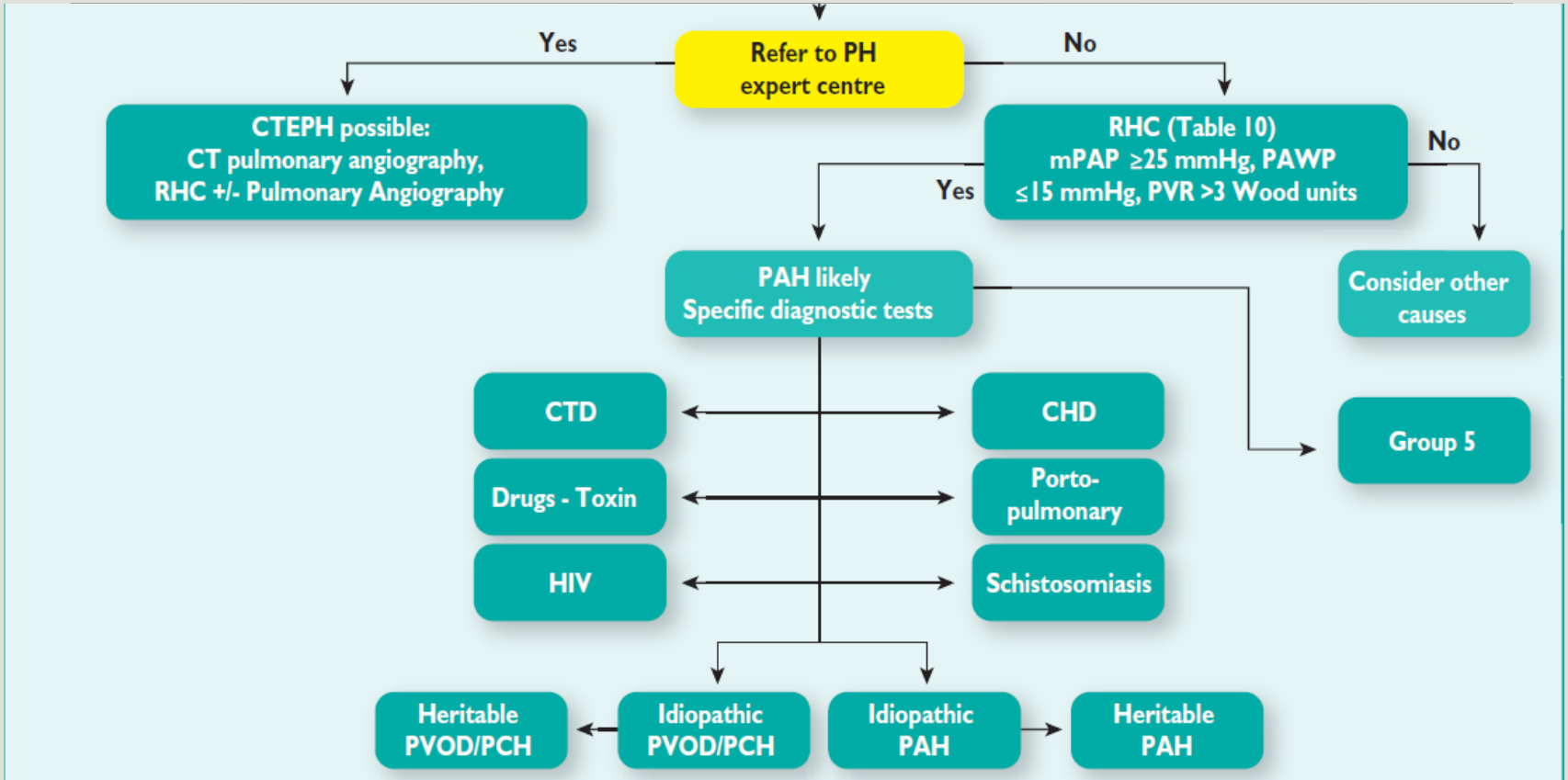
Table 8A Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension

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	

Diagnostic guidelines



Diagnostic guidelines



CHD = congenital heart diseases; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH = pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capillary hemangiomathosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.

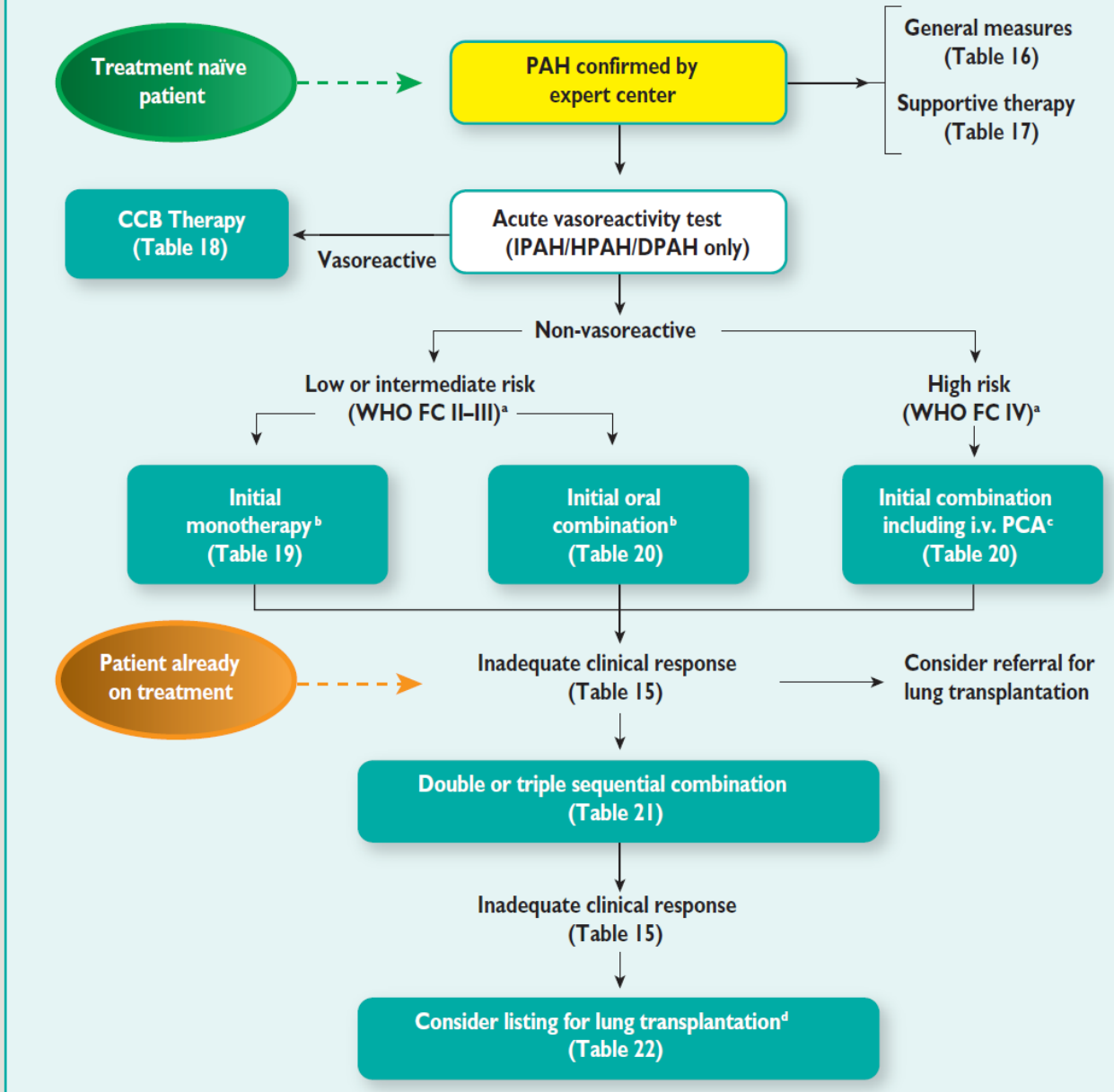
[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

Guidelines for risk assessment

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%

Follow up guidelines

	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]



CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.

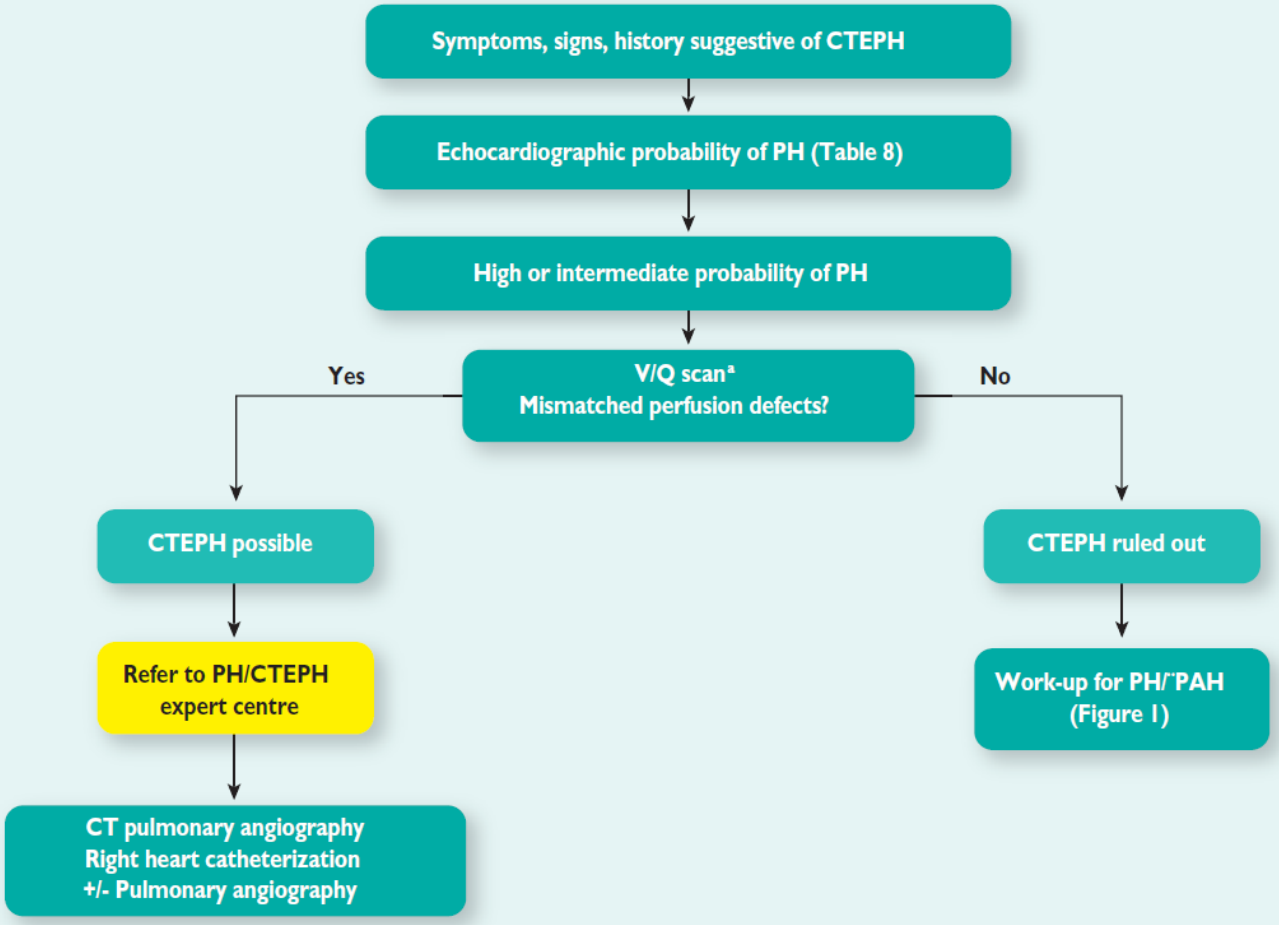
[a]Some WHO-FC III patients may be considered high risk (see Table 13).

[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.

[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.

[d]Consider also balloon atrial septostomy.

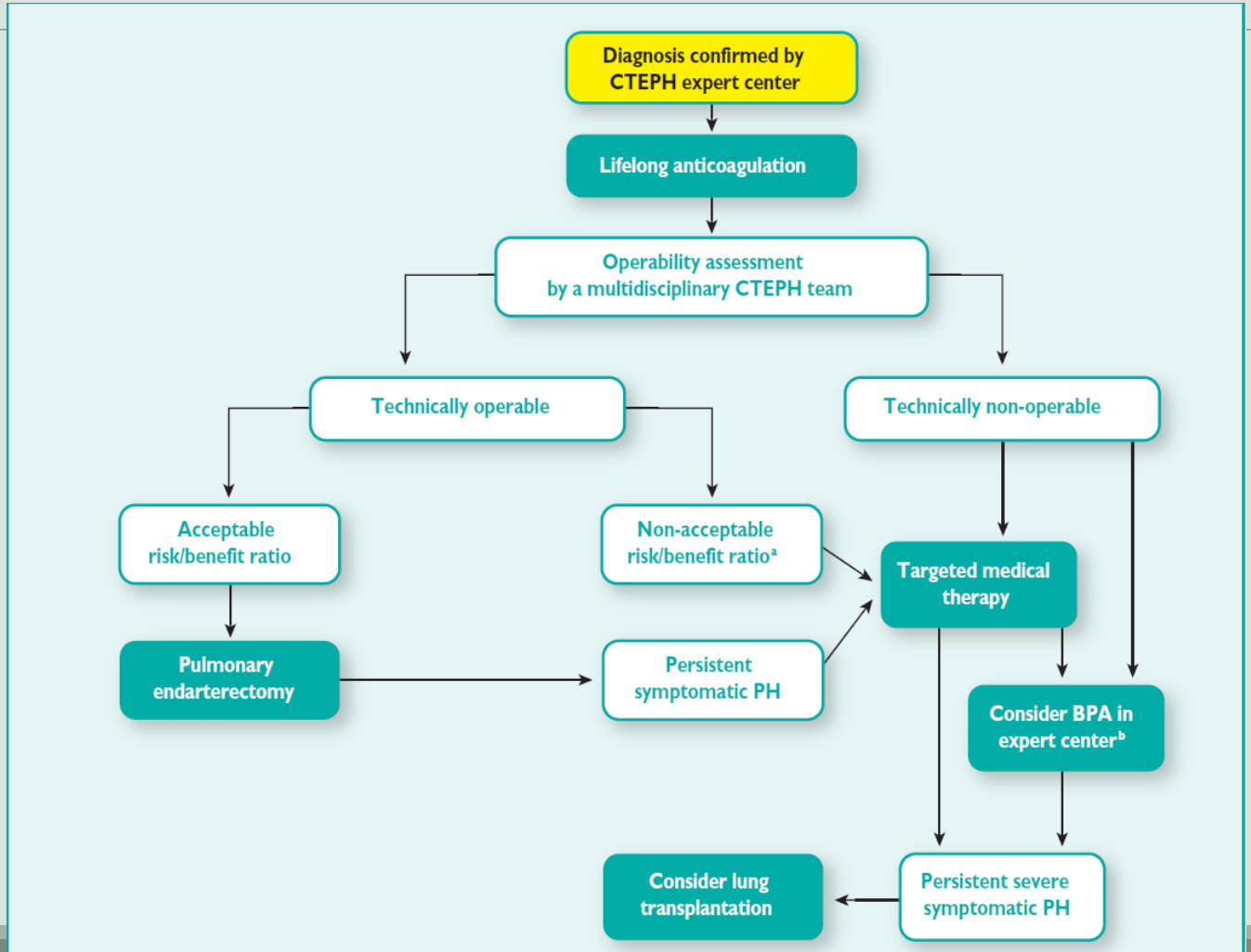
Chronic thromboembolic PH



CT = computed thomography; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; V/Q = ventilation/perfusion.

[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

Chronic thromboembolic PH



BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension.
[a]Technically operable patients with non-acceptable risk/benefit ratio can be considered also for BPA.
[b]In some centers medical therapy and BPA are initiated concurrently.

Pulmonary embolism

Pulmonary embolism is an occlusion or partial occlusion of the pulmonary artery by an embolus – mostly (95%) from deep vein thrombosis.

Embolus with infarction

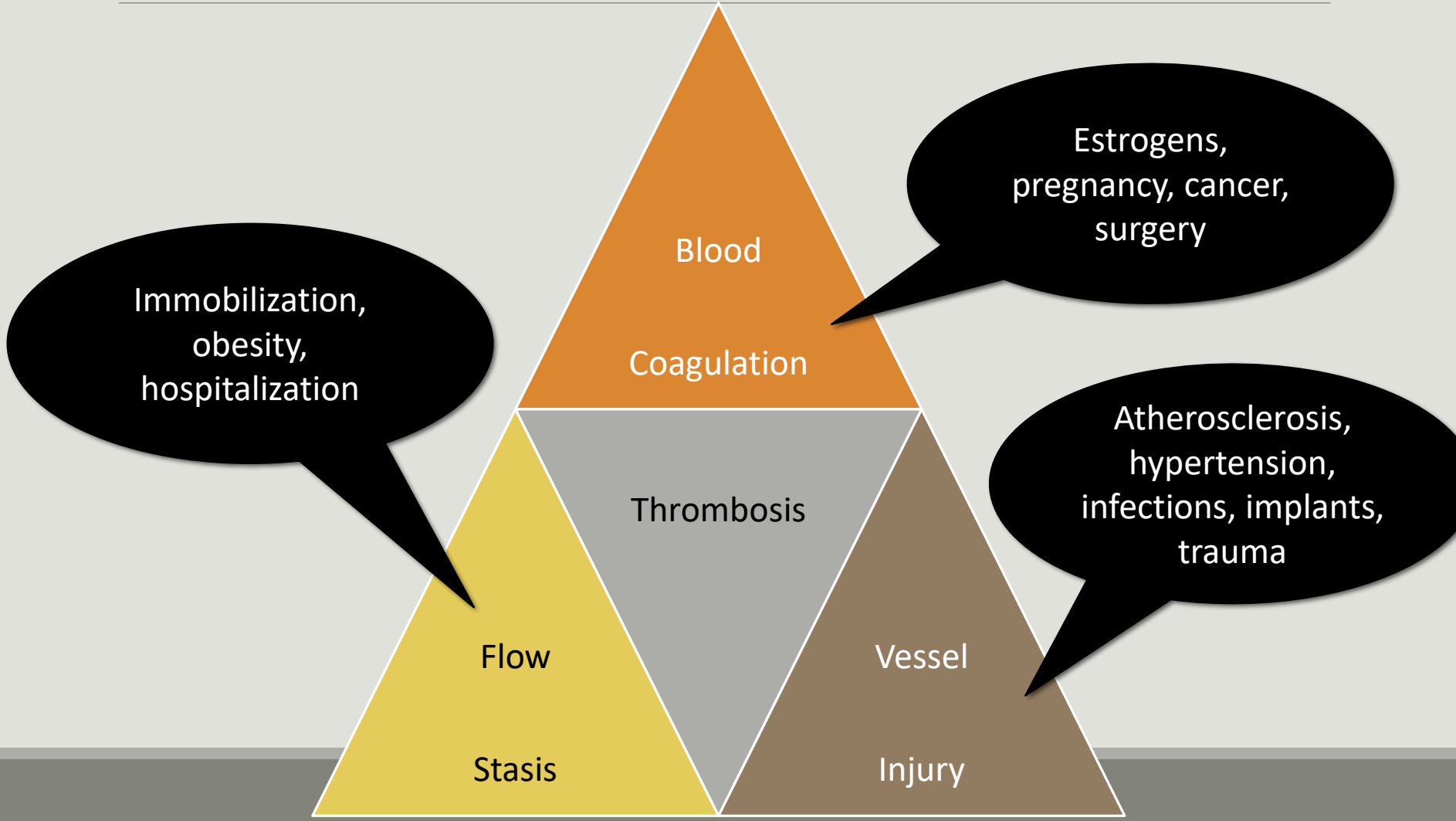
Embolus without infarction (bronchial circulation)

Massive occlusion

Multiple pulmonary emboli

- Chronic reccurent embolization

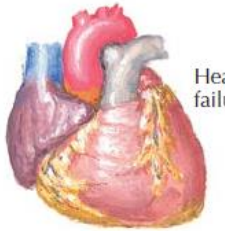
Virchow's triad



Predisposing Factors for Pulmonary Embolism

Venous stasis

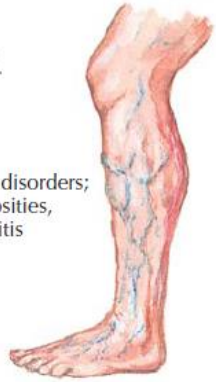
Prolonged bed rest



Heart failure

Prolonged sitting

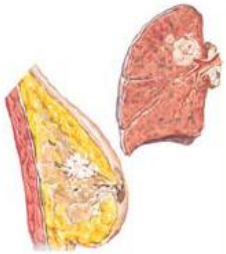
F. Netter M.D.
C. Machado M.D.



Local disorders; varicosities, phlebitis

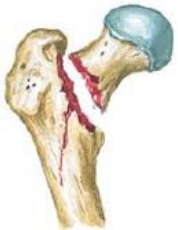
Coagulation disorders

Oral contraceptives



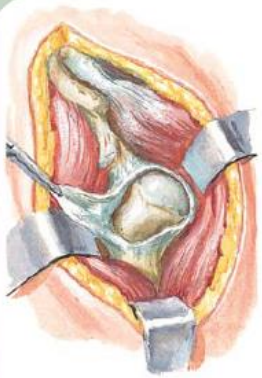
Malignancy

Trauma

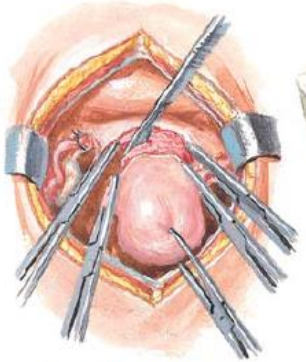


Fractures: also soft tissue (vessel) injury

Post-operative or post-partum

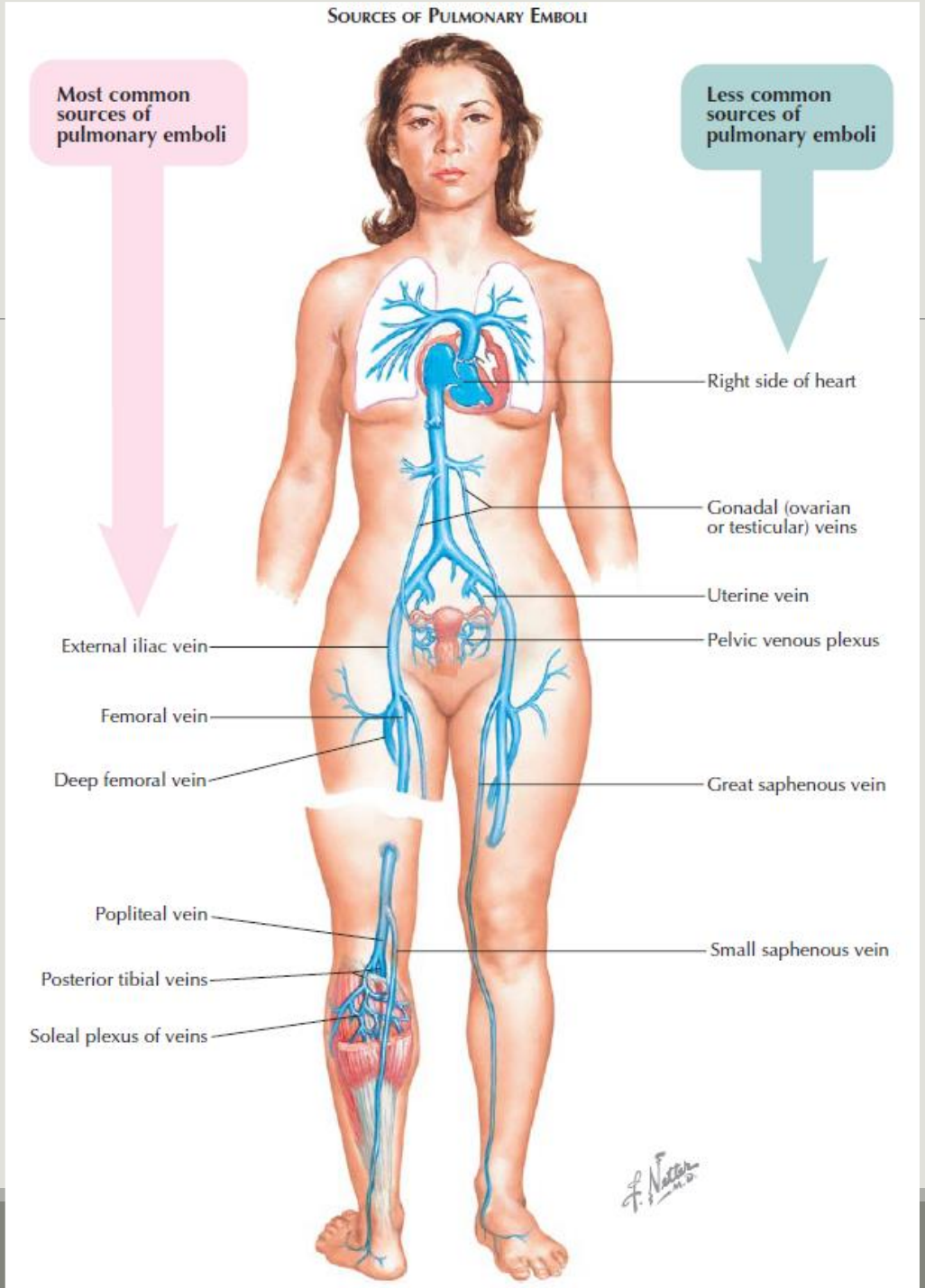


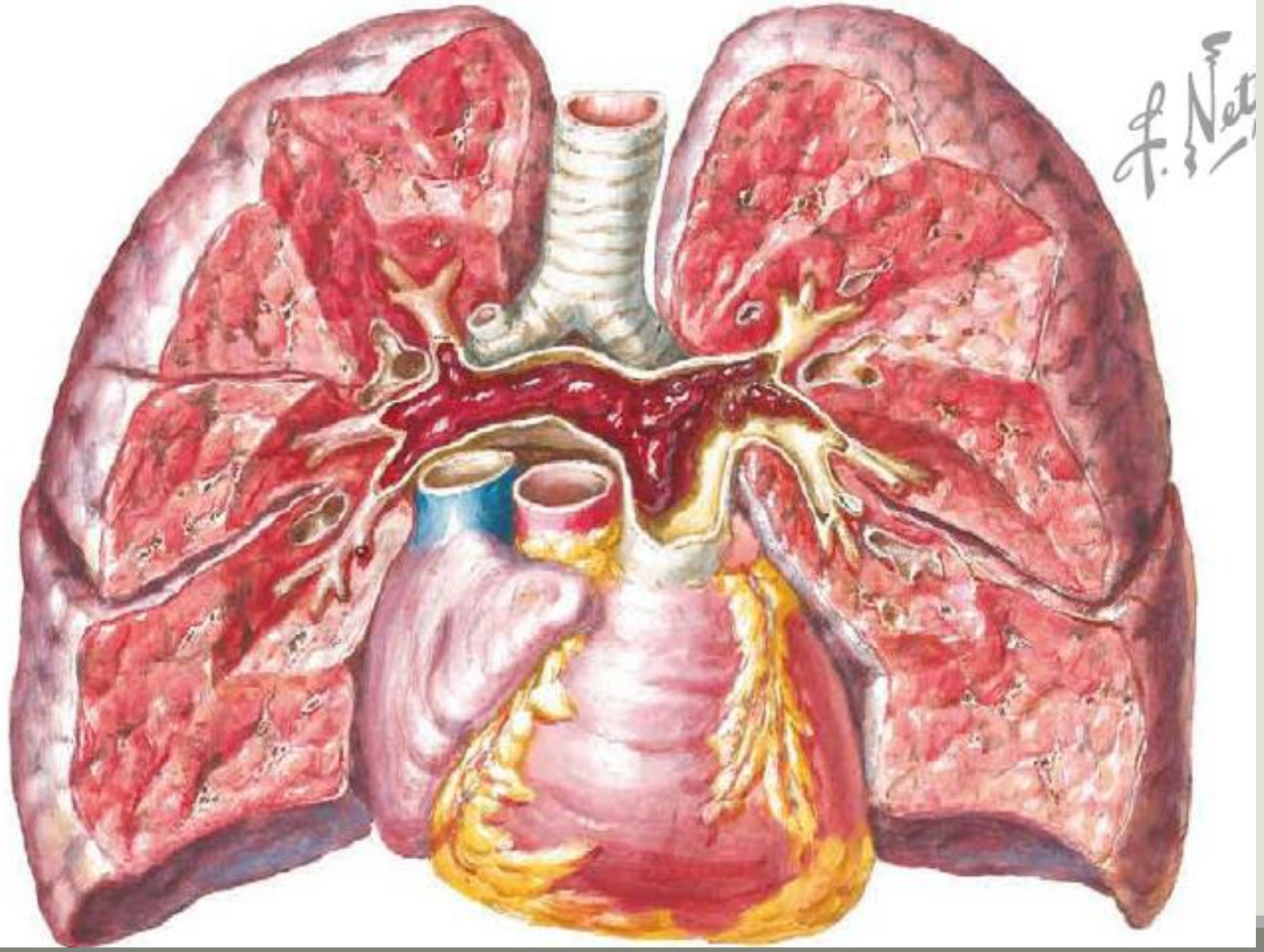
Hip operations



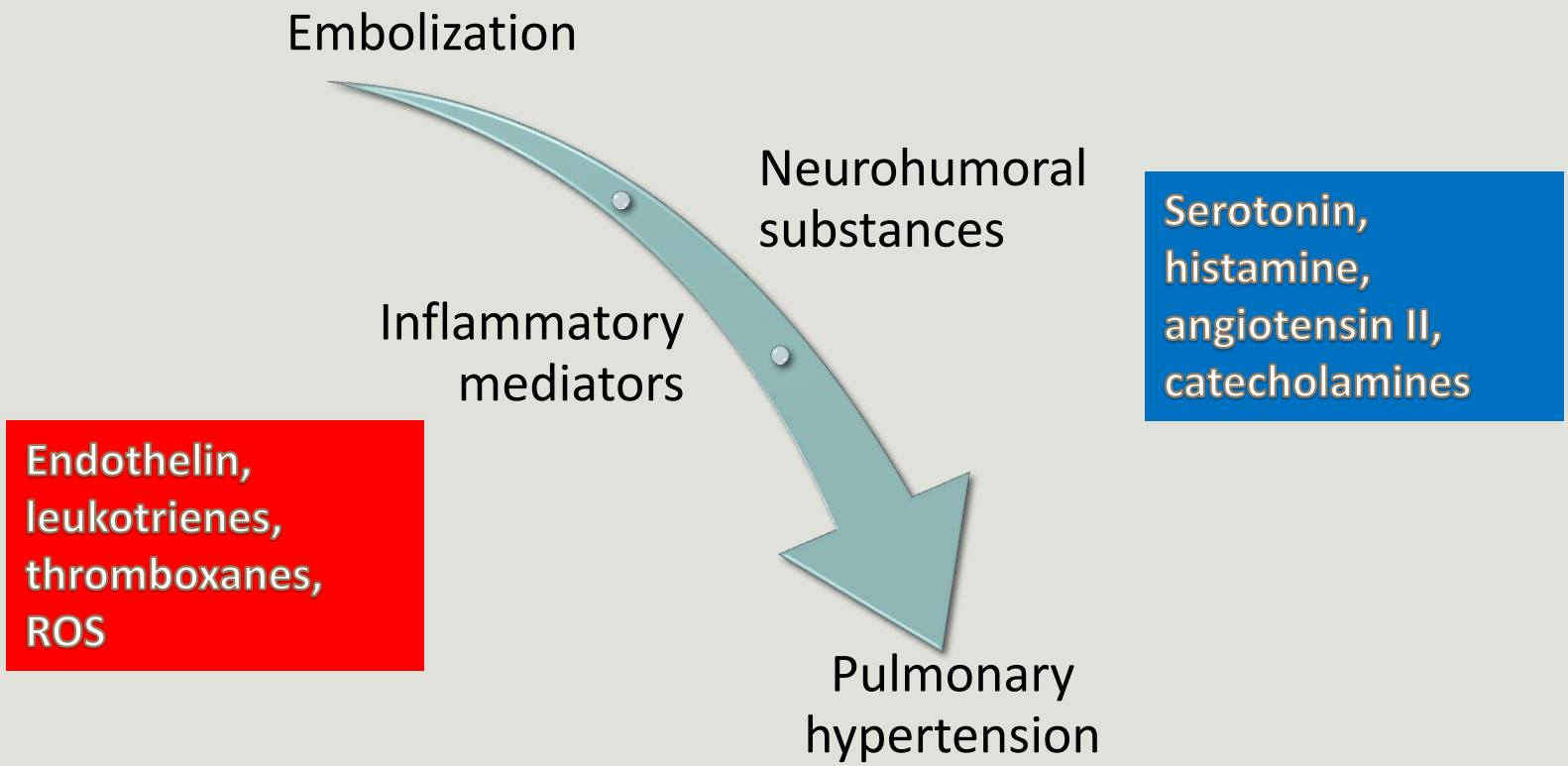
Extensive pelvic or abdominal operations

Phlegmasia alba dolens (milk leg)


Sources of Pulmonary Emboli
Most common sources of pulmonary emboli
Less common sources of pulmonary emboli
Right side of heart
Gonadal (ovarian or testicular) veins
Uterine vein
Pelvic venous plexus
External iliac vein
Femoral vein
Deep femoral vein
Great saphenous vein
Popliteal vein
Small saphenous vein
Posterior tibial veins
Soleal plexus of veins



Pulmonary embolism



Pulmonary embolism

Pathophysiology

- Hemodynamic changes
  - Pulmonary hypertension, decrease in cardiac output
- Changes in ventilation/perfusion
  - Hyperventilation, less surfactant production, alveolar collapse
- Hypoxemia
  - Less surfactant, inefficient perfusion of hypoventilated areas, right to left shunts
- Bronchoconstriction
  - Histamine from the embolus, wheezing
- Pulmonary infarction

Molecular pathogenesis

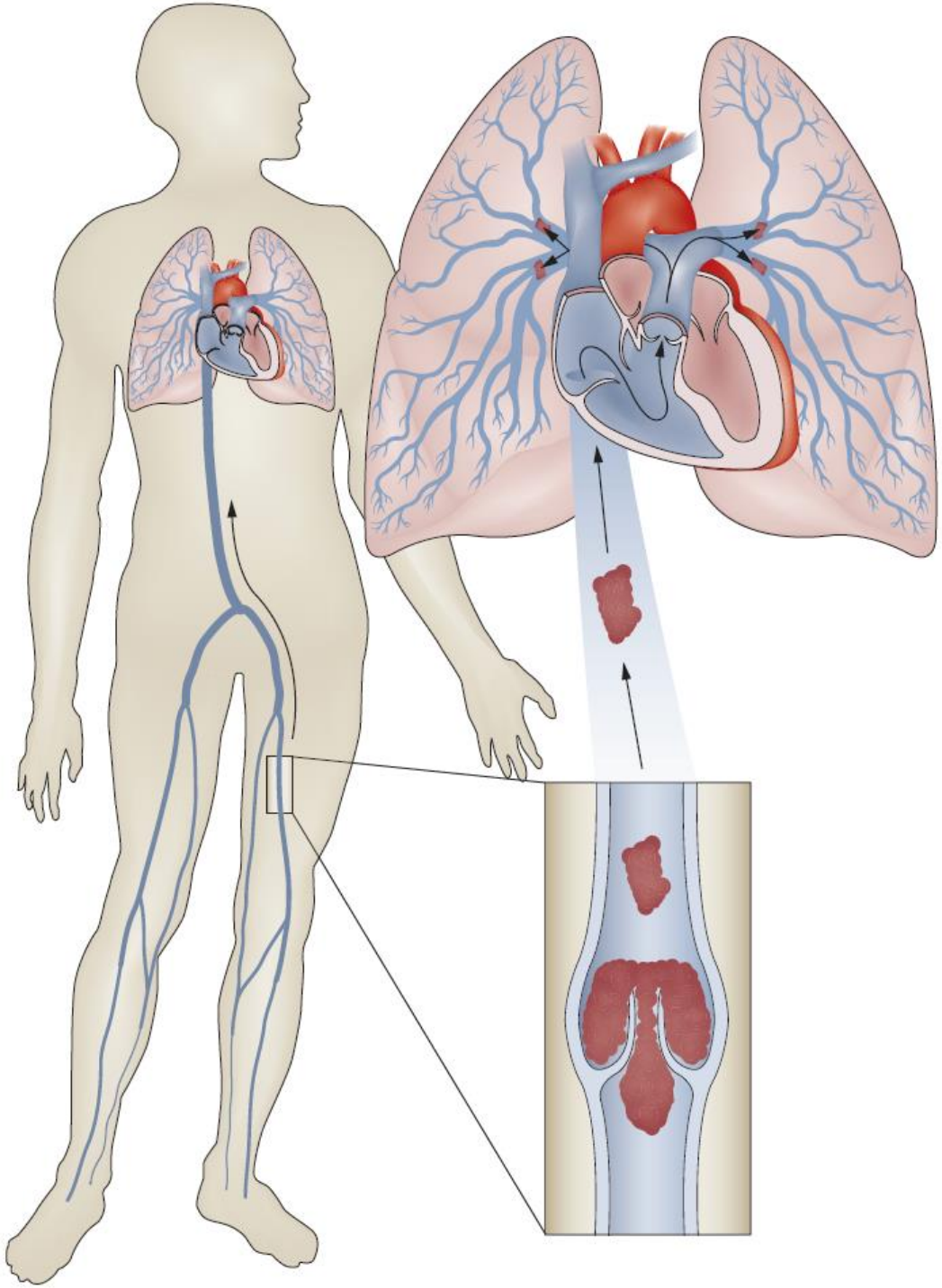
Decrease in endothelium-derived vasodilators

- NO, prostacyclin

Increase in vasoconstrictors

- Thromboxane, endothelin, VEGF

Functional and later structural changes



Venous stasis
Vessel injury
Hypercoagulability

↓

Thrombus formation

↓

Dislodgement of portion of thrombus

↓

Occlusion of part of pulmonary circulation

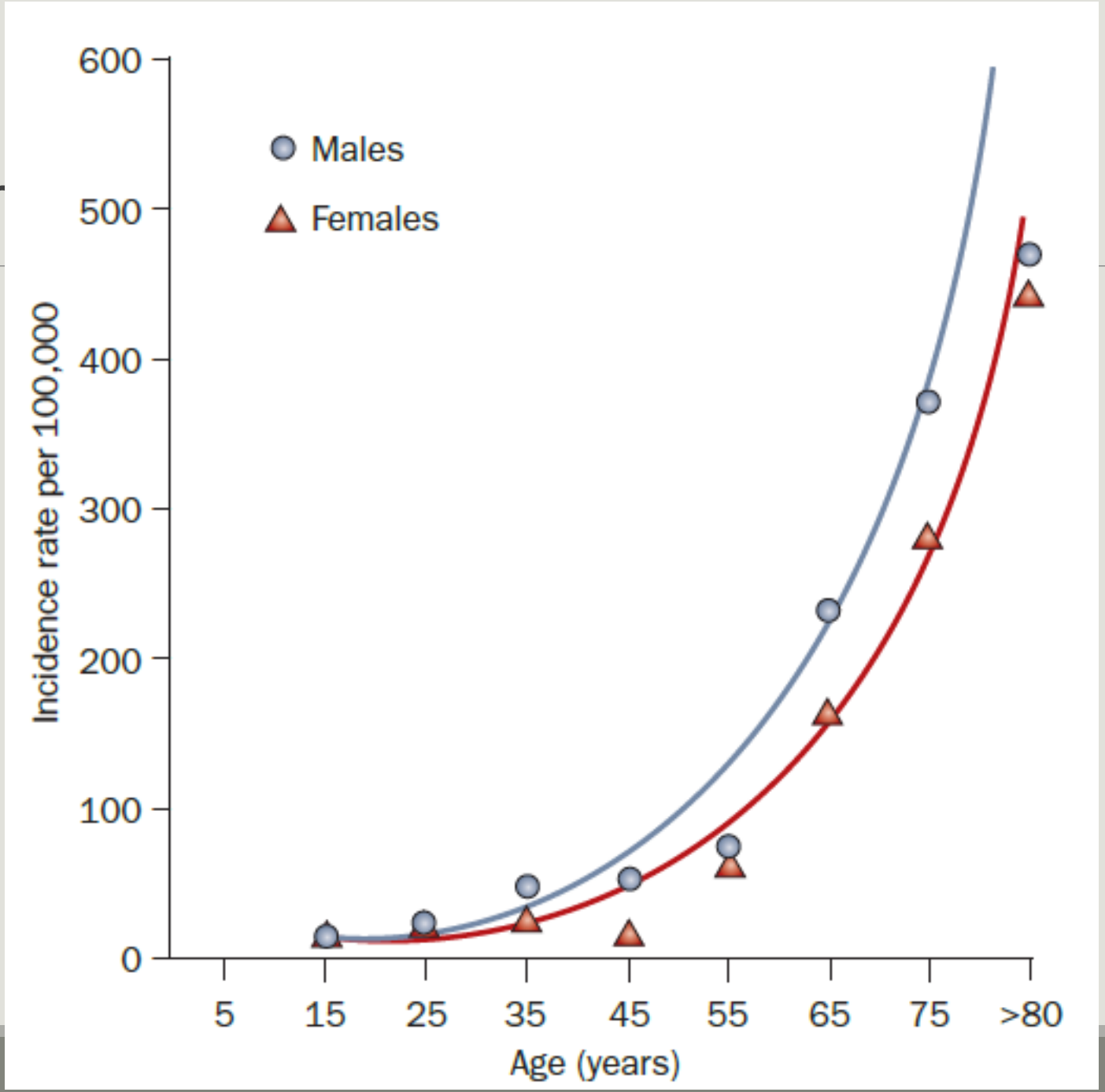
↓

Hypoxic vasoconstriction
Decreased surfactant
Release of neurohumoral and inflammatory substances
Pulmonary edema
Atelectasis

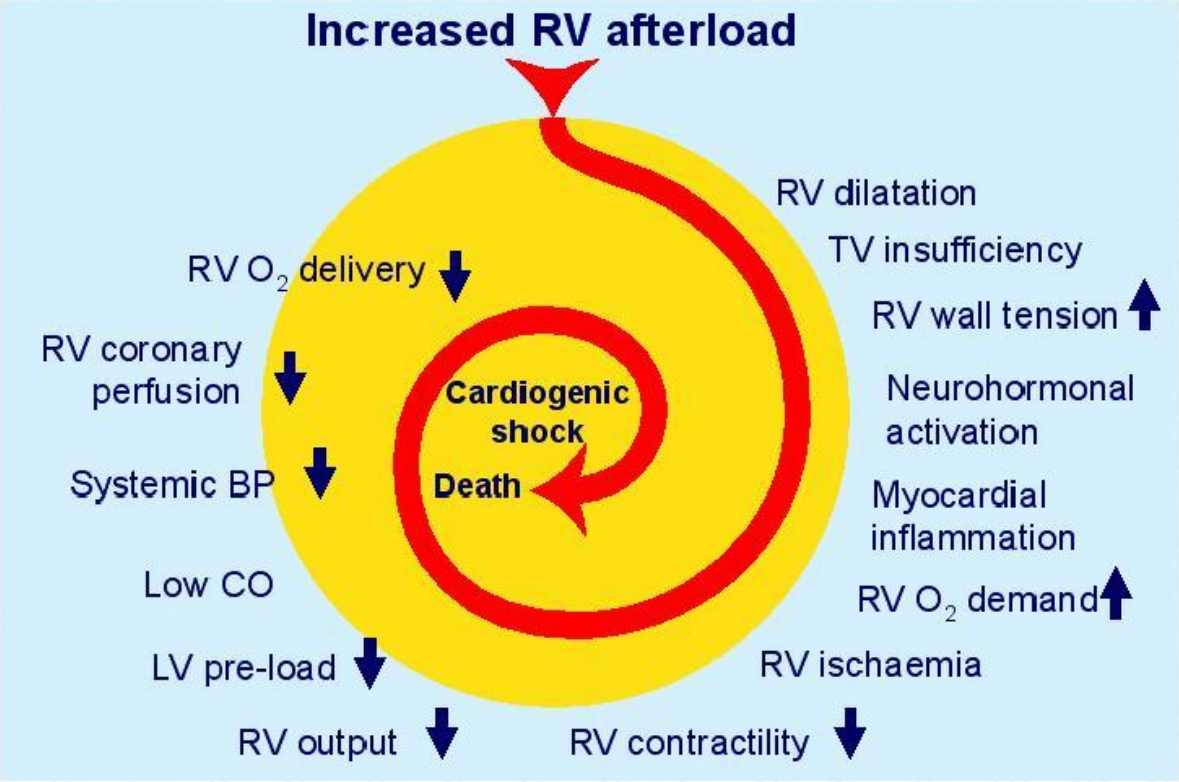
↓

Tachypnea
Dyspnea
Chest pain
Increased dead space
$\dot{V}/\dot{Q}$ imbalances
Decreased Pa_{O_2}
Pulmonary infarction
Pulmonary hypertension
Decreased cardiac output
Systemic hypotension
Shock

Ir


600
500
400
300
200
100
0
Incidence rate per 100,000
Males
Females
5
15
25
35
45
55
65
75
>80
Age (years)

Key factors contributing to haemodynamic collapse in acute pulmonary embolism



BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

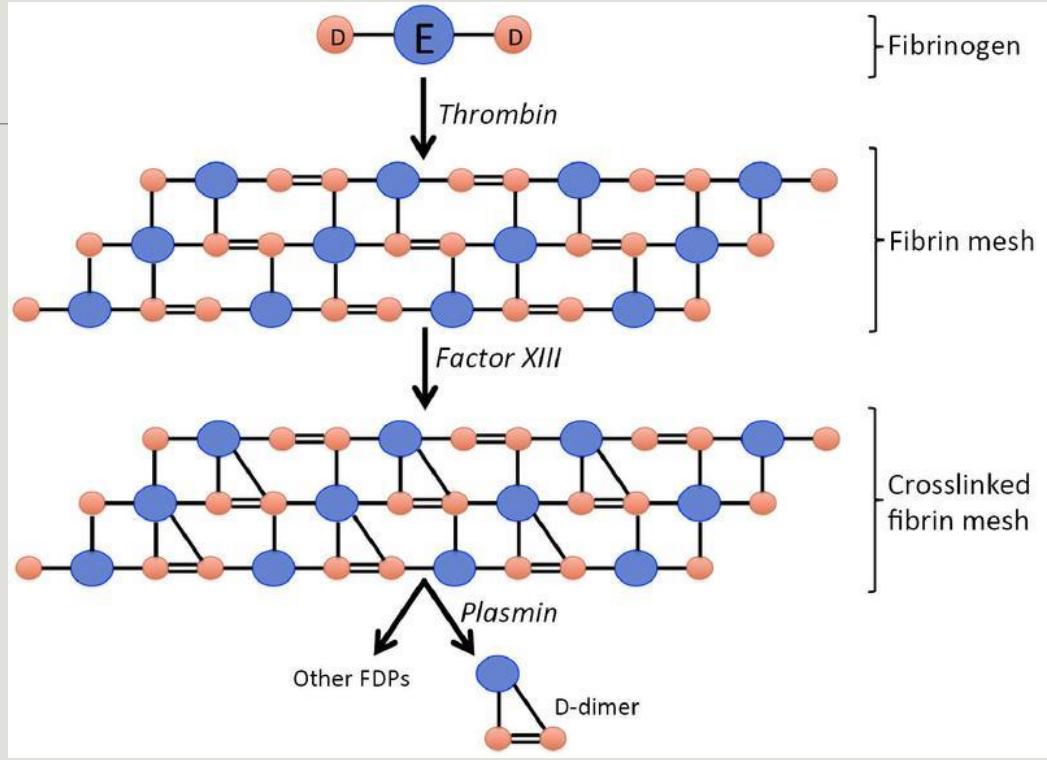
Diagnosis

Classic triad

- Dyspnea
- Pleuritic chest pain
- Hemoptysis

- Swollen, tender, warm, red calf

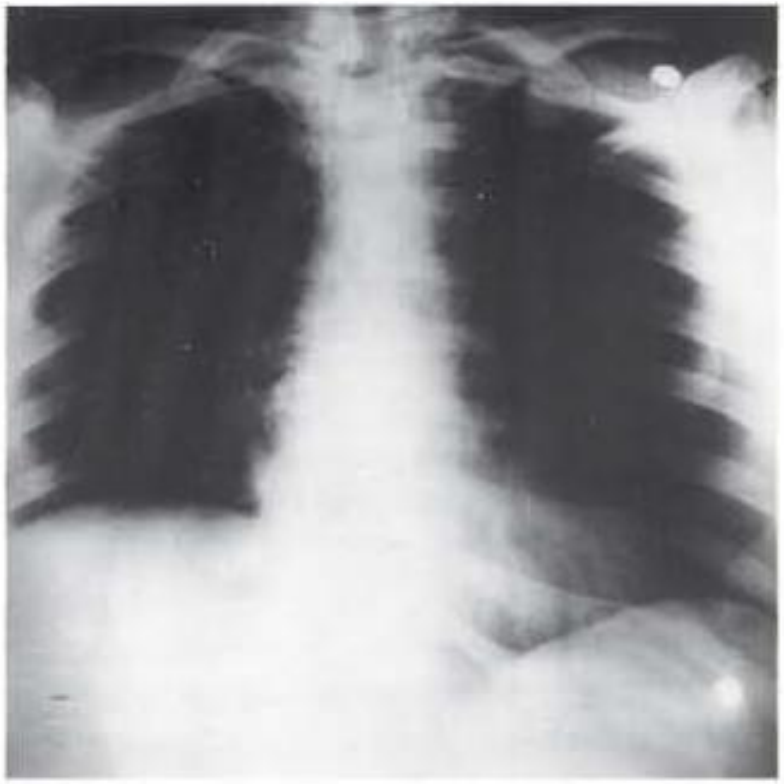
- ECG, X-ray
- Ventilation/perfusion scan
- CT angiography



- D-dimers – fibrin degradation products – high sensitivity, low specificity

Ventilation scan normal

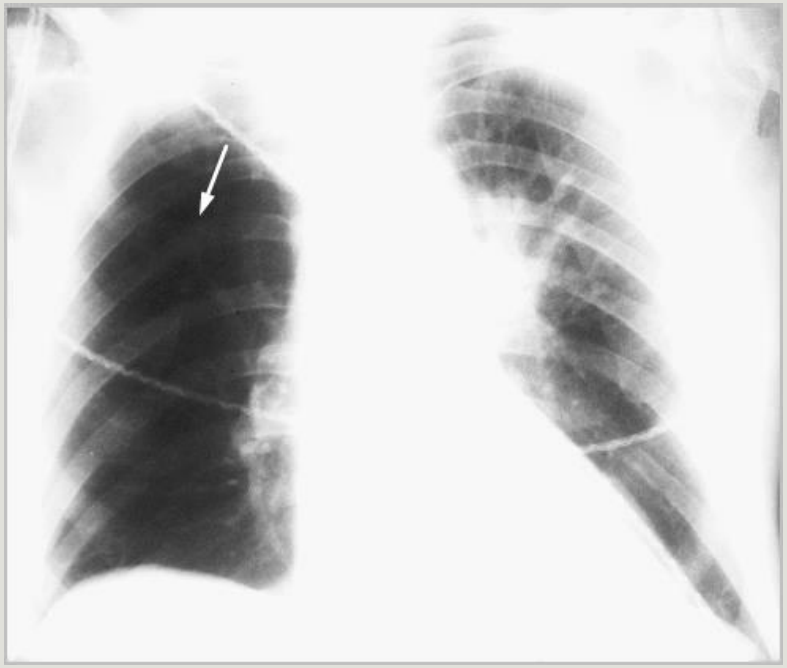
Perfusion scan reveals defects in right lung. Emboli in left lung not visualized



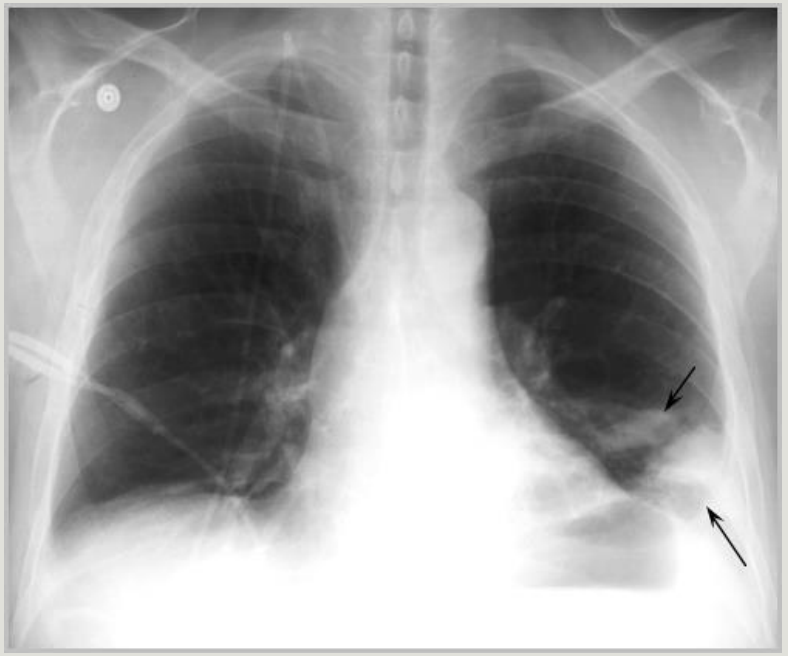
X-ray film often normal

Chest X-ray

Westermark sign – oligemia



Hampton hump – pulmonary infarction



Hampton's Hump

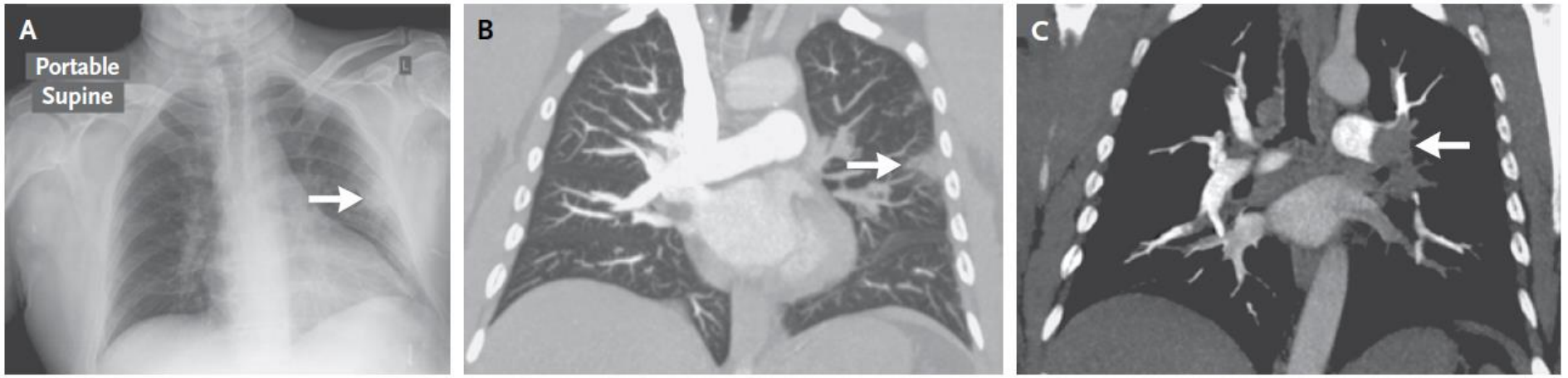
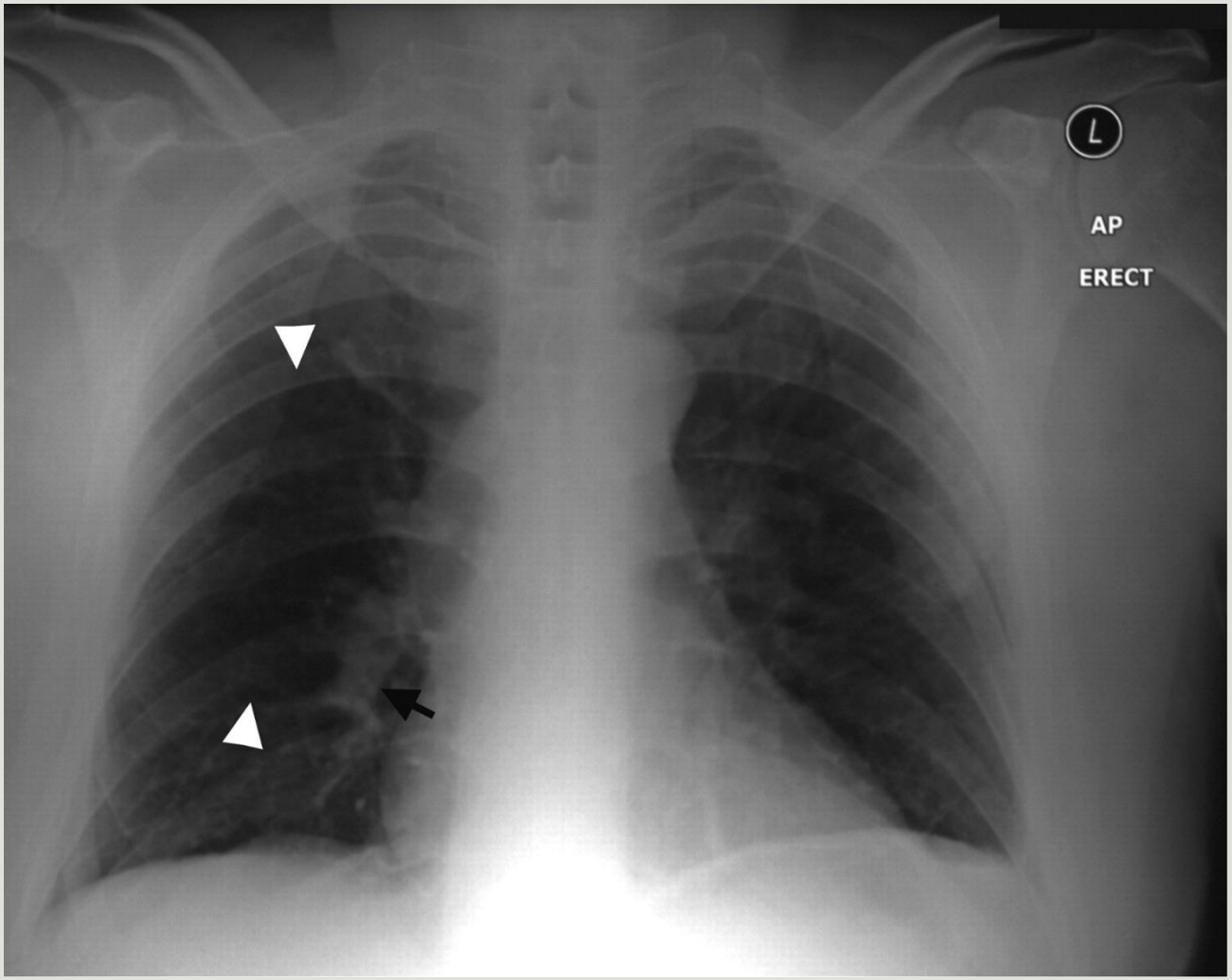


Figure 1. Chest radiograph demonstrating focal oligemia in the right lung (area between white arrowheads) Westermark sign and a prominent right descending pulmonary artery (black arrow) – Palla's sign.



Shiva Sreenivasan et al. Circulation. 2007;115:e211

Sudden onset of dyspnea and tachycardia in a predisposed individual is a cardinal clue.

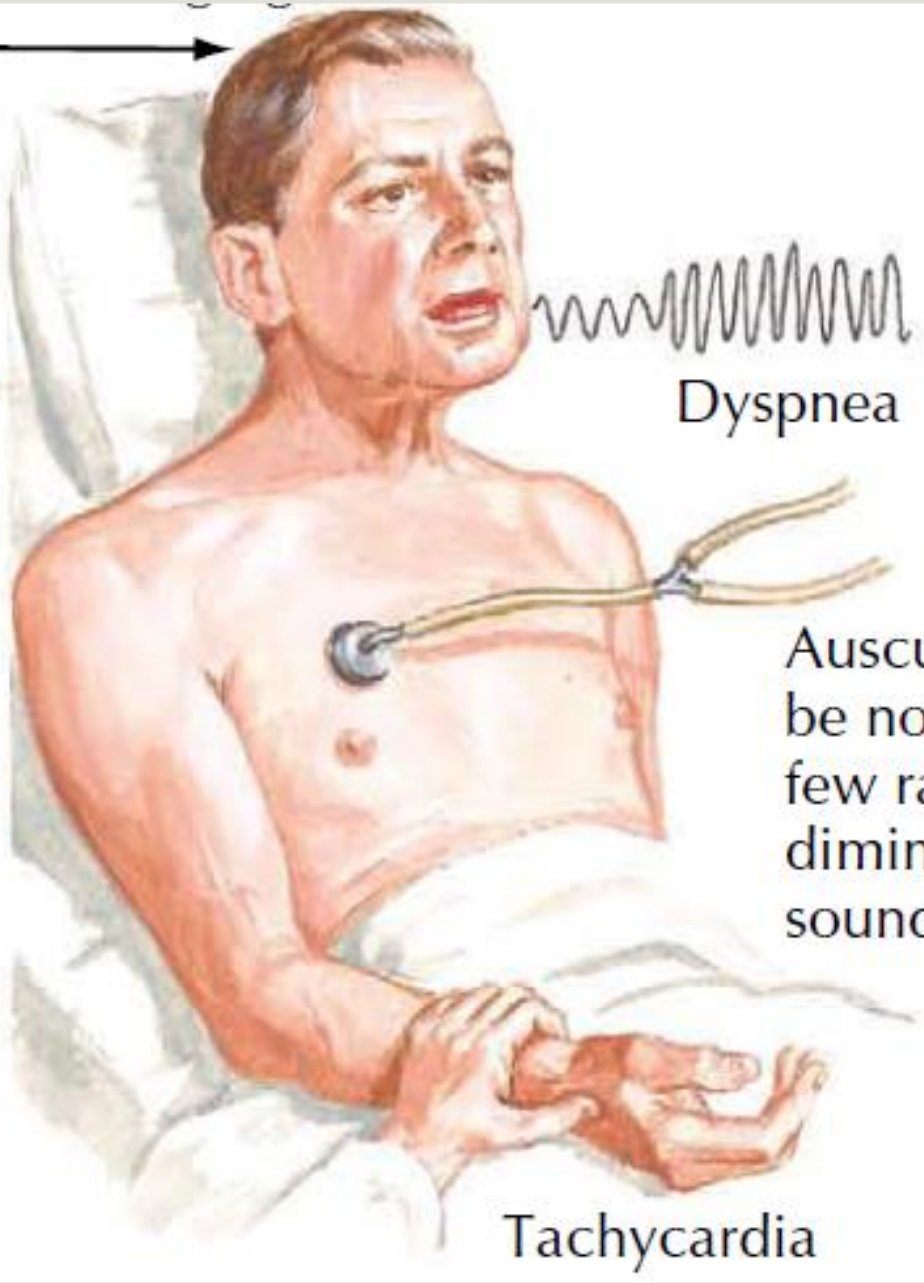


Table 6 Prevalence of symptoms and signs in patients with suspected PE according to final diagnosis

	PE confirmed ($n = 219$)	PE excluded ($n = 546$)
Symptoms		
Dyspnoea	80%	59%
Chest pain (pleuritic)	52%	43%
Chest pain (substernal)	12%	8%
Cough	20%	25%
Haemoptysis	11%	7%
Syncope	19%	11%
Signs		
Tachypnoea (≥20/min)	70%	68%
Tachycardia (>100/min)	26%	23%
Signs of DVT	15%	10%
Fever (>38.5°C)	7%	17%
Cyanosis	11%	9%

Philip Steven Wells, M.D., M.Sc

Pulmonary Embolism Wells Score

Share

Select Criteria:

- [ ] Symptoms of DVT (3 points)
- [ ] No alternative diagnosis better explains the illness (3 points)
- [ ] Tachycardia with pulse > 100 (1.5 points)
- [ ] Immobilization (>= 3 days) or surgery in the previous four weeks (1.5 points)
- [ ] Prior history of DVT or pulmonary embolism (1.5 points)
- [ ] Presence of hemoptysis (1 point)
- [ ] Presence of malignancy (1 point)

Results:

Total Criteria Point Count: **0**

Reset Form

Pulmonary Embolism Risk Score Interpretation

Score > 6:	High probability
Score >= 2 and <= 6:	Moderate probability
Score < 2:	Low Probability

Hints | References

The article referenced below also refers to a cut point of 4 points or less as PE unlikely as long as the specific D-Dimer test is negative. Refer to the original article below for all details.

Revised Geneva Score*

Characteristic	Points
Age older than 65 years	1
Previous deep venous thrombosis or pulmonary embolism	3
Surgery or fracture within 1 month	2
Active malignant condition	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate 75–94 beats/minute	3
Heart rate 95 beats/minute or more	5
Pain in response to lower-limb deep venous palpation, unilateral edema	4

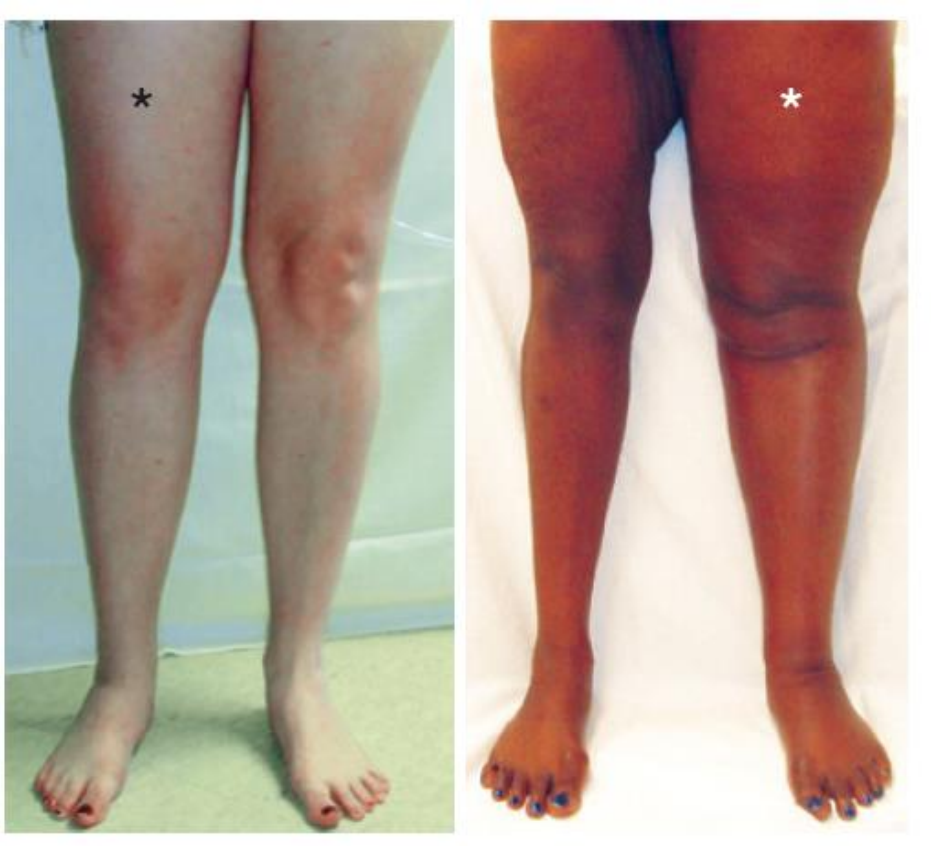
0–3 points indicates low clinical probability of pulmonary embolism (8% in the original validation study*)

4–10 points indicates intermediate clinical probability of pulmonary embolism (28% in the original validation study*)

≥11 points indicates high clinical probability of pulmonary embolism (74% in the original validation study*)

**Le Gal G. Prediction of pulmonary embolism in the emergency department: The revised Geneva score. Ann Intern Med 2006;144:165.*

Deep vein thrombosis



Guidelines

European Heart Journal (2014) **35**, 3033–3080
doi:10.1093/eurheartj/ehu283

ESC GUIDELINES

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

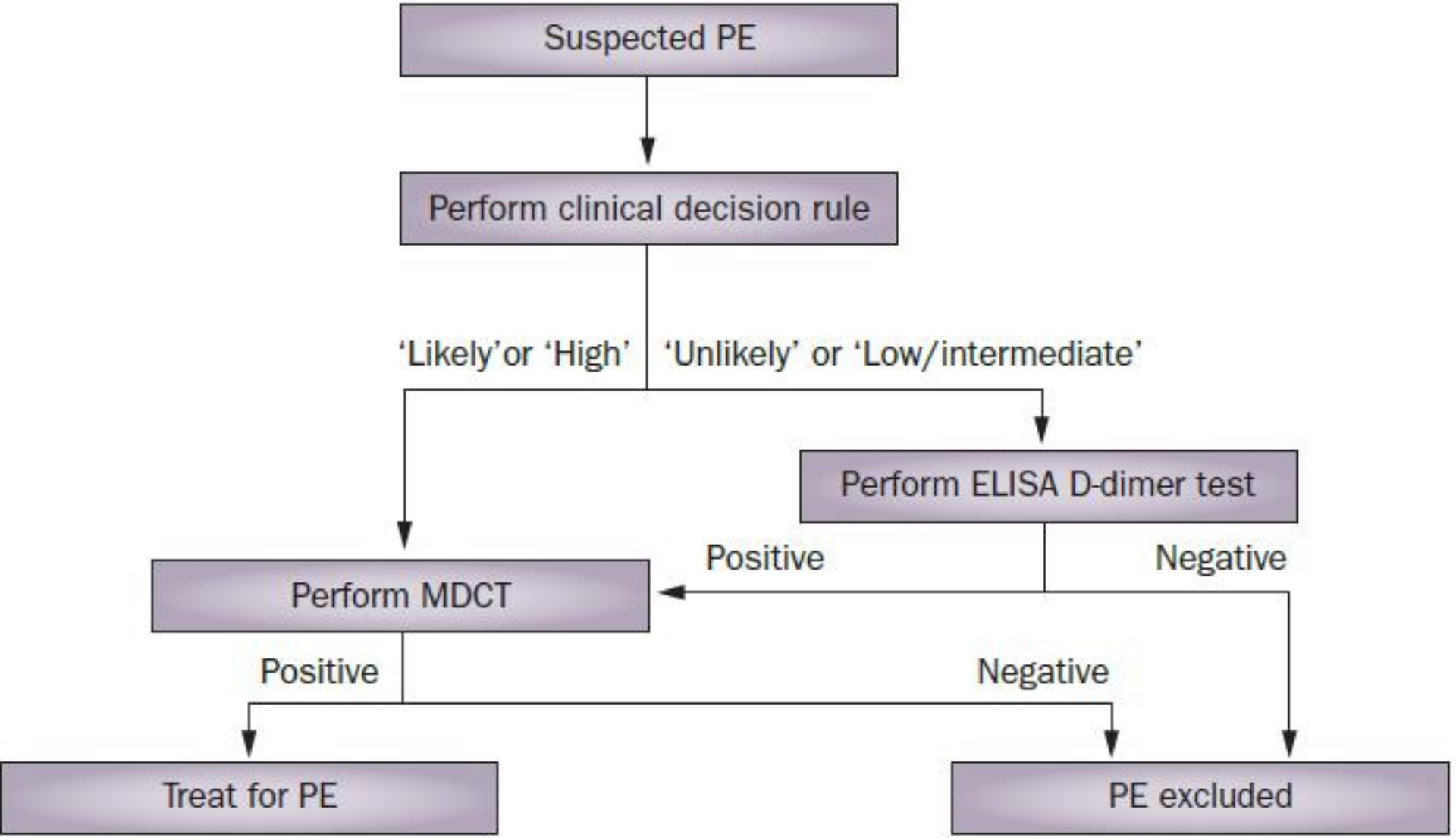
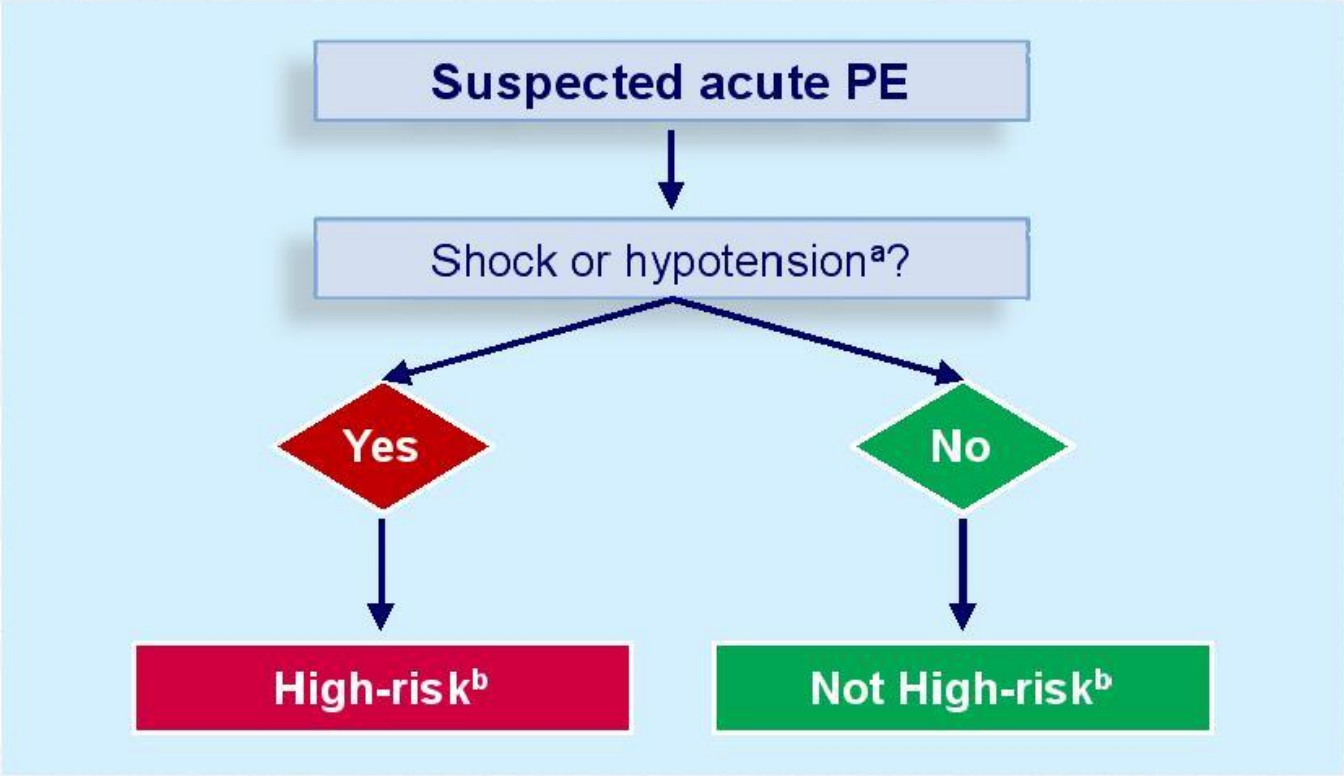


Figure 3 | Diagnostic approach to suspected acute pulmonary embolism. Abbreviations: ELISA, enzyme-linked immunosorbent assay; MDCT, multi-detector CT; PE, pulmonary embolism.

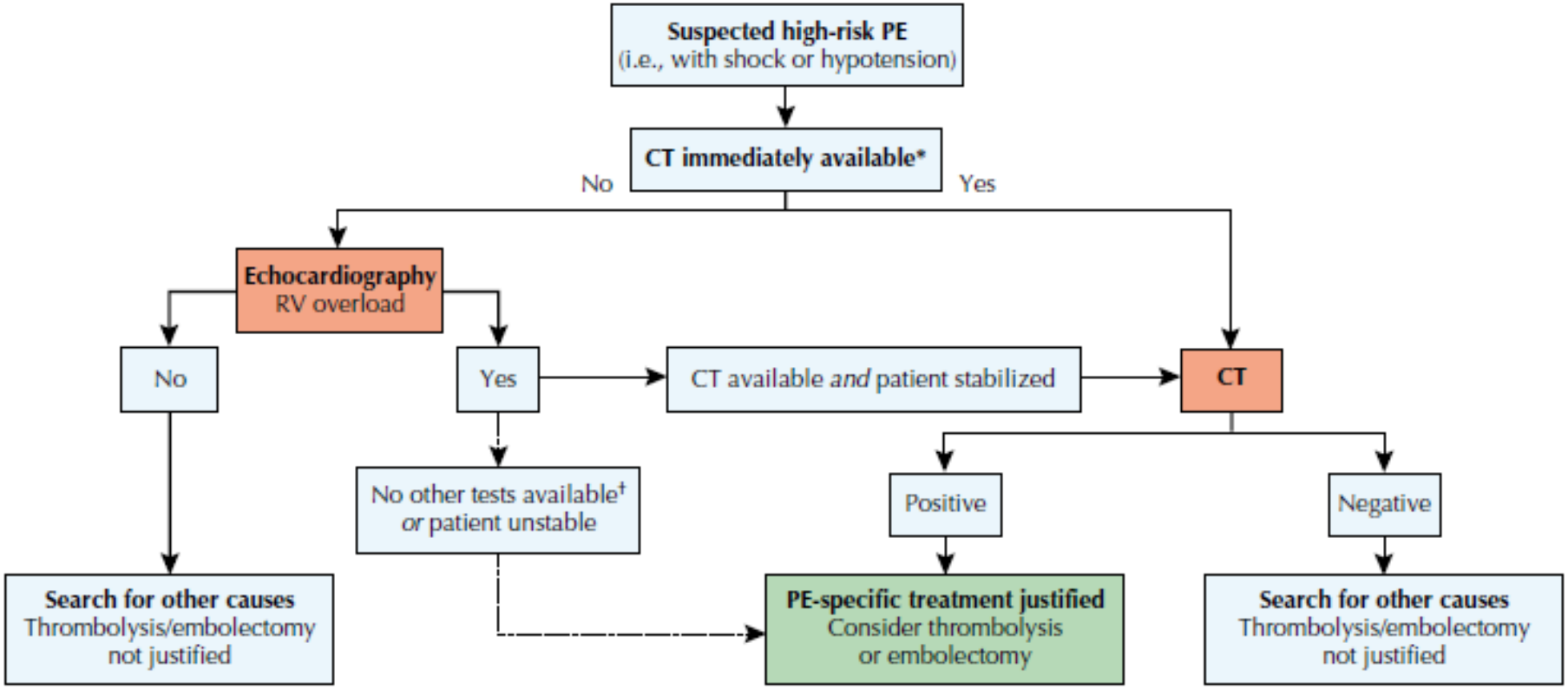
Initial risk stratification of acute PE



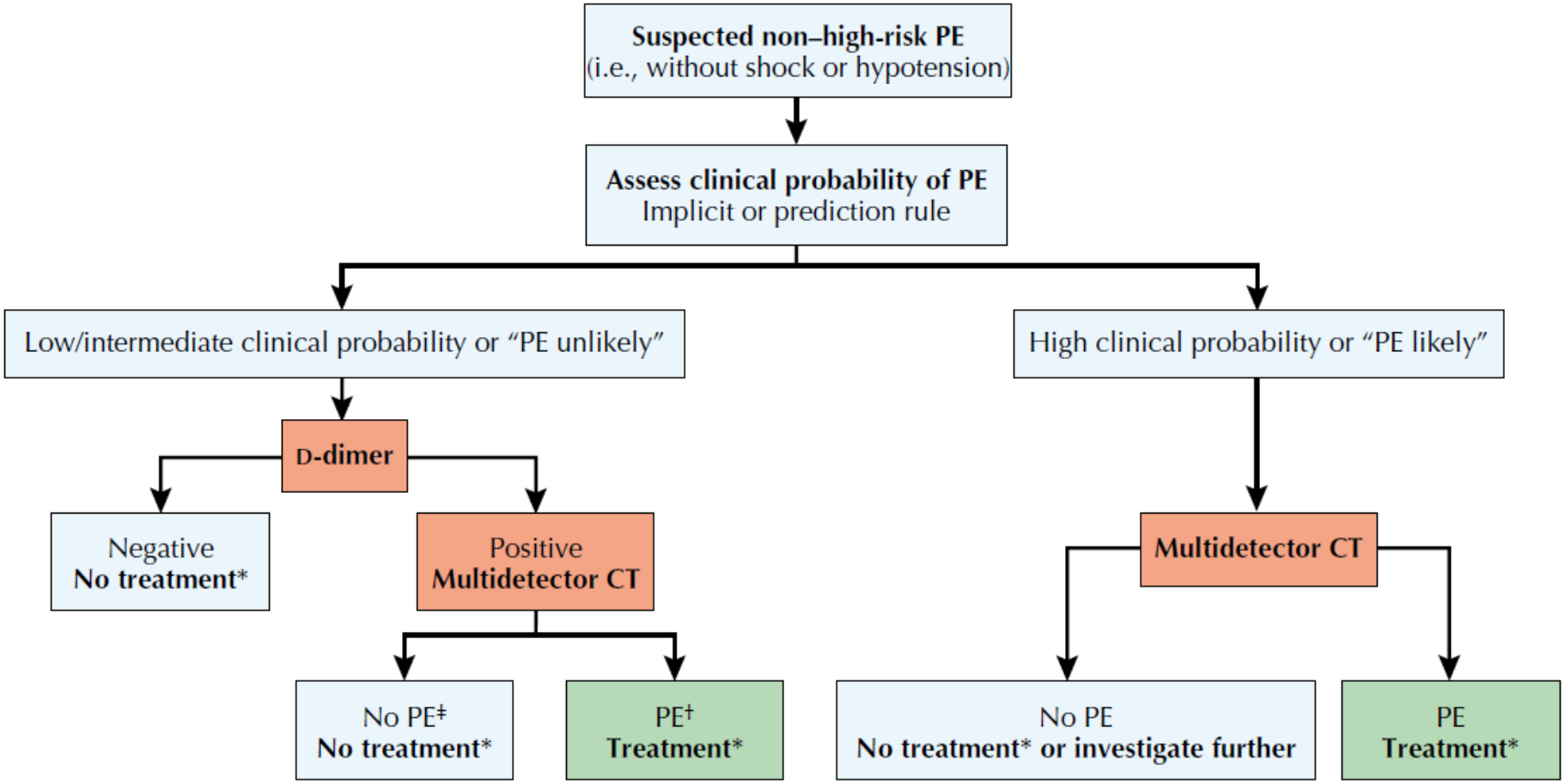
[a] Defined as systolic blood pressure <90 mmHg, or a systolic pressure drop by ≥40 mmHg, for >15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis.
[b] Based on the estimated PE-related in-hospital or 30-day mortality.

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Decision tree algorithm



Decision tree algorithm



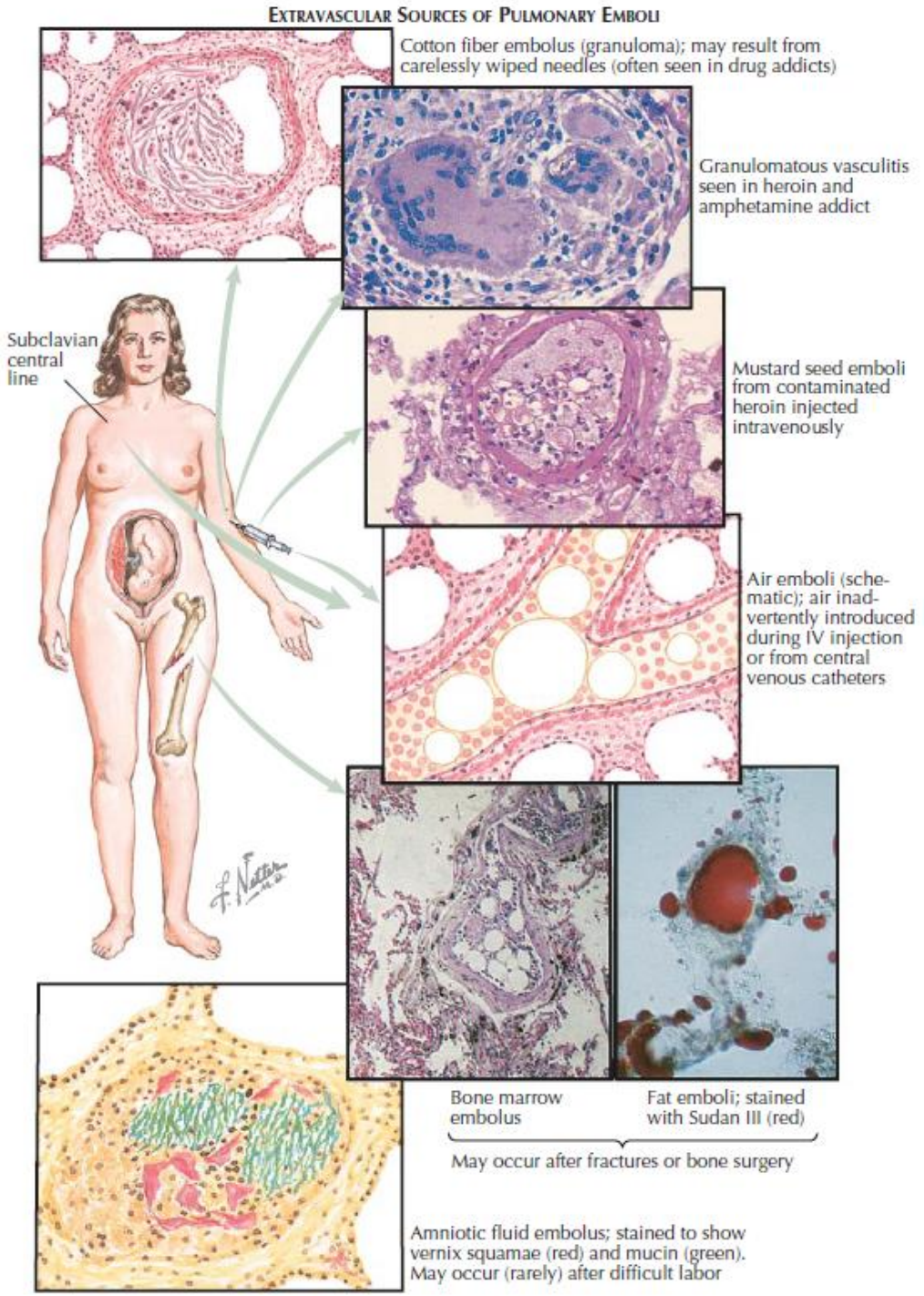
Decision matrix

Table 64-4 Decision Matrix for Patients with Suspected Pulmonary Embolism

	D-Dimer Negative	D-Dimer Positive	CT Negative	CT Positive
Wells score ≤ 4 "PE unlikely"	No CT No treatment	CT	No treatment	Treatment
Wells score > 4 "PE likely"	CT	CT	No treatment	Treatment

Exotic emboli

Material	Clinical Setting
Air	Cardiac surgery, neurosurgery, improper manipulation of central venous catheters
Amniotic fluid	Active labor
Fat	Long bone fracture, liposuction
Foreign body	Pieces of intravenous devices, talc
Oil	Lymphangiography
Parasite eggs	Schistosomiasis
Septic emboli	Endocarditis, thrombophlebitis
Thrombus	Deep venous thrombosis
Tumor	Renal cell carcinoma with invasion of vena cava



Differential diagnosis

Pulmonary thromboembolism vs pulmonary hypertension

Pneumonia

Valvular diseases

Acute myocardial infarction

Acute heart failure

Pericarditis

Aortic rupture

Pleural diseases

Treatment

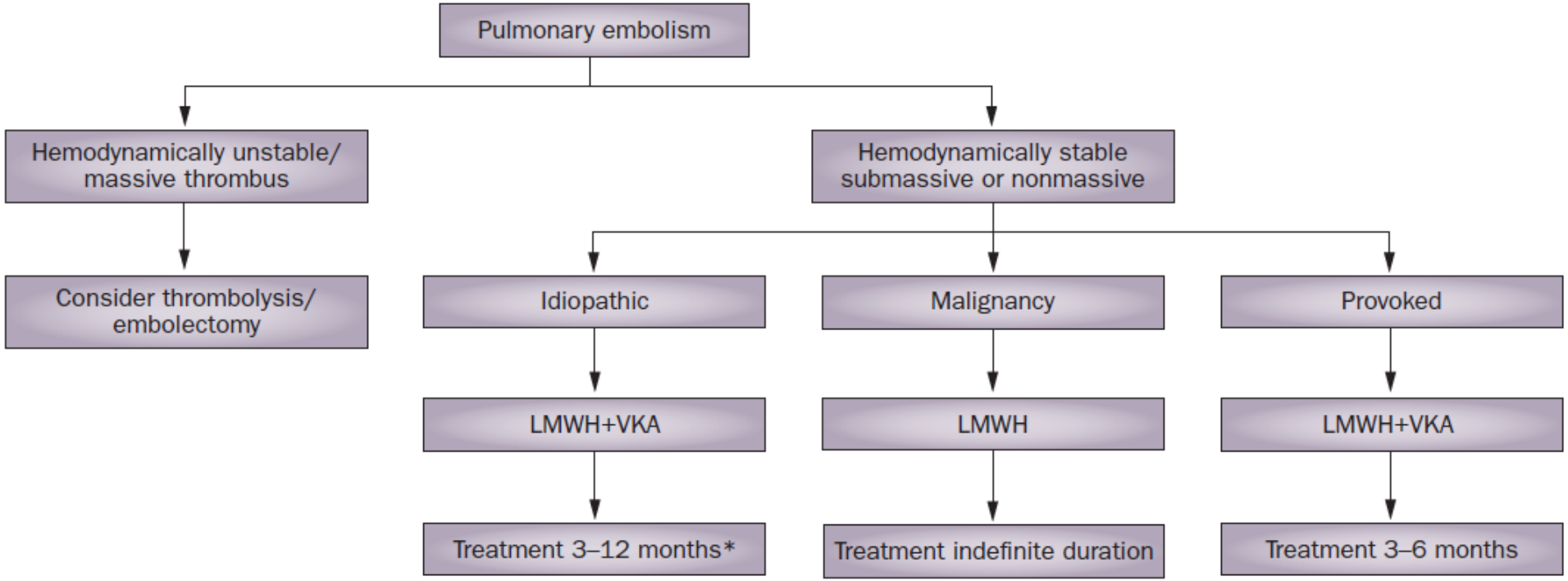


Figure 2 | Overview of treatment strategies for patients with pulmonary embolism. *Consider prolonged treatment after counseling of the patient. Abbreviations: LMWH, low-molecular-weight heparin; VKA, vitamin-K antagonist.

Treatment

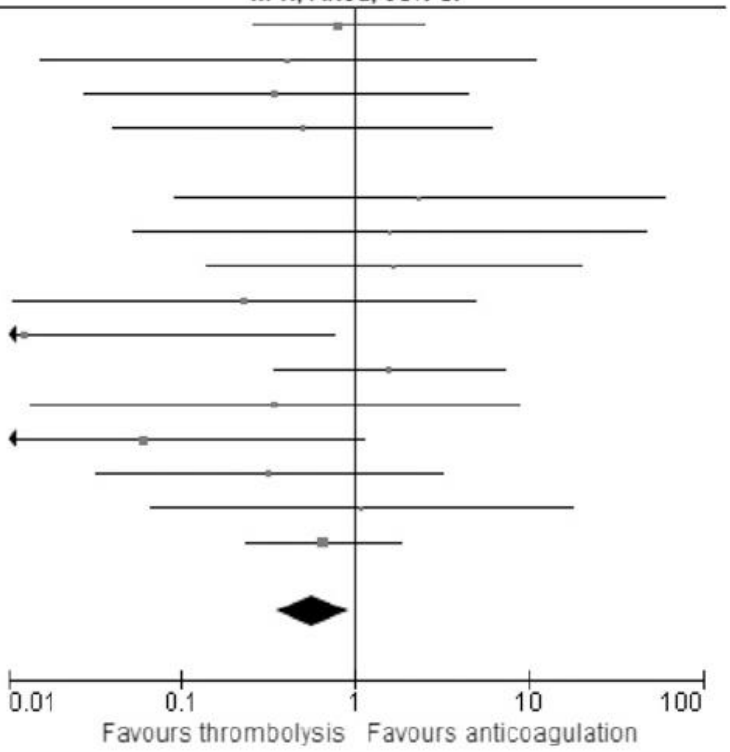
Thrombolysis or surgical thrombectomy

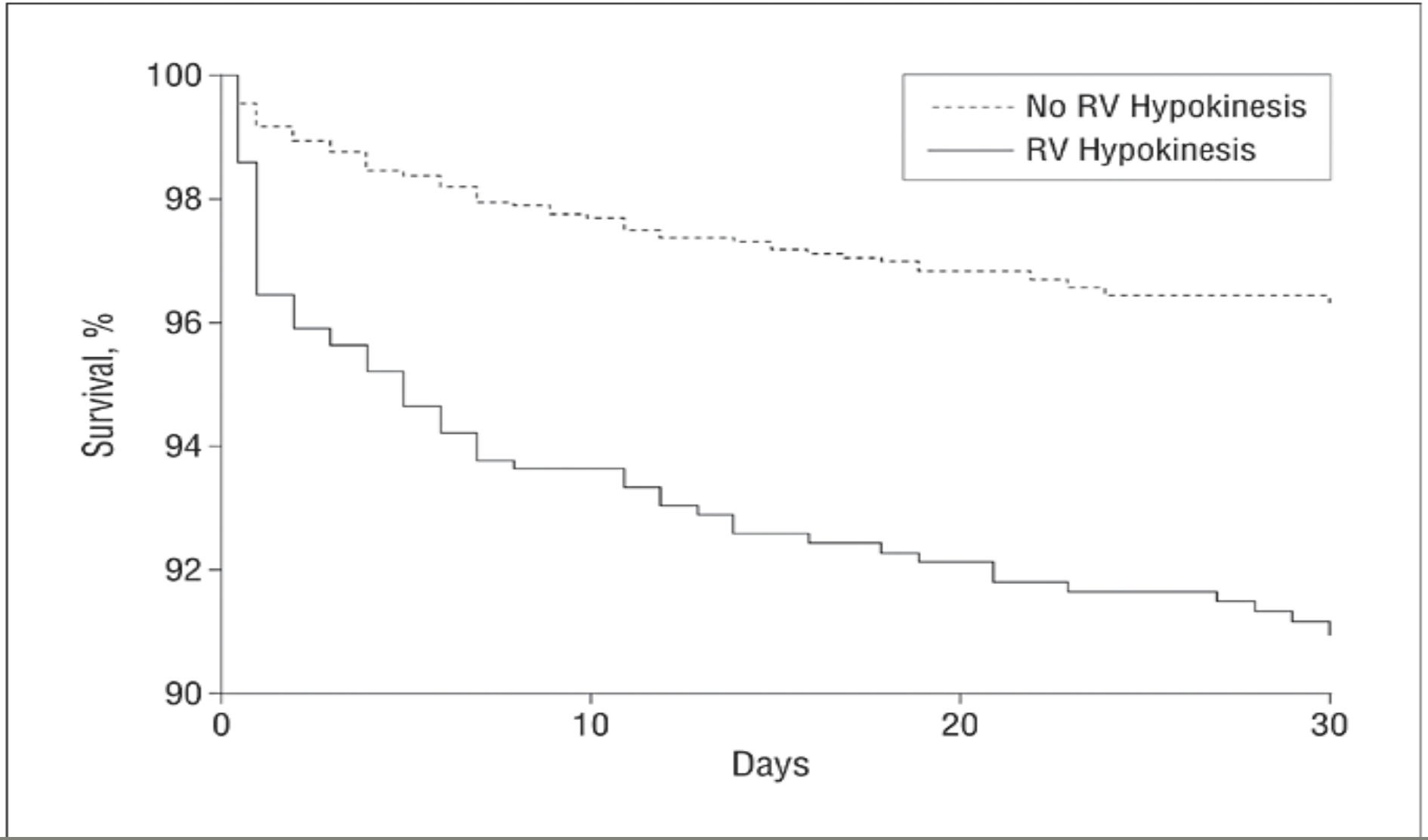
Heparin, warfarin, vena cava inferior filter

Study or Subgroup	Thrombolysis Events	Thrombolysis Total	Anticoagulation Events	Anticoagulation Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
UPET 1970	6	82	7	78	15.2%	0.80 [0.26, 2.50]	1970
Tibbutt et al 1974	0	13	1	17	2.9%	0.41 [0.02, 10.83]	1974
Ly et al 1978	1	14	2	11	4.8%	0.35 [0.03, 4.42]	1978
Dotter et al 1979	1	15	2	16	4.1%	0.50 [0.04, 6.17]	1979
Marini et al 1988	0	20	0	10		Not estimable	1988
Levine et al 1990	1	33	0	25	1.2%	2.35 [0.09, 60.24]	1990
PIOPED 1990	1	9	0	4	1.3%	1.59 [0.05, 47.52]	1990
PAIMS2 1992	2	20	1	16	2.3%	1.67 [0.14, 20.23]	1992
Goldhaber et al 1993	0	46	2	55	5.2%	0.23 [0.01, 4.92]	1993
Jerjes-Sanchez et al 1995	0	4	4	4	9.3%	0.01 [0.00, 0.77]	1995
MSPPE-3 2002	4	118	3	138	6.1%	1.58 [0.35, 7.20]	2002
TIPES 2009	0	28	1	30	3.3%	0.35 [0.01, 8.83]	2009
Fasullo et al 2011	0	37	6	35	15.1%	0.06 [0.00, 1.12]	2011
MOPETT 2013	1	61	3	60	6.8%	0.32 [0.03, 3.13]	2013
TOPCOAT 2014	1	40	1	43	2.1%	1.08 [0.07, 17.81]	2014
PEITHO 2014	6	506	9	499	20.5%	0.65 [0.23, 1.85]	2014
Total (95% CI)		**1046**		**1041**	**100.0%**	**0.57 [0.35, 0.92]**	
Total events	24		42				

Heterogeneity: $Chi^2 = 10.61$, $df = 14$ ($P = 0.72$); $I^2 = 0\%$

Test for overall effect: $Z = 2.28$ ($P = 0.02$)




100
98
96
94
92
90
Survival, %
0
10
20
30
Days
No RV Hypokinesis
RV Hypokinesis

Pulmonary embolism

Key points

- Venous thromboembolism, and more specifically pulmonary embolism, is a frequently occurring and potentially fatal condition for which improved diagnosis and treatment are necessary
- Both inherited and acquired risk factors for pulmonary embolism have been identified, including thrombophilia, surgery, cancer, immobilization, and previous venous thromboembolism
- The clinical diagnosis of pulmonary embolism can be difficult because of variation in signs and symptoms; for accurate diagnosis, several diagnostic tests should be incorporated in an integrated approach
- Fewer than 20% of patients with suspected pulmonary embolism actually have the condition; the main initial challenge is to adequately exclude a diagnosis of PE
- The first diagnostic step is to assess the clinical probability of pulmonary embolism using a standardized score, followed by D-dimer testing and, if necessary, multidetector CT pulmonary angiography or ventilation–perfusion scanning
- The diagnostic strategy and the choice of imaging test depend on the clinical status of the patient and the availability of diagnostic tools

Pulmonary embolism

Key points

- Pulmonary embolism (PE) can be effectively treated with anticoagulant medication
- Initial therapy for PE comprises low-molecular-weight heparin, unfractionated heparin, or fondaparinux, and is followed by long-term treatment with oral vitamin-K antagonists
- Duration of long-term anticoagulation is usually 3–12 months and depends on type of PE, risk of recurrence, risk of major bleeding, and the patient's preference
- Tailoring the duration of treatment using biomarkers, such as D-dimer level or presence of residual vein thrombosis, is not yet recommended
- Patients with PE who are hemodynamically unstable (massive PE) should be treated with thrombolysis
- Currently, insufficient evidence exists that hemodynamically stable patients with right ventricular dysfunction (submassive PE) benefit from thrombolysis

Cor pulmonale

Examination

1. Definition
2. Classification
3. Epidemiology
4. Etiology
5. Pathogenesis
6. Symptoms & Signs
7. Complications
8. Prevention & Diagnosis & Therapy

Definition

Cor pulmonale

Pulmonary heart disease

Syndrome with **right-sided** ventricular hypertrophy, dilation or heart failure due to vascular **resistance** in the **lung** circulation

not due to systemic causes

„Lungs cause the heart to fail“

Classification

Acute

- ARDS, lung thromboembolism...

Chronic

- COPD, sleep apnea, lung thromboembolism...

Epidemiology

10% of all cases of heart failure

5-year mortality 70-80%

In 50% the cause is COPD

- Chronic bronchitis
- Lung emphysema

Etiology

Pulmonary hypertension

- Primary pulmonary hypertension
- Alveolar hypoxia – pulmonary vasoconstriction (sleep apnea)
- Lung disorders – lung tissue damage (COPD, interstitial lung disease, rheumatid disorders)
- Blood viscosity (blood clots, polycythemia)

Pathogenesis

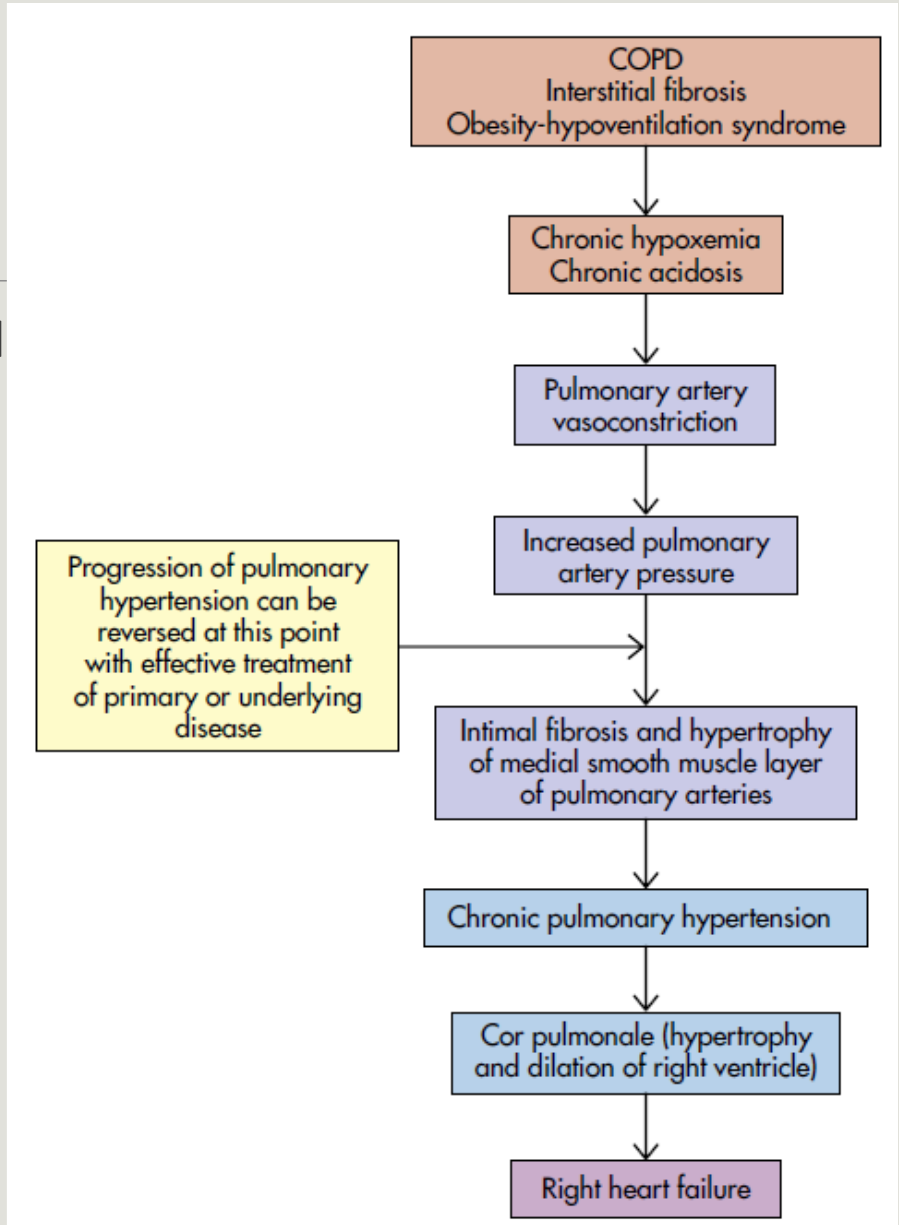
Right ventricular afterload is increased

Hypertrophy or Dilation?

- Acute or Chronic

Mortality predictors

- Age > 65 years
- Bed rest > 72 hours
- Tachycardia, tachypnoe



Symptoms & Signs

Fatique

Dyspnea

Cyanosis

Chest pain

Hepatomegaly

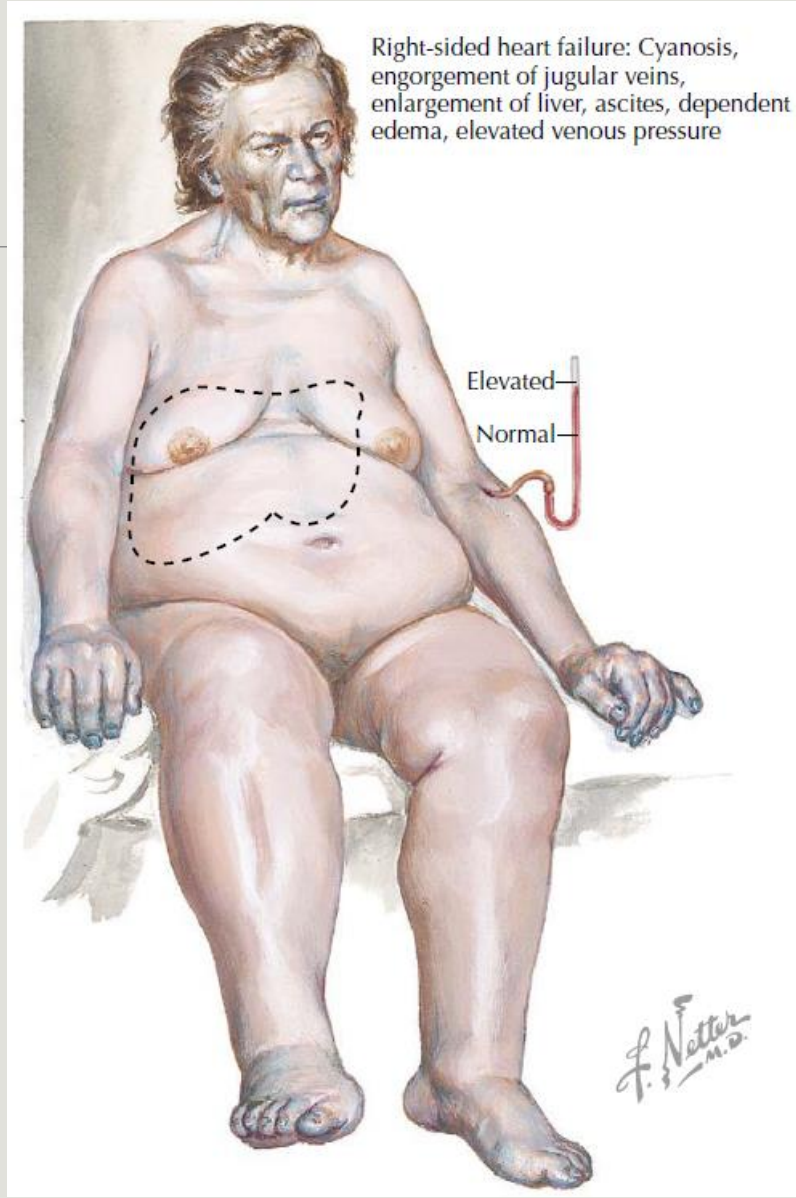
Ascites

Jaundice

Raised jugular venous pressure

Abnormal heart sounds

Right ventricular hypertrophy



Complications

Peripheral hypoxia

Backward failure of the right heart

Arrhythmias

Polycythemia – stroke

Liver failure

Renal failure

Neurological complications

- Syncope, cognitive deficits

Prevention & Diagnosis & Therapy

Causal prevention

Prevention and therapy of lung diseases

Discontinuing smoking

Patient history

Auscultation, Chest X-ray, ECG – right axis deviation, echocardiography, BNP, arterial gases

Causal treatment

Diuretics, anticoagulants, oxygen, transplantation?

PH online

Animation of PAH

https://www.youtube.com/watch?v=9a4untSzLzg

Khan Academy

https://www.youtube.com/watch?v=KtkR_NTte4M

Brown University lecture

https://www.youtube.com/watch?v=3bopVnVwPGQ

PE online

MEDCRAM lecture

https://www.youtube.com/watch?v=4C6BB56fG1M

Final notes

Without heparin prophylaxis 84% of patients will have pulmonary thromboembolism after hip or knee replacement.

Pulmonary embolization is the most common preventable cause of death in hospitalized patients.

80% of pulmonary emboli occur without prior symptoms

In 25-50% of autopsies of hospitalized patients pulmonary thromboemboli are found.

They are diagnosed in only 10-20% of cases antemortem.

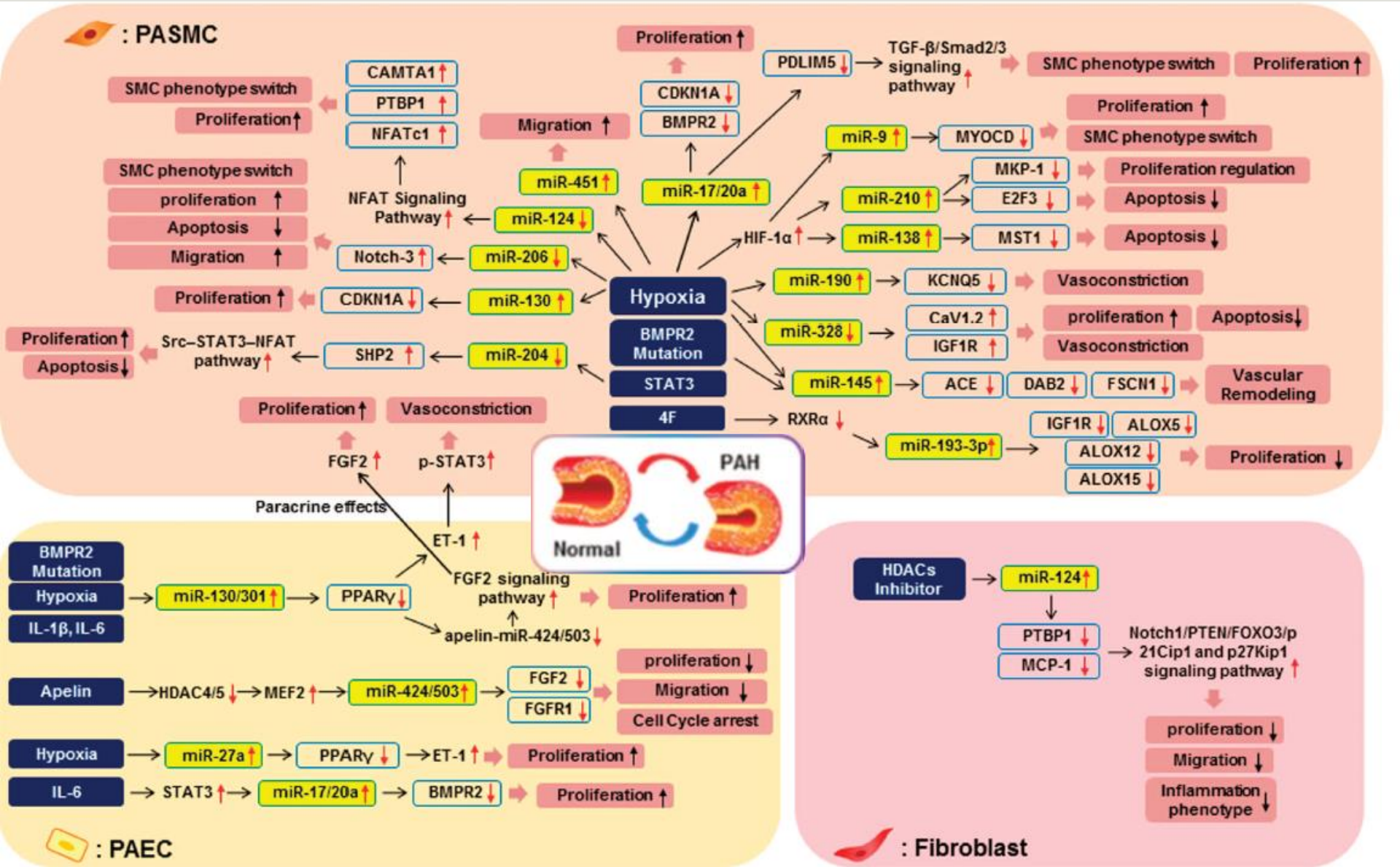
Most of the cases remain undiagnosed.

2/3 of deaths due to pulmonary emboli occur within 30 minutes.

Early treatment is effective.

Final notes

We seem to know a lot about the pathogenesis of pulmonary hypertension.


: PASMC
Proliferation
PDLIM5
TGF-β/Smad2/3 signaling pathway
SMC phenotype switch
Proliferation
CAMTA1
PTBP1
NFATc1
SMC phenotype switch
Proliferation
Migration
CDKN1A
BMPR2
miR-9
MYOCD
Proliferation
SMC phenotype switch
SMC phenotype switch
proliferation
Apoptosis
Migration
NFAT Signaling Pathway
miR-451
miR-124
miR-17/20a
miR-210
MKP-1
E2F3
Proliferation regulation
Apoptosis
HIF-1α
miR-138
MST1
Apoptosis
Notch-3
miR-206
Proliferation
CDKN1A
miR-130
Hypoxia
miR-190
KCNQ5
Vasoconstriction
Proliferation
Apoptosis
Src–STAT3–NFAT pathway
SHP2
miR-204
BMPR2 Mutation
STAT3
4F
miR-328
CaV1.2
IGF1R
proliferation
Vasoconstriction
miR-145
ACE
DAB2
FSCN1
Vascular Remodeling
Proliferation
Vasoconstriction
RXRα
IGF1R
ALOX5
miR-193-3p
ALOX12
ALOX15
Proliferation
FGF2
p-STAT3
Paracrine effects
PAH
Normal
ET-1
BMPR2 Mutation
Hypoxia
IL-1β, IL-6
miR-130/301
PPARγ
FGF2 signaling pathway
Proliferation
apelin-miR-424/503
Apelin
HDAC4/5
MEF2
miR-424/503
FGF2
FGFR1
proliferation
Migration
Cell Cycle arrest
Hypoxia
miR-27a
PPARγ
ET-1
Proliferation
IL-6
STAT3
miR-17/20a
BMPR2
Proliferation
: PAEC
HDACs Inhibitor
miR-124
PTBP1
MCP-1
Notch1/PTEN/FOXO3/p 21Cip1 and p27Kip1 signaling pathway
proliferation
Migration
Inflammation phenotype
: Fibroblast

Final notes

We seem to know a lot about the pathogenesis of pulmonary hypertension.

But we are far from understanding the disease processes.

So, how can we maximize the benefits for the patients?

...by following the guidelines.

petercelec@gmail.com