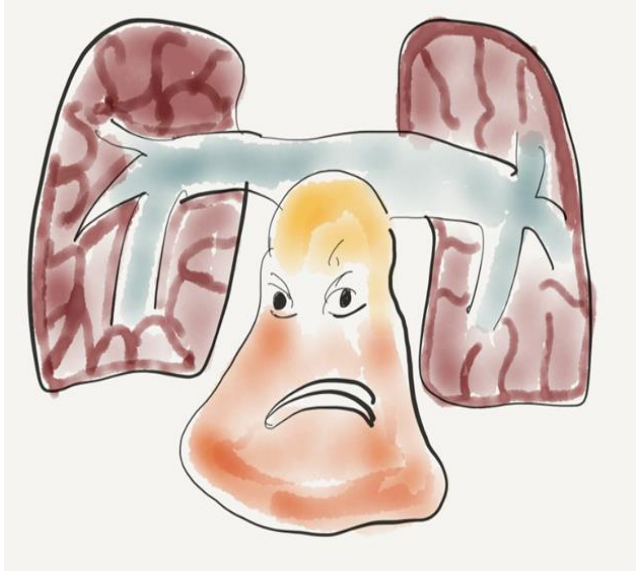
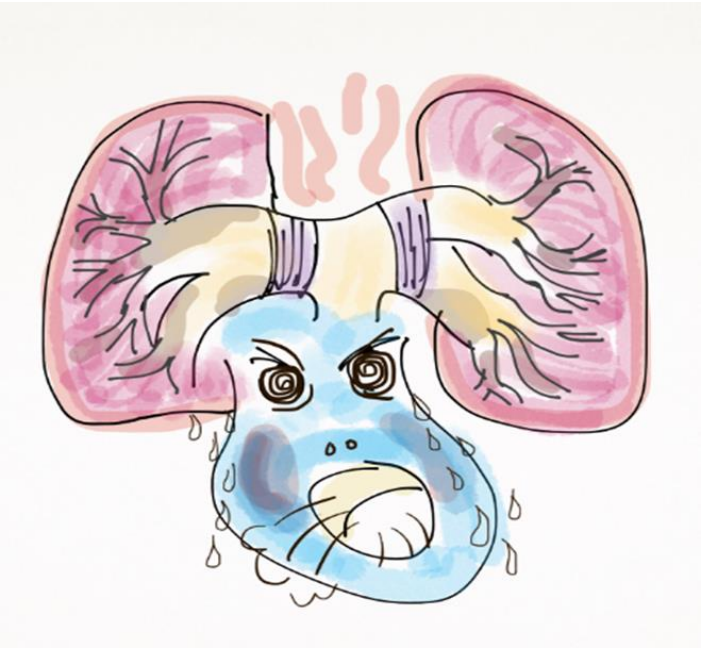
Evaluation and management when patients have PH and lung disease



인제의대 해운대백병원
장항제

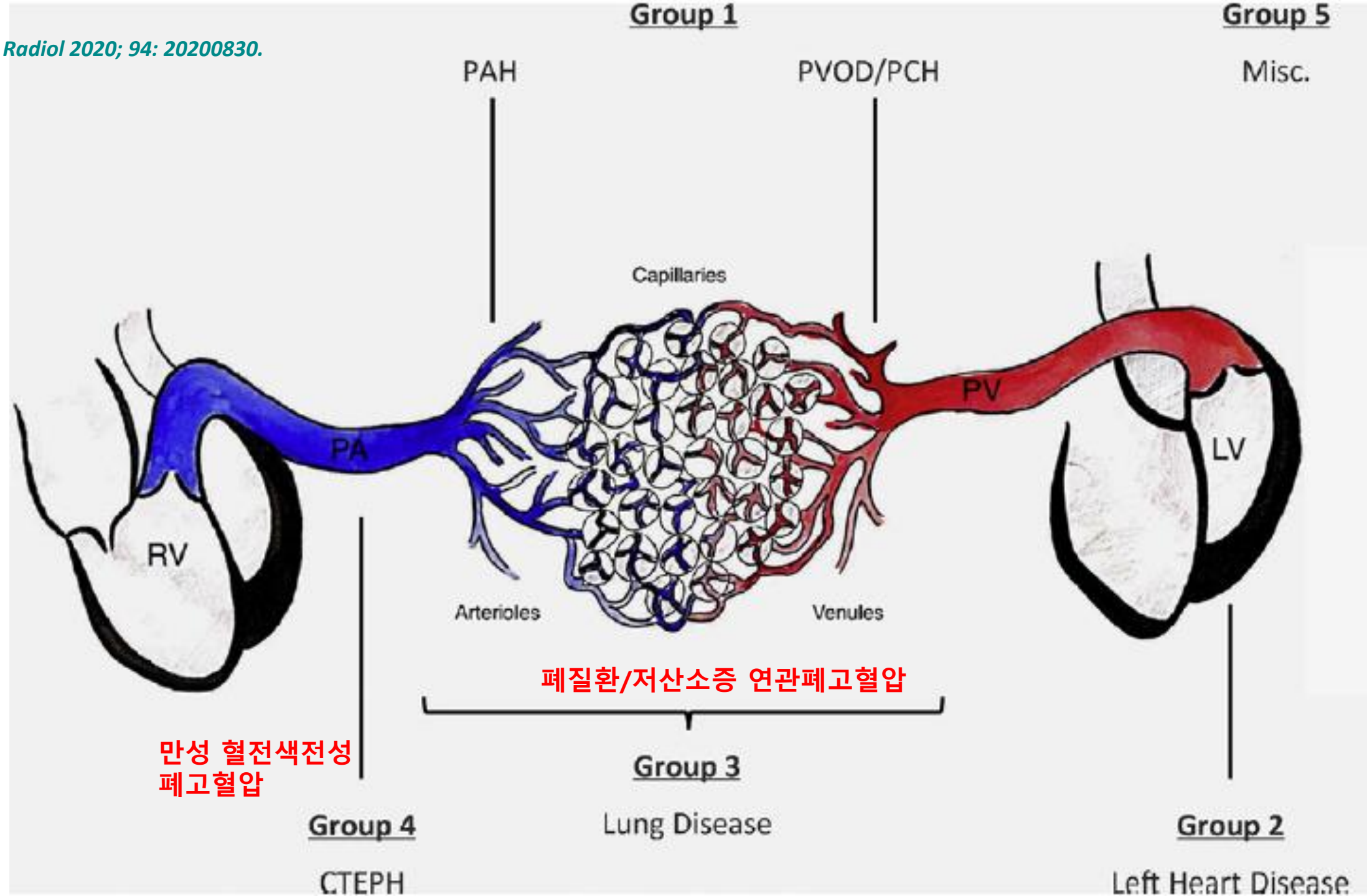


Contents

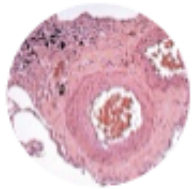
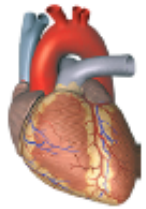
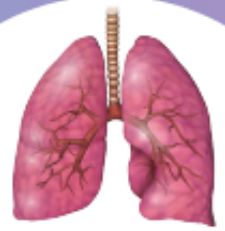
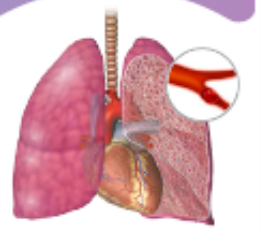
- PH 를 유발하는 급성/만성 폐질환과 병태생리
- 호흡기 의사가 PH를 인지하는 증상,징후,검사결과

  어떻게 해석하는가?
- PH associated chronic lung disease 에서
  Severe vs. Non-severe 로 나누어 판단하는 이유는?
- Rt. heart catheterization (우심도자) 어떤 환자, 언제 해야하나? 위험한가?
- Underlying lung disease 에 대한 optimized care 는
  정말로 PH를 호전시키는가?
- PAH-specific drugs 투여 고려해야 하는 환자군은?

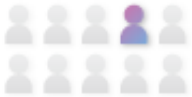
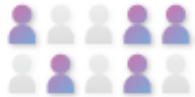
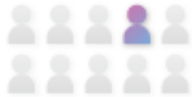
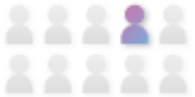
Br J Radiol 2020; 94: 20200830.



Clinical Classification

Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematologic disorders • Systemic disorders

Prevalence

Rare	Very common	Common	Rare	Rare
				

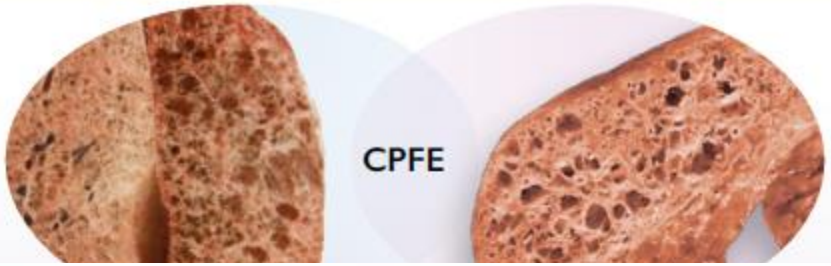
Therapeutic Strategies

Medical therapy • PAH drugs • CCB in responders **Lung transplantation**	**IpcPH:** • Treatment of LHD[a] **CpcPH:** • Treatment of LHD[a] • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	**Surgical therapy:** • PEA **Interventional:** • BPA **Medical therapy:** • PH drugs	**Optimized treatment of underlying disease** • Potentially: PAH drugs (trials)

ESC ERS

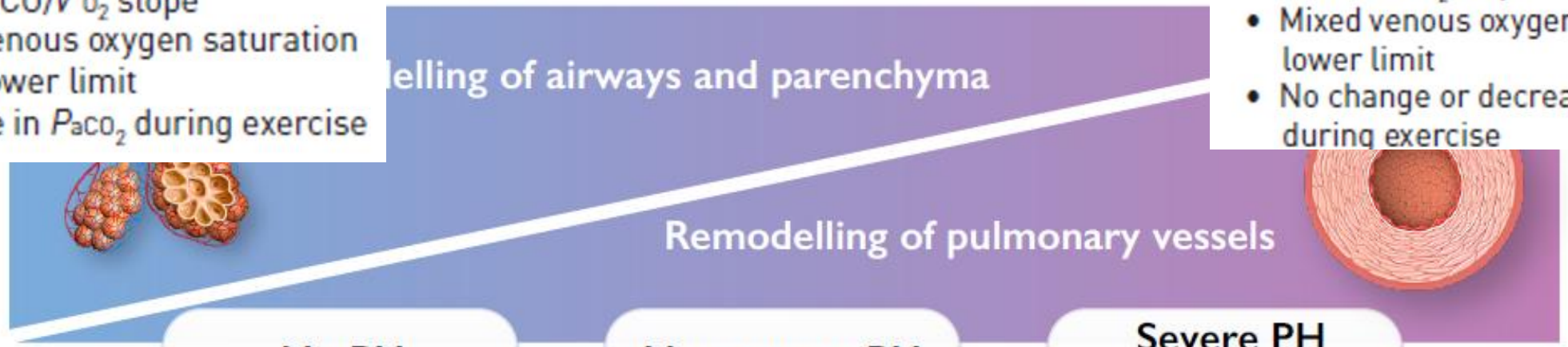
Features of exhausted ventilatory reserve:

- Reduced breathing reserve
- Normal oxygen pulse
- Normal $CO/\dot{V}O_2$ slope
- Mixed venous oxygen saturation above lower limit
- Increase in P_{aCO_2} during exercise



Features of exhausted circulatory reserve:

- Preserved breathing reserve
- Reduced oxygen pulse
- Low $CO/\dot{V}O_2$ slope
- Mixed venous oxygen saturation at lower limit
- No change or decrease in P_{aCO_2} during exercise



	No PH	Non-severe PH	Severe PH (PVR >5 WU)
Prevalence	~70%	~20%	~5–10%

Mostly ventilatory exercise limitation

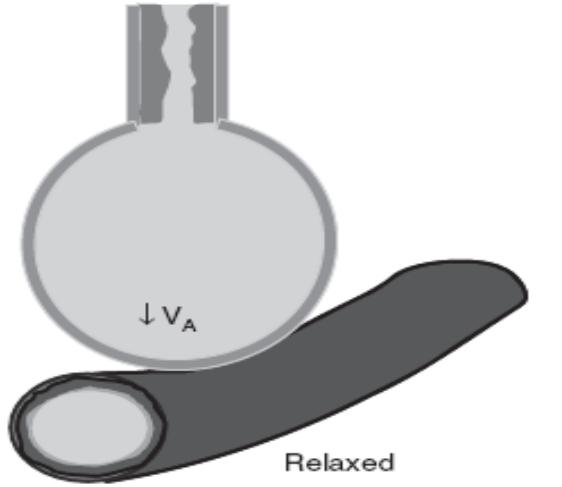
Mostly circulatory exercise limitation

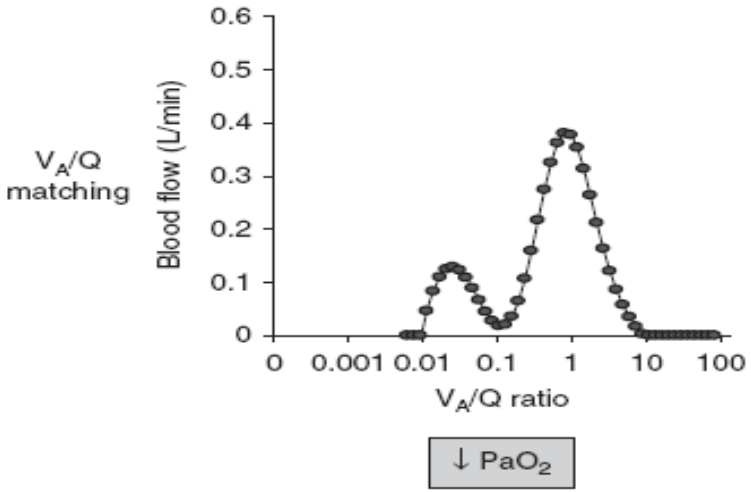
Hypoxaemia at rest and/or during exercise

exercise limitation
exercise limitation
Hypoxaemia at rest and/or during exercise

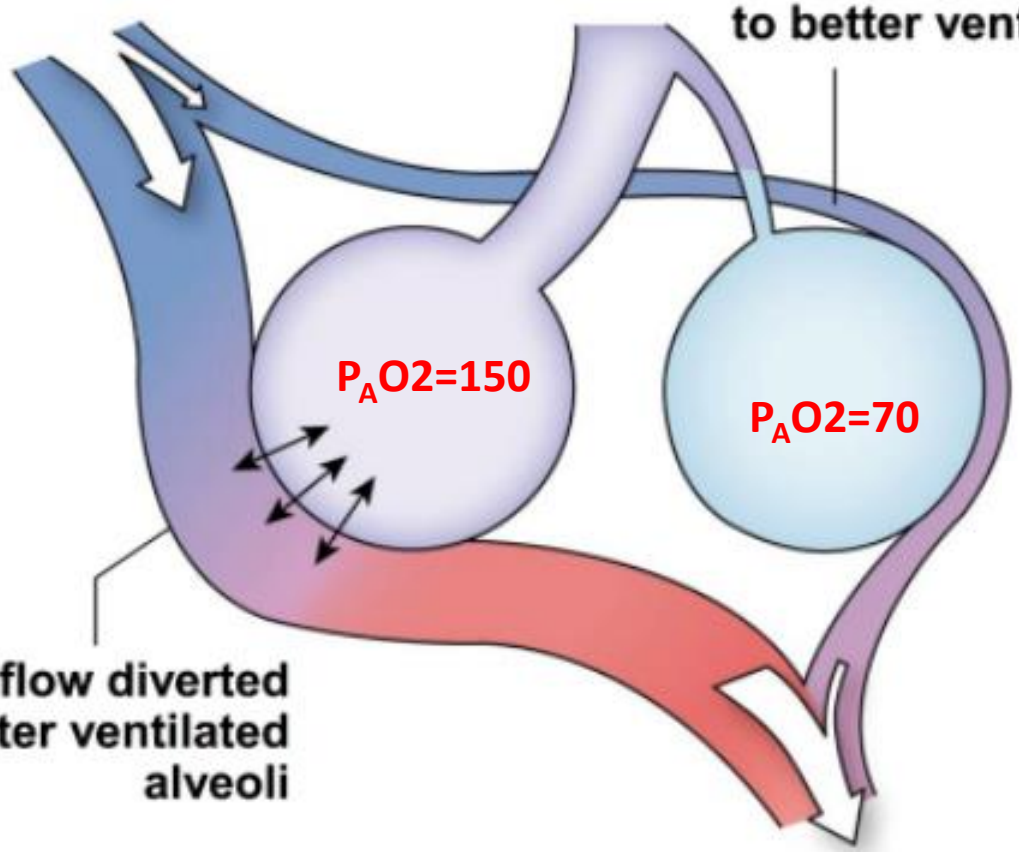
ESC ERS

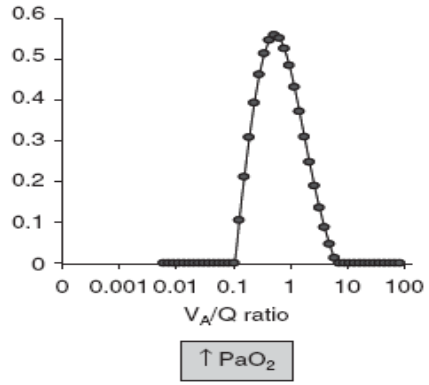
Hypoxic **P**ulmonary **V**asoconstriction (**HPV**)





Decreased tissue P_{O_2} around underventilated alveoli constricts their arterioles, diverting blood to better ventilated alveoli.





Pathophysiology of **PH-lung diseases**

- Acute

Hypoxic pulmonary vasoconstriction

Acute PTE
Air/Fat/amniotic embolism
ARDS
Severe pneumonia
Aspiration

- Sub-acute

PA pressure ↑ → **vascular remodeling**

→ **RV dilatation**

- **Chronic**

→RV Hypertrophy

RV contractility ↓ → RV failure

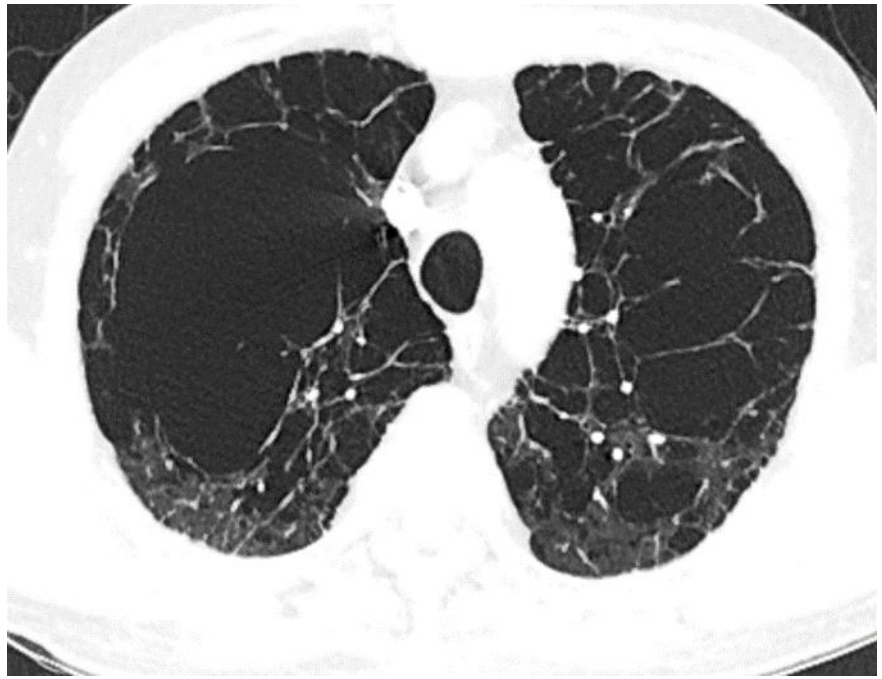
Chronic lung disease
: ILD
COPD
TBDL

폐고혈압을 유발하는 폐질환은?
만성 chronic

만성폐쇄성폐질환 COPD

Slow progression

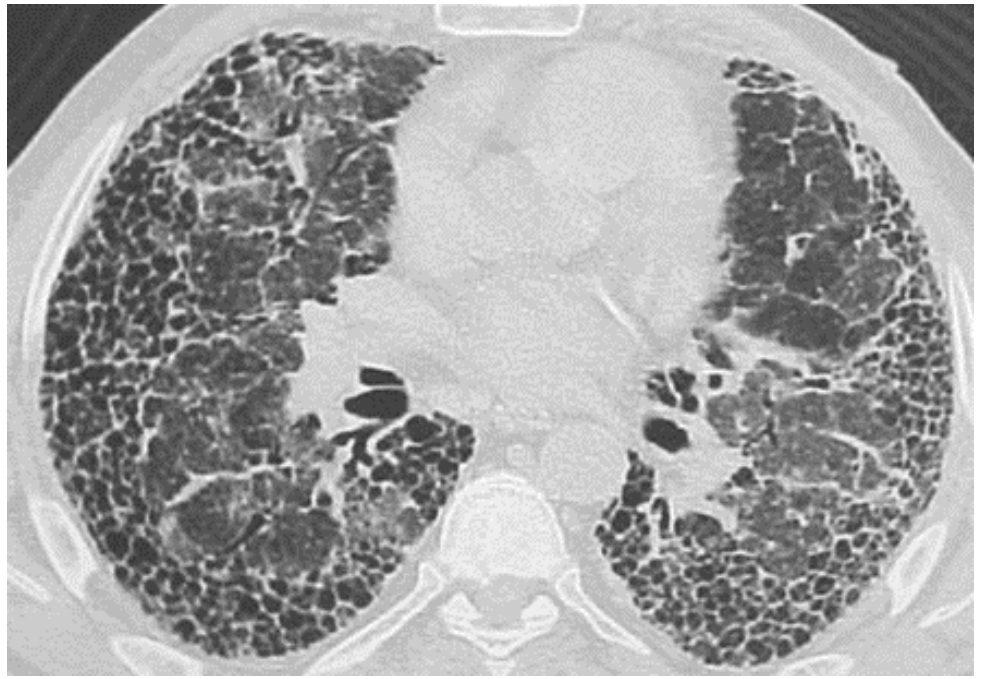
Prevalence > 50% (severe 1-5%)



간질성폐질환 ILD

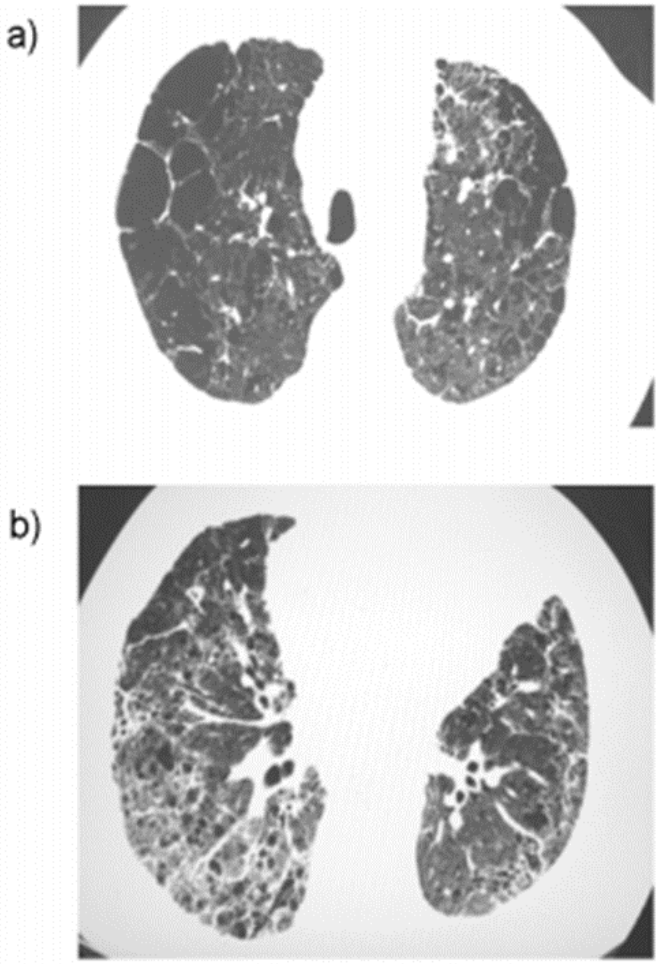
Rapid progression

Prevalence 8-40% (severe < 10%)



폐고혈압을 유발하는 폐질환은?
만성 chronic

- **Combined pulmonary fibrosis and emphysema (CPFE)**



40 patients with CPFE and PH
27 patients (68%) had severe PH

Parameters	Mean±SD
Age	68±2
FEV1 % predicted	**78±18**
FVC % predicted	**86±19**
FEV1/FVC	75±18
DLco % predicted	**24±14**
6MWD (m)	244±126
SpO2 decrease test	**-15±8**
Mean PAP (mmHg)	**40±9**
CO $L \cdot m^{-1}$	4.7±1.3
PVR $dyn \cdot s \cdot cm^{-5}$	521±205

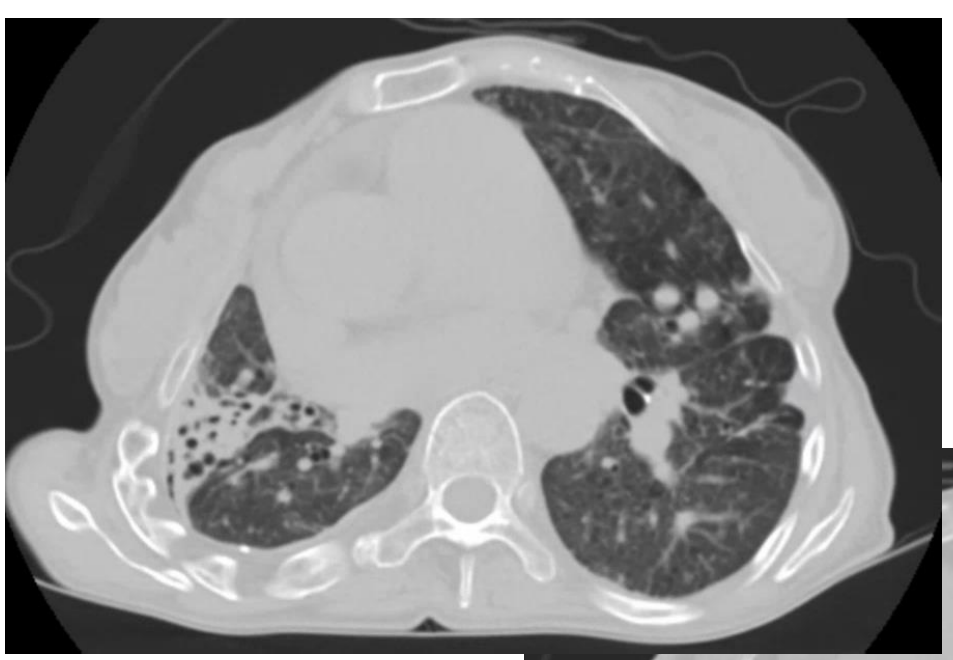
Rapid progression

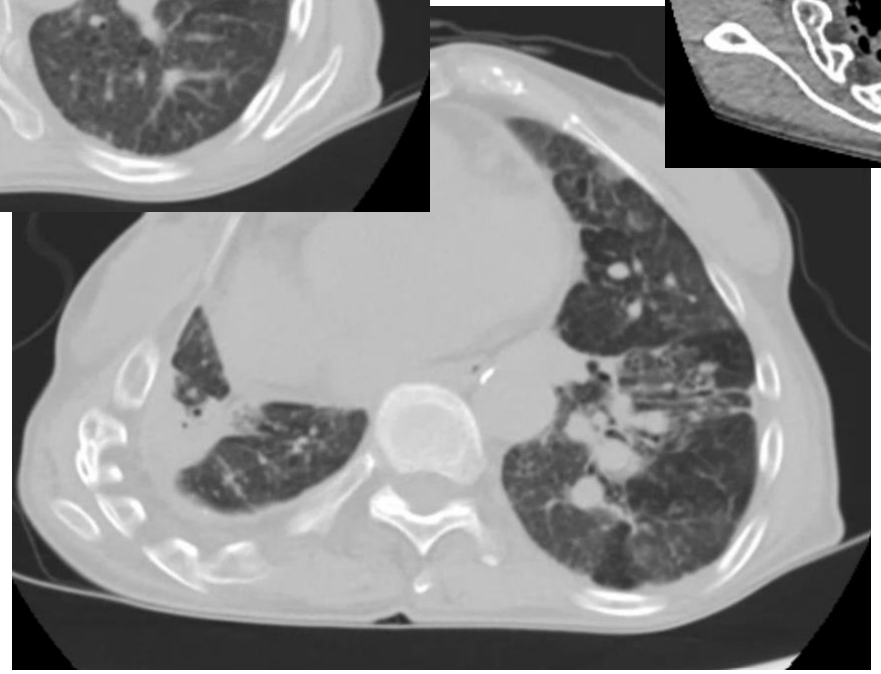
Prevalence ~50%

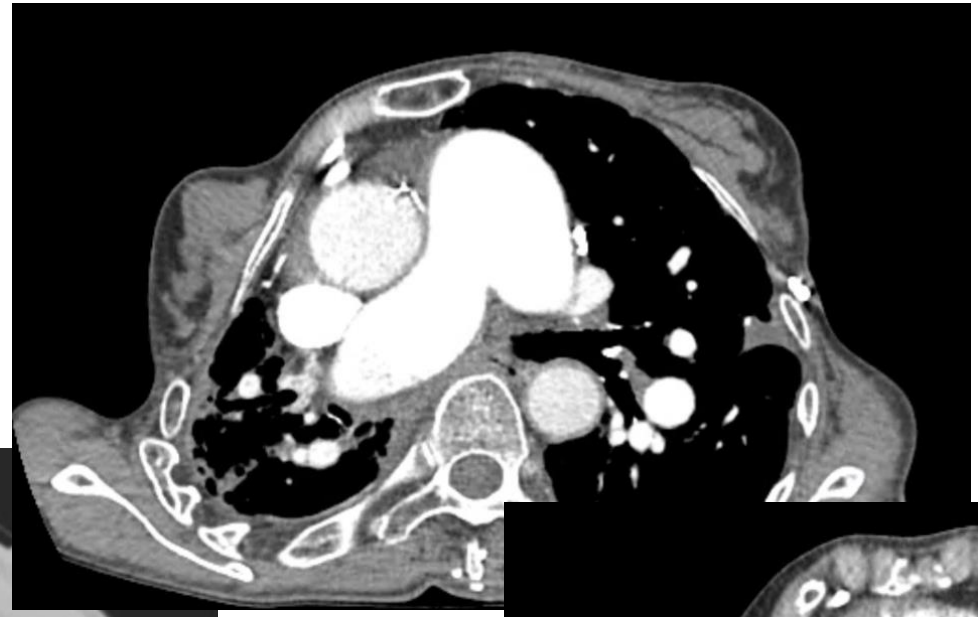
Severe PH ~ 70%

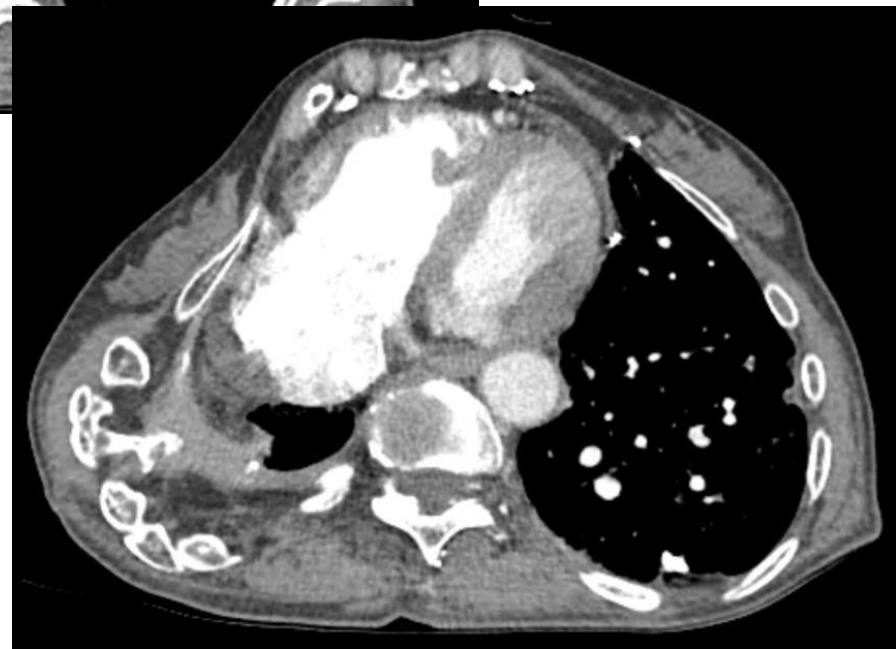
Cottin et al. Eur Respir J 2010; 35: 105–111

TB destroyed lung

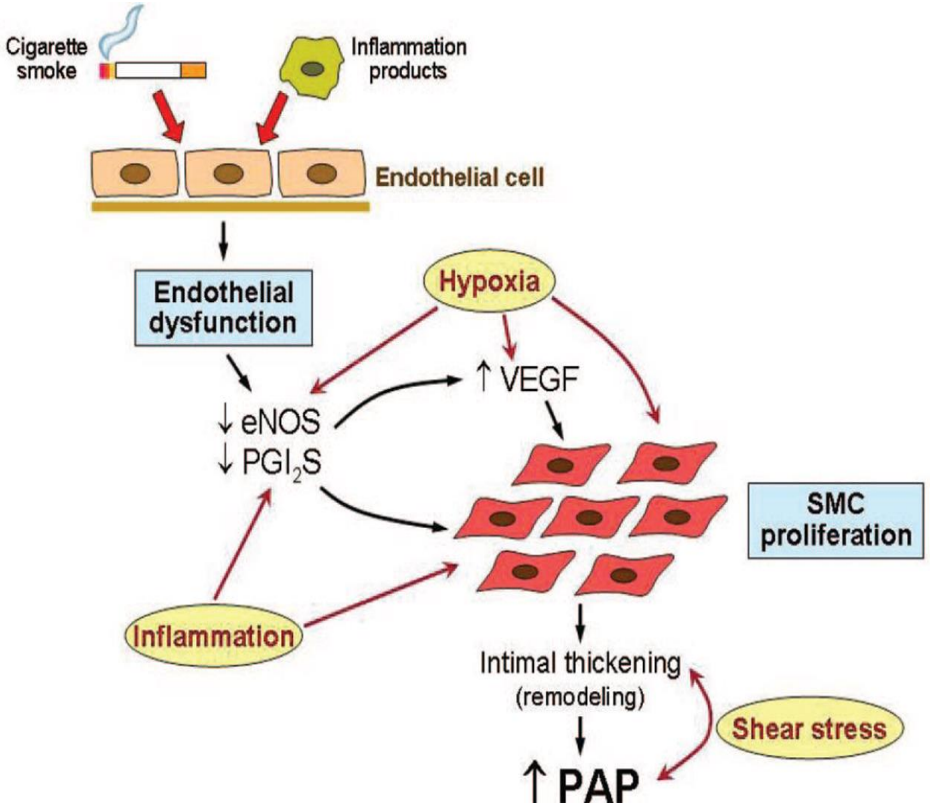




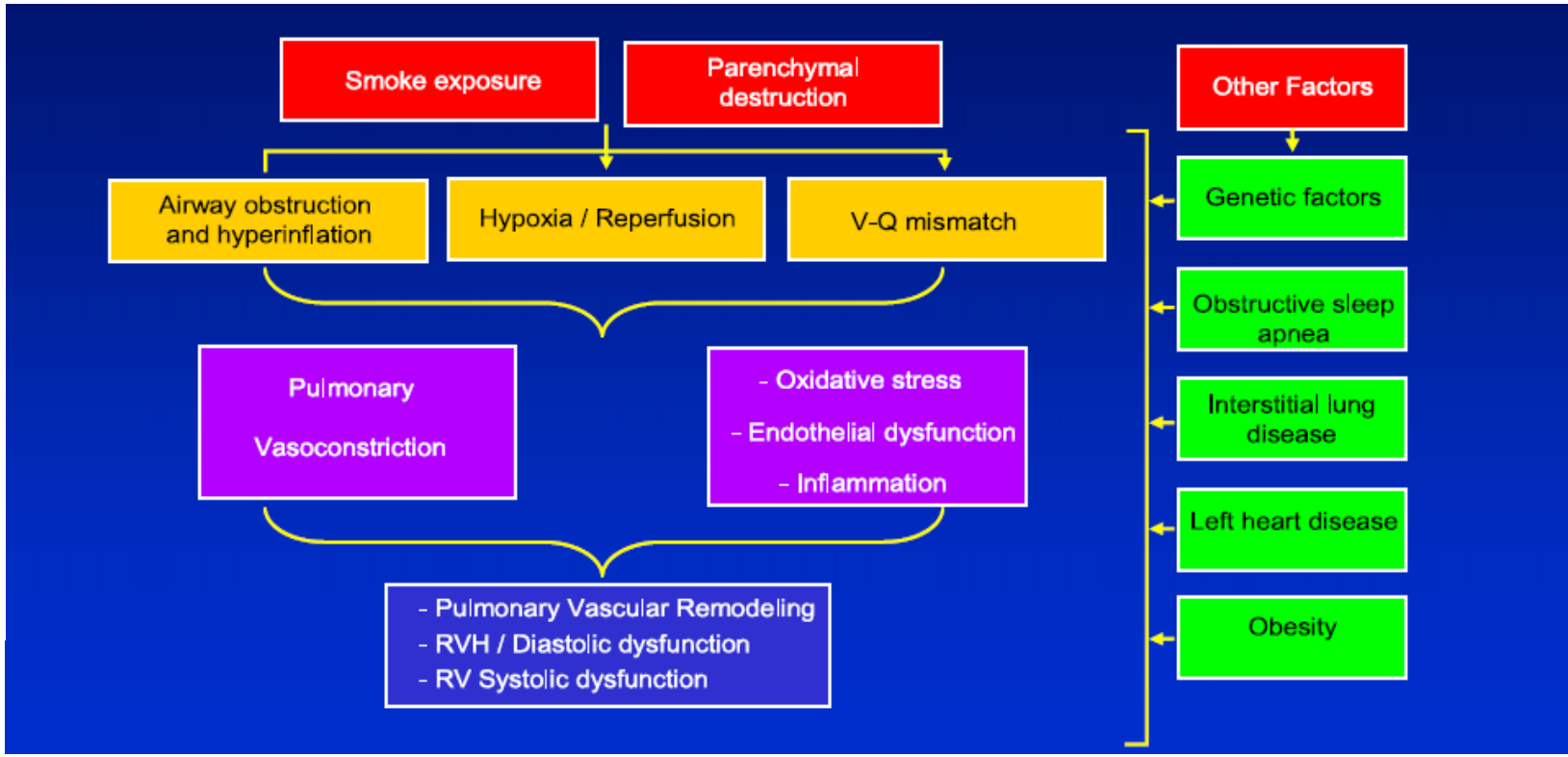




Pathogenesis of PH in COPD
Endothelial dysfunction
+ multi-factorial process

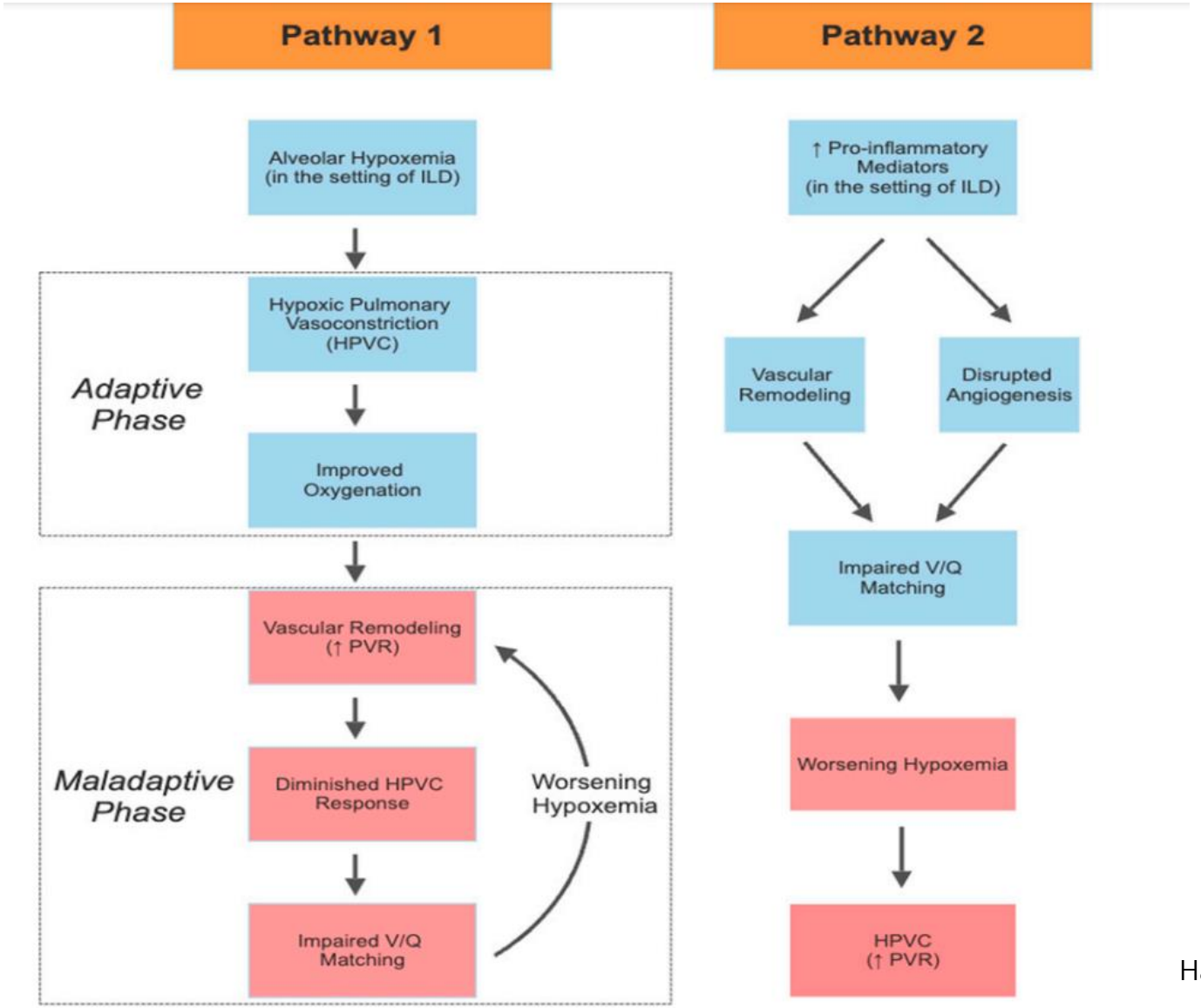


Peinado et al. CHEST 2008; 134:808–814



Minai et al. CHEST 2010; 137(6)(Suppl):39S–51S

Pathophysiology of **PH-ILD**: **Complex and not fully understood!**



Haynes ZA et al, Cells. 2023 Oct 1;12(19)

PH Symptom : Non-specific!

Chronic Lung diseases (CLD) without PH vs. CLD with PH

Early

Late

Symptoms

- Dyspnoea on exertion (WHO-FC)
- Fatigue and rapid exhaustion
- Dyspnoea when bending forward (bendopnoea)
- Palpitations
- Haemoptysis
- Exercise-induced abdominal distension and nausea
- Weight gain due to fluid retention
- Syncope (during or shortly after physical exertion)

Rare symptoms due to pulmonary artery dilation[a]

- Exertional chest pain:
  dynamic compression of the left main coronary artery
- Hoarseness (dysphonia):
  compression of the left laryngeal recurrent nerve (cardiovocal or Ortner´s syndrome)
- Shortness of breath, wheezing, cough, lower respiratory tract infection, atelectasis:
  compression of the bronchi

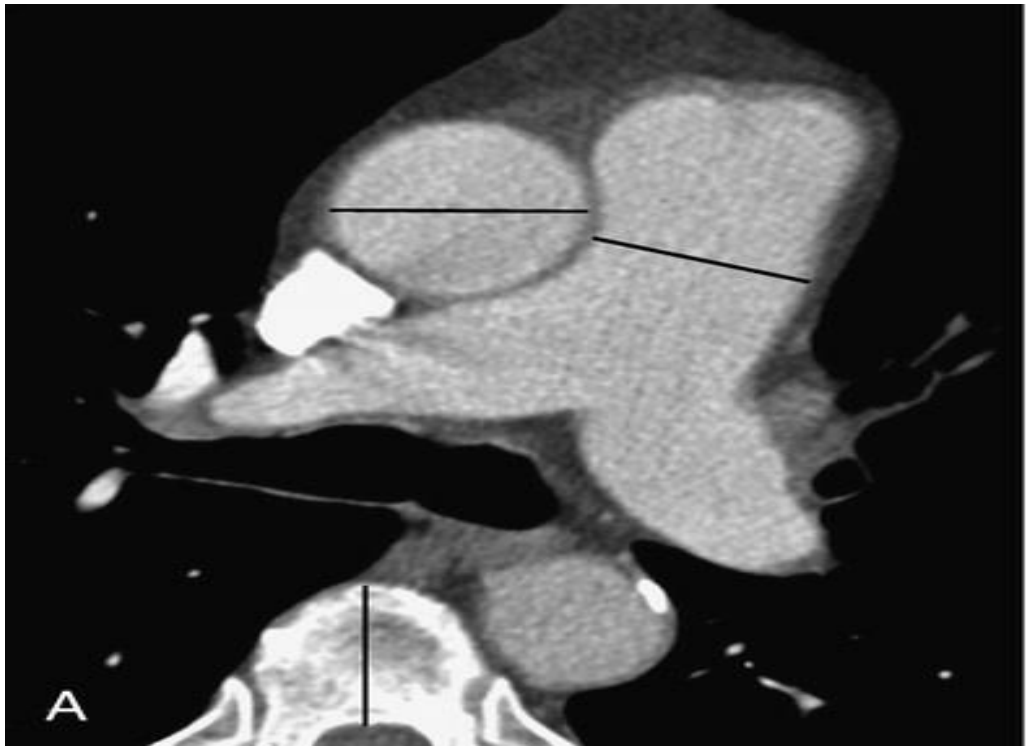
ESC ERS

Findings Suggestive of **Pulmonary Hypertension**

in Chronic Lung diseases

History	Syncope Dizziness
P/Ex	JVP ↑ Peripheral edema Ascites
Pulmonary function test	Severely reduced DLco
6 minute walk test	Severely reduced, worsening Marked desaturation
CT	RV:LV ratio >1 Increased PA:Ao ratio (>0.9)
Lab test	Elevated BNP or NT-proBNP

CT for detecting PH



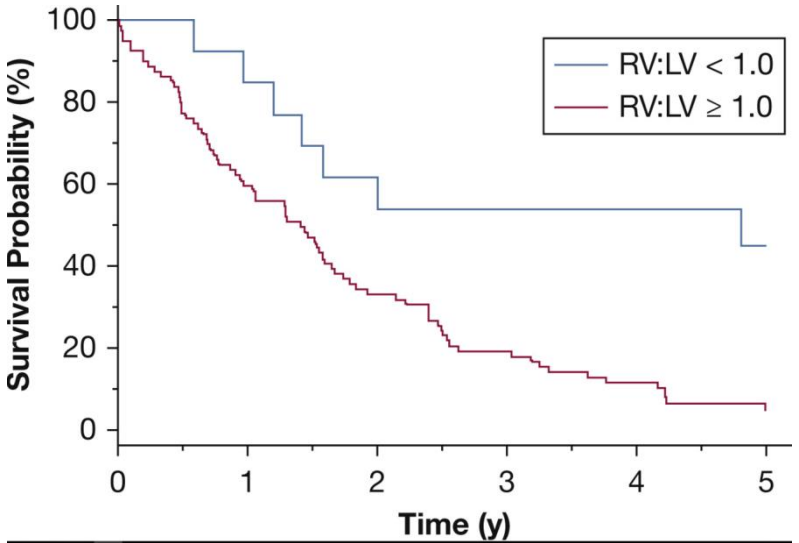
The ratio of the main pulmonary artery to ascending aorta diameter on imaging may predict PH in both COPD and IPF,
with a ratio >1 (range 0.9–1.1) suggested as a threshold

Dornia C, et al. J Comput Assit Tomogr 2012;36:175-180

RV:LV ratio at CT angiogram – automated AI

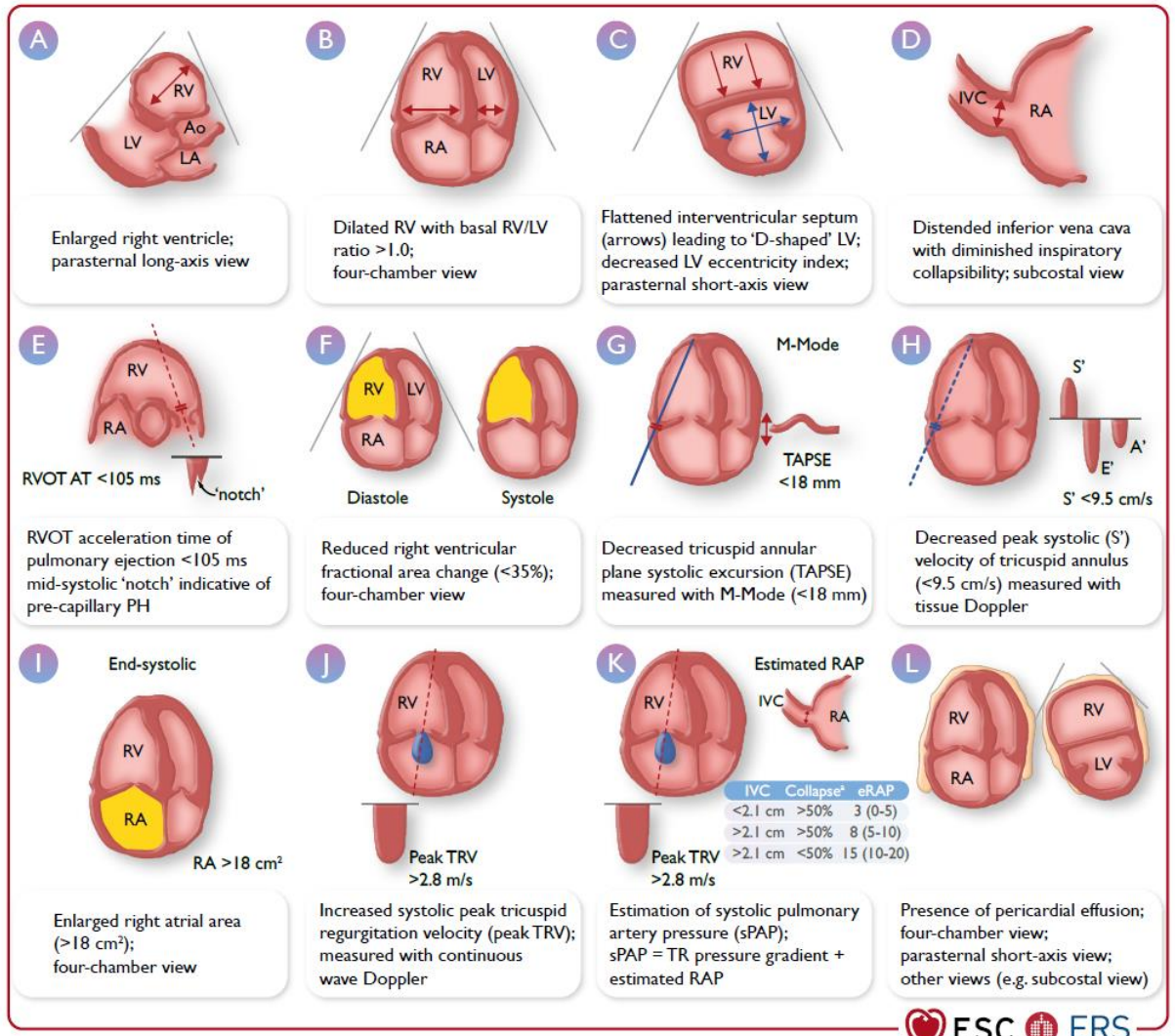
Predicts Mortality in Interstitial Lung Disease

S Bax et al Chest. 2020 Jan;157(1):89-98.

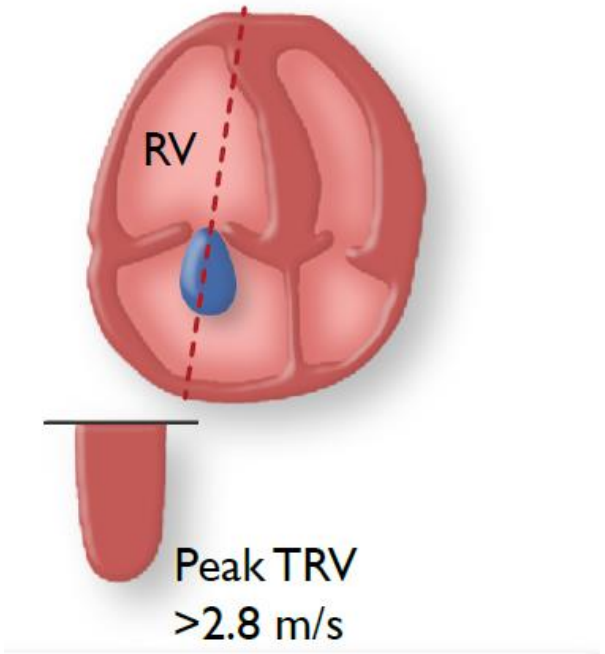


호흡기의사 관점

– 만성폐질환자 심초음파 리포트 해석



Estimation of systolic pulmonary artery pressure (sPAP)



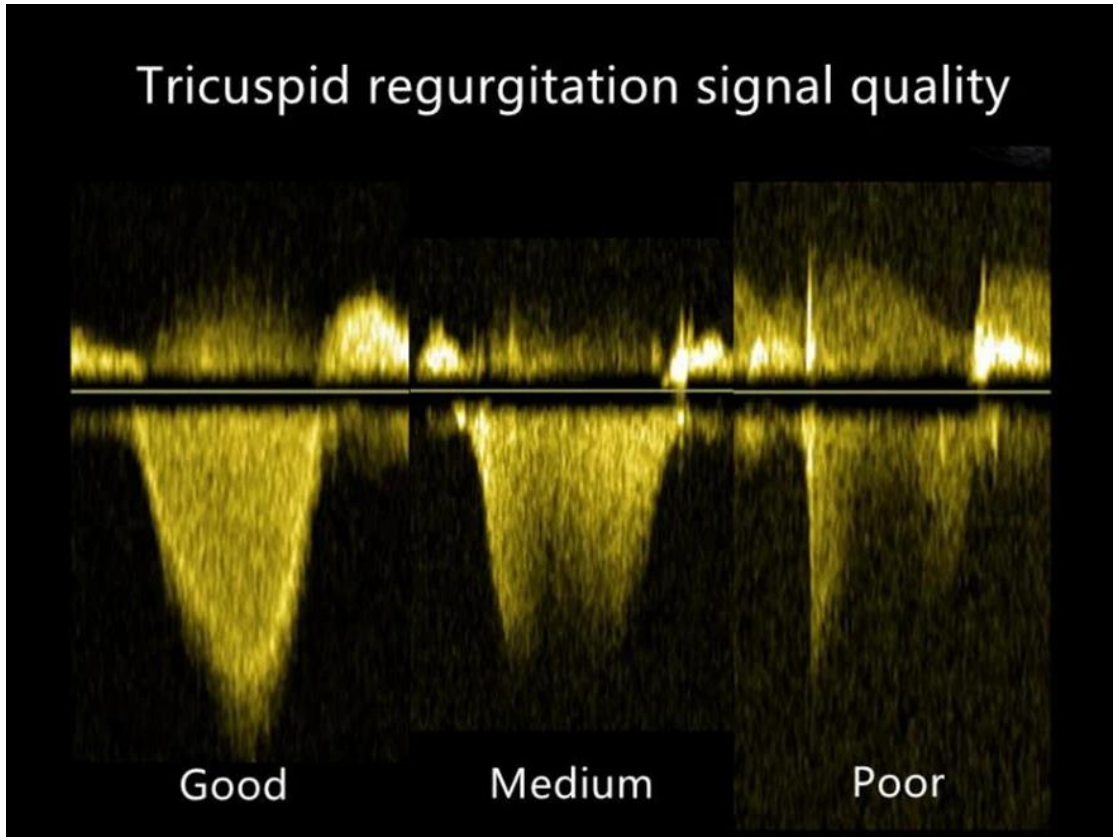
- sPAP = $4[\text{TR Vmax}]^2$ + estimated RAP

IVC	Collapse[a]	eRAP
<2.1 cm	>50%	3 (0-5)
>2.1 cm	>50%	8 (5-10)
>2.1 cm	<50%	15 (10-20)

- Commonly poor sonic window!
- Commonly unmeasurable TR Vmax
- Tendency to overestimate PAP
- Accuracy of echo in patients with advanced respiratory diseases is low

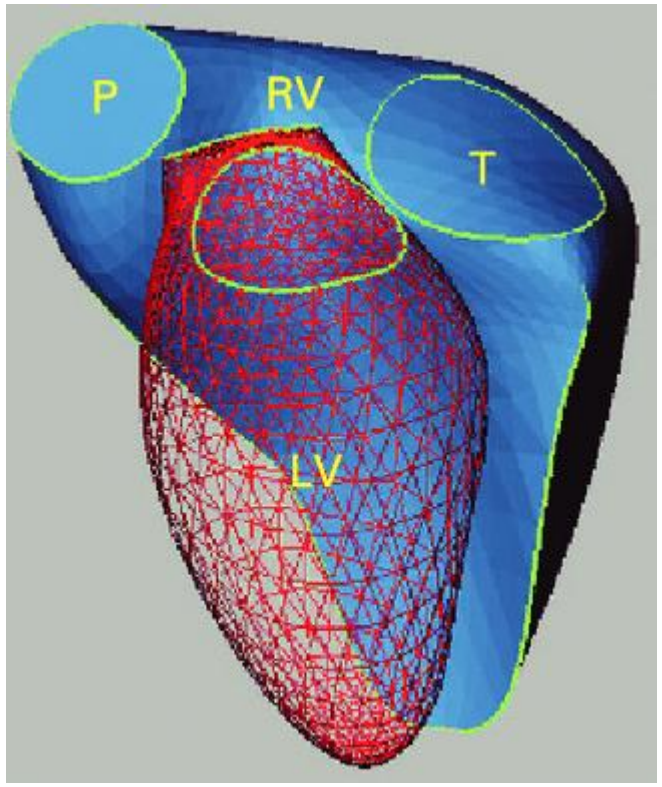
→ Severe PH 추정 위해서는 other echo signs of PH 중요

The accuracy of Doppler echocardiography

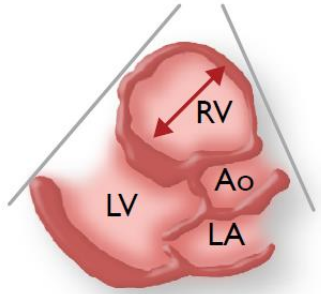


Lv et al. BMC Medical Imaging (2022) 22:91

Right heart function - evaluation by echo

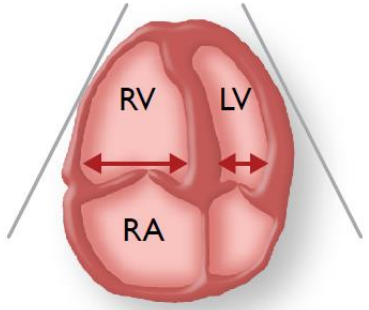


A



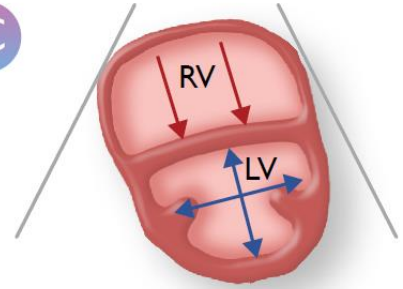
Enlarged right ventricle;
parasternal long-axis view

B



Dilated RV with basal RV/LV ratio >1.0;
four-chamber view

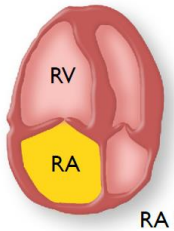
C



Flattened interventricular septum (arrows) leading to 'D-shaped' LV; decreased LV eccentricity index; parasternal short-axis view

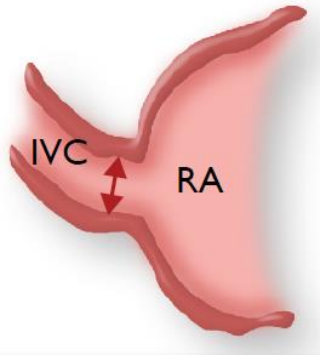
I

End-systolic

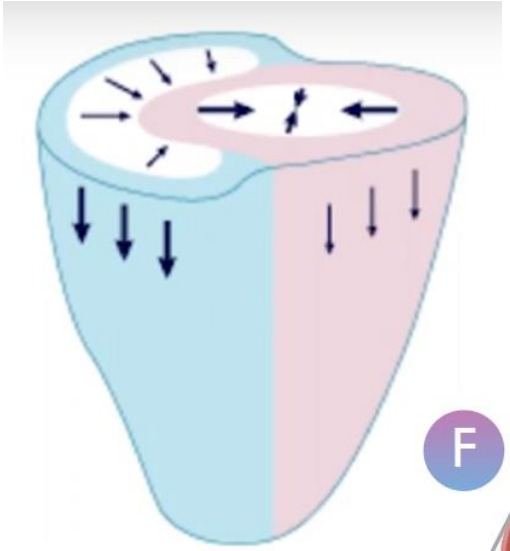


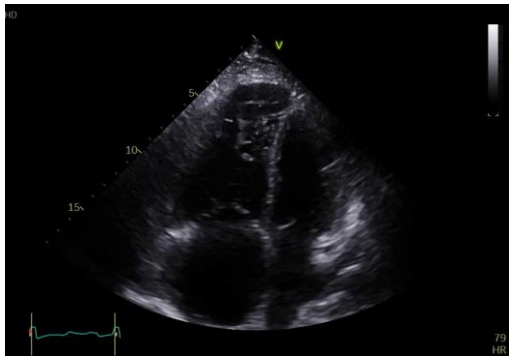
RA >18 cm^2

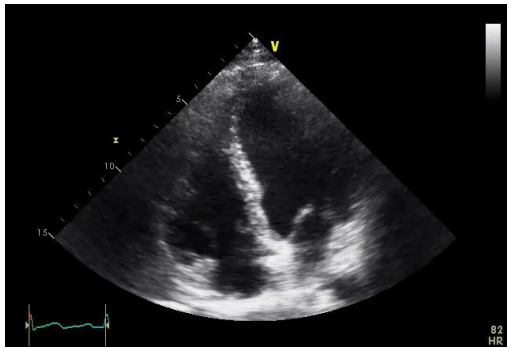
Enlarged right atrial area (>18 cm^2);
four-chamber view

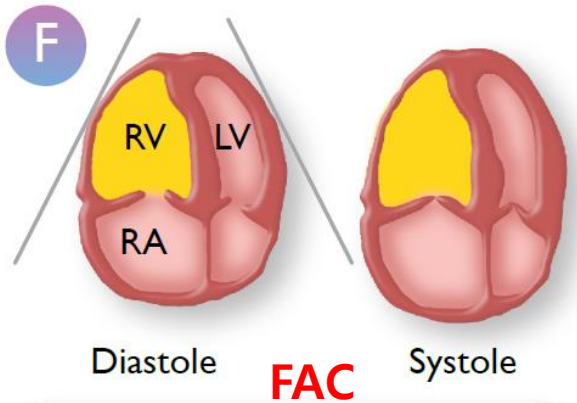


Right heart function - evaluation by echo



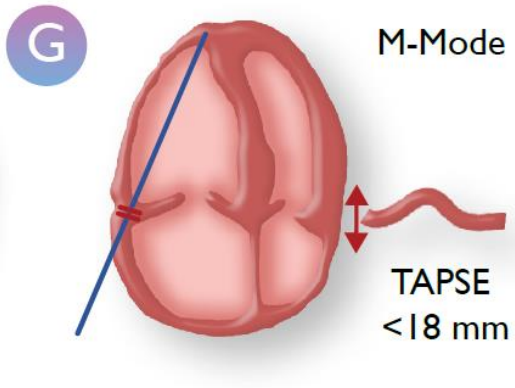




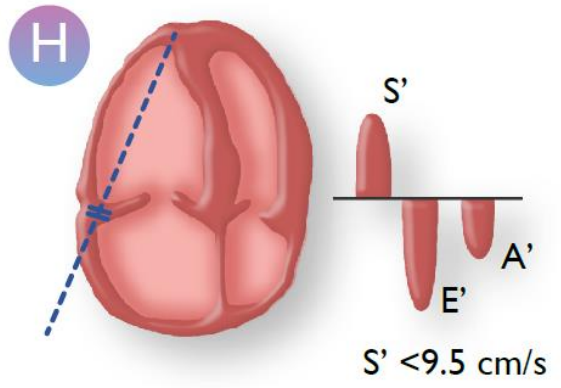


FAC

Reduced right ventricular fractional area change (<35%); four-chamber view



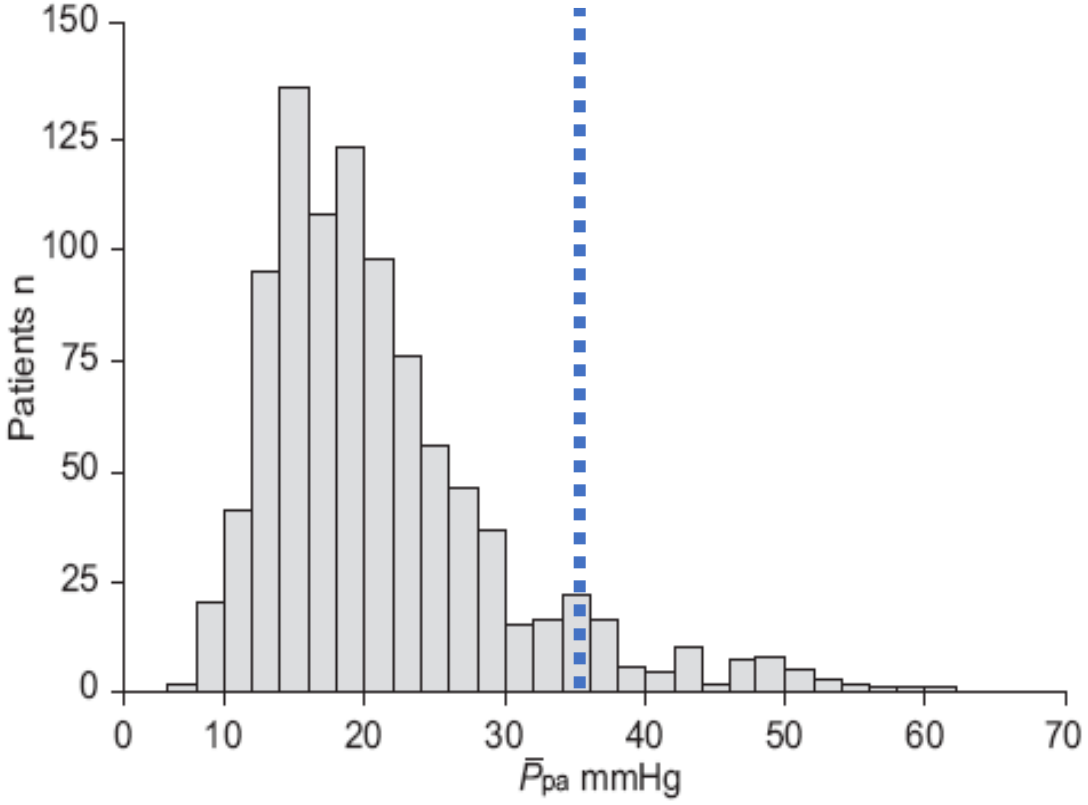
Decreased tricuspid annular plane systolic excursion (TAPSE) measured with M-Mode (<18 mm)



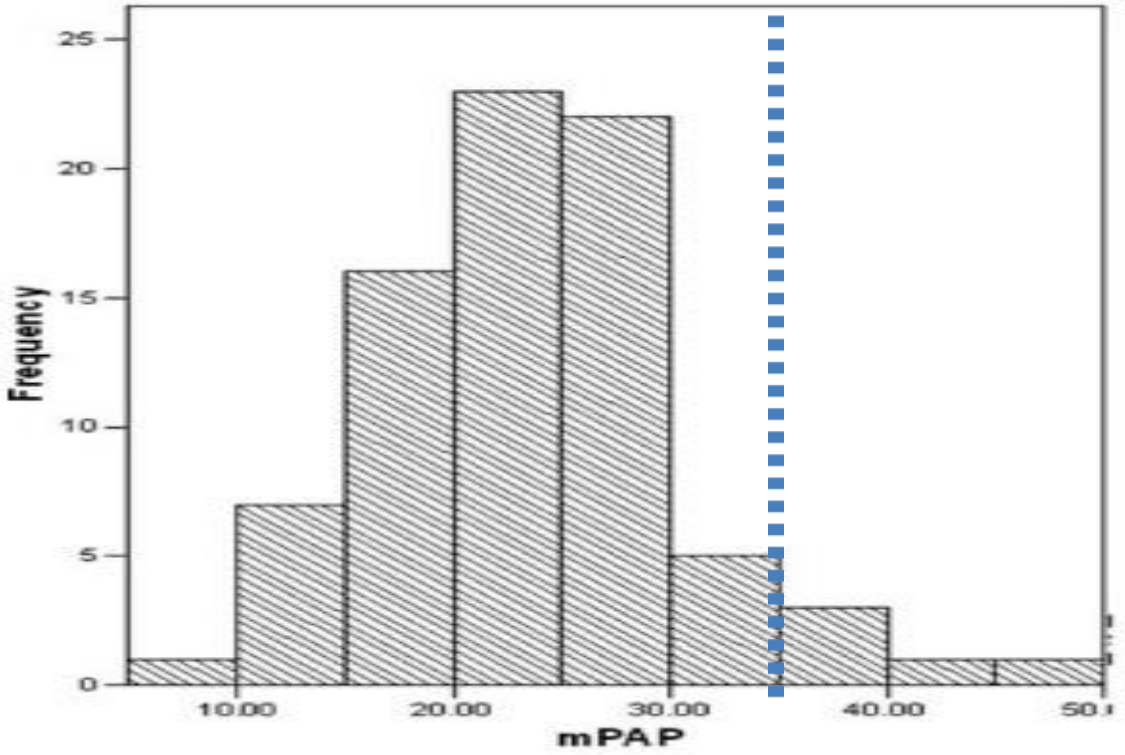
Decreased peak systolic (S') velocity of tricuspid annulus (<9.5 cm/s) measured with tissue Doppler

Mean PAP in patients with COPD and IPF

COPD



IPF

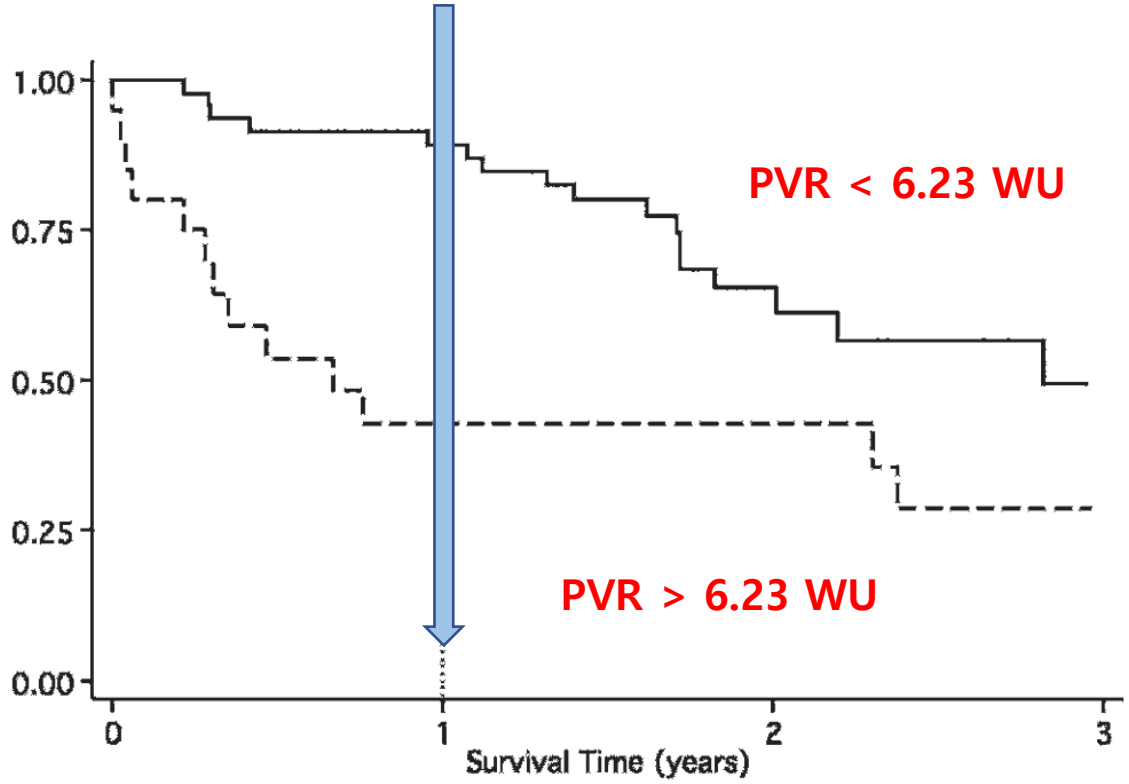


Chaouat et al. Am J Respir Crit Care Med 2005;172: 189–194

Lettieri CJ, et al. CHEST 2006; 129:746 –752

PVR predicts early mortality
in patients with diffuse fibrotic lung disease and suspected PH

Hospital records of consecutive patients with difuse lung diseases undergoing right heart catheterization (RHC) were reviewed (n=66)

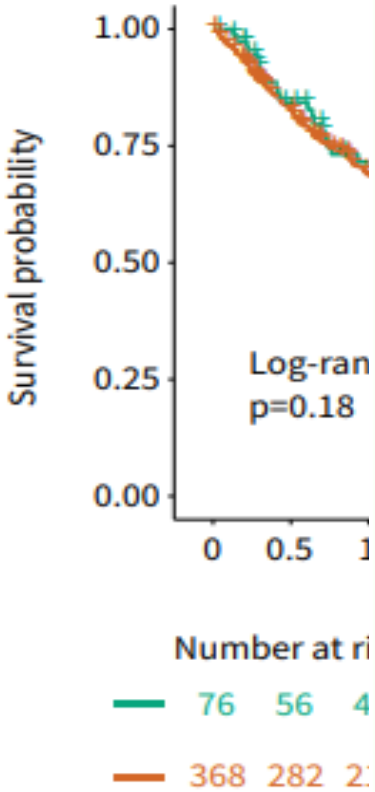


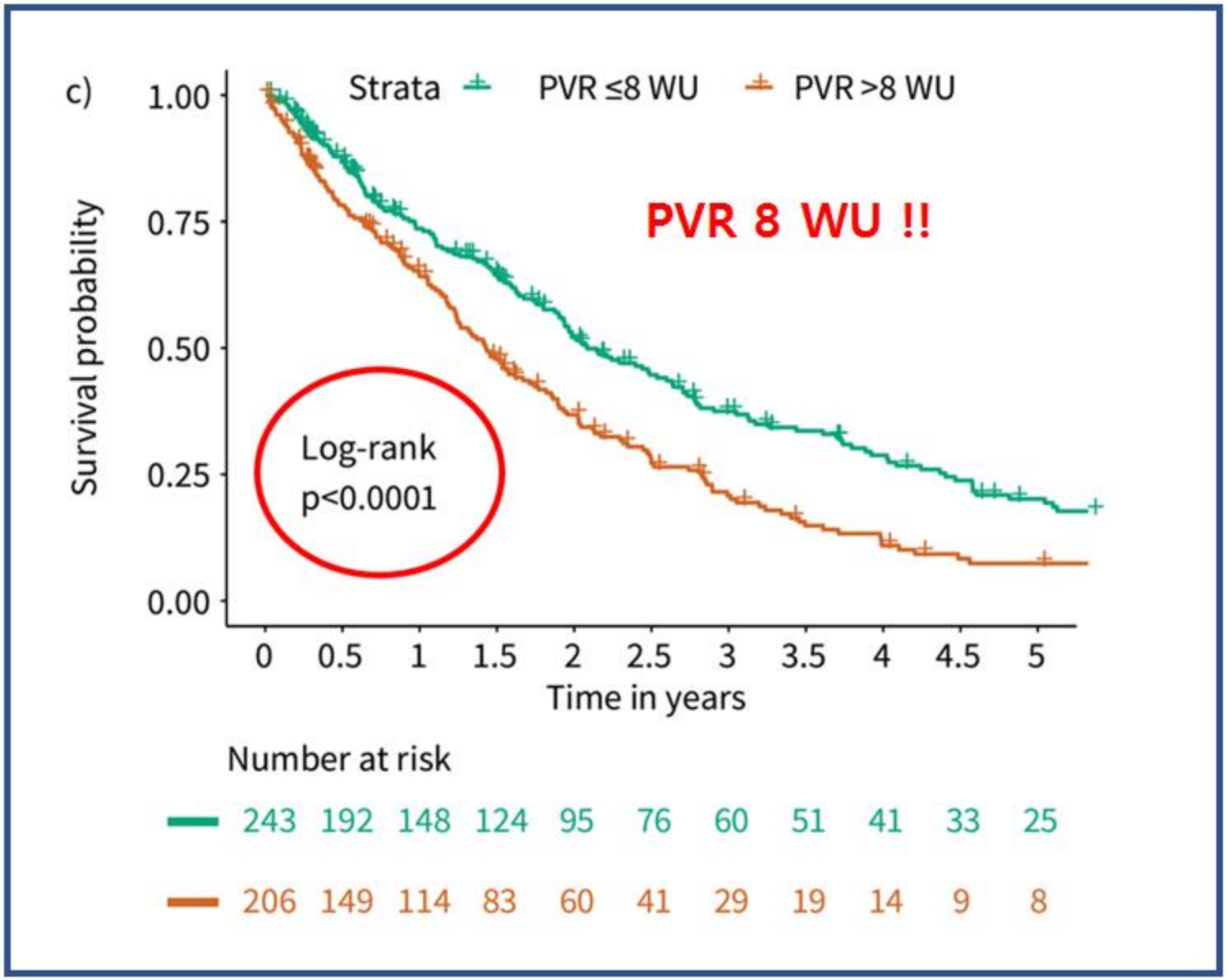
TJ Corte et al, Thorax 2009;64:883–888.

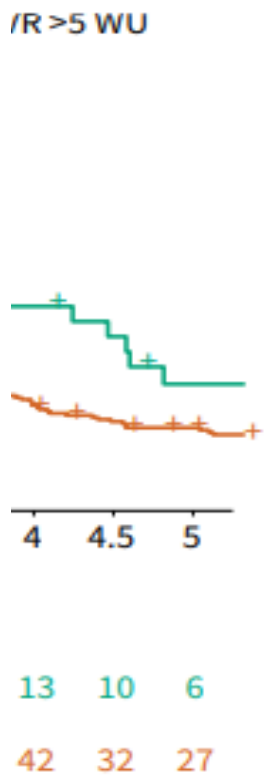
PVR provic
with PH-ILI

in patients

- **449 patient**







Olsson KM, et l. Eur Respir J 2021; 58: 2101483

Definition of severe PH-LD

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

2015 ESC/ERS guidelines for PH

Terminology	Hemodynamics
No PH	PAPm ≤ 20mmHg
Non-severe PH	**PAPm > 20mmHg** **PVR ≤5WU**
Severe PH	**PAPm > 20mmHg** **PVR >5 WU**

2022 ESC/ERS guidelines for PH

Pulmonary vascular resistance **PVR （ Wood units ）**

- Quantitative value for **right ventricular afterload**.

Ohm's law V=IR

Pressure gradient=Flow x Resistance

혈관저항= 압력차이/심박출량

- 저항 (R) = $\frac{\text{압력차이 Pressure gradient}}{\text{유량 Flow}}$

$$\frac{\text{(input pressure – output pressure)}}{\text{blood flow}}$$

$$\frac{\textbf{Mean PA pressure - left atrial pressure (PCWP)}}{\textbf{Cardiac output}}$$

ex) $\frac{\textbf{15 – 10}}{\textbf{5}}$ **= 1 WU**

Pulmonary vascular resistance (PVR)

$$PVR = \frac{mPAP - PCWP}{CO}$$

$$PVR = \frac{15 - 10}{5} = 1.0 \text{ Wood units}$$

$$PVR = \frac{35 - 10}{5} = 5.0 \text{ Wood units}$$

Pulmonary vascular resistance (PVR)

$$PVR = \frac{mPAP - PCWP}{CO}$$

$$PVR = \frac{35 - 10}{5} = 5.0 \text{ Wood units}$$

$$PVR = \frac{25 - 10}{3} = 5.0 \text{ Wood units}$$

Pulmonary vascular resistance (PVR)

$$PVR = \frac{mPAP - PCWP}{CO}$$

$$PVR = \frac{15 - 10}{5} = 1.0 \text{ Wood units}$$

$$PVR = \frac{30 - 20}{5} = 2.0 \text{ Wood units}$$

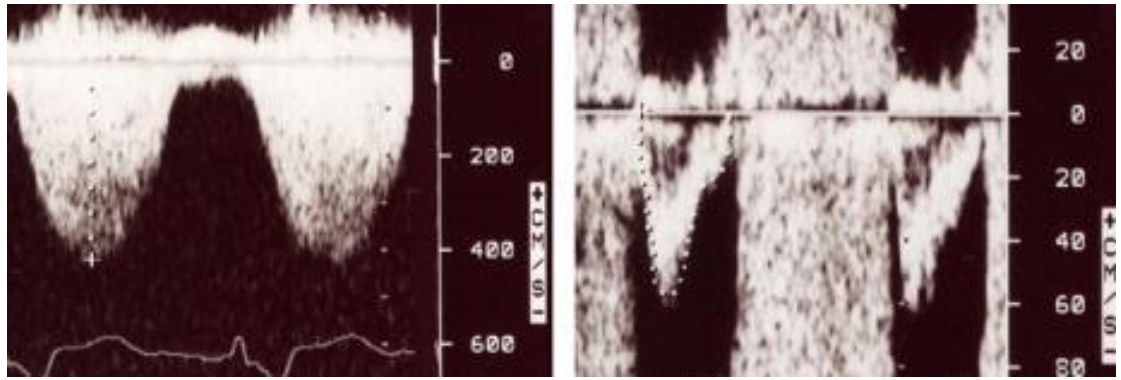
Pulmonary vascular resistance (PVR)

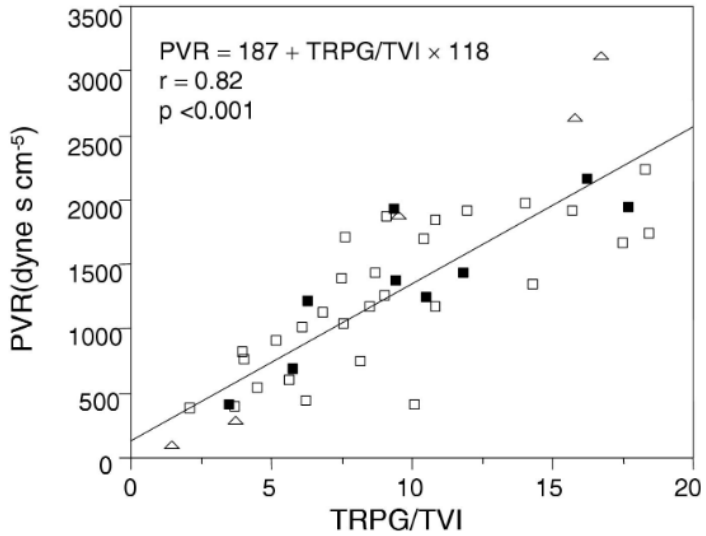
$$PVR = \frac{mPAP - PCWP}{CO}$$

$$PVR = \frac{35 - 15}{10} = 2.0 \text{ Wood units}$$

“High-flow mediated PH

Non-invasive test로 high PVR 예측할 수 있을까?



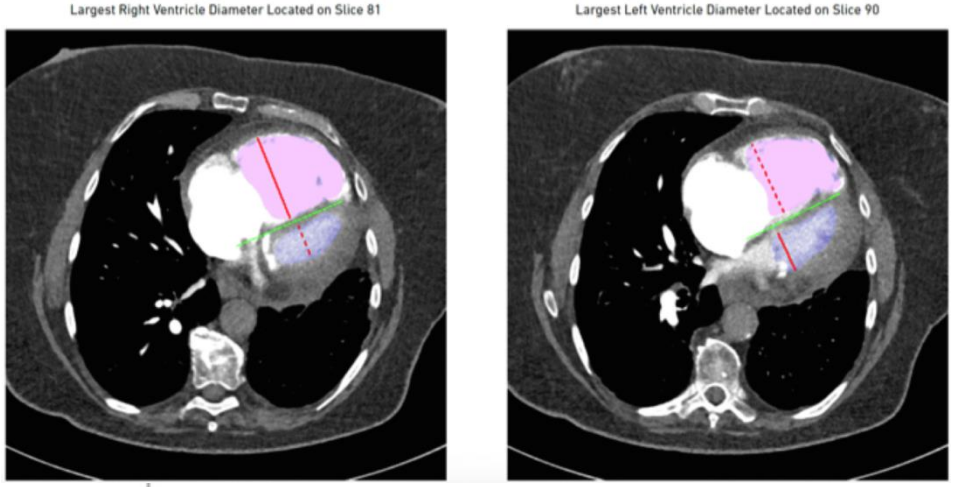


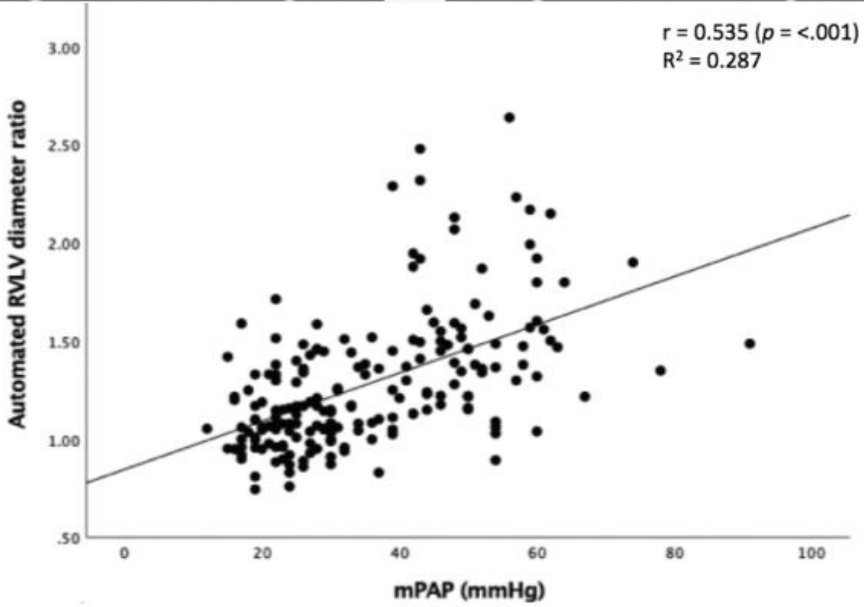
Peak tricuspid regurgitant pressure gradient (TRPG) → pulmonary artery pressure
RVOT time–velocity integral (TVI) → pulmonary blood flow

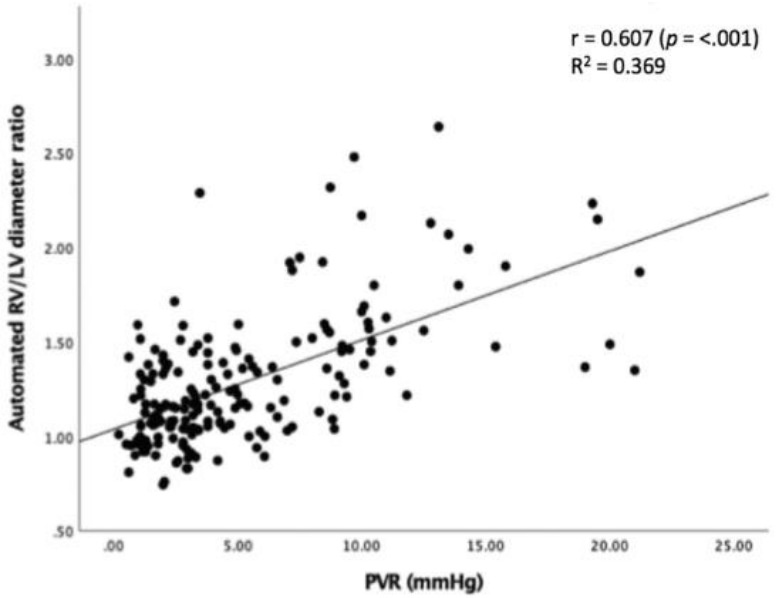
H Kouzu wt al, Am J Cardiol. 2009 Mar 15;103(6):872-6

Automated AI derived RV:LV diameter ratio in CTPA

To predict PH at right heart catheterization







P F P Charters et al Clin Radiol. 2022 Jul;77(7):e500-e508

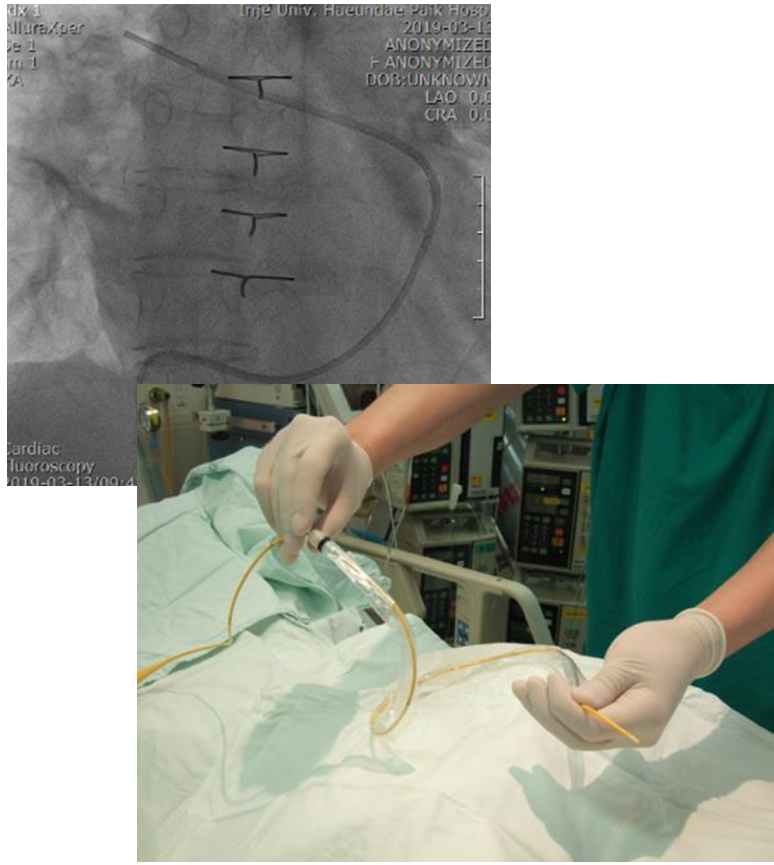
Rt. Heart catheterization (RHC) 반드시 해야 하나?

- **Golden standard** to confirm pulmonary hypertension
- DDx> Group 2 PH associated with Lt heart disease
  PCWP, direct mearsure of LVEDP

- Group 2 이외 다른 그룹간에 hemodynamic 구별 안됨

- inconclusive echocardiographic findings in cases with a high level of suspicion and potential therapeutic implications

- Candidate for lung transplantation

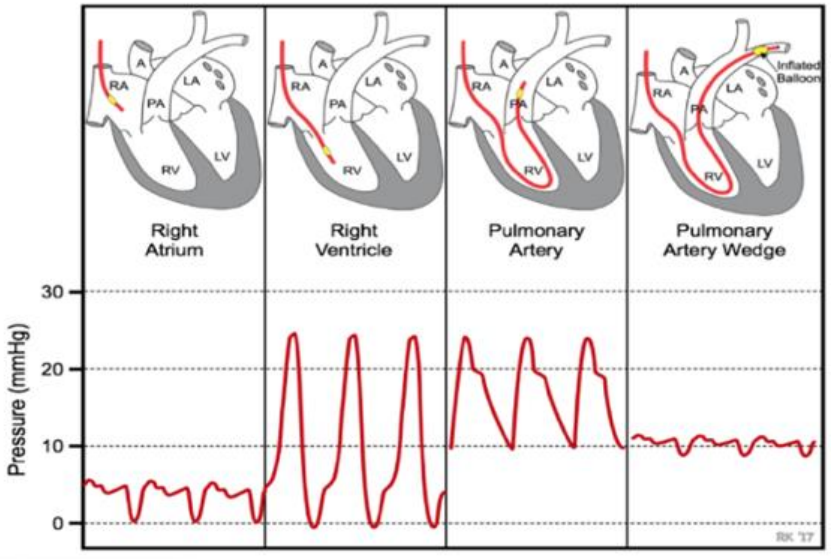


In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions	I	C

2022 ESC/ERS guidelines for PH

Right heart catheterization (RHC)

- The risk of major complications is usually < 1%,
- the risk of mortality of 0.05%



Rare complications may include:

Ventricular tachycardia

Cardiac tamponade

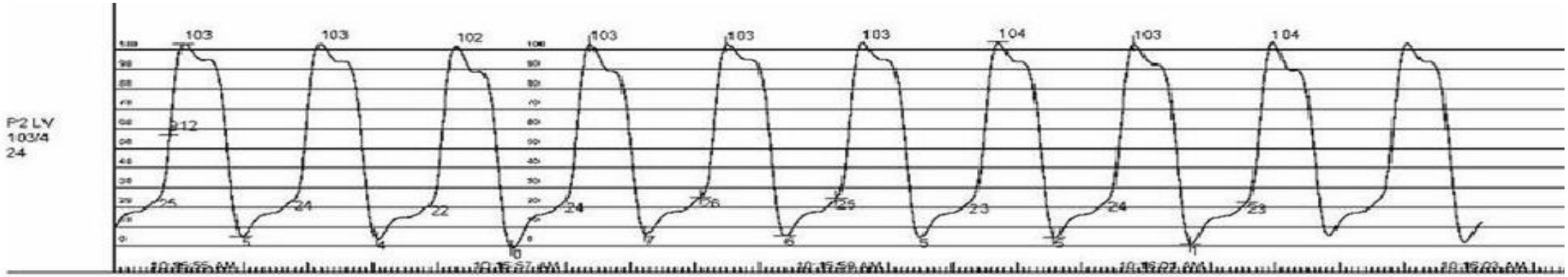
Infection

Air embolism

Pulmonary artery rupture

Direct measurement of LVEDP in case of in-conclusive PCWP

LVEDP=24 mmHg



$$PVR = \frac{mPAP - PCWP}{CO}$$

$$PVR = \frac{34 - 24}{5} = 2.0 \text{ Wood units}$$

증례 #1

우심도자술이 필요했던

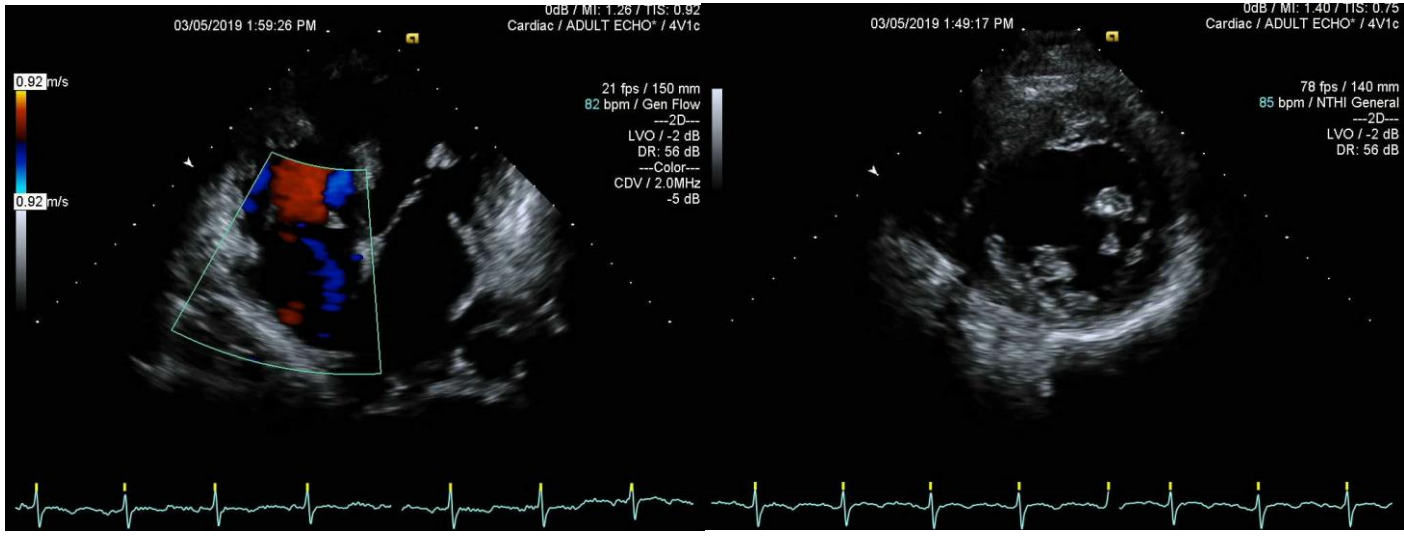
증례 #1 58/F,
Chief complaint: Worsening exertional dyspnea, several months

- WHO dyspnea Fc III
- spO2 89% body Wt. 35kg, no peripheral edema

- **Past History > :**
- **VSD closure operation 13 years ago**
- **생체 간이식 9년전**
- 간이식 후 신부전 chronic renal failure
- ESRD, hypertension
- 2년 전부터 **hemodialysis** 주 2회

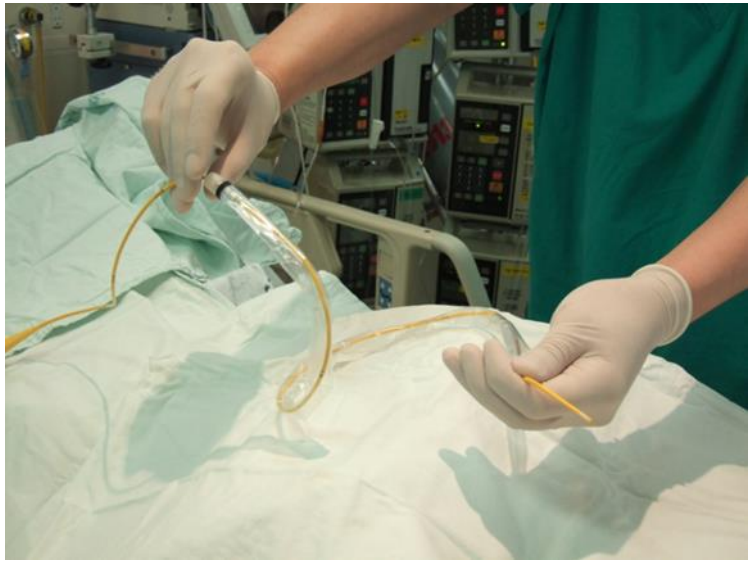
Echocardiography

- Enlarged LA **43.6 mm**
- with normal LV wall thickness.
- No RWMA with normal global LV systolic function. LV EF 61%
- **E/E'=15.5**
- TR of Grade III/IV
- **Peak TR velocity 4.2 m/s**
- TAPSE 16.7



간이식 수술전　ICU 에서　시행한 우심도자술 (RHC)

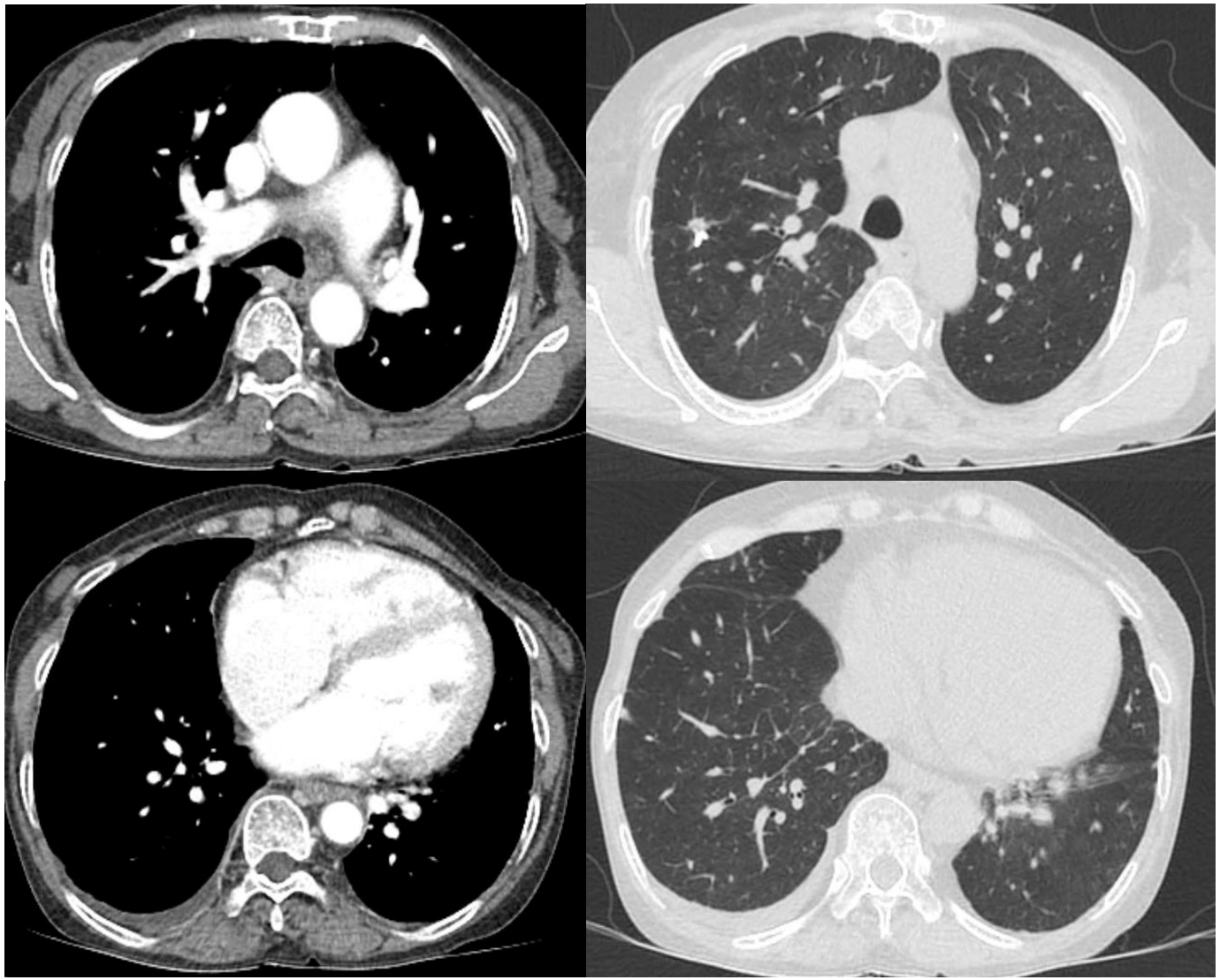
- Mean PAP 26~28 mmHg
- Cardiac output　4.1 L/min
- PCWP 12 mmHg
- PVR 3.66 WU



Portopulmonary hypertension (PoPH)

PoPH patients with mild PH
(mPAP 25–35 mmHg and/or PVR is < 400 dynes.s/cm5)
can be considered for liver transplant in experienced centers. (1B)

Obstructive pulmonary disease



Bronchiolitis obliteranse

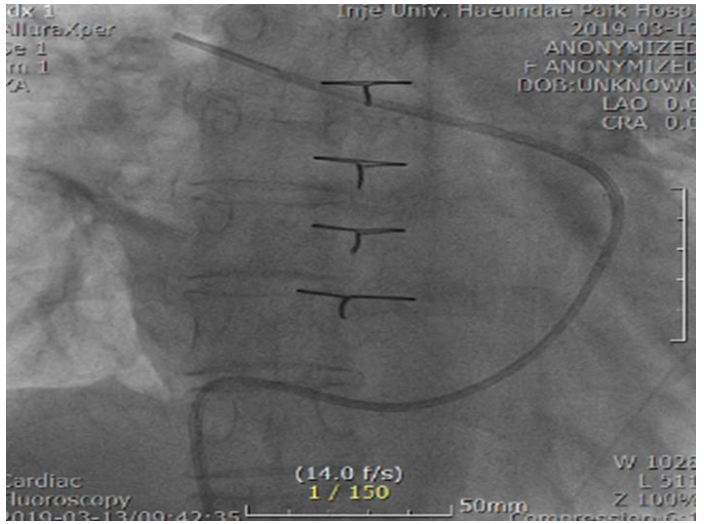
FVC 71% **FEV1 58%**

FEV1/FVC 65%

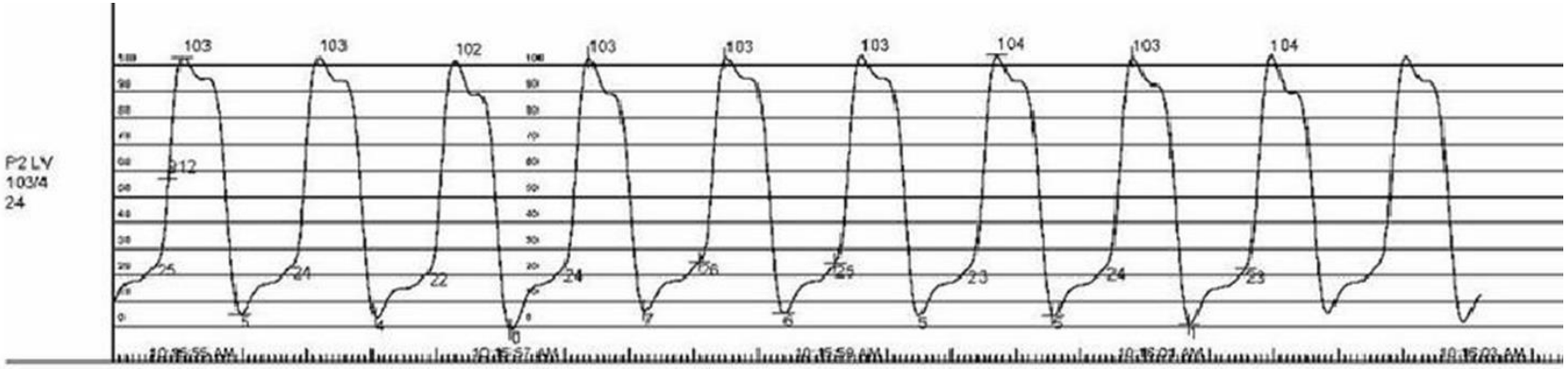
DLco 47%

RHC in cardiac cath lab

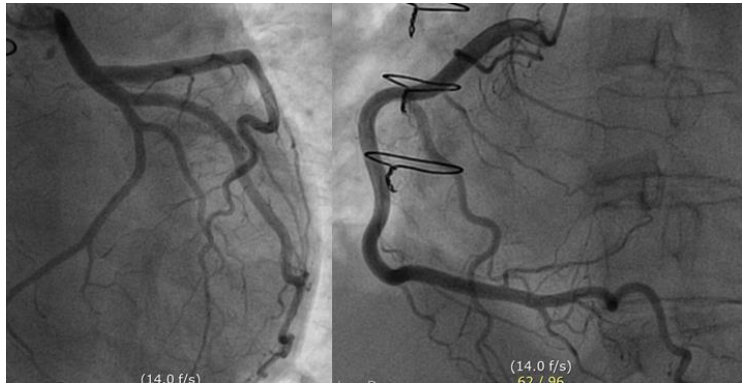
- PAP 48/33 mmHg mean PAP **40** mmHg
- **PCWP 24** mmHg
- Cardiac output 3.4 L/min
- **RA 21** mmHg
- **PVR 5** WU

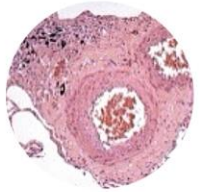
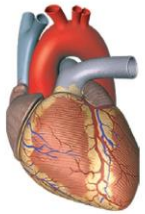
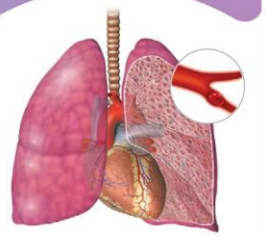


LVEDP=24 mmHg



Coronary angiogram: normal



Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematological disorders • Systemic disorders
PREVALENCE				
Rare	Very common	Common	Rare	Rare
THERAPEUTIC STRATEGIES				
Medical therapy • PAH drugs • CCB in responders **Lung transplantation**	**IpcPH:** • Treatment of LHD[a] **CpcPH:** • Treatment of LHD[a] • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	**Surgical therapy:** • PEA **Interventional:** • BPA **Medical therapy:** • PH drugs	**Optimized treatment of underlying disease** • Potentially: PAH drugs (trials)

Eur Heart J, Volume 43, Issue 38, 7 October 2022, Pages 3618–3731

Treatment

- Group II PH - High PCWP, LVEDP → 낮추는 치료
  전신부종은 없지만 투석전문의와 상의 dry Wt. 점진적으로 줄이기
  혈압조절 약물 ARB CCB

- Obstructive pulmonary disease
  : inhaled long acting bronchodilator and steroid
  PO aminophyllline
  pulmonary rehabiliation

- **Group I associated PAH 가능성에 대한 치료는 일단 보류**

Follow up

- 9개월 후 follow up **Rt. heart cath**

- mPAP 40 → **39**
- PCWP 24 → **17**
- C.O 3.4 → **4.9**
- RAP 21 → 15
- PVR 5 → 4

- 이후 2년 follow up
- 1년 전부터 **sildenafil** 20 mg t i d 추가
- 현재 WHO **Fc II 유지** , doing well resting spo2 94%

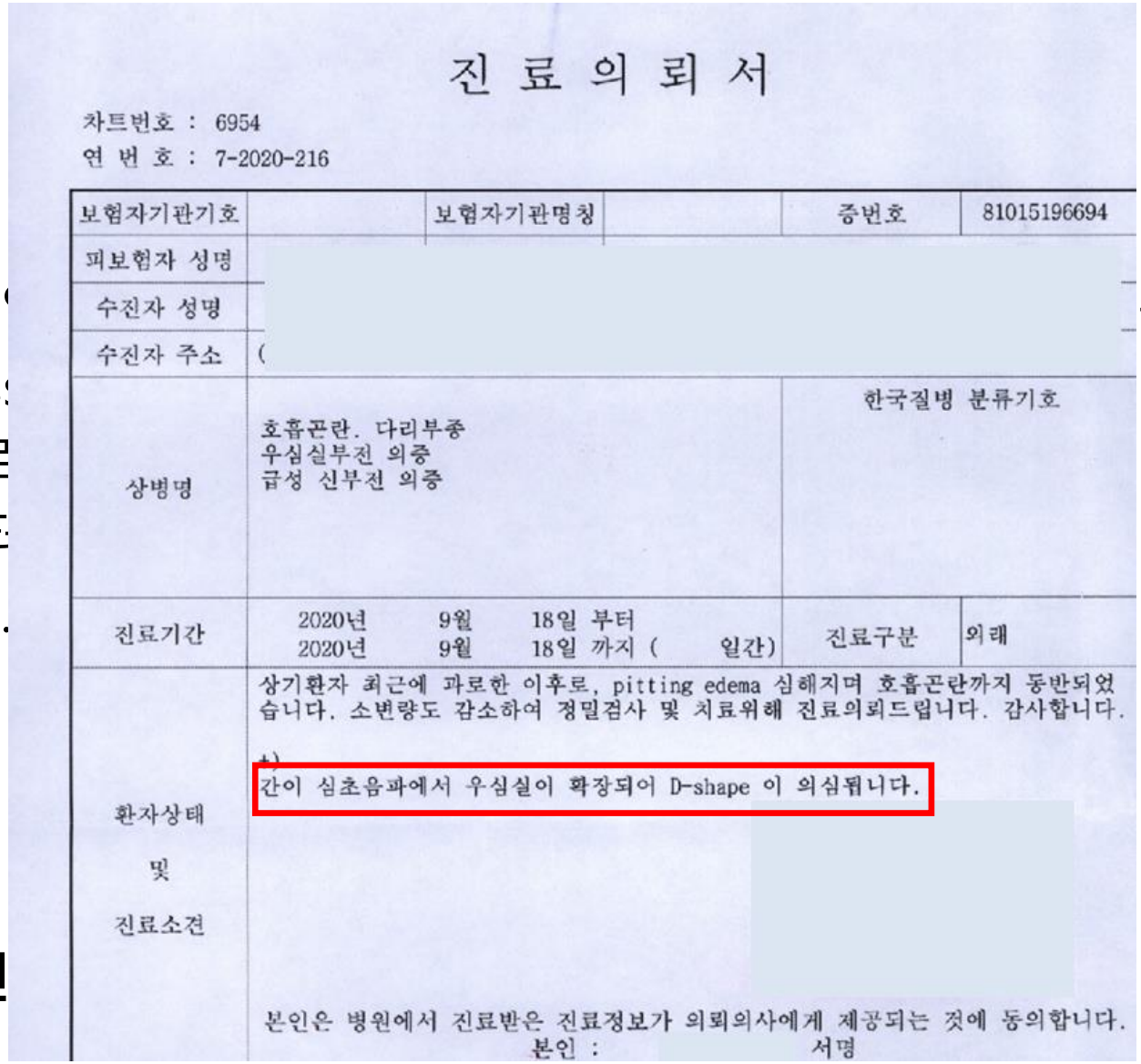
증례 #2　PH associated with lung disease

우심도자술이 필요없었던 증례

하지만 시행 했던

증례#2

- **67/남자**
- C.C : 내원 10
- Present illnes
  한달 전 피로
  7-8년 전부터
  느꼈다고 함.
- 가족력 : 어머
- 과거력
  - **40갑년 현**



진 료 의 뢰 서

차트번호 : 6954
연 번 호 : 7-2020-216

보험자기관기호		보험자기관명칭		증번호	81015196694
피보험자 성명					
수진자 성명					
수진자 주소	(				
상병명	호흡곤란. 다리부종 우심실부전 의증 급성 신부전 의증			한국질병 분류기호	
진료기간	2020년 9월 18일 부터 2020년 9월 18일 까지 (일간)			진료구분	외래
환자상태 및 진료소견	상기환자 최근에 과로한 이후로, pitting edema 심해지며 호흡곤란까지 동반되었습니다. 소변량도 감소하여 정밀검사 및 치료위해 진료의뢰드립니다. 감사합니다. +) 간이 심초음파에서 우심실이 확장되어 D-shape 이 의심됩니다.				

본인은 병원에서 진료받은 진료정보가 의뢰의사에게 제공되는 것에 동의합니다.
본인 : 서명

증례#2

체계별 문진 (review of system)

전반적 위약 (+)

기침/가래 (+/+)

호흡곤란 (+, 움직이면)

chest discomfort/palpitaion (+/-)

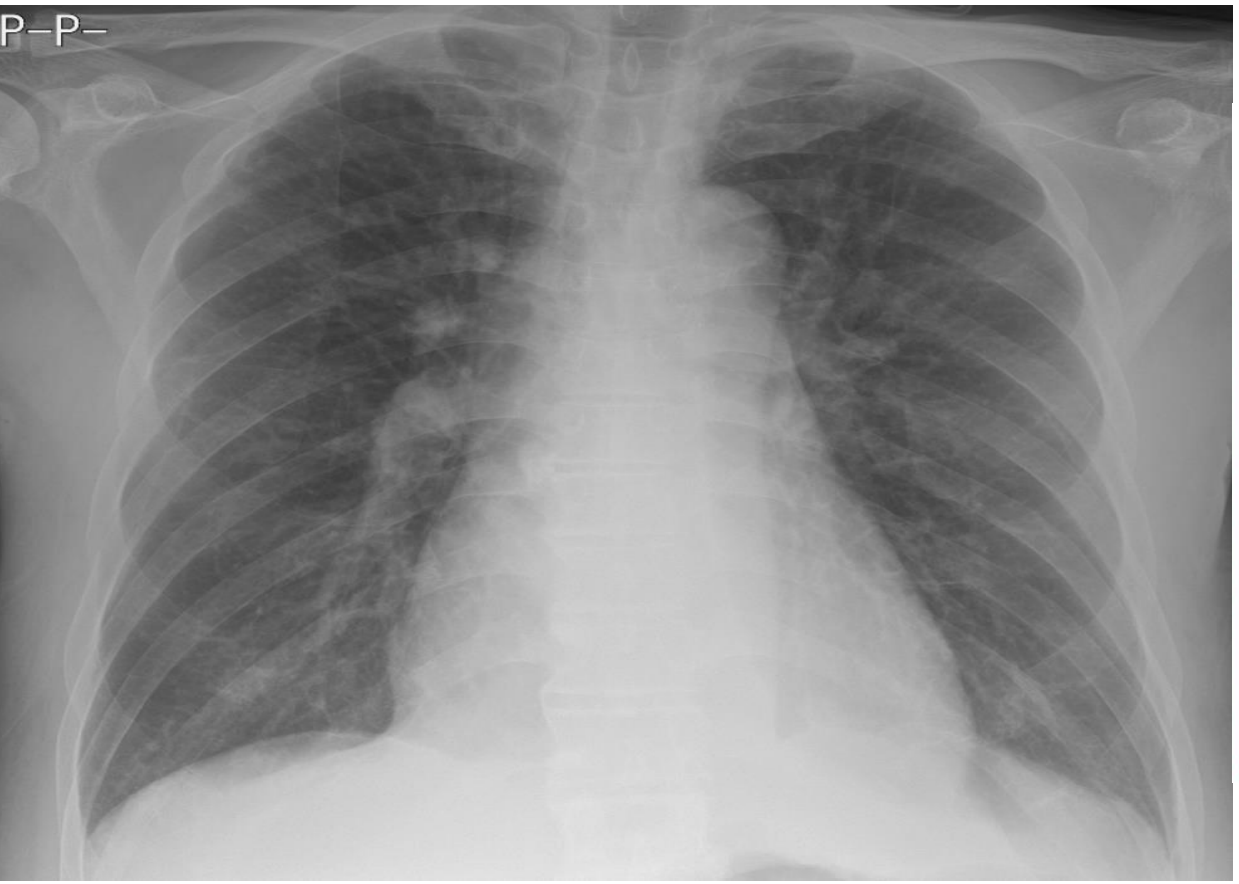
소변 양 감소, 색 진해짐

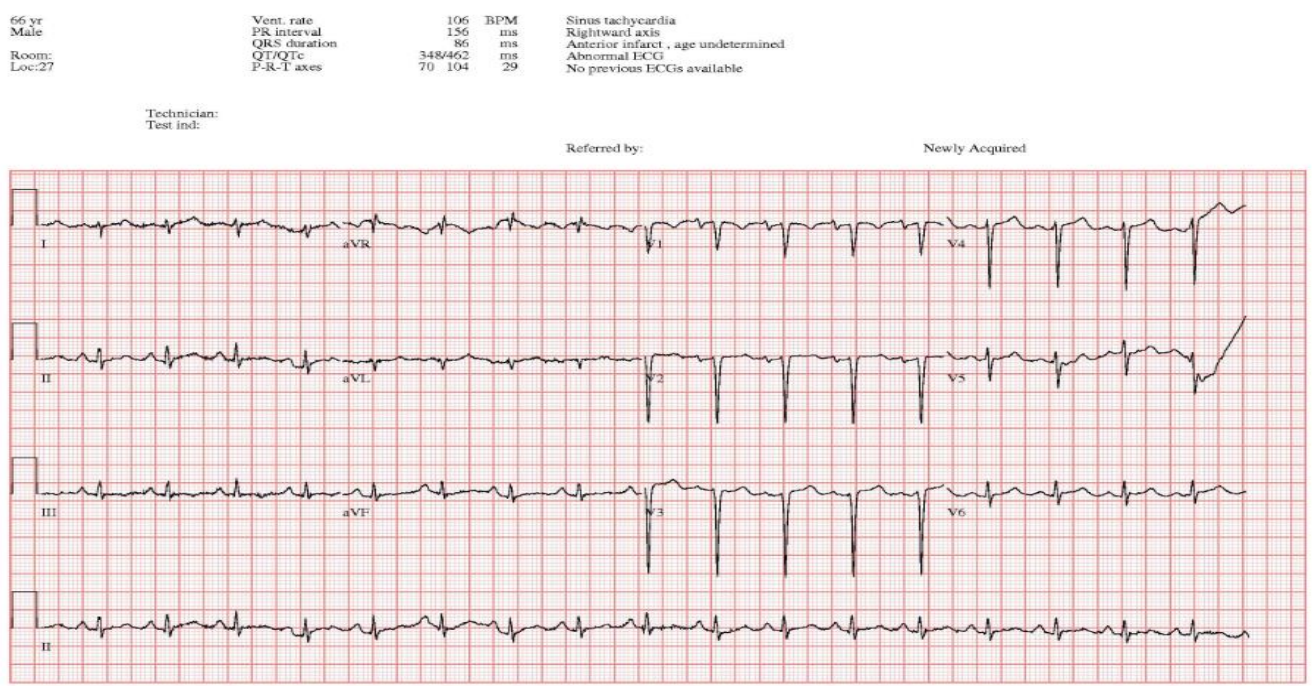
신체검진 (P/Ex)

혈압 : 143/82mmHg, 체온 : 36.8℃, 맥박수 : 107회/분, 호흡수 : 20회/분)

의식 명료 천명음 (-) 수포음 (-) 심잡음 (-)

양측 하지 부종 (++/++) pitting

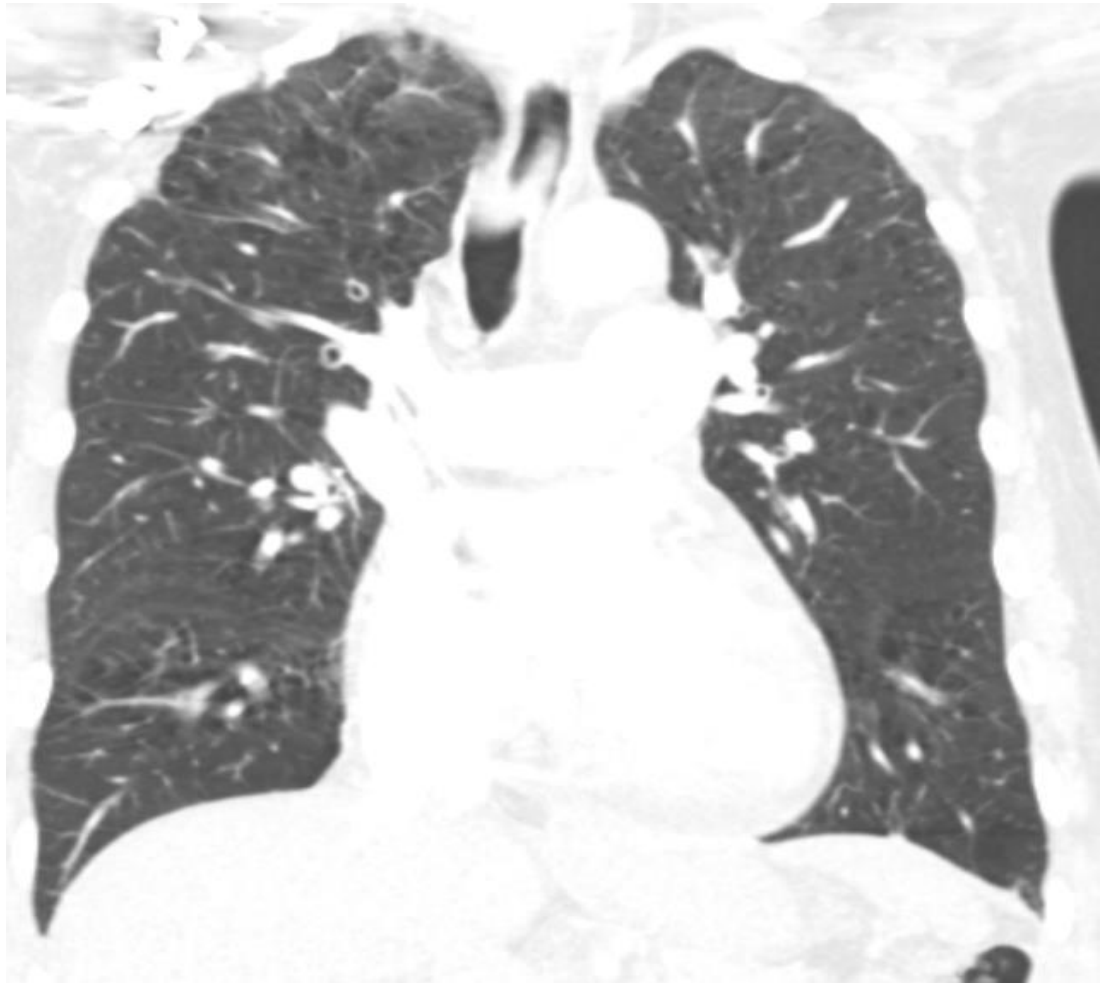


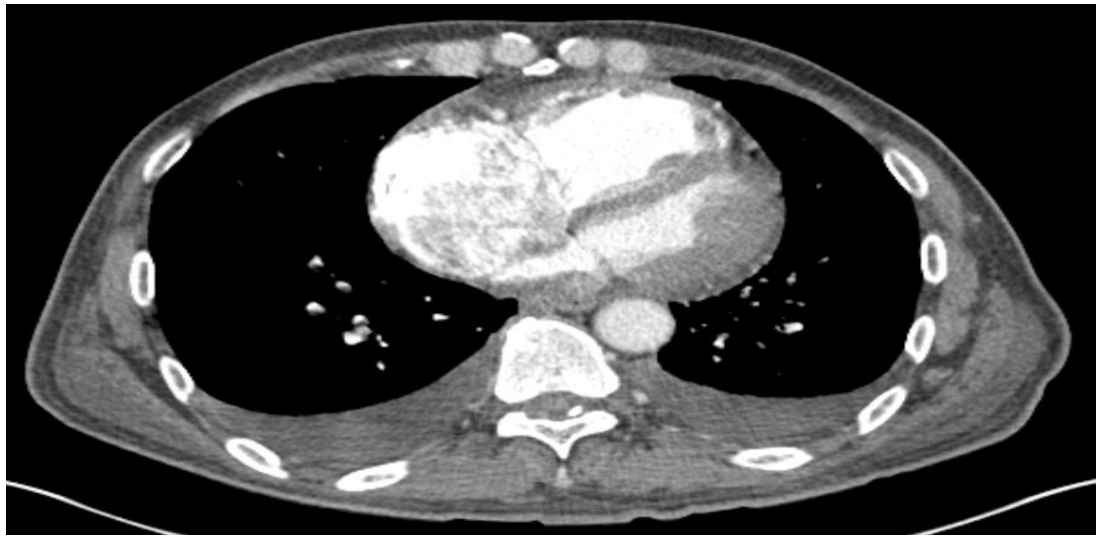


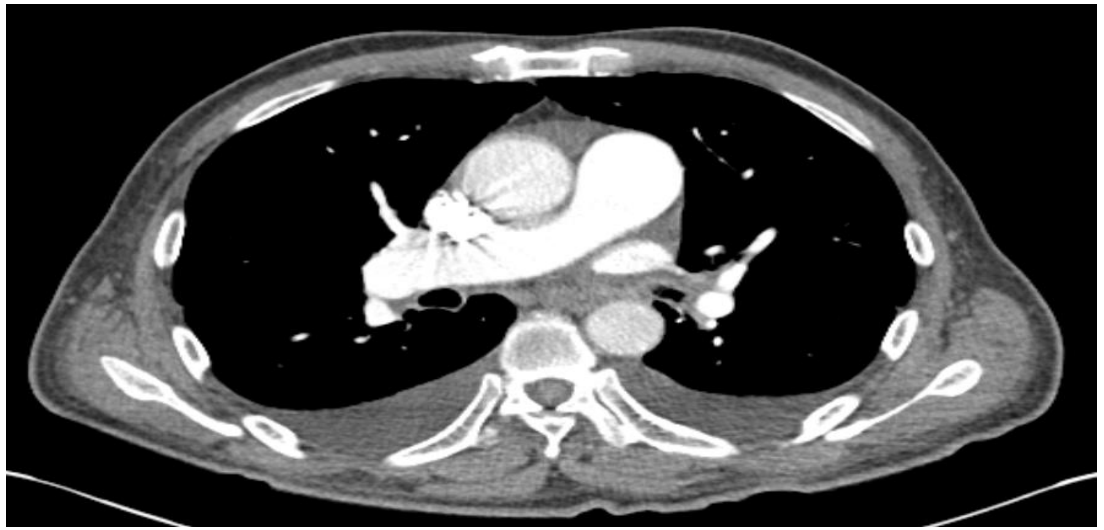
CBC WBC 52300- **Hb18.5**- plt 155k

pro-BNP 2872 pg/mL

Chest embolism CT

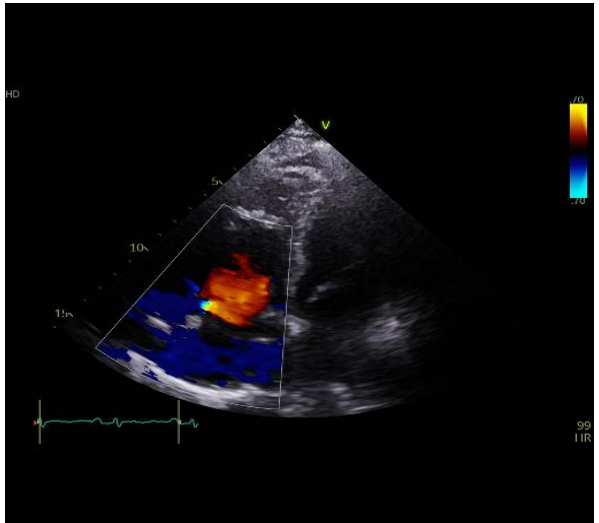


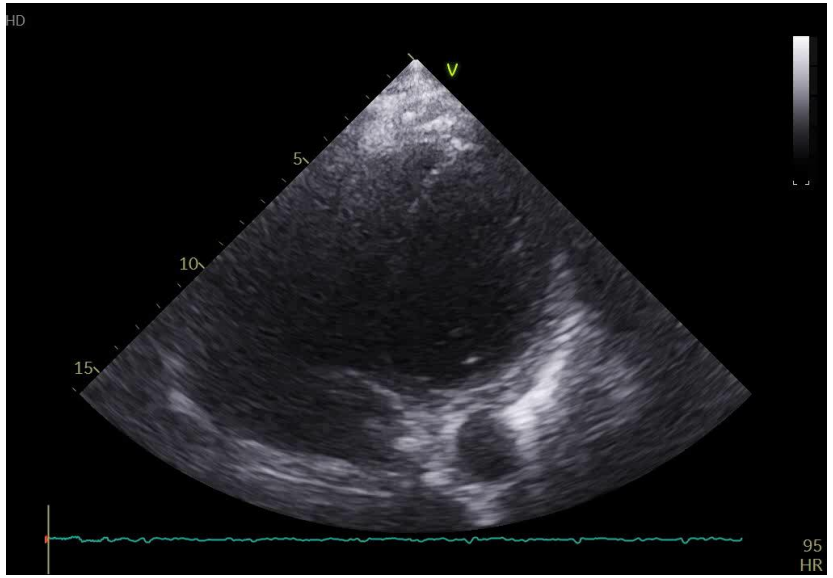


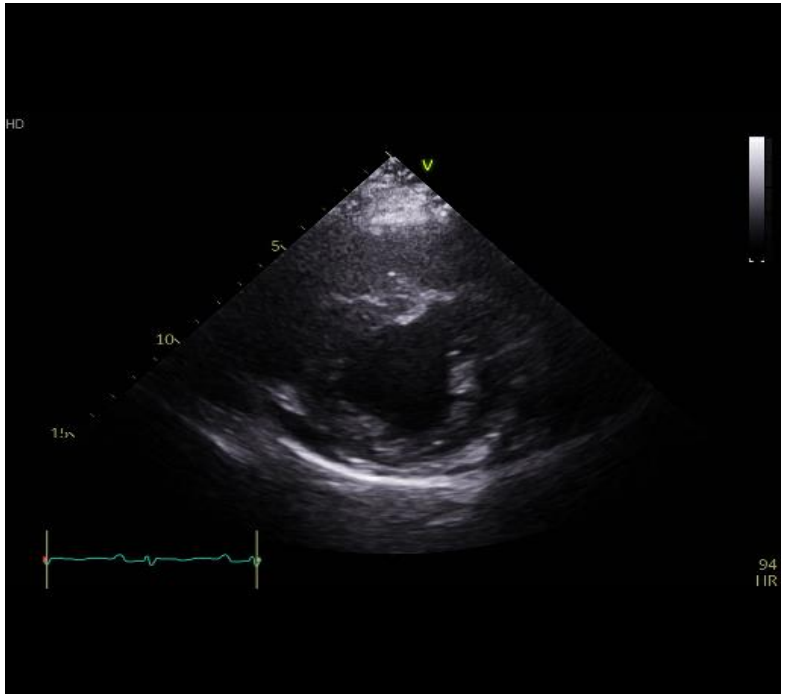


ICU admission #3 Echocardiography

- Enlarged RA & RV dimension
- No RWMA with normal global LV systolic function.
- Decreased RV contractility(FAC = 16%).
- **TR Vmax 3.29 m/s** (RVSP =48.3 mmHg)







일반병실 입원 HD#2 ,,,,

응급실 내원 직후 spO2 60% 저하 보여 nasal prong O2 투여하며 조절

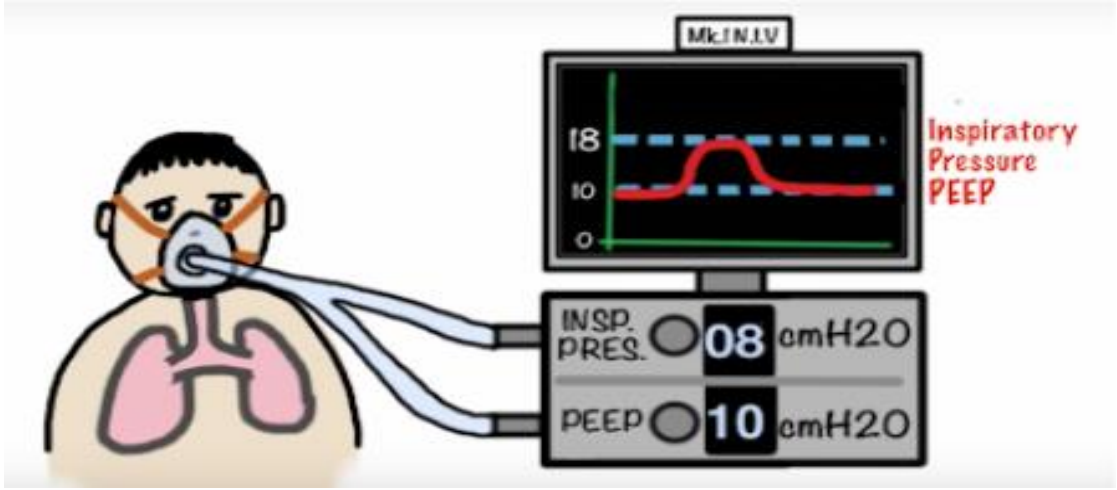
A2009194261 2020-09-19 13:21	C2009185991 2020-09-18 20:33
7.16	7.49
144	42
116	182
1.10	0.83
22.6	8.7
11.9	7.5
34.2	30.9
51.3	32.0
55.7	33.3
97	100

Decreased mentality → intubated

ICU admission #3

- 2일 후 weaning, extubation 성공!

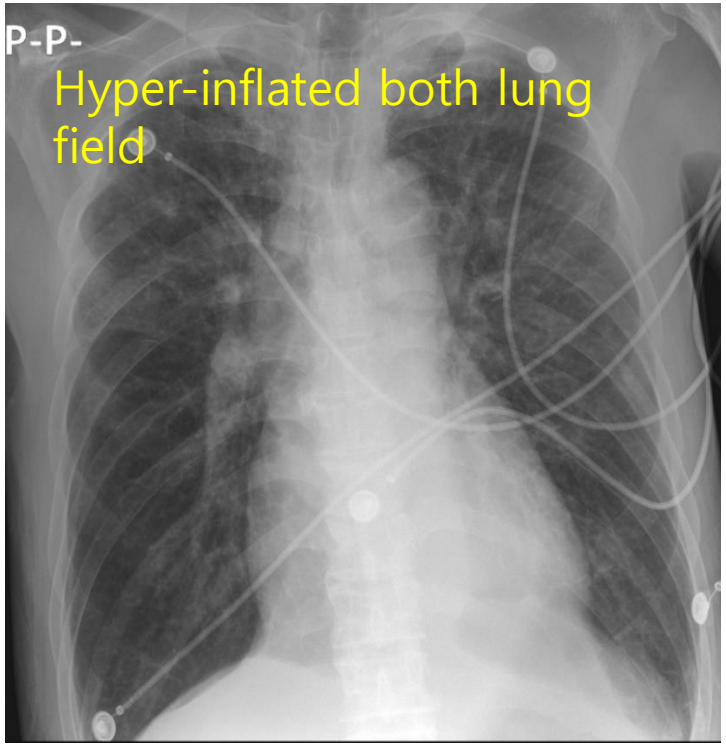
- Intermittent Non-invasive positive pressure ventilation (NIPPV)



ICU admission #6 일반병실 전동 대기 중,,,,,,

- Room air 로 spO2 96% → spO2 70%
- Wheezing ++ in thorax ABGA : pH 7.15 **pCO2 109**

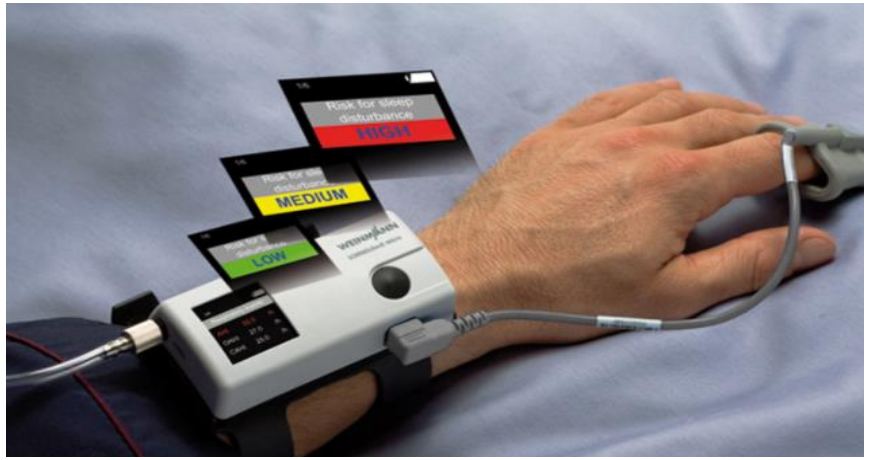
- → Re-intubation → ventilator care, steroid Tx
  4일 후 다시 extubation



Home ventilator 로 NIPPV 적용하며 일반병동 전동대기 중,,,

- Room air 상태로 intermittent NIPPV 적용 중
- **NIPPV 적용 안하는 수면 중에 desaturation down to spO2 ~80%** 자주 목격됨

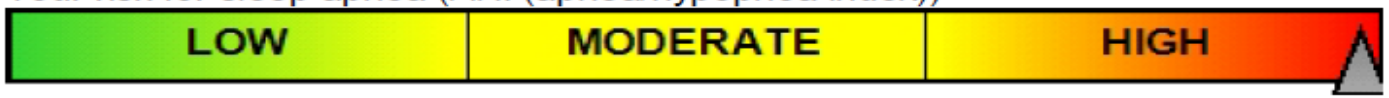
-→ portable somnography (간이 수면 검진기) 시행하기로 함



간이수면검진기 결과

Risk summary

Your risk for sleep apnea (AHI (apnea/hypopnea index))



Risk for fragmented sleep (AAI)

Respiration

AHI (apnea/hypopnea index)	27.0 / h (< 5 / h)	oAHI (obstructive AHI)	**25.4 / h**
AI (apnea index)	**24.5 / h**	cAHI (central AHI)	**1.4 / h**
HI (hypopnea index)	**2.6 / h**	snoring	**0 %**
longest apnea	**59 s**	flattening	**1 %**
mean apnea duration	**19 s**		

Oxygen

Oxygen desaturation index	**23.7 / h**	Time below 95 %	**06:12:44 [100 %]**
lowest saturation	65 % (90–96 %)	Time below 90 %	**02:02:31 [33 %]**
mean saturation	89 % (94–98 %)	Time below 85 %	**00:31:12 [08 %]**
		Total hypoxemia duration (SpO2 <90% for >5 min.)	**00:39:49 [11 %]**

Heart rate

mean pulse rate	**86 / min**	highest pulse rate	98 / min (60–90 / min)
		lowest pulse rate	38 / min (50–70 / min)

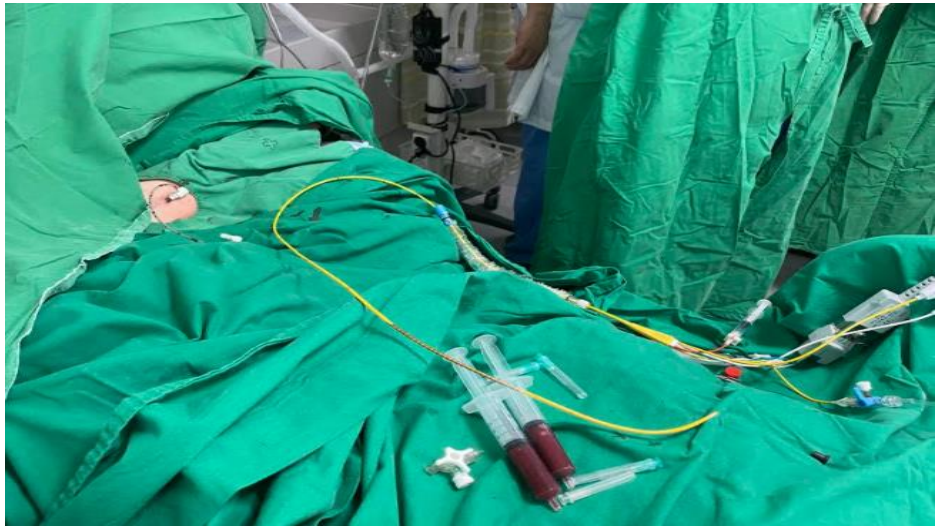
Diagnosis

#1 Pulmonary hypertension with Rt. heart failure
#2 COPD with asthma = probable ACOS
#3 recurrent hypercapnic respiratory failure
#4 obstructive sleep apnea

Impression >>
PH due to COPD or OSA
vs.
lung disease (COPD, OSA) + Combined idiopathic PAH ?

Bedside Rt. Heart catheterization in ICU

- **PAP 36/21 mean PAP 27 mmHg**
- PCWP 10 mmHg
- Cardiac output (thermodilution) 3 회 평균 10.1 L/min
- PVR 1.683 WU/㎡
- SvO2 76%

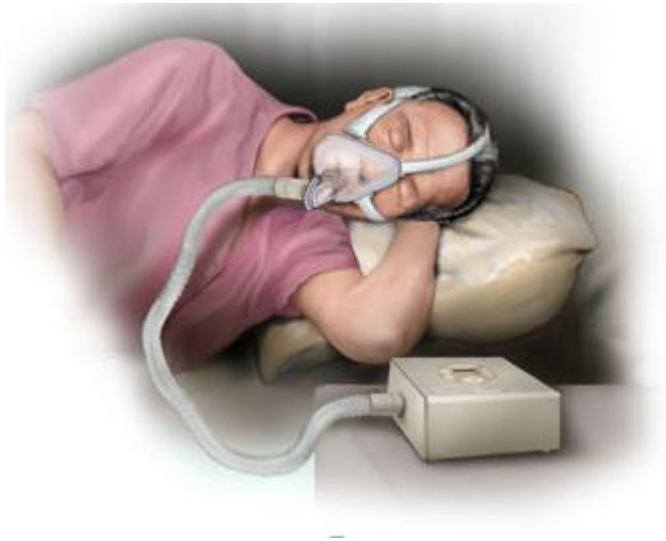


Discharge and follow up
optimizied care of underlying lung disease

- Home NIV – BiPAP titration

  Day – evening – night

  → **Only at Nighttime**



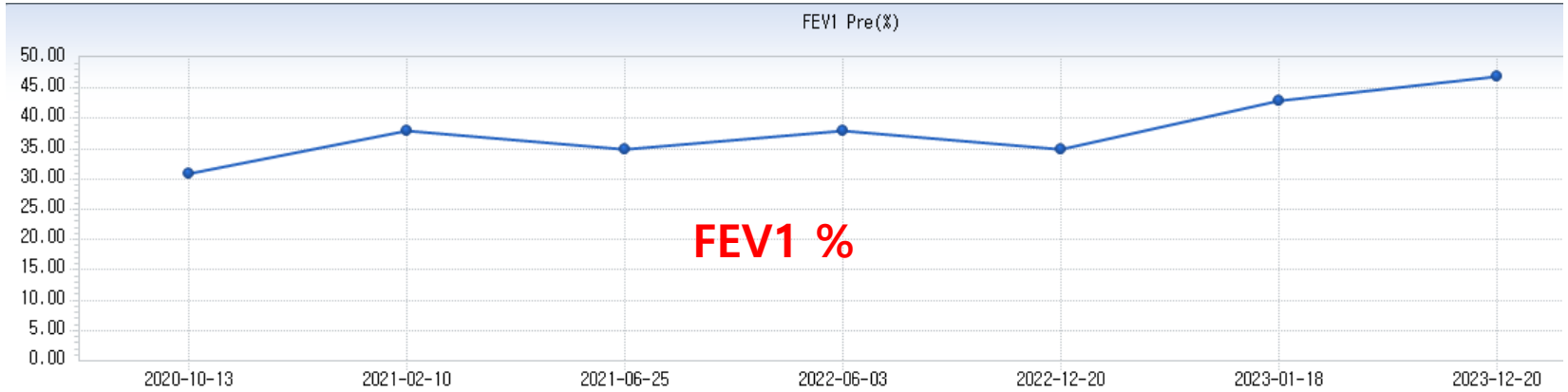
- Maintaining normocapnia

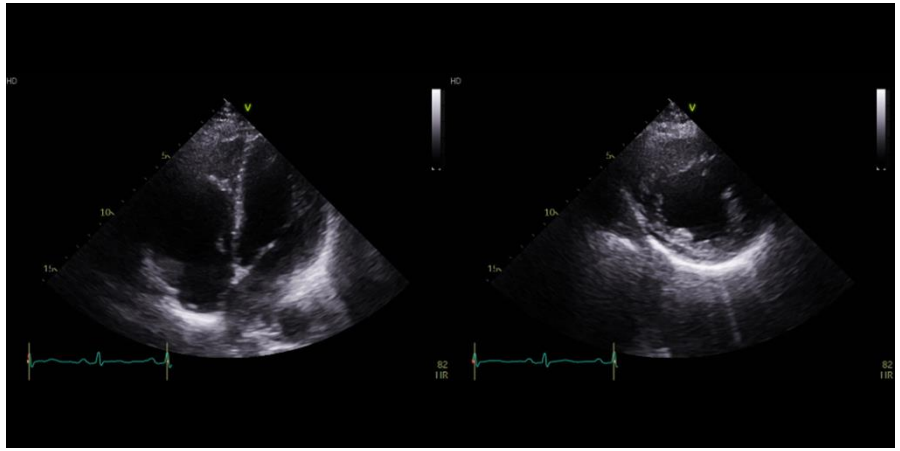
PH	7.35 ~ 7.45		7.444
PCO_2	35.0 ~ 45.0	mmHg	42.7
PO_2	75.0 ~ 100.0	mmHg	80.6

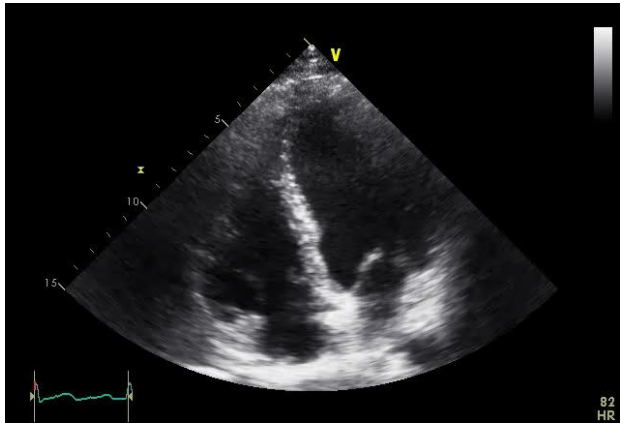
Discharge and follow up
optimized care of underlying lung disease

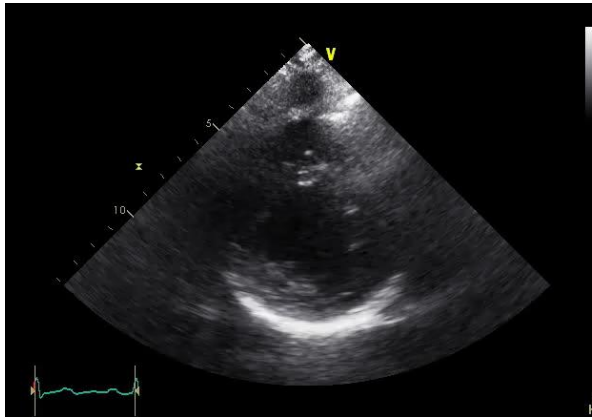
Spirometry

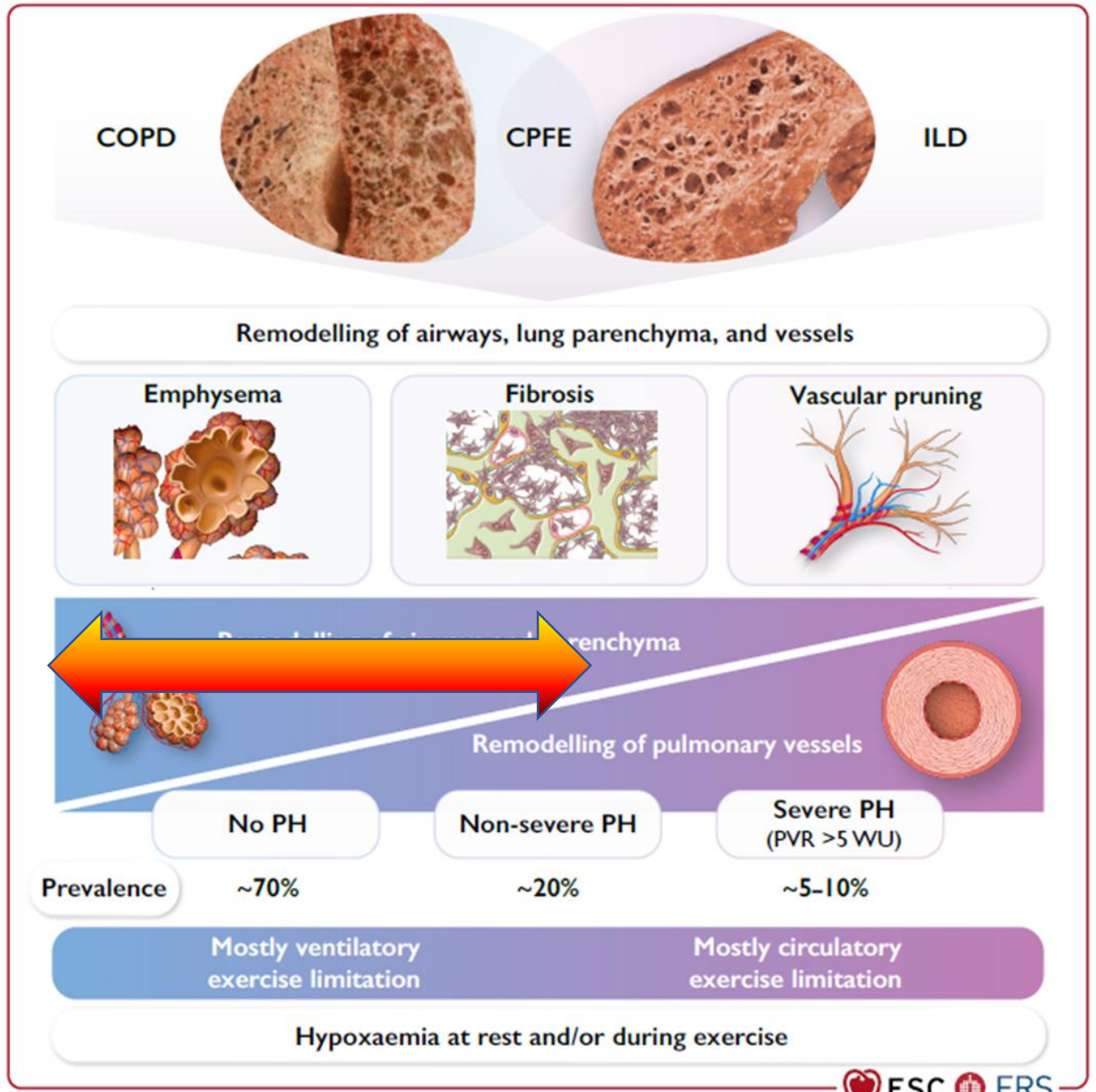
FVC	Liters	4.77	3.45	72
FEV1	Liters	3.57	1.12	31










COPD
CPFE
ILD
Remodelling of airways, lung parenchyma, and vessels
Emphysema
Fibrosis
Vascular pruning
Remodelling of pulmonary vessels
No PH
Non-severe PH
Severe PH
(PVR >5 WU)
Prevalence
~70%
~20%
~5–10%
Mostly ventilatory exercise limitation
Mostly circulatory exercise limitation
Hypoxaemia at rest and/or during exercise
ESC ERS

General treatment for group 3 PH

- 기저 폐질환 약물 치료 최적화
- Home O2 , portable O2 on ambulation
- Hypercapnia → home NIPPV (NIV)
- Sleep disordered breathing
- Rehabilitation
- Vaccination

Pulmonary hypertension associated with ILD (PH-ILD)

Annals of Internal Medicine | ORIGINAL RESEARCH

Treatment of Idiopathic Pulmonary Fibrosis With Ambrisentan

A Parallel, Randomized Trial

Ganesh Raghu, MD; Juergen Behr, MD; Kevin K. Brown, MD; Jim J. Egan, MD; Steven M. Kawut, MD; Kevin R. Flaherty, MD; Fernando J. Martinez, MD; Steven D. Nathan, MD; Athol U. Wells, MD; Harold R. Collard, MD; Ulrich Costabel, MD; Luca Richeldi, MD; Joao de Andrade, MD; Nasreen Khalil, MD; Lake D. Morrison, MD; David J. Lederer, MD; Lixin Shao, MD; Xiaoming Li, PhD; Patty S. Pedersen, BSN; A. Bruce Montgomery, MD; Jason W. Chien, MD; Thomas G. O'Riordan, MD, and the ARTEMIS-IPF Investigators*

BUILD-1: A Randomized Pla… ontrolled Trial of Bosentan in Idiopathic Pulm… ibrosis

Talmadge E. King, Jr.[1], Jürgen Behr[2], Kevin K. Brown[3], Roland M. … ancaster[5], Joao A. de Andrade[6], Gerd Stähler[7], Isabelle Leconte[8], Sébastien Roux[8], and Ganesh Raghu …

BUILD-3: A Randomized, Controlled Tria… …entan in Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr.[1], Kevin K. Brown[2], Ganesh Raghu[3], Roland M. du Bois[4], David A. Lynch[5], Dominique Valeyre[7], Isabelle Leconte[8], Adele Morganti[8], Sébastien Roux[8], and Juergen Behr[9]

ORIGINAL ARTICLE

Bosentan in Pulmonary Hypertension Asso… … Fibrotic Idiopathic Interstitial Pneumoni…

Tamera J. Corte[1,2*], Gregory J. Keir[1,3*], Konstantinos Dimo… …ward[5], Paul A. Corris[6], Lisa Parfitt[4], Claire Foley[7], Monica Yanez-Lopez[7], Daphne Babalis[7], P… …by M. Maher[1], Elizabeth A. Renzoni[1], Lisa Spencer[8], Charlie A. Elliot[9], Surinder S. Birring[10], Kat… …illy[11], Michael A. Gatzoulis[4], Athol U. Wells[1], and Stephen J. Wort[4,12]; for the BPHIT Study Group

Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study

Steven D Nathan, Jürgen Behr, Harold R Collard, Vincent Cottin, Marius M Hoeper, Fernando J Martinez, Tamera J Corte, Anne M Keogh, Hanno Leuchte, Nesrin Mogulkoc, Silvia Ulrich, Wim A Wuyts, Zhen Yao, Francis Boateng, Athol U Wells*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

The Idiopath… …nary Fibrosis Clinical Research Network*

…GLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis

Martin Kolb, M.D., Ganesh Raghu, M.D., Athol U. Wells, M.D., Jürgen Behr, M.D., Luca Richeldi, M.D., Birgit Schinzel, Dipl.Stat., Manuel Quaresma, Lic., Susanne Stowasser, M.D., and Fernando J. Martinez, M.D., for the INSTAGE Investigators*

…EST

Original Research

DIFFUSE LUNG DISEASE

Sild… …reserves Exercise Capacity in Patient… …ith Idiopathic Pulmonary Fibrosis and Right-sided Ventricular Dysfunction

*MeiLan K. Han, MD; David S. Bach, MD; Peter G. Hagan, MD; Eric Yow, MS; Kevin R. Flaherty, MD, FCCP; Galen B. Toews, MD; Kevin J. Anstrom, PhD; and Fernando J. Martinez, MD, FCCP; for the IPFnet Investigators**

Recommendations for PH associated with lung disease and/or hypoxa - 2022 ESC/ERS

Recommendation Table 23B

	GRADE			
Recommendations	**Quality of evidence**	**Strength of recommendation**	**Class[a]**	**Level[b]**
PDE5is may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres)	Very low	Conditional	**IIb**	**C**
The use of PDE5is in patients with ILD and non-severe PH is not recommended	Very low	Conditional	**III**	**C**

Inhaled treprostinil may be considered in patients with PH associated with ILD[734]	**IIb**	**B**
The use of ambrisentan is not recommended in patients with PH associated with IPF[740]	**III**	**B**
The use of riociguat is not recommended in patients with PH associated with IIP[181]	**III**	**B**
The use of PAH medication is not recommended in patients with lung disease and non-severe PH[e]	**III**	**C**

Inhaled Treprostinil in PH due to Interstitial Lung Disease

INCREASE trial *N Engl J Med* 2021; 384:325-334

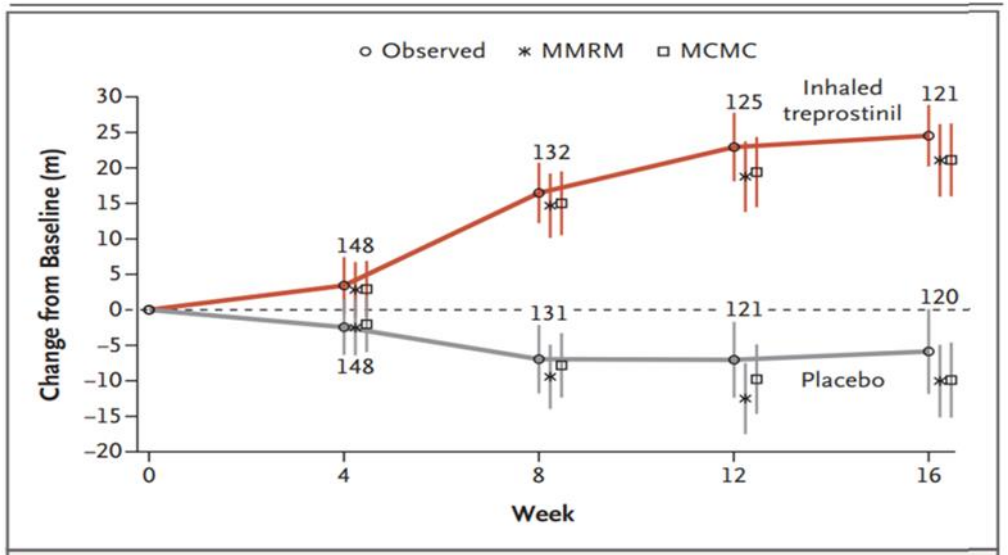
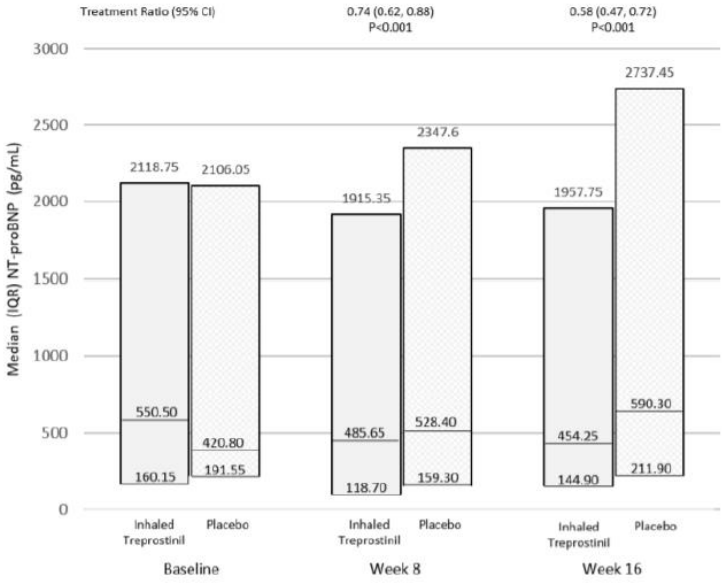
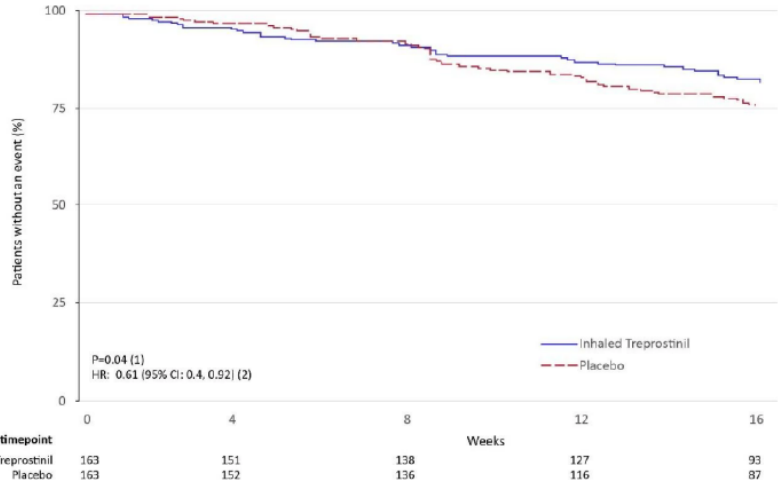


Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.



6MWT – exercise capacity ↑
NT-proBNP ↓
Risk of clinical worsening ↓

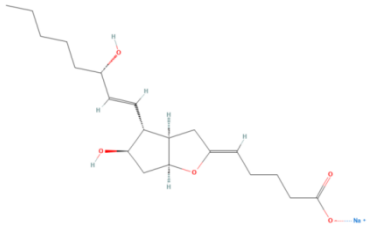


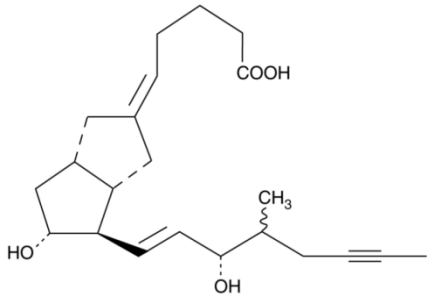
INCREASE trial
Greater treatment effect in higher **PVR** & **NT-proBNP**

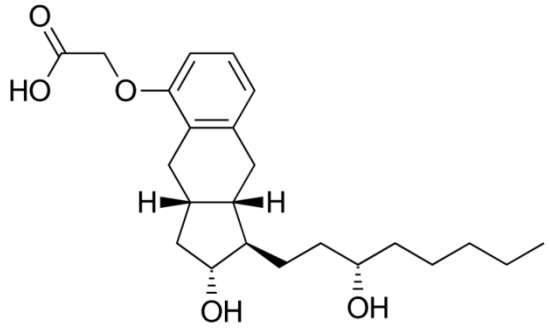
	Inhaled treprostinil (n)	Placebo (n)	Placebo-corrected difference in week-16 FVC, mL	p value
Pulmonary vascular resistance, Wood units				
<5·275	64	75	−1·6 (47·9; −95·9 to 92·8)	0·97
≥5·275	65	49	112·5 (52·6; 9·0 to 215·9)	0·033
NT-proBNP, pg/mL				
<503·85	62	75	19·9 (53·7; −86·3 to 126·1)	0·71
≥503·85	63	47	94·4 (47·4; 0·7 to 188·2)	0·048

Placebo-corrected difference in week-16 FVC stratified by median baseline clinical characteristics

Prostanoids – for **inhalation**







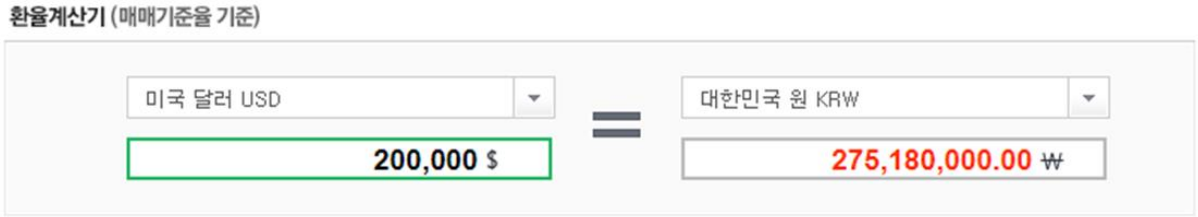
2024.7.5 국내 품목허가 취득
진료상 필수약제로 보험약가 신청

IPF 산정특례 대상으로 추진 예정

Epoprostenol Sodium

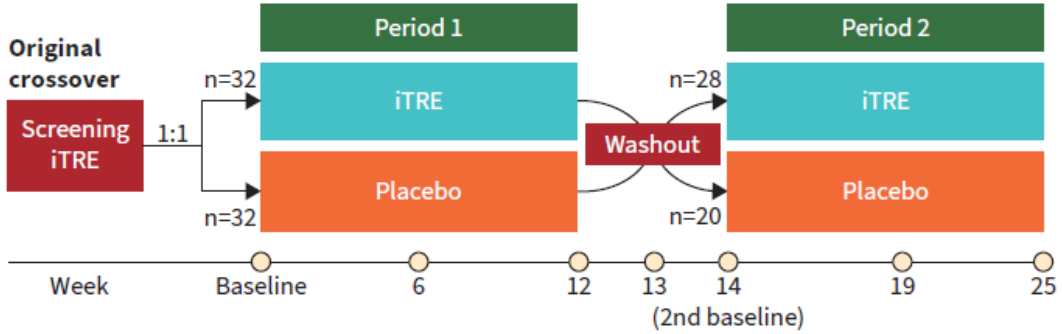
Iloprost
현재 국내사용중

Treprostinil



S.D. Nathan et al,
Eur Respir J. 2024 Jun 6;63(6)

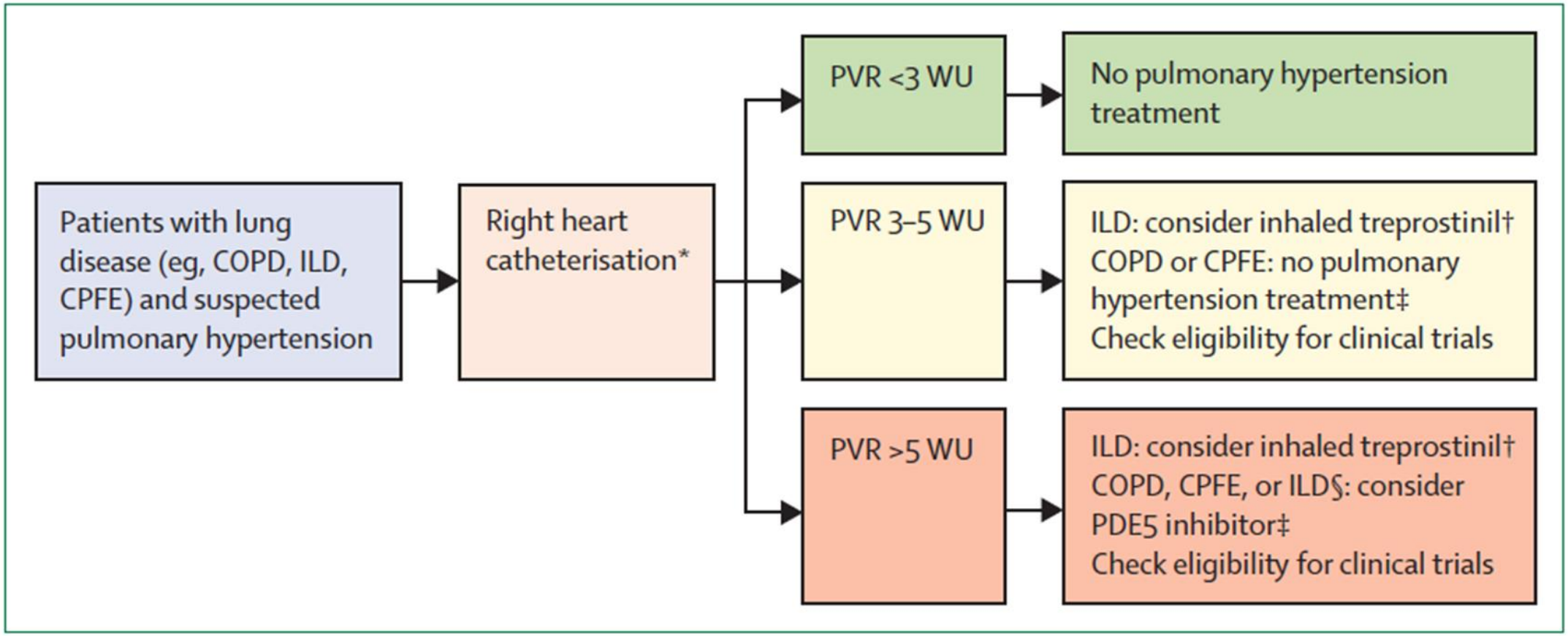
Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results



76 patients (FVC 74.8±17.6, FEV1 42.6±18.4 Dlco 30.4±12.5)
moderate to severe PH
based on RHC : mPAP ⩾30 mmHg, PVR ⩾4 WU
Resting spO2 ⩾90%

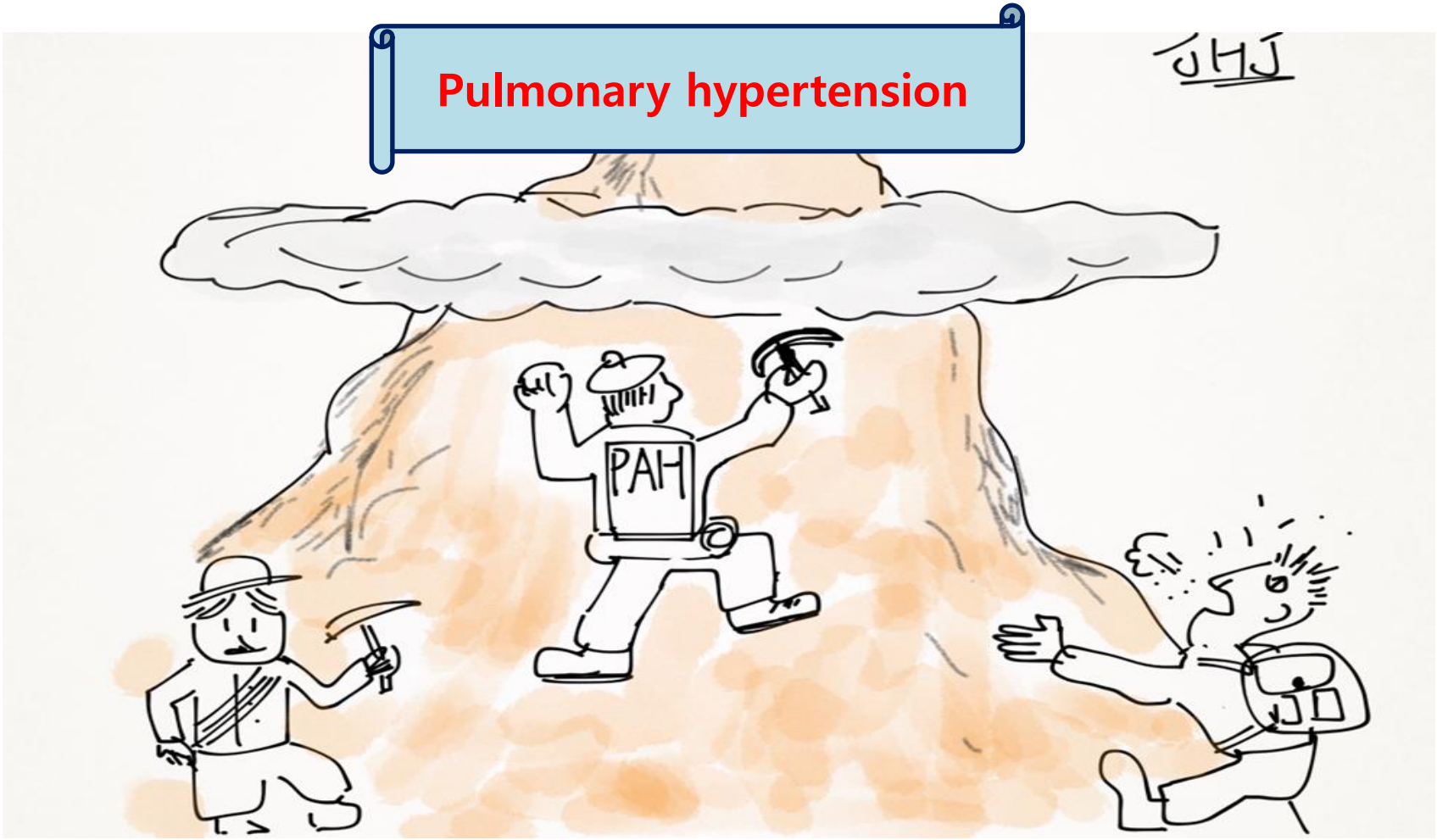
The study was terminated early
increased the risk of serious adverse events
suggestive evidence of an increased risk of mortality.
The change in 6MWD was numerically worse

Treatment guidance of PH associated chronic lung disease



Lancet Respir Med 2023;11: 820–35

감사합니다!



Extent of lung disease		
Normal or mildly impaired: • FEV_1 >60% pred (COPD) • FVC >70% pred (IPF) • Low diffusion capacity in relation to obstructive/restrictive changes	Pulmonary function testing	Moderate to very severely impaired: • FEV_1 <60% pred (COPD) • FVC <70% pred (IPF) • Diffusion capacity "corresponds" to obstructive/restrictive changes
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan[¶]	Characteristic airway and/or parenchymal abnormalities
Haemodynamic profile		
Moderate-to-severe PH	Right heart catheterisation Echocardiogram	Mild-to-moderate PH
Ancillary testing		
Present	Further PAH risk factors (*e.g.* HIV, connective tissue disease, *BMPR2* mutations, *etc.*)	Absent
Features of exhausted circulatory reserve: • Preserved breathing reserve • Reduced oxygen pulse • Low $CO/\dot{V}O_2$ slope • Mixed venous oxygen saturation at lower limit • No change or decrease in P_{aCO_2} during exercise	Cardiopulmonary exercise test[+] (P_{aCO_2} particularly relevant in COPD)	Features of exhausted ventilatory reserve: • Reduced breathing reserve • Normal oxygen pulse • Normal $CO/\dot{V}O_2$ slope • Mixed venous oxygen saturation above lower limit • Increase in P_{aCO_2} during exercise
Predominant haemodynamic profile		Predominant obstructive/restrictive profile

Natnan et al. Eur Respir J 2019; 53: 1801914

PH-Lung Disease (LD) or PAH with LD ?

Vascular phenotype ?