YONSEI UNIVERSITY

Practical issues in lung transplantation in PAH and PH-Lung

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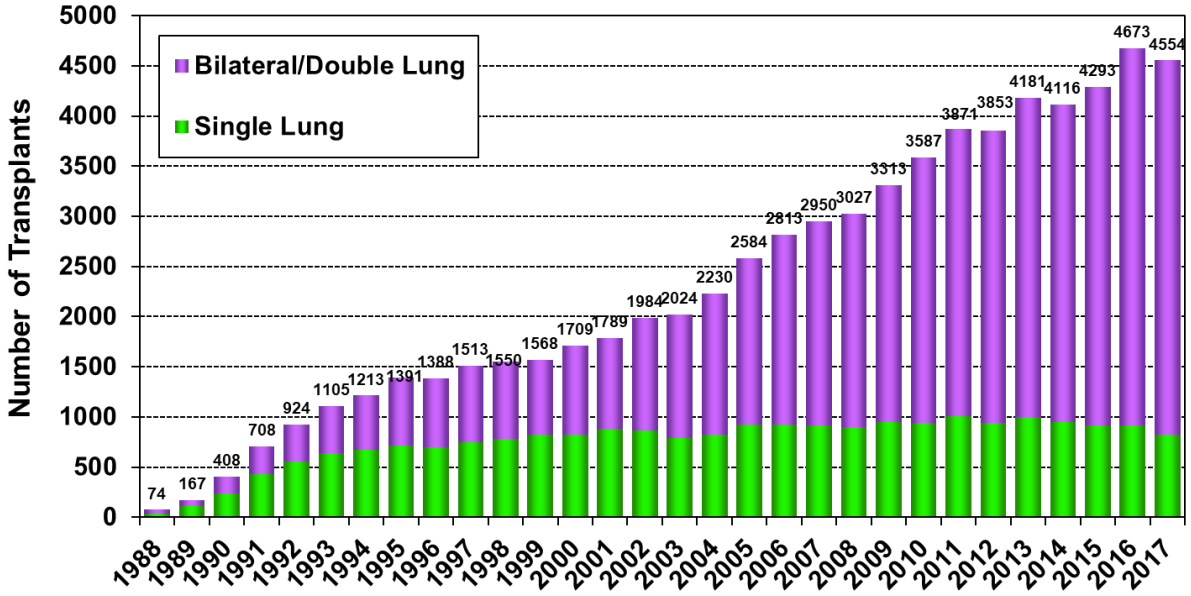
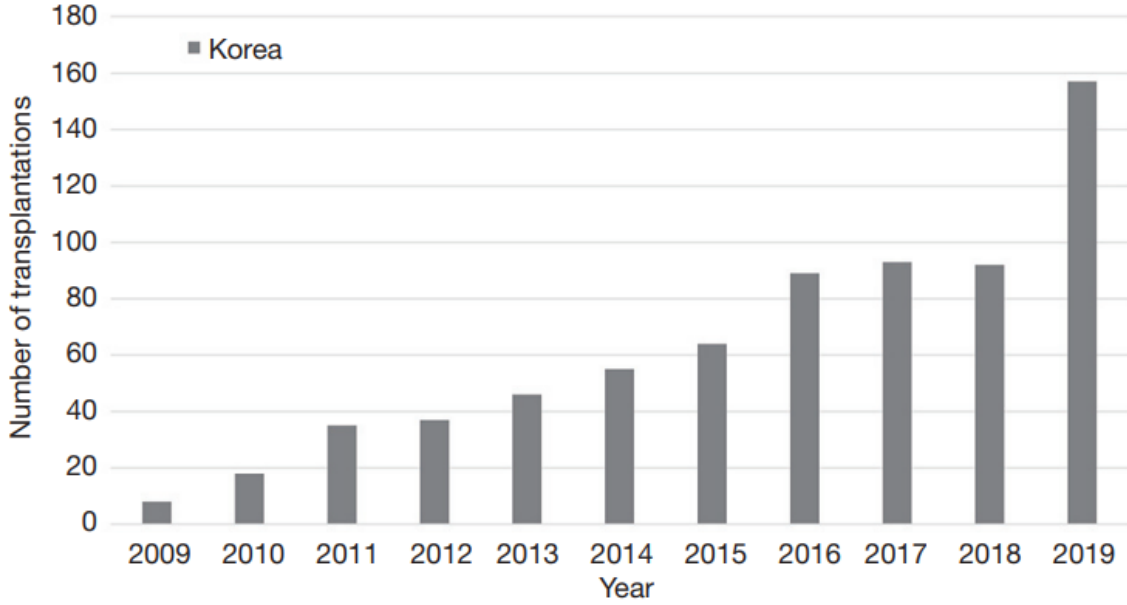
Severance

Introduction

Lung transplantation, How many?

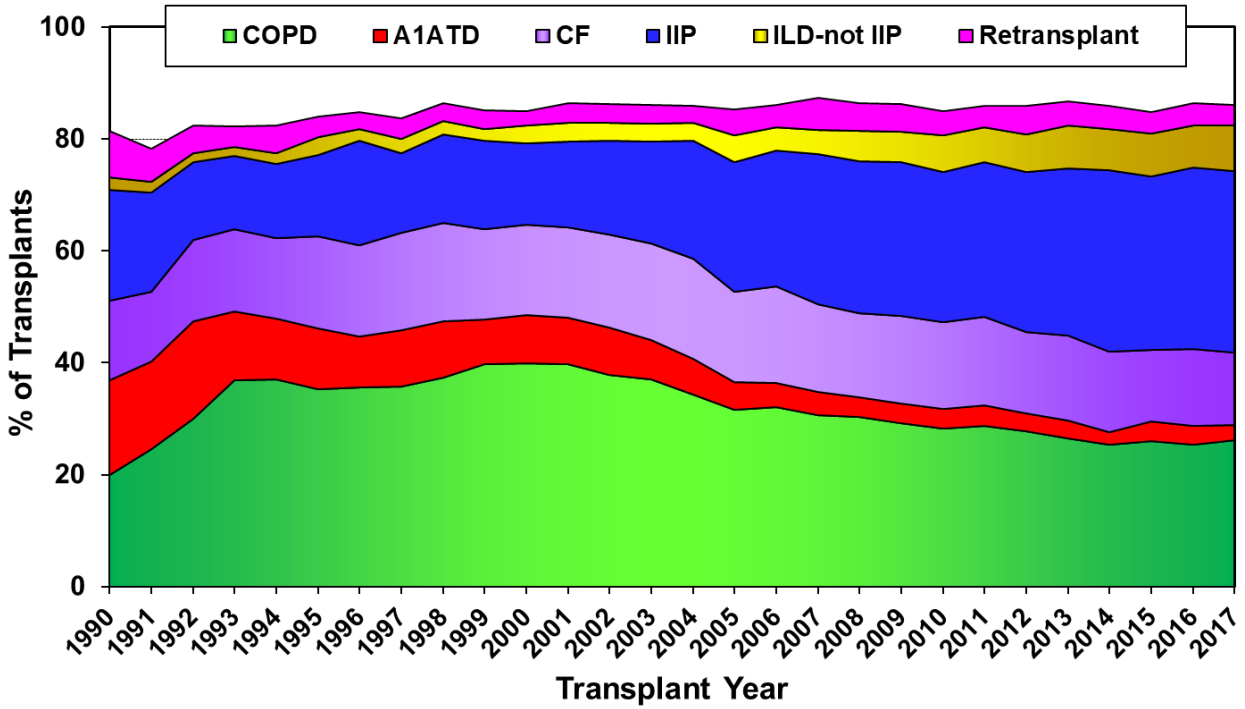


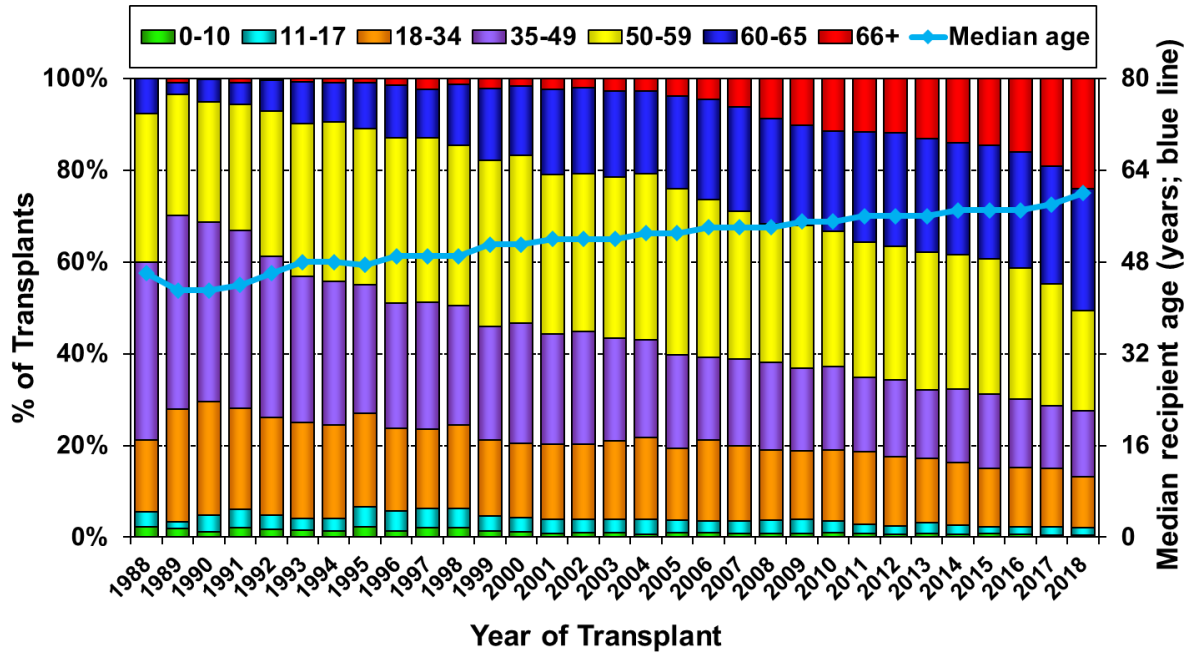


JHLT 2019; 38(10):1015-1066

Y. H. Jeong, D. K. Kim, S. Choi *Current Challenges in Thoracic Surgery* (2022)

Lung transplantation: Diagnosis?





JHLT. 2021 Oct; 40(10): 1023-1072

JHLT. 2019 Oct; 38(10): 1015-1066

Lung transplantation: Diagnosis?

IPF	268 (49.9)
Post-transplant BO	34 (6.3)
Bronchiectasis	28 (5.2)
Primary pulmonary hypertension	18 (3.4)
Lymphangioleiomyomatosis	14 (2.6)
Emphysema	5 (1.0)
Eisenmenger syndrome	3 (0.6)
Asbestosis	3 (0.6)
Cystic fibrosis	2 (0.4)
Others	189 (35.2)

Y. H. Jeong, D. K. Kim, S. Choi *Current Challenges in Thoracic Surgery* (2022

Lung transplantation, status

표 2-2-45. 뇌사 이식 (폐) - 응급도별

(단위: 건)

구분	2017	2018	2019	2020	2021
계	93	92	157	150	167
Status0	46	51	107	101	124
Status1	44	38	45	45	42
Status2		2	5	2	1
Status3	3	1		2	

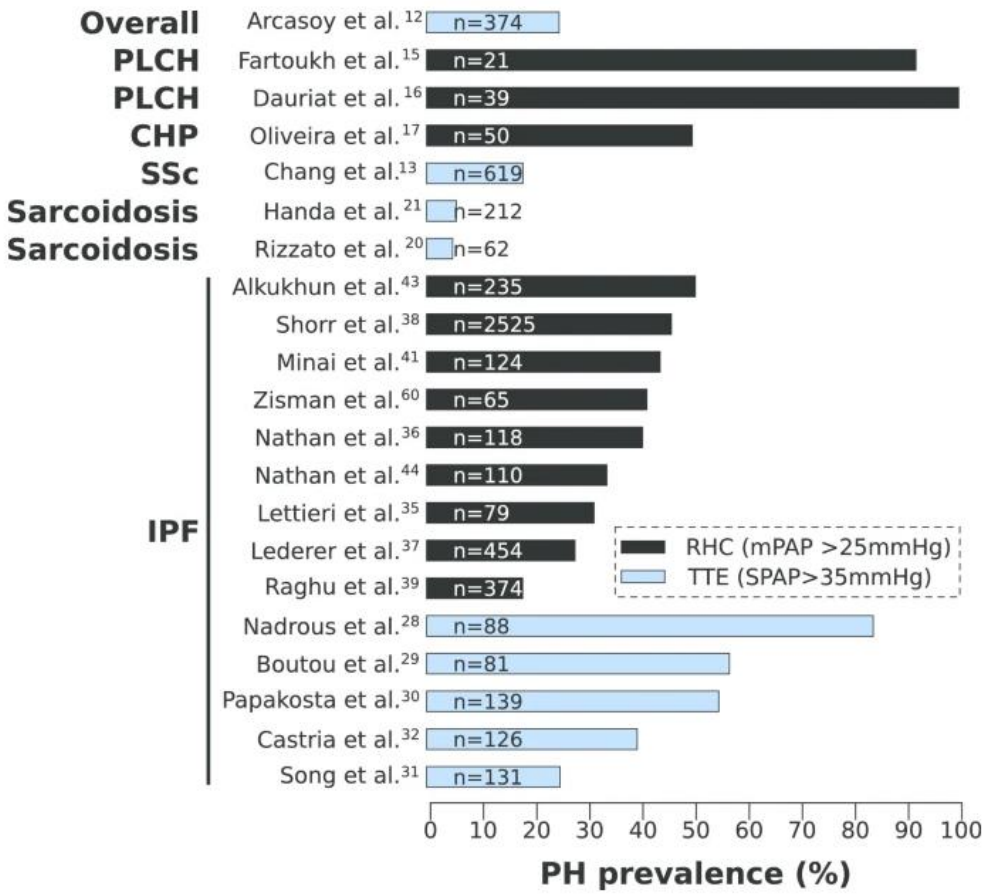
2020년도 장기 등 이식 및 인체조직기증 통계연보

폐이식 응급도

0	**인공호흡기 혹은 에크모를 달고 있는 환자**
1	산소 투여없이 동맥산소압 55mmHg 미만
	평균폐동맥압>65mmHg, 우심방압>15mmHg
	심장박출지수 < 2L/min/L^2
	동맥혈검사 이산화탄소압> 80mmHg
	입원 환자 중 고유량 비캐뉼라 사용(60%, 30L이상)
2	폐기능 검사에서 1초 강제 호기량(FEV1) <25%
	산소 없이 측정한 동맥혈 가스 검사상 PaO2 <60 mmHg
	평균 우심방 혈압이 10-15 mmHg 인 경우
	평균 폐동맥 압력이 55-65 mmHg 인 경우
	심박출지수 2-2.5L/min/m2 인 경우
	동맥혈 검사상 70 mmHg ≦PCO2 <80 mmHg인 경우
	폐확산능<30% 인 경우
3	단독 폐이식이 필요한 경우
	폐기종, 폐고혈압, 간질성폐질환인 경우
	폐기능 검사에서 노력 호기량이 30% 미만인 경우
	호흡부전증으로 3번 이상 입원한 경우

PH in Lung Transplantation

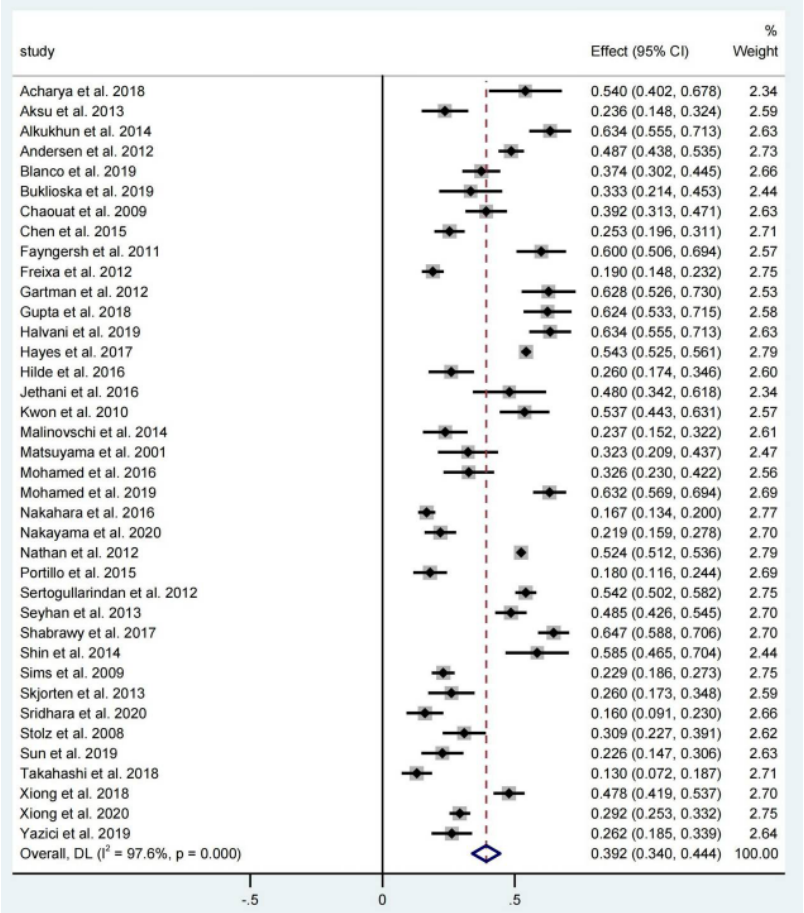
Prevalence of Pulmonary hypertension in PF patients



Ruffenach et al. Respir Res (2020) 21:303

Pooled Prevalence of COPD-Related PH

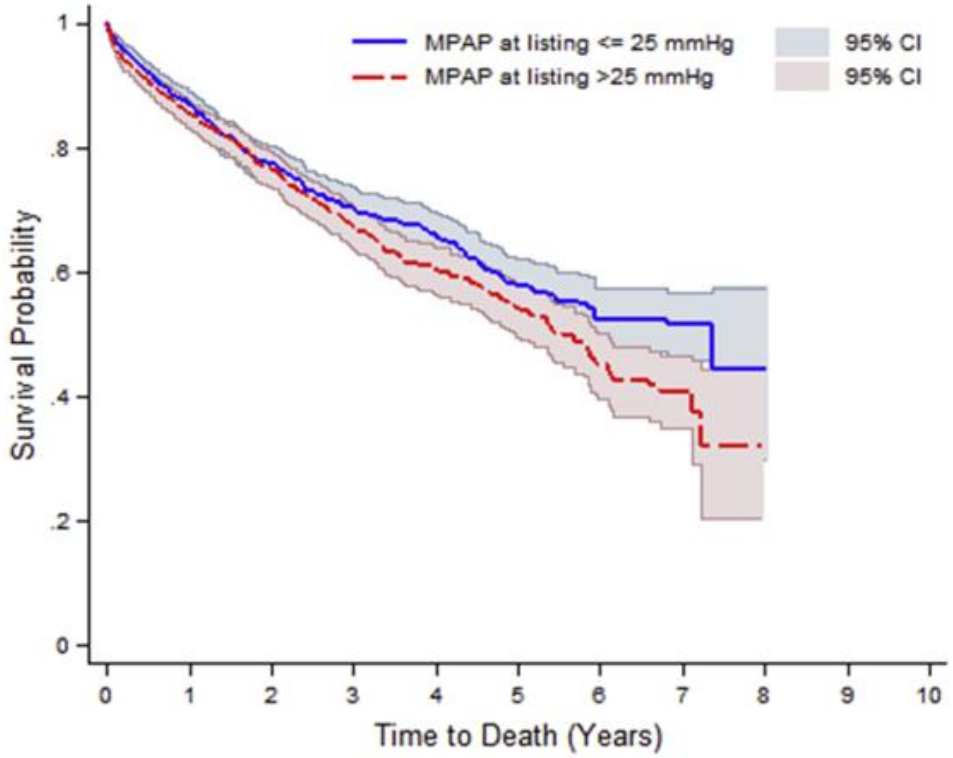
Overall COPD-related PH prevalence was approximately 39.2%



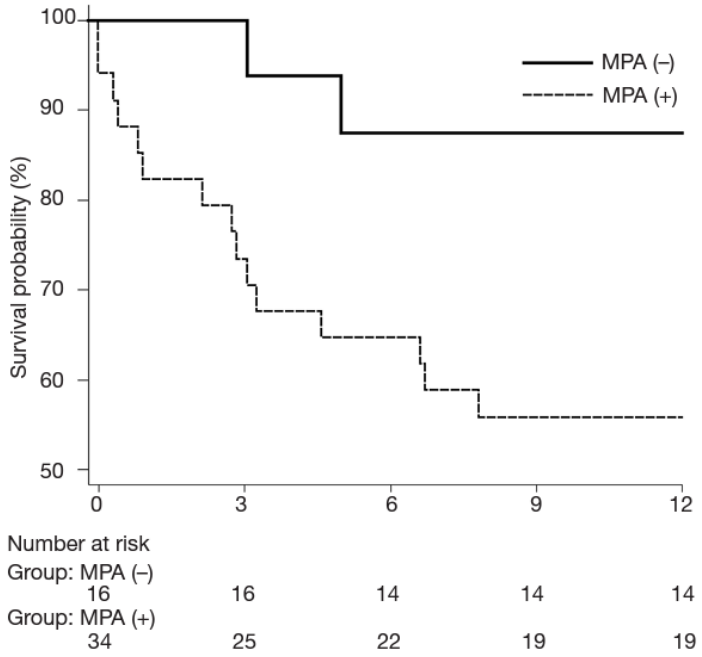
Int J Chron Obstruct Pulmon Dis. 2022; 17: 1365–1379.

PH, poor prognosis in lung Transplantation

3362 COPD LTx recipient



1 year mortality

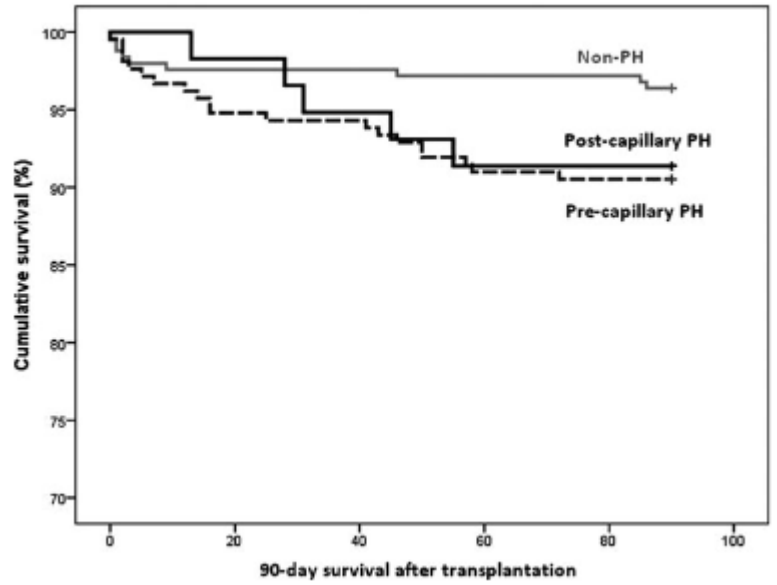


J Thorac Dis 2018;10(3):1578-1587

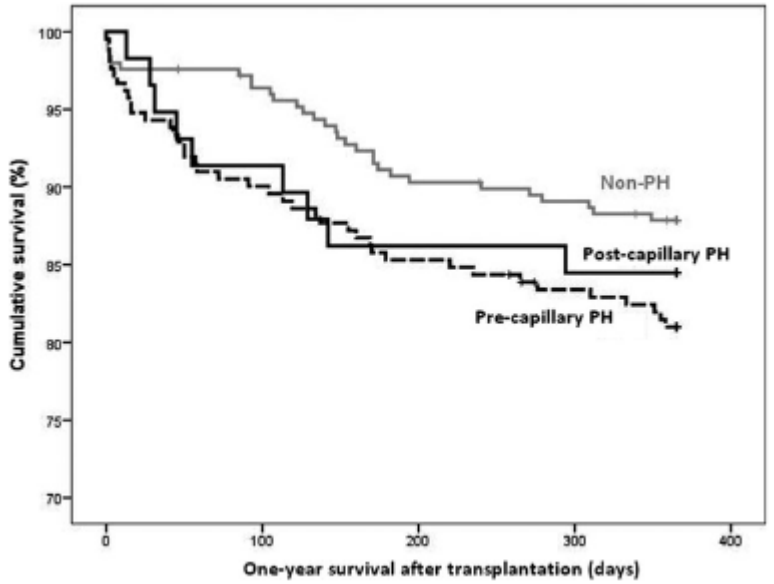
D. Hayes Jr. et al. Respiratory Medicine 128 (2017) 10

PH, poor prognosis in lung Transplantation

90 D mortality

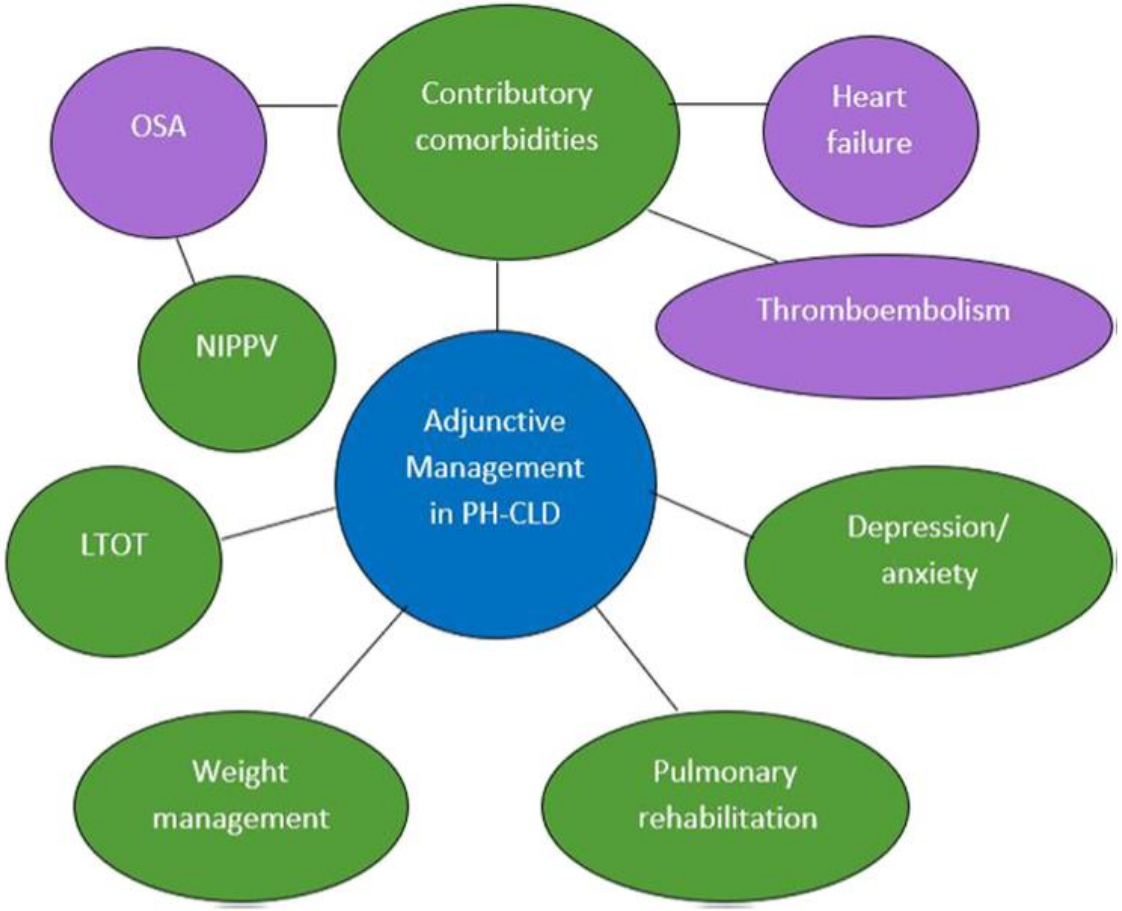


1 Y mortality



Clin Transplant 2016: 30: 357–364

Management of PH, pre-transplantation



Cardiol Clin 40 (2022) 77–88

Management of PH, in ICU

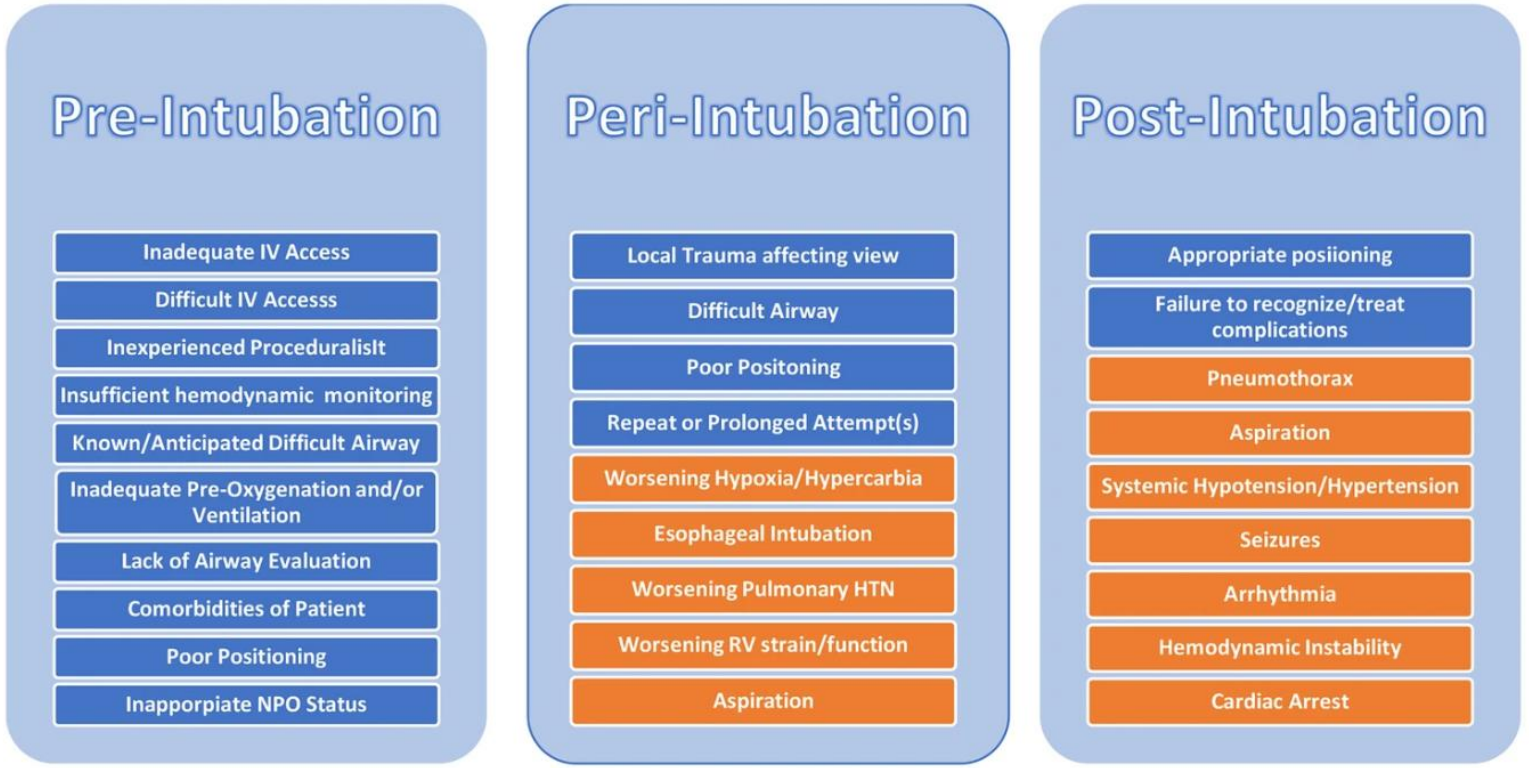
Management of PH, in ICU

- Intubation
- VV vs. VA
- Post-op Care

Management of PH, in ICU

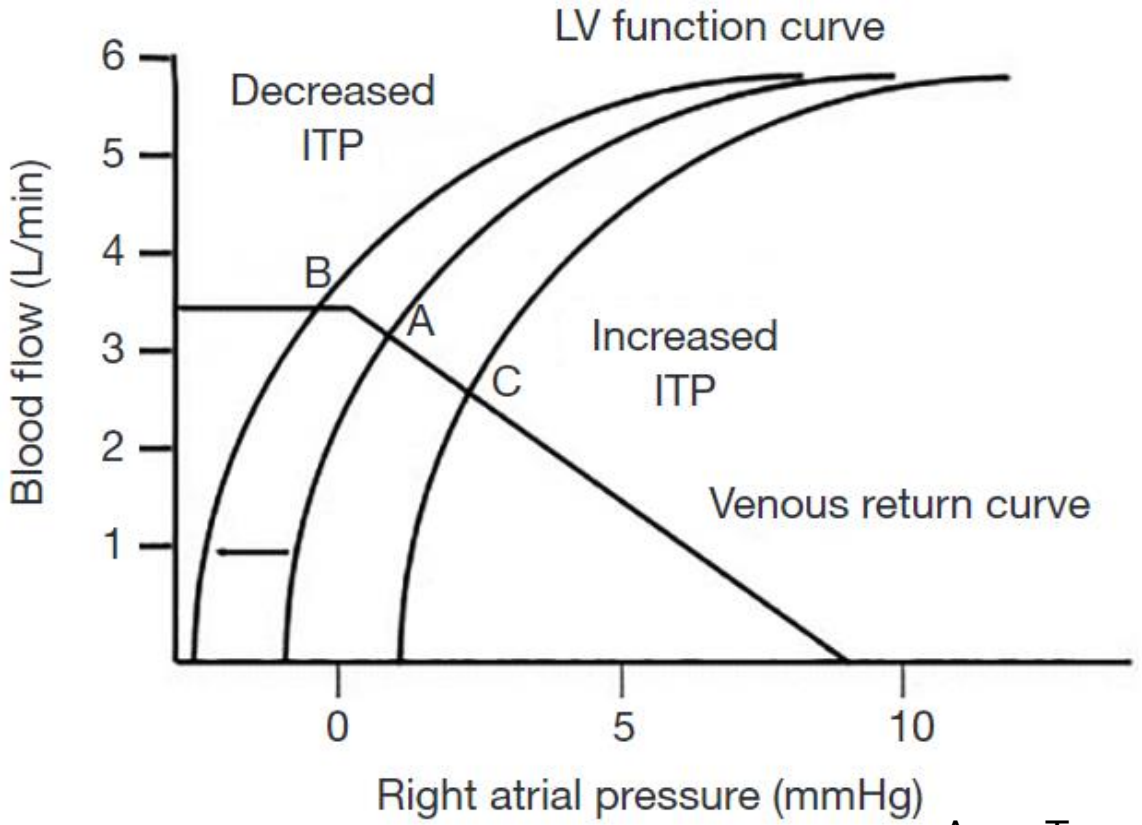
- **Intubation**
- VV vs. VA
- Post-op Care

Challenges and complications associated with endotracheal intubation



Heart Fail Rev. 2022 Sep;27(5):1807-1817.

Heart lung interaction



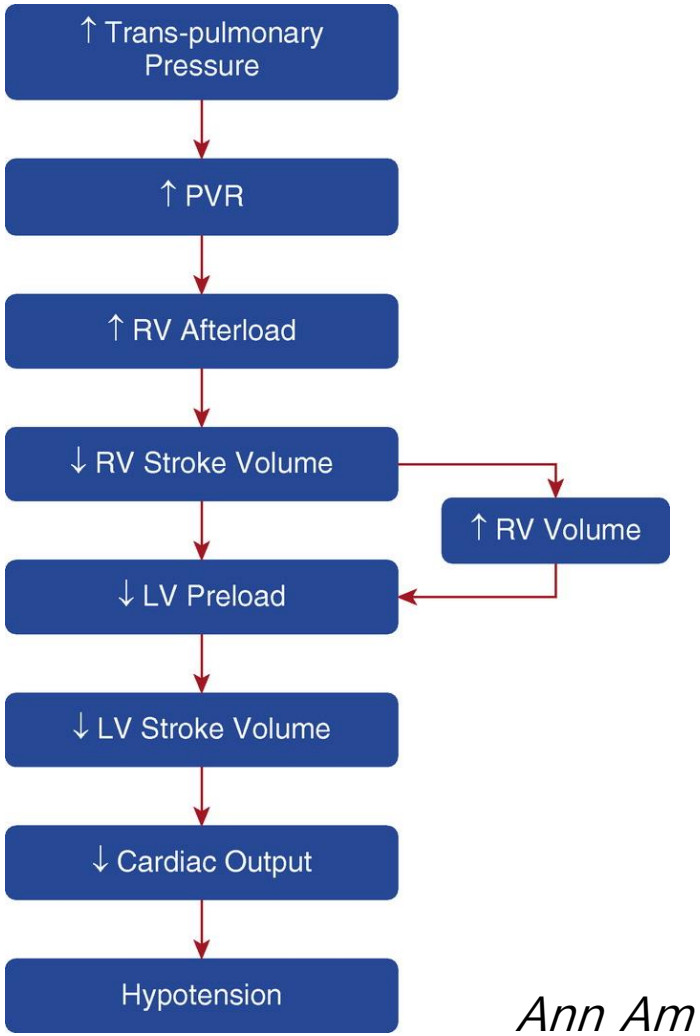
A: Apneic baseline

B: Spontaneous inspiration

C: Positive pressure inspiration

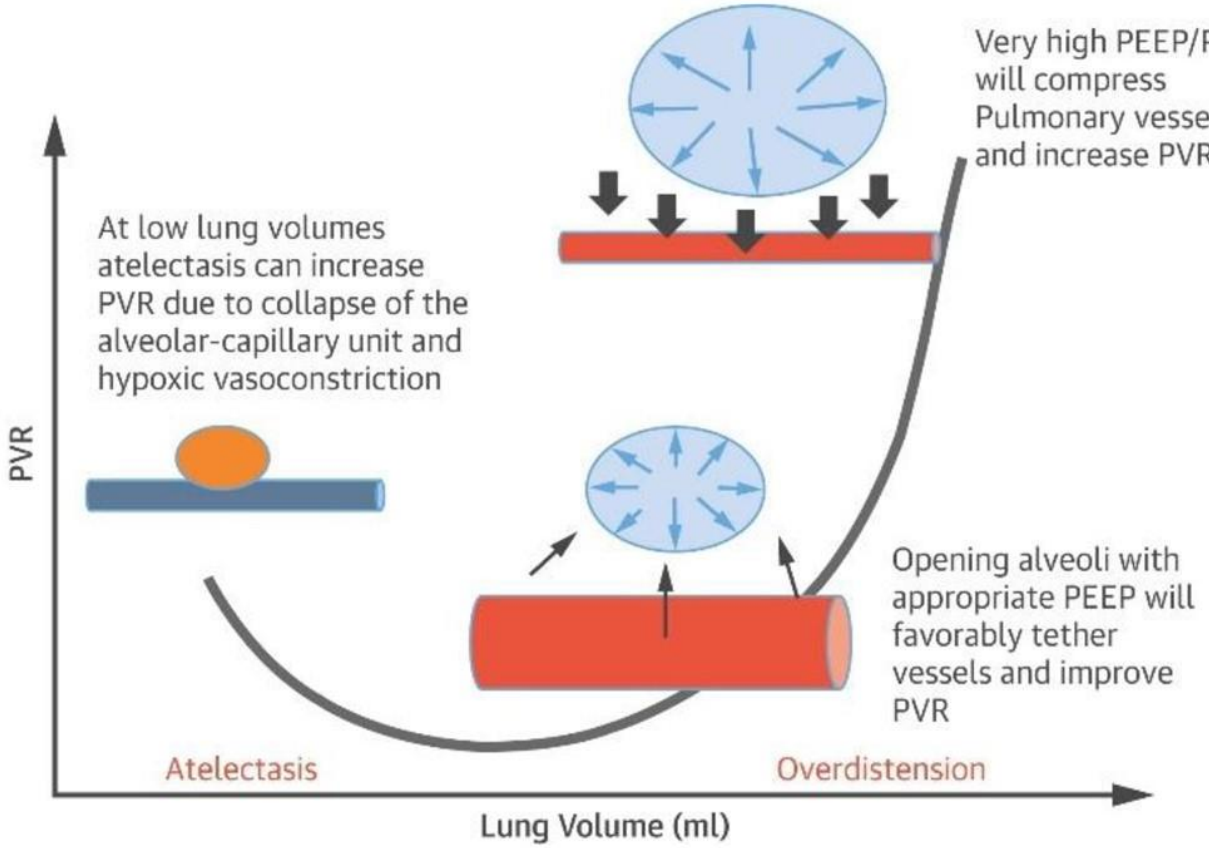
Ann Transl Med. 2018 Sep; 6(18): 349

Effects of mechanical ventilation on RV hemodynamics that lead to systemic hypotension



Ann Am Thorac Soc . 2018 Mar;15(3):383-389

PEEP or not



Eur Heart J Acute Cardiovasc Care. 2022 Jan 12;11(1):77-83.

Pharmacological options for rapid sequence intubation(RSI)

Drug	Mechanism	Advantages	Side effects	Dose	Duration of action
Sedatives					
Etomidate	Ultra-short acting nonbarbiturate general anesthetic	• Little effect on hypotension	• Suppresses adrenal cortisol production	0.2–0.6 mg/kg	3–5 min (dose-dependent)
Ketamine	NMDA and glutamate receptor antagonist	• Catecholamine • Bronchodilation	• May increase blood pressure • Raise ICP	1–2 mg/kg	15–30 min
Midazolam	GABA receptor	• No reported advantage	• Dose-dependent reduction in myocardial contractility • Hypotension	0.2–0.3 mg/kg	1–6 h
Propofol	GABA receptor modulator	• Bronchodilation	• Suppress myocardial contractility • Hypotension • Discolored urine (green tint) • Myoclonus	1.5 to 3 mg/kg	10 min
NMBAs					
Succinylcholine	Depolarizing agent acting on post-synaptic cholinergic receptors of the motor endplate	• Shortest acting	• Many contraindications • Malignant hyperthermia • Rhabdomyolysis • Hyperkalemia • Trismus/fasciculations • Bradycardia • Increased ICP	1.5 mg/kg	6–10 min
Rocuronium	Nondepolarizing agent acting on synaptic nicotinic receptors at the neuromuscular junction	• No effects on heart rate or blood pressure	• IgE-induced anaphylaxis	1–1.2 mg/kg	45 min
Vecuronium	Nondepolarizing agent blocking the nicotinic acetylcholine receptor at the postjunctional membrane of the neuromuscular junction	• No reported advantage	• Bronchospasm • Hypotension • Sinus tachycardia • Erythema • Urticaria • Flushing • Pruritus • Hypersensitivity • Anaphylaxis	0.1–0.2 mg/kg	45–60 min

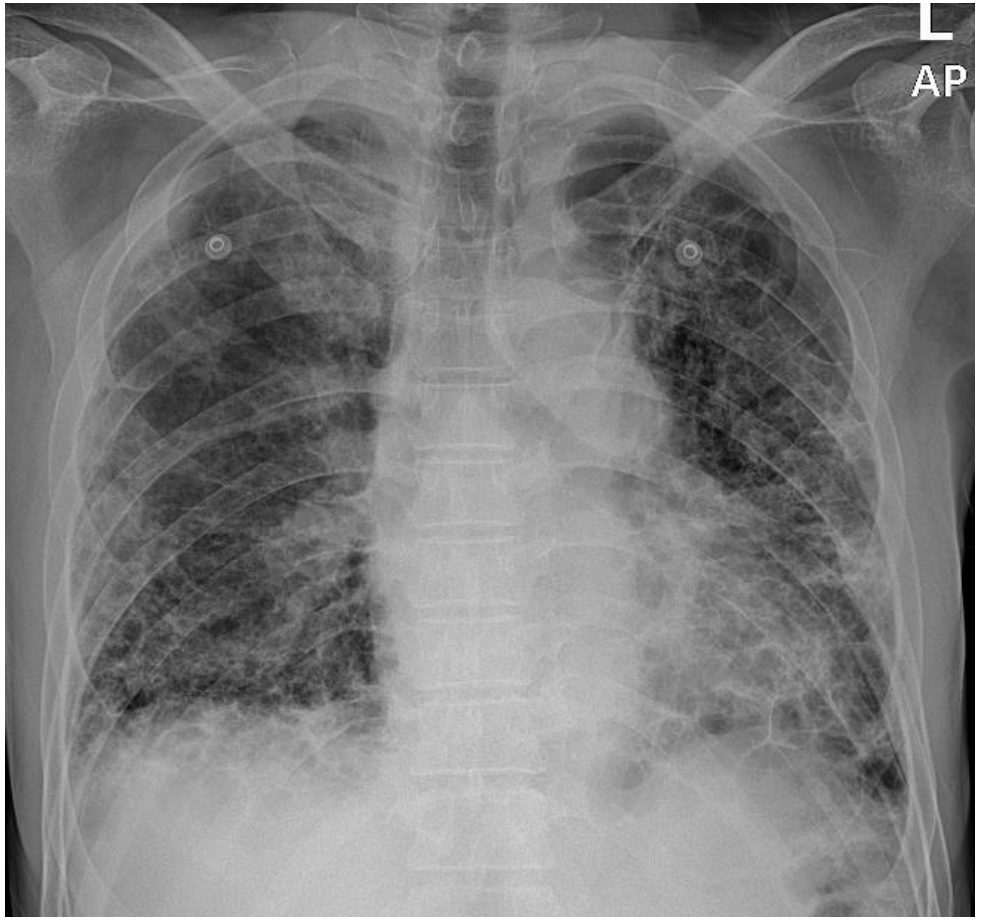
Heart Fail Rev. 2022 Sep;27(5):1807-1817.

RSI medication in PH

Sedatives	
Etomidate	**Less hemodynamic effects compared to propofol in rodent models**
Ketamine	**Minimize hypotension during RSI and improve coronary artery and end organ perfusion**
Propofol	Recommended to avoid propofol due to vasodilator and cardiac depressive properties
Midazolam	In combination ketamine and rocuronium, have been utilized successfully with vasopressors for intubation in stable preoperative PH

Heart Fail Rev. 2022 Sep;27(5):1807-1817.

Case A: PH-ILD



- M/52
- Post-ARDS fibrosis
  - r/o unclassifiable ILD
- Resting hypoxia
  - O2 3L/min
- PFT
  - FVC 1.36(32%) FEV1 1.21(38%) ratio 89 DLco 6.3(34%)

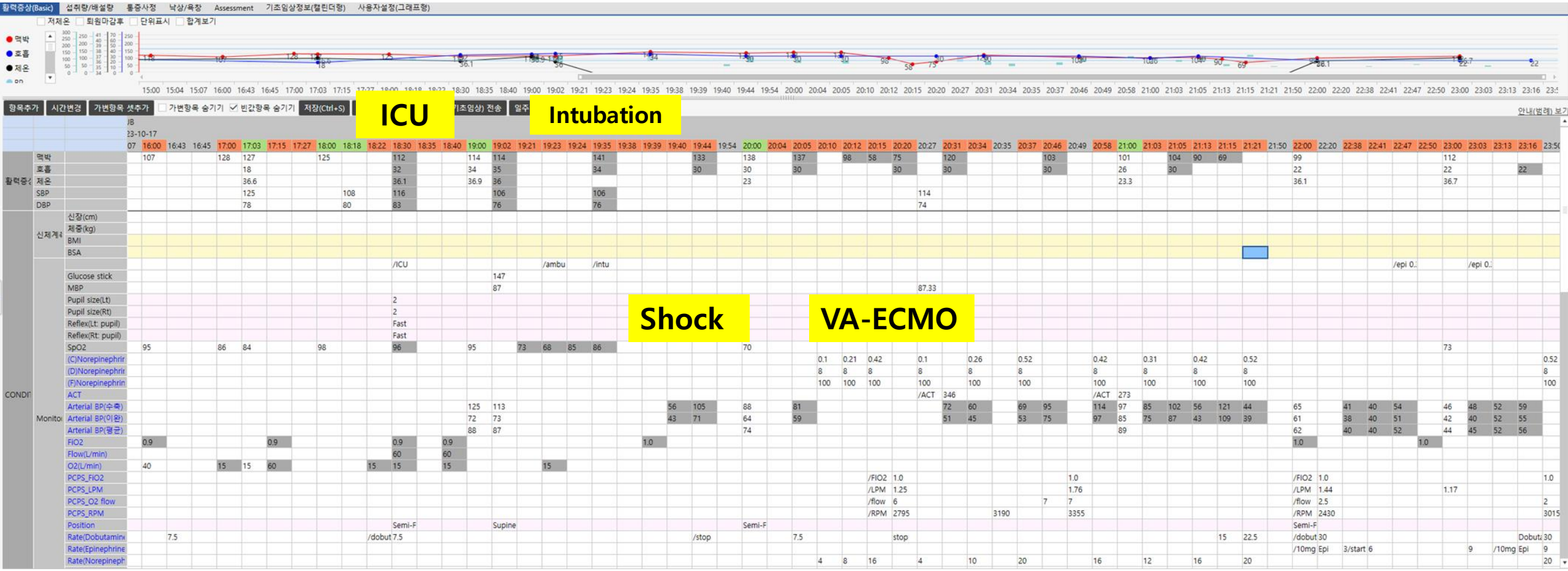
Case A: PH-ILD

Baseline TTE (2023.10.10)

1. Severe pulmonary hypertension (RVSP : 92mmHg) with poor collapsible IVC (18mm)
2. Enlarged RA and RV with reduced RV systolic function (RV TDI S' : 11cm/s, FAC : 27%)
3. Severe TR(GIII-IV/IV) with dilated TV annulus (40mm)
4. D-shaped LV (LVEDD/ESD : 39/25mm) with normal LV systolic function (EF : 68%)
5. Dilated pulmonary trunk (MPA: 36mm, LPA: 20mm, RPA: 20mm)
6. Slightly dilated sinus of Valsalva (38mm) and ascending aorta (37mm)
7. Minimal pericardial effusion

<Pulmonary HTN baseline>
1. TAPSE/sPAP ratio : 0.18
2. RV TDI S': 11cm/s
3. RV strain: - 14.0%
4. RA area: 20.9cm2
5. Geometry (LV eccentricity index) : 1.34

Case A : Aggravation hypoxia



CASE A: f/u TTE

2023.10.18, ECMO D1

>> bed side ehco 시행하였습니다.

EF 20전후로 LV function 저하되었으며
기존의 RV failure 굉장히 심한 상태입니다.

다만 LV function은 VA echmo fighting 에 의한 저하소견인지 shock, desaturation status 지속으로 인한 stress로 발생한 건지 알 수 없는 상태입니다.
official echo 판독 필요합니다.

CASE A: f/u TTE

Post ECMO TTE(2023.10.19) ECMO D2

ICU portable echo: Lung T 대기자, IPF, ECMO apply (2023.10.17-)
* compared with previous echo (2023.10.10) *

1. Severe pulmonary HTN (RVSP: 80mmHg)
2. Enlarged RA and RV with reduced RV systolic function (FAC: 28%)
3. Moderate TR (G III-IV ->II-III/IV, VCW: 0.58cm) with dilated TV annulus (37mm)
4. Small sized, D-shaped LV (LVEDD/ESD: 37/22mm) with normal LV systolic function (EF: 74%)
5. Dilated pulmonary trunk (MPA: 35mm, RPA: 22mm, LPA: 19mm)
6. Dilated sinus of Valsalva (41mm)

CASE A: Progress

TTE, 2wks after ECMO

Impression

*ICU portable echo: Lung T 대기자, IPF, ECMO apply (2023.10.17-)
*Cmpared with previous echo (2023.10.19)

1. Severe pulmonary HTN (RVSP: 80->130mmHg)
2. Enlarged RA and RV with reduced RV systolic function (FAC: 29%)
3. Moderate TR (GII-III/IV) with dilated TV annulus (40mm)
4. Small sized, D-shaped LV (LVEDD/ESD: 30/23mm) with normal LV systolic function (EF: 69%)
5. Dilated pulmonary trunk (MPA: 35mm, RPA: 22mm, LPA: 23mm)
6. Dilated sinus of Valsalva (41mm) and ascending aorta (36mm)

CASE A: Progress

TTE, post lung Transplantation

ICU portable TTE : S/P Lung transplantation double (2023.11.02)
- Compared with previous echo (23.11.01)
**Very poor echo window d/t dressing site로 echo parameter에 limitation있습니다
**Only subcostal window was available

1. Decreased to normal range of RVSP (111->26mmHg) with poorly collapsible IVC (17mm)
2. Enlarged RA and RV with normal RV systolic function (FAC : 26->37%)
3. Trivial TR (G II-III->trivial)
4. Normal sized LA and LV with normal LV systolic function (LVEDD/ESD : 41/24mm, LVEDD/BSA: 25mm/m2, EF : 75%)

Management of PH, in ICU

- **Intubation : Be prepared for RV failure**
  - RSI medication : Etomidate or ketamine >> propofol
  - Consider VA-ECMO stand-by
  - Keep previous medication including PH-medication

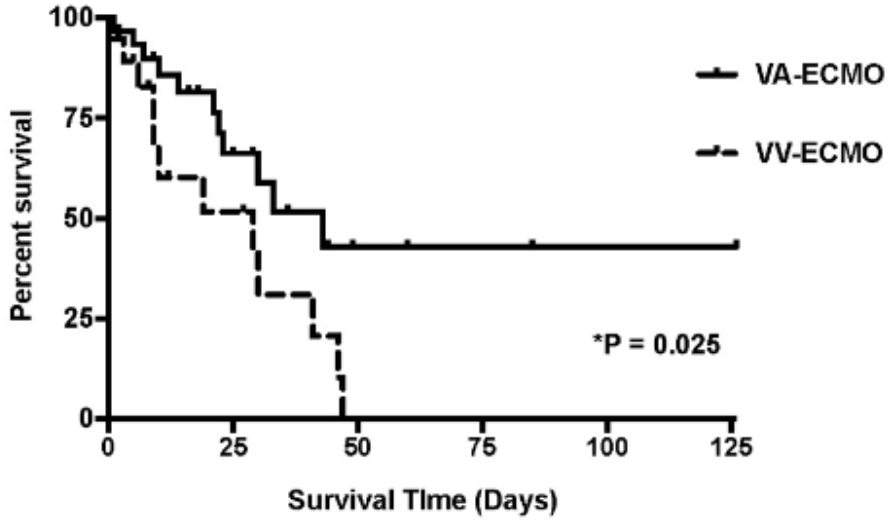
Management of PH, in ICU

- Intubation
- **VV vs. VA**
- Post-op Care

Management of PH in ICU : ECMO

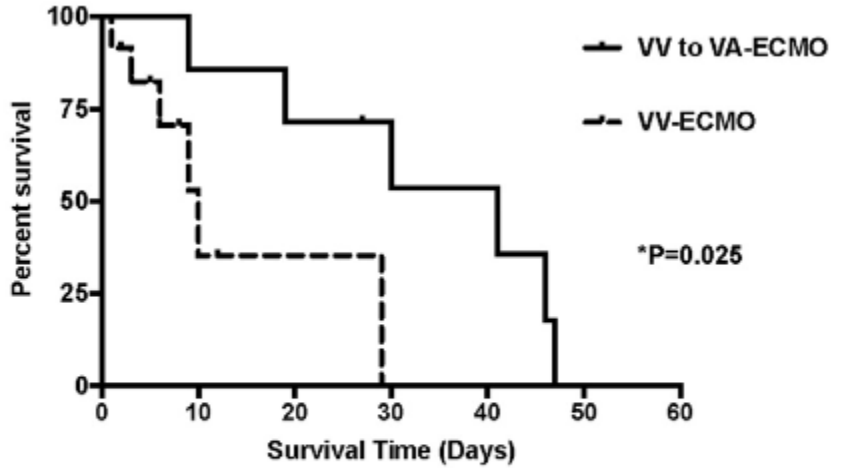
End-stage ILD with PH

Variables	Total	VV	VA	*p* Value[a]	VV ECMO		*p* Value[a]	VA ECMO		*p* Value[a]
					Transplanted	Deceased		Transplanted	Deceased	
Number of patients	50	19	31		7	12		20	11	



No. at Risk						
VV-ECMO	19	6	0	0	0	0
VA ECMO	31	11	3	2	1	1

*Comparisons by Log Rank Test



No. at Risk						
VV to VA-ECMO:	7	6	5	4	3	0
VV-ECMO:	12	3	1	0	0	0

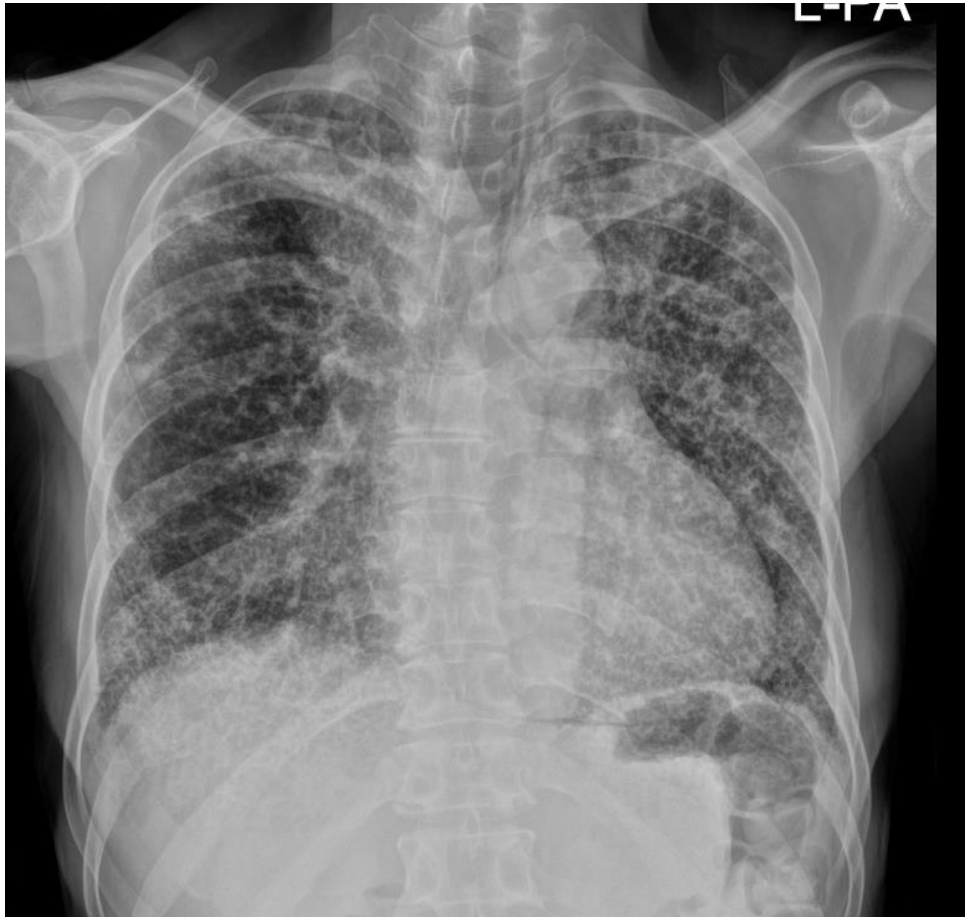
*Comparison by Log Rank Test.

Ann Thorac Surg 2018;106:1812–9

VV vs. VA

- **Fitfalls of VA ECMO**
  - Bleeding
  - Thrombo-embolic risk
  - Harlequin syndrome
  - LV distension
  - Infections
  - Limb ischemia

Case B: PH-ILD



- M/63
- IPF
- Resting hypoxia
  - O2 L/min
- PFT
  - FVC 1.60(39%) FEV1 1.50(52%) ratio 94 DLco 4.1(25%)

CASE B: Baseline TTE

Pre lung transplantation evaluation : IPF

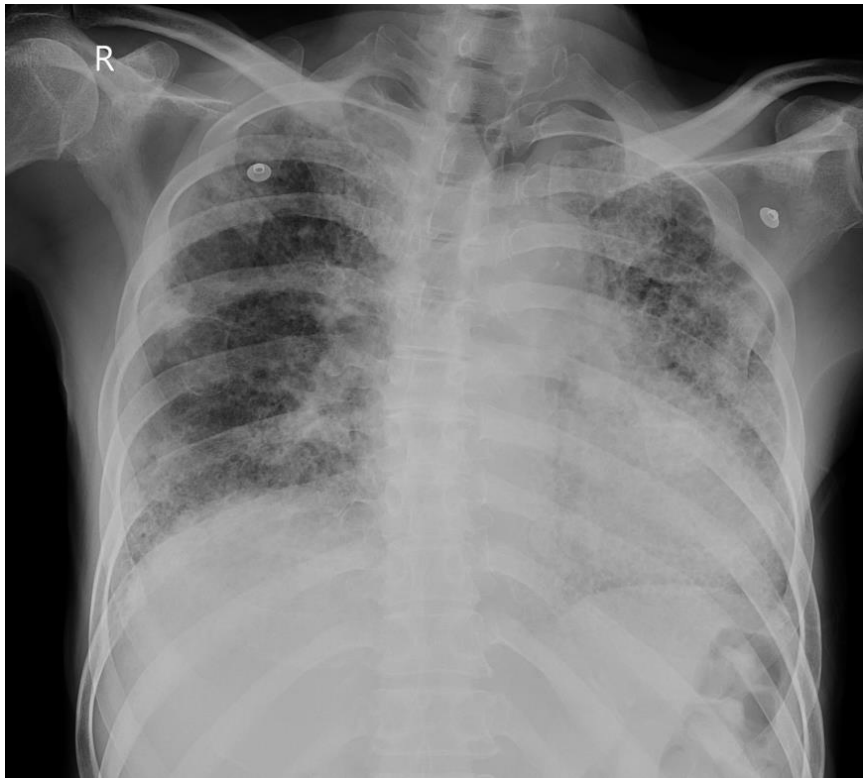
1. Enlarged RA and RV with hypokinesia of RV free wall (FAC: 30%)
2. Moderate pulmonary hypertension (RVSP: 61mmHg) with well collapsible IVC
3. Small LV(LVEDD/ESD: 41/30mm) with normal global LV systolic function (EF: 56%)
4. Relaxation abnormality of LV filling pattern (E/E': 8)
5. Concentric remodeling of LV

<폐고 복잡>

1. TR V max: 3.75m/sec 2. RAP: 5mmHg 3. TR area: 0.25cm2 4. TV TDI S': 12cm/s
5. TAPSE: 1.64cm 6. RVOT acceleration time: 231.8ms
7. RVOT VTI: 7.7cm
8. LVOT VTI: 10.2cm 9. Tei-index: 0.69

CASE B: Aggravation hypoxia, ICU

2019.4.26



2019.4.26, MV+VV-ECMO

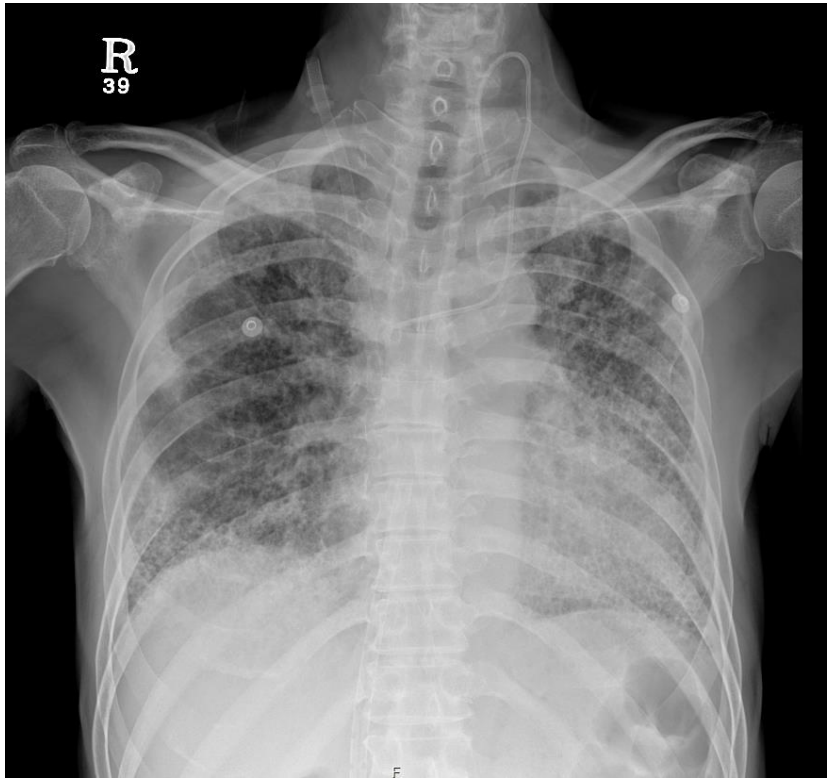
CASE B: f/u TTE(19.4.27)

Portable TTE for follow up : IPF (lung transplantation 대기상태), VV ECMP insertion status
Compared with previous echo (2019.01.08)

1. Mild global hypokinesia of LV
2. Enlarged RA and RV with akinesia of RV freewall and reduced global RV systolic function (FAC: 30 -> 27%)
3. Mild pulmonary HTN with decreased RVSP (61 -> 42mmHg)
4. No significant interval change of LV (LVEDD/ESD: 41/30 -> 43/32m)
   with preserved global LV systolic function (EF: 56 -> 54%)
5. Relaxation abnormality of LV filling pattern (E/e': 8 -> 9)

CASE B: Progress

- 2019.4.28 VV-ECMO+HFNC



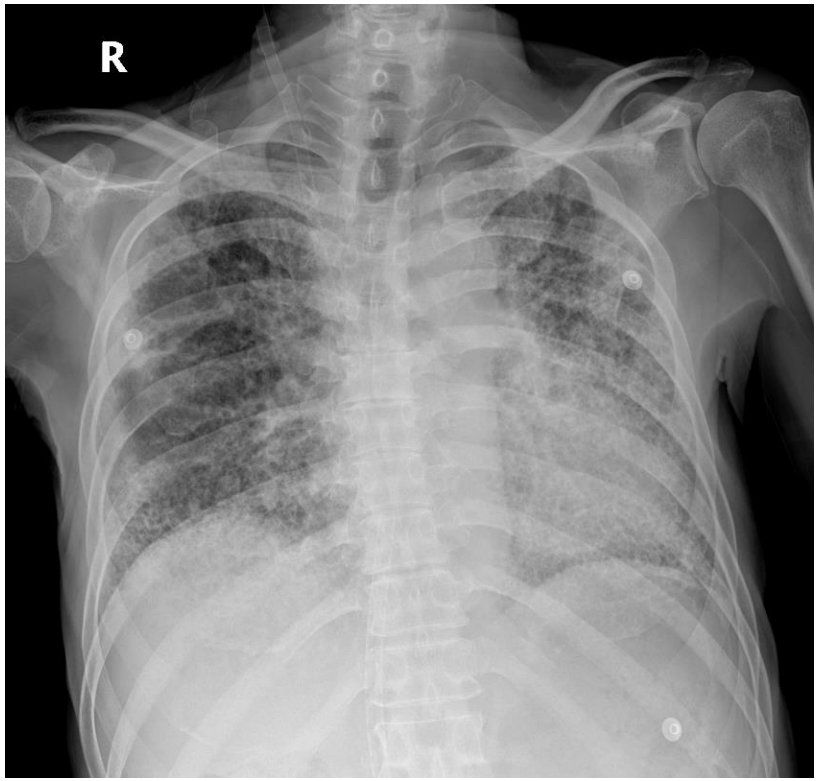
CASE B: Progress

19.5.13 TTE (ECMO D-17)

ICU limited portable echo F/U for RV function, EF, RWMA: IPF (lung transplantation 대기), VV ECMP inserted status
Compared with previous echo (2019.05.08)

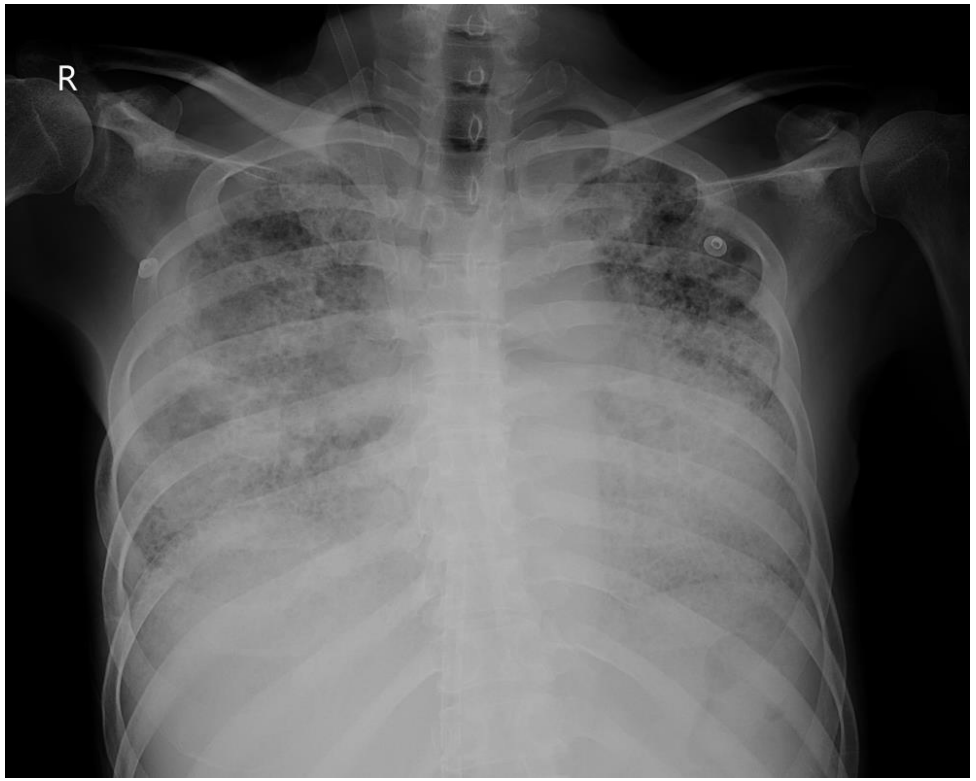
1. Still borderline enlarged RV with still reduced RV systolic function (FAC: 32 -> 34%).
   - but preserved longitudinal motion of RV base (TV TDI S': 14-> 13cm/s).
2. Moderate pulmonary HTN (RVSP: 59mmHg).
3. Normal sized LV, LA and normal global LV systolic function (EF: 65%), without interval change.
4. Relaxation abnormality of LV filling pattern (E/e': 10).

19.5.13 CXR



CASE B: Progress

19.5.19 VV-ECMO+HFNC, D-23



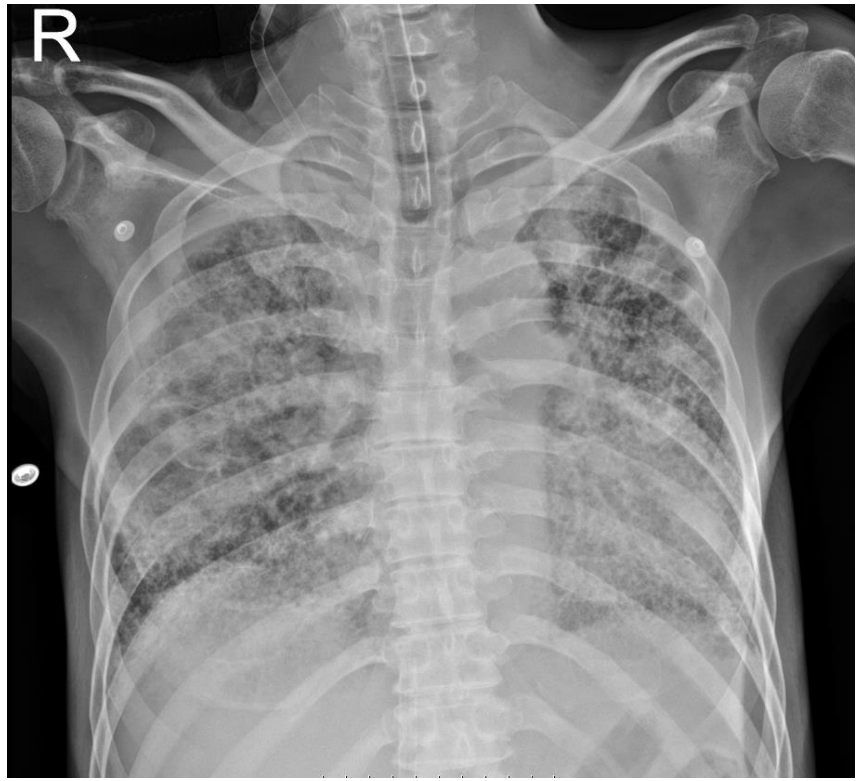
f/u TTE 19.5.20

ICU limited portable echo F/U for EF, RV function,RVSP: IPF (lung transplantation 대기), VV ECMP inserted status
Compared with previous echo (2019.05.13)

1. Still borderline enlarged RV and RA with still reduced RV systolic function (FAC: 34-> 34%)
   - but preserved longitudinal motion of RV base (TV TDI S': 13-> 13cm/s)
2. Moderate pulmonary HTN (RVSP: 59-> 54mmHg) with D-shaped LV
3. Normal sized LV, LA and normal global LV systolic function (EF: 72%), without interval change

CASE B: Progress

- 19.5.21, ECMO D-25, MV+VAV d/t Cardiac arrest



CASE B: Progress

TTE 19.5.22

ICU limited portable echo for EF, RV function,RVSP evaluation: IPF (LT 대기), post ROSC
Compared with previous echo (2019.5.20)

1. Severe global hypokinesia of LV and RV.
2. Normal sized LV with reduced global LV systolic function (EF: 72->28% by biplane).
3. Enlarged RA and RV with reduced RV systolic function (S': 5.8cm/s).
4. Mild TR(GI/IV) with moderate pulmonary hypertension (RVSP: 54mmHg).

TTE 19.5.24

ICU portable echo: Lung T 대기, IPF s/p VV ECMO insertion, post ROSC
- Compared with previous echo (2019.05.22), (2019.04.27)

1. Moderate pulmonary HTN (RVSP: 54-> 50mmHg) with poorly collasible IVC
2. No significant change in enlarged RA and RV with RVH (5.8mm)
3. Akinesia of RV freewall with reduced RV systolic function (FAC: 27-> 24%),
   but relatively preserved longitudinal motion (TV TDI S': 11cm/s)
4. Improved to mild global hypokinesia of LV
5. Decreased normal sized LV (EDD/ESD: 52/41-> 40/30mm, ESD/BSA: 25mm/m2)
   with improved to preserved LV systolic function (EF: 28-> 53%)
6. Relaxation abnormality of LV filling pattern (E/e': 9-> 11)
7. Small amount of pericardial effusion at RA (0.57cm), RV (0.54cm)
8. Slightly dilated sinus of Valsalva (36mm)
9. Dilated MPA (36mm), RPA (18mm), and LPA (19mm)

CASE B: Progress

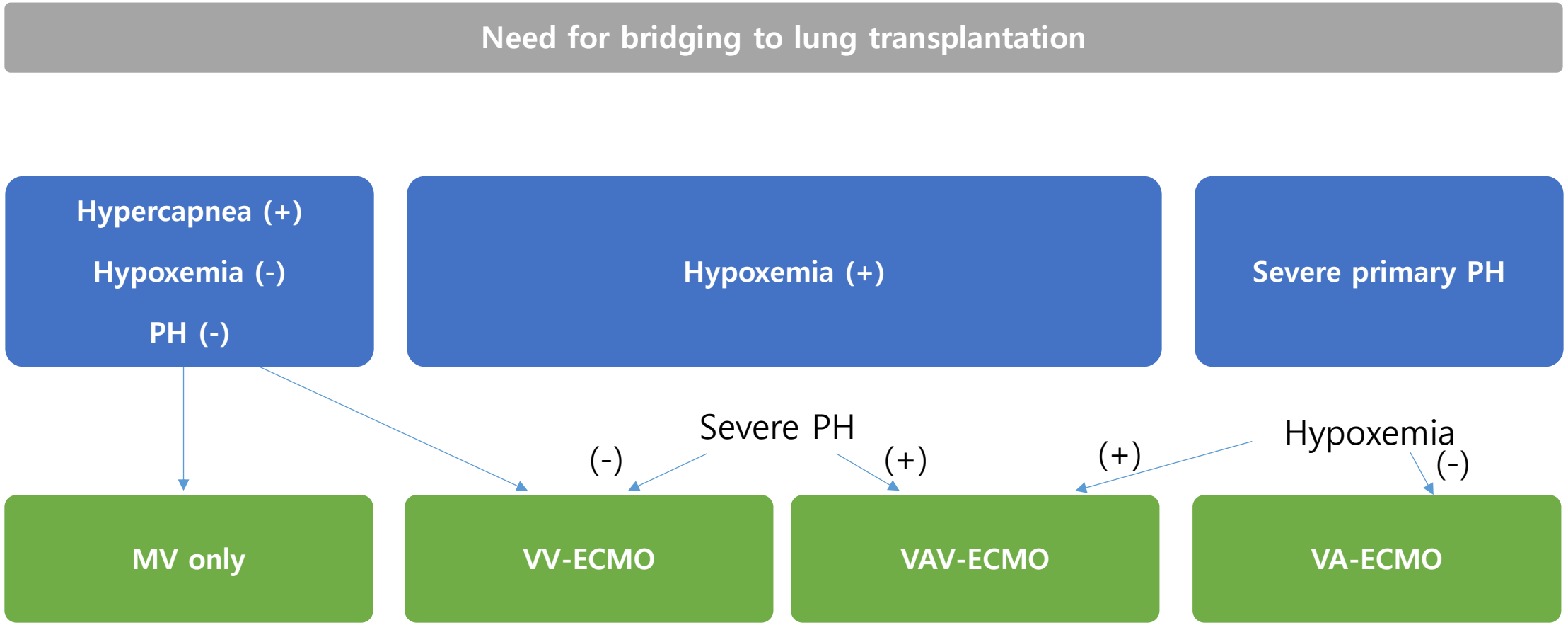
- **Lung transplantation, double 2019.5.25**

ICU portable echo: S/P Lung transplatation (2019.05.25)
* Compared with previous echo (2019.05.24)
** Only available of subcoastal window 로 인하여 정확한 평가가 어렵습니다. **

1. Mild pulmonary HTN (RVSP: 50->39mmHg) with poorly collapsible IVC (15mm)
2. Still enlarged RA, RV with improved RV function (FAC: 24->33%)
3. Preserved LV systolic function (EF: 53->53%)

VV vs. VA

폐이식 매뉴얼, 세브란스병원
Ann Thorac Surg. 2017 Aug;104(2):412-419.



Issues in ICU: General management

TABLE 2. RECOMMENDED MONITORING OF THE CRITICALLY ILL PATIENT WITH SEVERE PULMONARY ARTERIAL HYPERTENSION

Parameter	Modality	Treatment Goal
Renal function	Urinary catheter	Maintain kidney function and diuresis. In general a net negative fluid balance is required
	Serum creatinine	
Liver function	AST, ALT, bilirubin	Reduce hepatic congestion
		Maintain hepatic perfusion
Cardiac function	Central venous line (central venous pressure, Scv_{O_2})	Improvement in cardiac function demonstrated by an increase in cardiac output with improvement (reduction) in right atrial pressures
	Pulmonary arterial catheter (RA pressure, cardiac index, PAPm, PVR, $S\bar{v}_{O_2}$)	$Scv_{O_2} > 70\%$
		$S\bar{v}_{O_2} > 65\%$
	Echocardiography	Improve LV filling
Tissue perfusion/oxygenation	Lactate	<2.0 mmol/L
Neurohormonal markers	Brain natriuretic peptides (BNP or NT-proBNP)	Reduction in BNP levels
Myocardial perfusion	Systemic blood pressure (noninvasive or invasive)	Ensure adequate systemic diastolic pressure (>60 mm Hg)
	ECG	Avoid/treat tachycardia/tachyarrhythmia
	Troponin	Optimize myocardial perfusion (negative troponin)

Am J Respir Crit Care Med. 2011 Nov 15;184(10):1114-24

Issues in ICU: PH monitoring

- **Physical examination**
  - Elevated jugular venous pressure with a large v wave, a loud P2 component of the second heart sound, and palpable RV heave
  - Hepatomegaly, ascites, and peripheral oedema
  - Low pulse pressure &cool extremities
- **Echocardiography**
- **Laboratory exam**
  - BNP, Troponin, liver enzyme
- **Pulmonary artery catheter (PAC)**

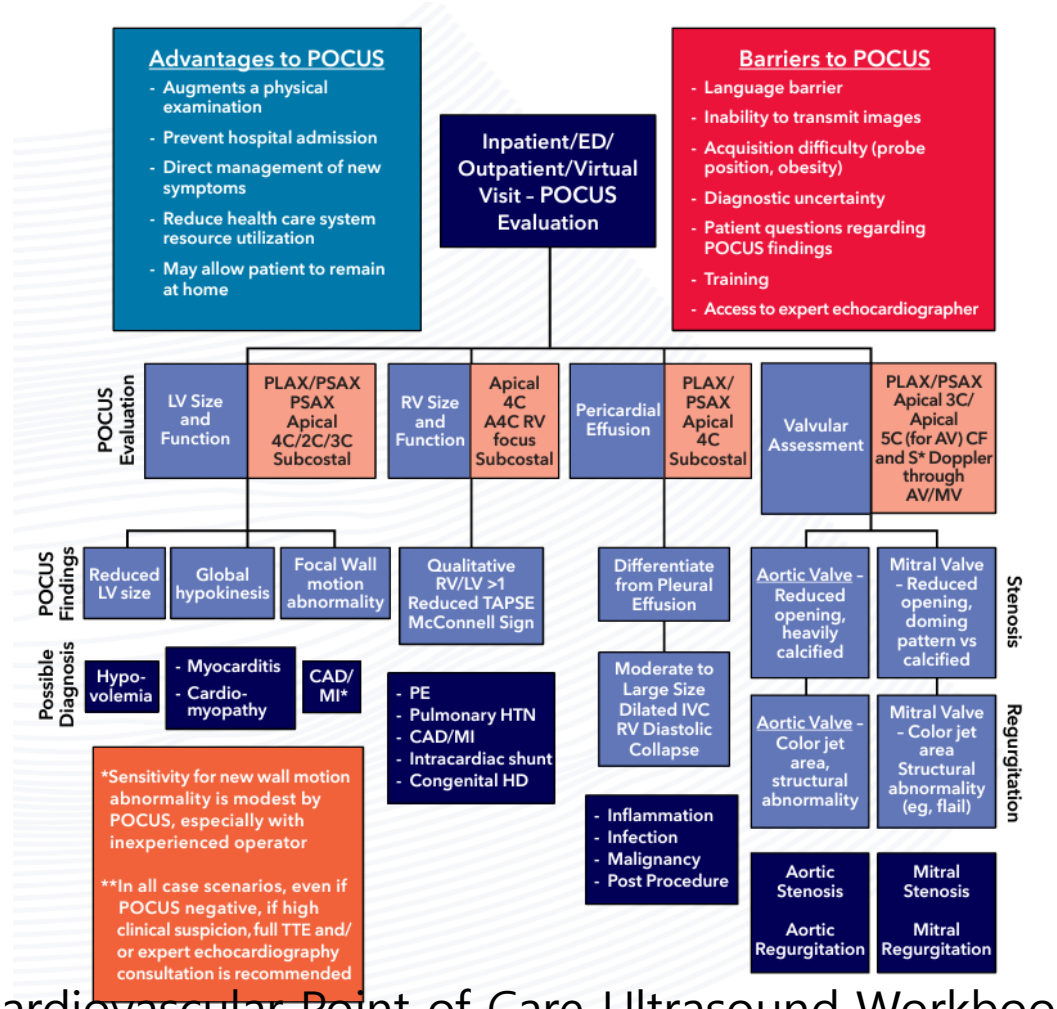
Issues in ICU: PH monitoring

TABLE 2. Echocardiographic Parameters of RV Function

Parameter	View		Abnormal Value
	TEE	TTE	
RV:LV area ratio	ME four chamber	Apical four chamber	> 0.6
LV eccentricity index	TG midpapillary short axis	Parasternal midpapillary short axis	> 1
RVFAC	ME four chamber	Apical four chamber	< 35%
TAPSE	Deep TG RV	Apical four chamber	< 1.6 cm
Peak velocity of systolic excursion at the annulus	Deep TG RV	Apical four chamber	< 10 cm/s
Pulmonary artery flow acceleration time	Ascending aortic short-axis	Parasternal RV outflow	< 100 ms

Chest. 2015 Mar;147(3):835-846.

Issues in ICU: PH monitoring



Cardiovascular Point of Care Ultrasound Workbook, American college of cardiology

Issues in ICU: Time is ticking

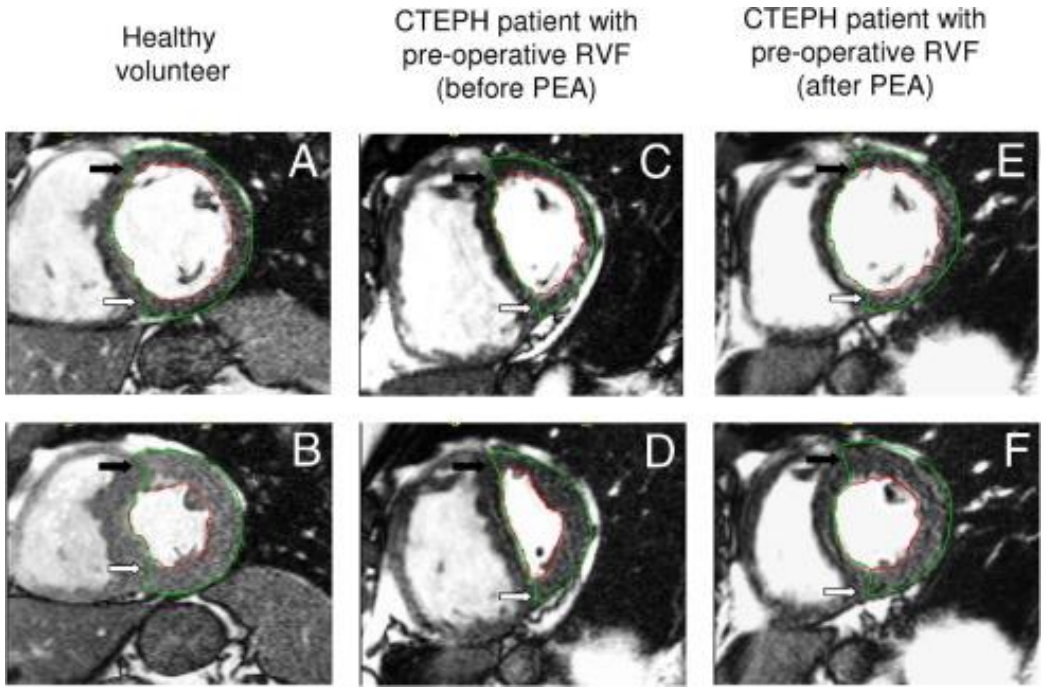
[표 8] 폐 응급도 판별기준

구분	폐 응급도 기준
응급도0	입원한 환자로 다음 한 가지 이상 해당 하여야 한다..(8일 이내 재등록, 19세 미만 이식대기자는 재등록 횟수 제한이 없으며, 19세 이상은 8일마다 3회까지 등록 가능) ① 호흡부전증으로 인공호흡기(Intubation ventilator)를 부착중인 환자 ② 체외막형 심폐기를 가동 중인 환자
응급도1	다음 한 가지 이상 해당하여야 한다. (60일마다 재등록하며 검사결과는 검사시점과 상관없이 인정한다) ① 산소 투여 없이 측정한 동맥혈 가스 검사상 PaO2〈 55mmHg ② 평균 폐동맥혈압 〉65mmHg, 또는 평균 우심방 혈압 〉15mmHg ③ Cardiac index〈 2L/min/m2 인 경우 ④ 동맥혈검사 상 PCO2≧80mmHg인 경우 ⑤ 입원환자 중 고유량 비강 캐뉼라(highflow nasal cannula) 30L FiO2≧ 0.6으로 2주 이상 유지중인 경우(유지 중에만 인정) ⑥ 인공호흡기나 체외막형 심폐기를 적용 중인 이식대기자 중 응급도 0에 해당되지 않는 경우
응급도2	다음 한 가지 이상 해당하여야 한다.(등록시점 30일 이내의 검사결과로 등록할 수 있으며 180일마다 연장할 수 있다. 검사결과는 처음 등록시점 검사결과만으로 연장 가능) ① 폐 기능 검사에서 1초 강제 호기 량 (FEV1)〈 25% ② 산소 투여 없이 측정한 동맥혈가스 검사 상 PaO2〈 60mmHg ③ 평균 우심방 혈압이 10-15mmHg인 경우 ④ 평균 폐동맥압력이 55-65mmHg인 경우 ⑤ Cardiac index가 2-2.5L/min/m2인 경우 ⑥ 동맥혈 검사 상 70mmHg ≦ PCO2 〈 80mmHg인 경우 ⑦ DLCO 〈 30%인 경우

Management of PH, in ICU

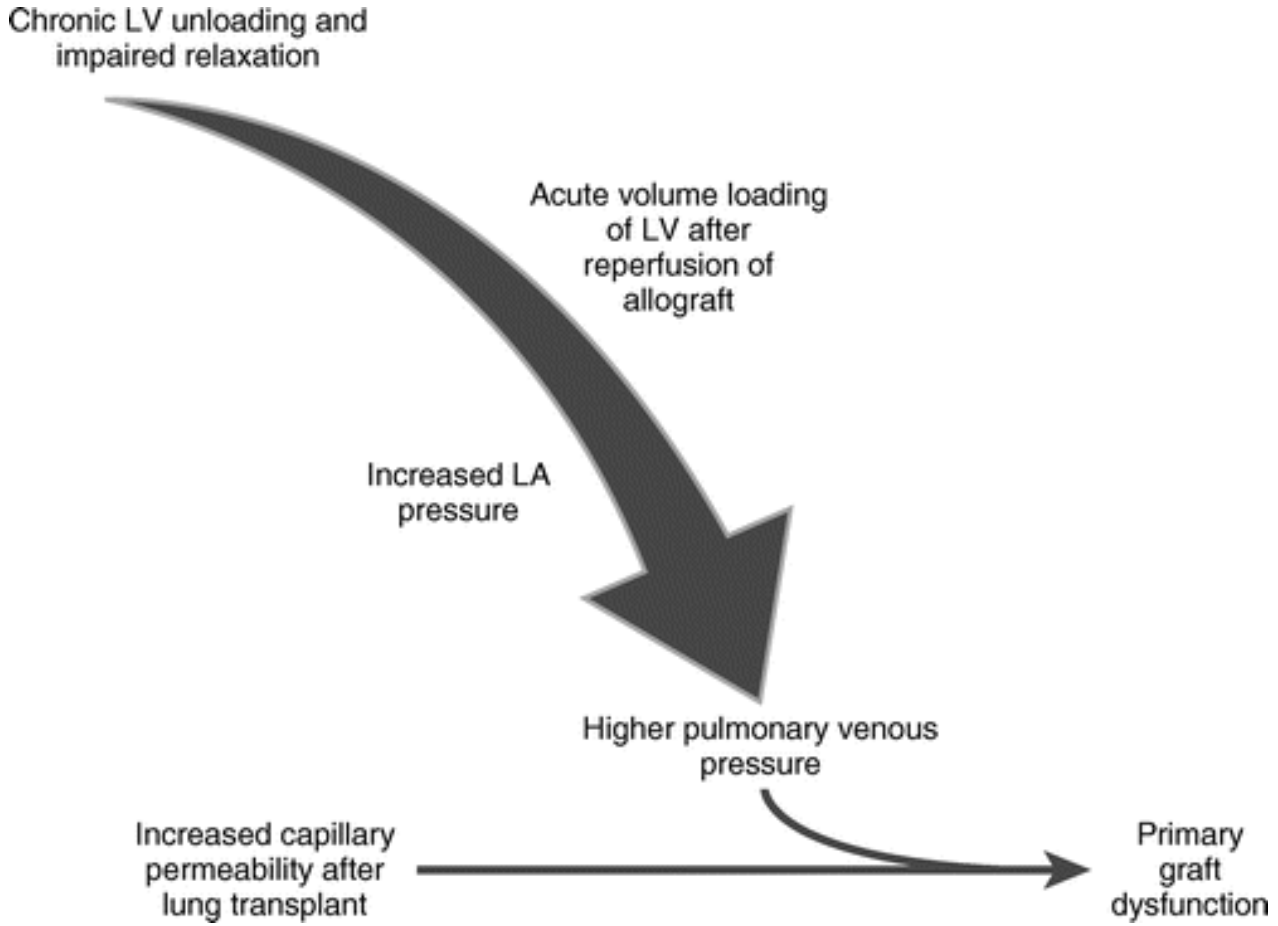
- Intubation
- VV vs. VA
- **Post-op Care**

RV failure → LV wall mass ↓ ↓



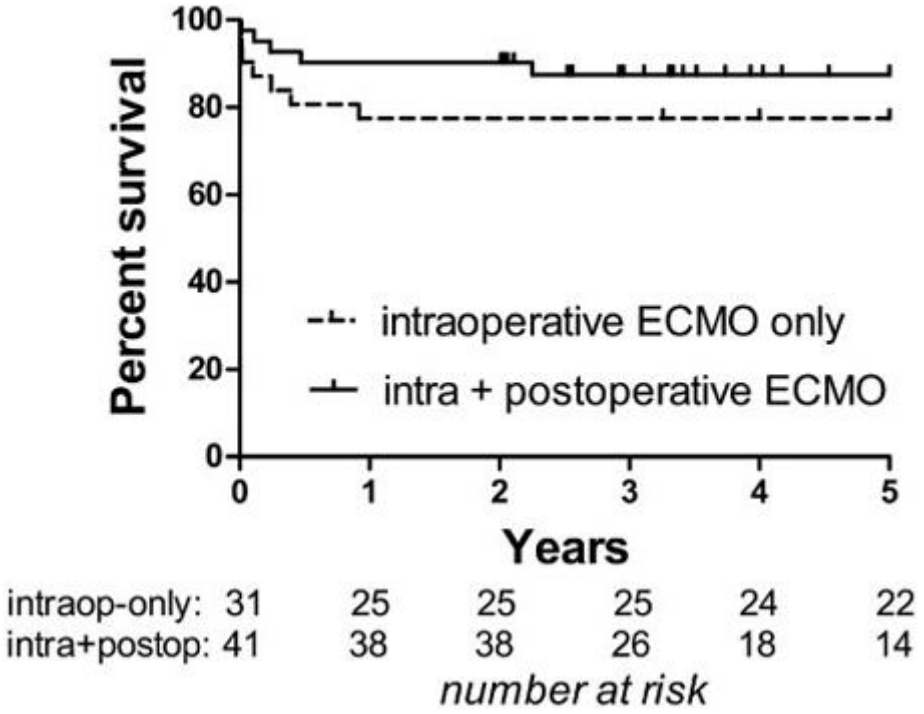
J Am Coll Cardiol. 2011 Feb 22;57(8):921-8.

After lung transplantation



Am J Respir Crit Care Med. 2016 Jun 15;193(12):1392-400.

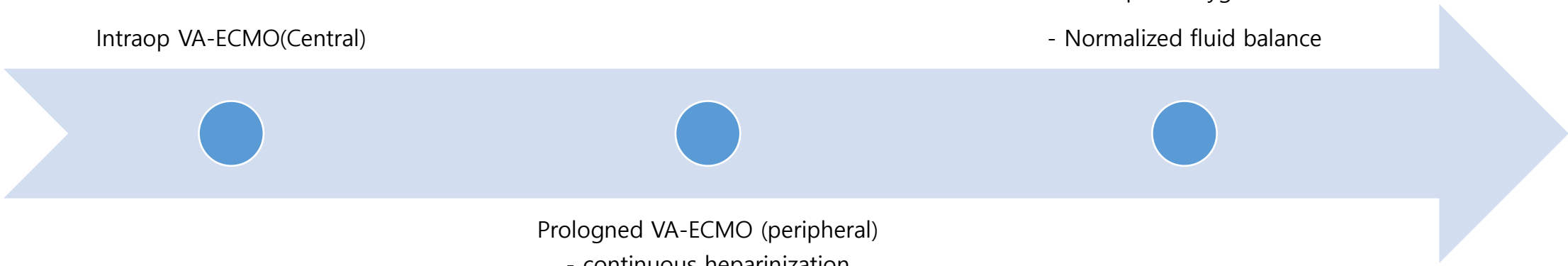
Prolonged ECMO after lung T



European Journal of Cardio-Thoracic Surgery 53 (2018) 178–185

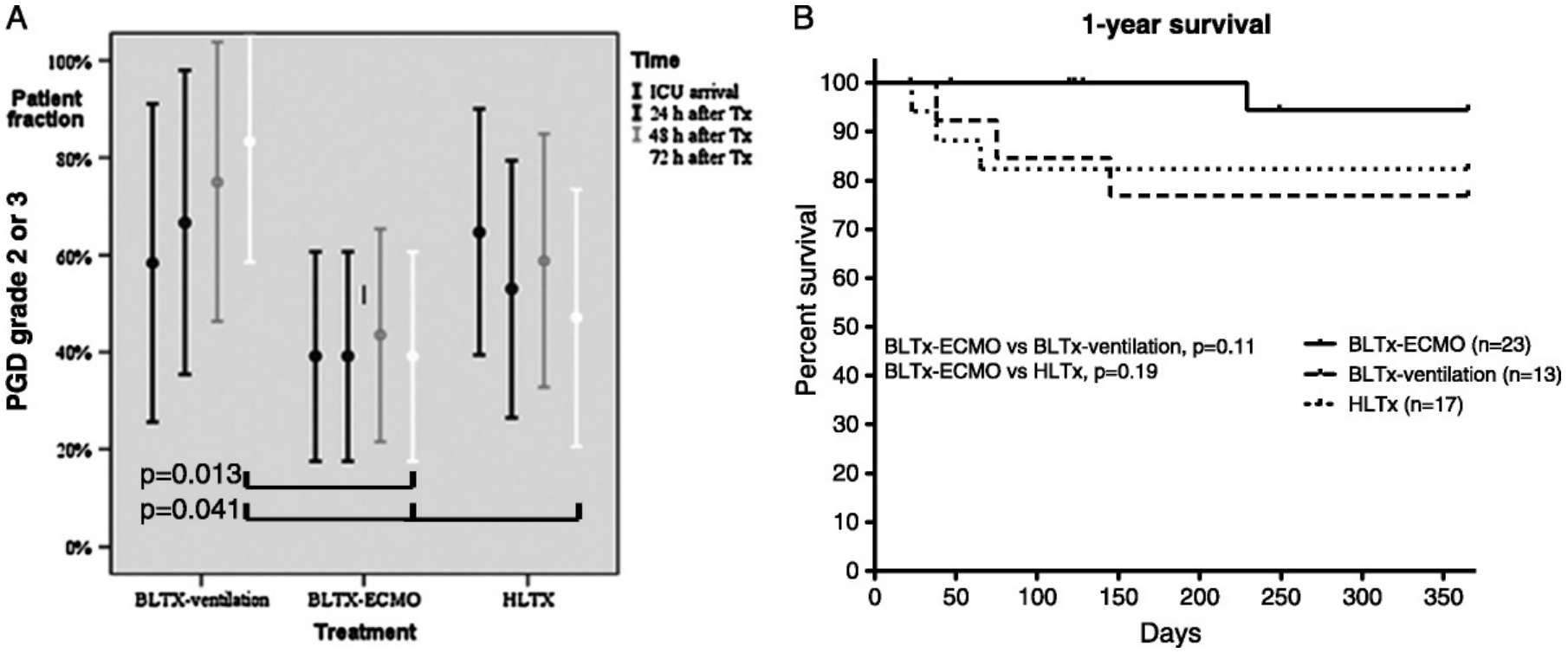
VA ECMO after transplantation in PH

Vienna



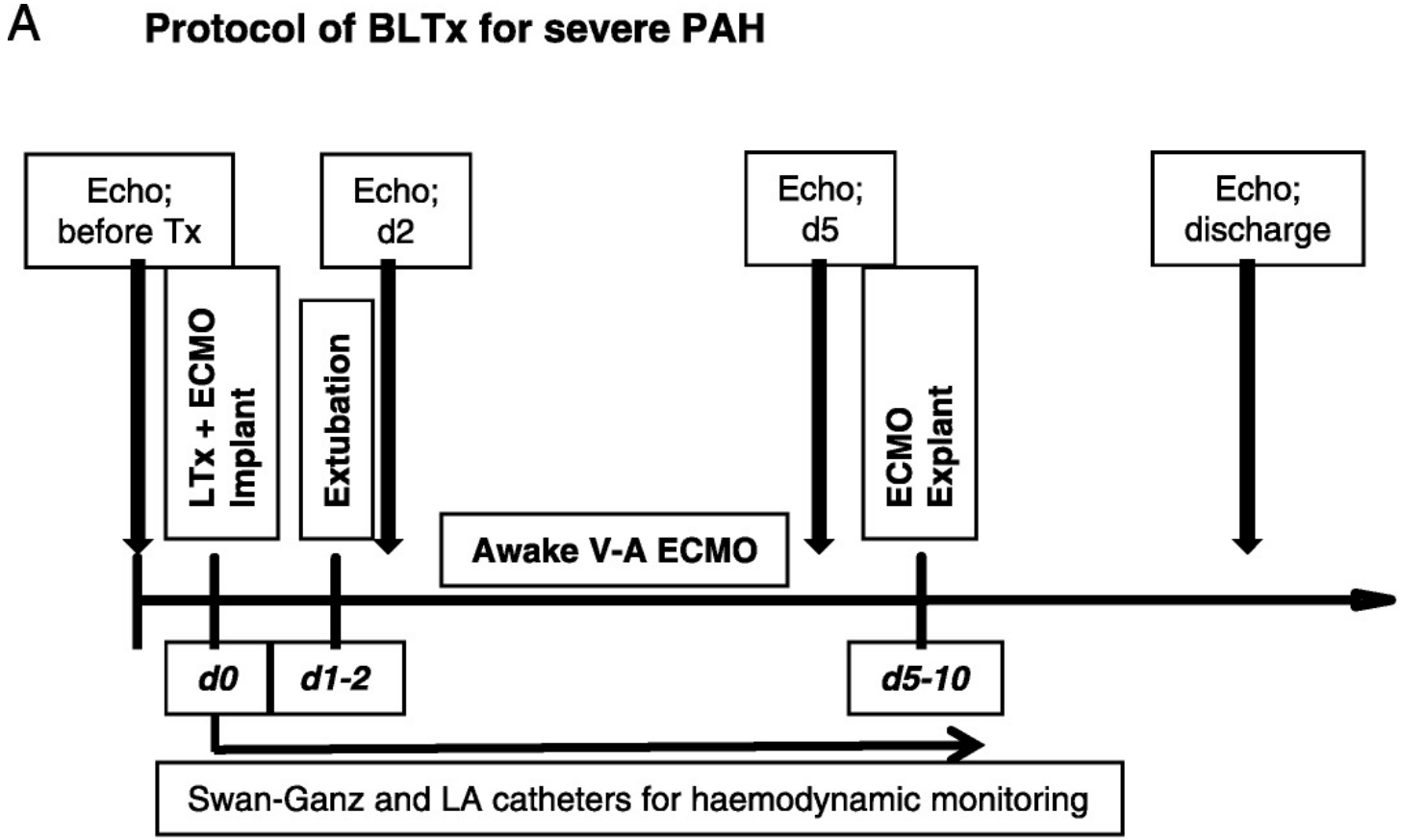
European Journal of Cardio-Thoracic Surgery 53 (2018) 178–185

VA ECMO after transplantation in PH



Transplantation. 2015 Feb;99(2):451-8.

VA ECMO after transplantation in PH



Hannover, Germany

Transplantation. 2015 Feb;99(2):451-8.

Take home message

- Pulmonary hypertension is prevalent in lung transplantation candidates

- In ICU
  - During intubation and mechanical ventilation
    - Prepared for cardiogenic shock, especially RV failure

  - VA-ECMO should be considered in severe PH, not only as a bridging strategy but also as post-operative care

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COLLEGE OF MEDICINE