長庚醫療財團法人
CHANG GUNG MEDICAL FOUNDATION

MV management in ARDS with vv ECMO

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20191207 09:20－10:00

Outlines

- Introduction of ARDS
  - Lung protective strategy in ARDS
- ECMO in ARDS
- MV setting in ARDS with ECMO
- Summary

ARDS: CXR and CT

Baby Lung

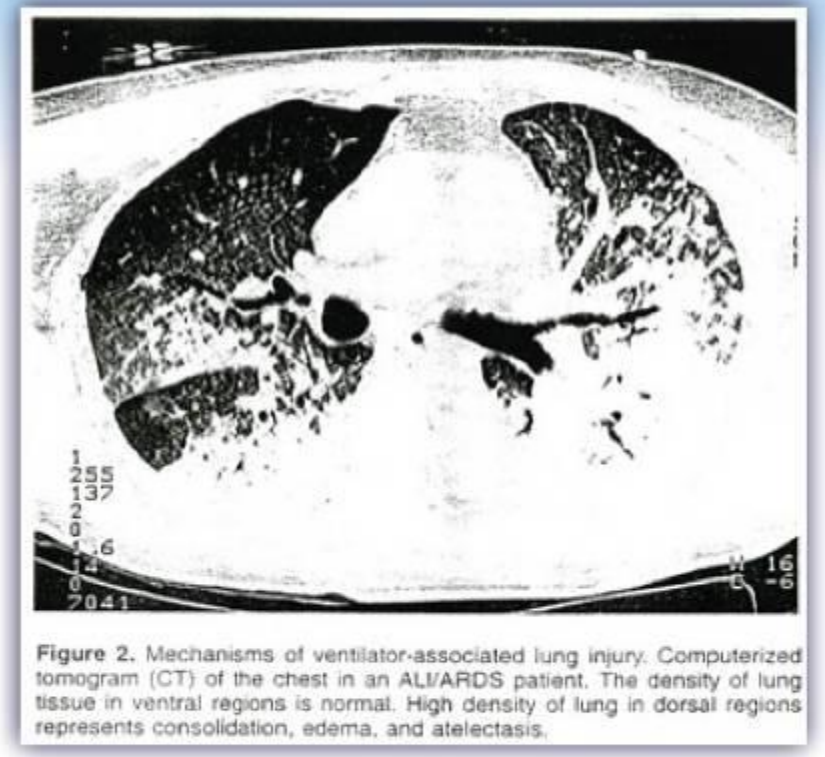


Figure 2. Mechanisms of ventilator-associated lung injury. Computerized tomogram (CT) of the chest in an ALI/ARDS patient. The density of lung tissue in ventral regions is normal. High density of lung in dorsal regions represents consolidation, edema, and atelectasis.

Berlin definition

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg $<$ PaO_2/FIO_2 $\leq$ 300 mm Hg with PEEP or CPAP $\geq$5 cm H_2O[c]
Moderate	100 mm Hg $<$ PaO_2/FIO_2 $\leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O
Severe	PaO_2/FIO_2 $\leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Chest radiograph or computed tomography scan.

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [$PaO_2/FIO_2 \times$ (barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Intensive Care Med (2012) 38:1573–1582

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

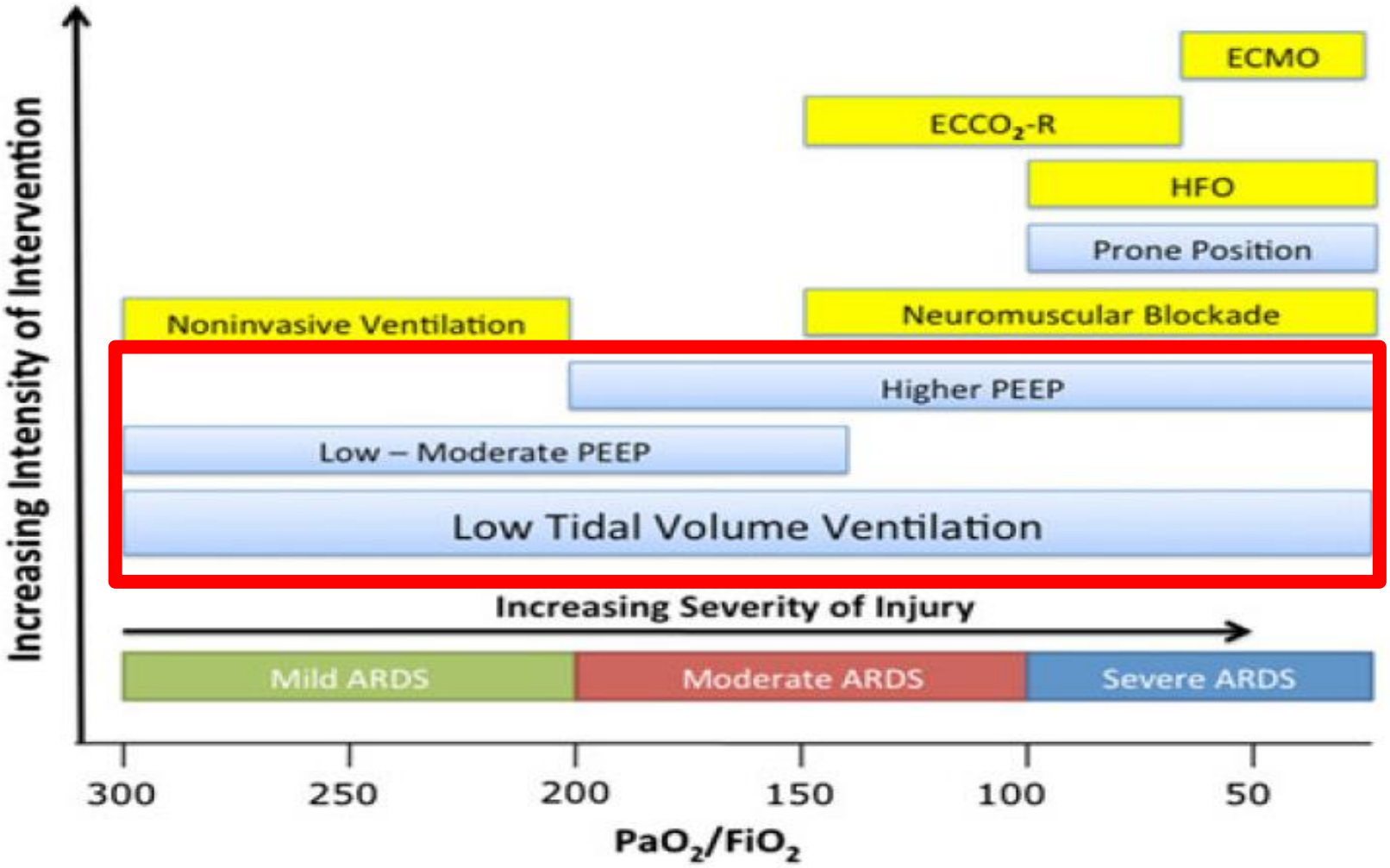
Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Tài Pham, MD; Eddy Fan, MD, PhD; Laurent Brochard, MD, HDR; Andres Esteban, MD, PhD; Luciano Gattinoni, MD, FRCP; Frank van Haren, MD, PhD; Anders Larsson, MD, PhD; Daniel F. McAuley, MD, PhD; Marco Ranieri, MD; Gordon Rubenfeld, MD, MSc; B. Taylor Thompson, MD, PhD; Hermann Wrigge, MD, PhD; Arthur S. Slutsky, MD, MASc; Antonio Pesenti, MD; for the LUNG SAFE Investigators and the ESICM Trials Group

- **LUNG SAFE study**
- 2014 winter, 50 countries, 459 ICUs, 2377 patients
- ARDS prevalence:
  - 10.4% ICU admissions; 23% of requiring MV.
  - Mild: 30.0%; Moderate: **46.6%;** Severe: 23.4%
- Hospital mortality

  -Mild: 34.9%; moderate: 40.3%; severe: 46.1%

<Bellani G et al JAMA 2016;315:788-800>

Therapeutic Options with Berlin Definition



<Niall D. Ferguson et al,Intensive Care Med 2012;38:1573–82>

From VALI to MODS to Death

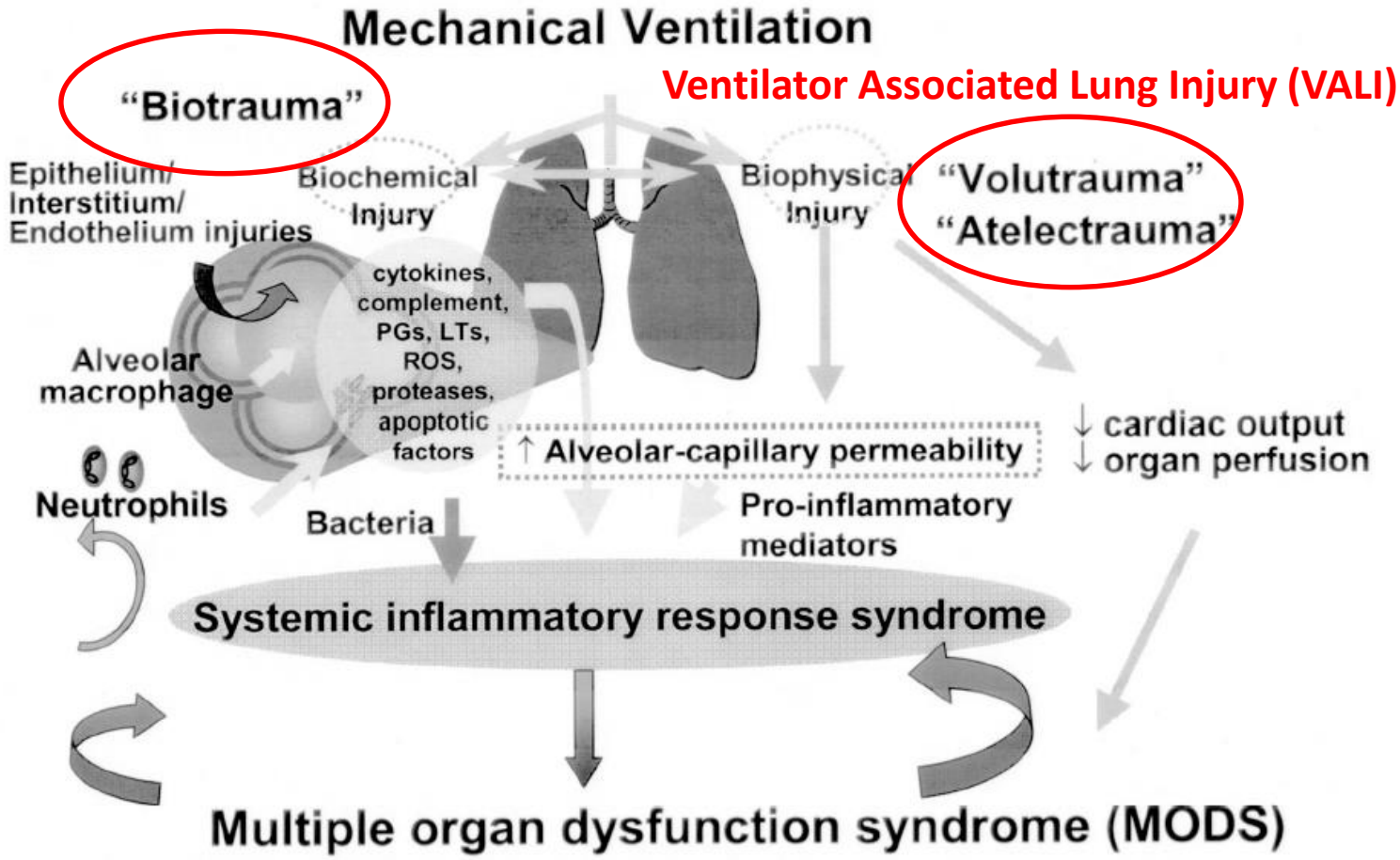
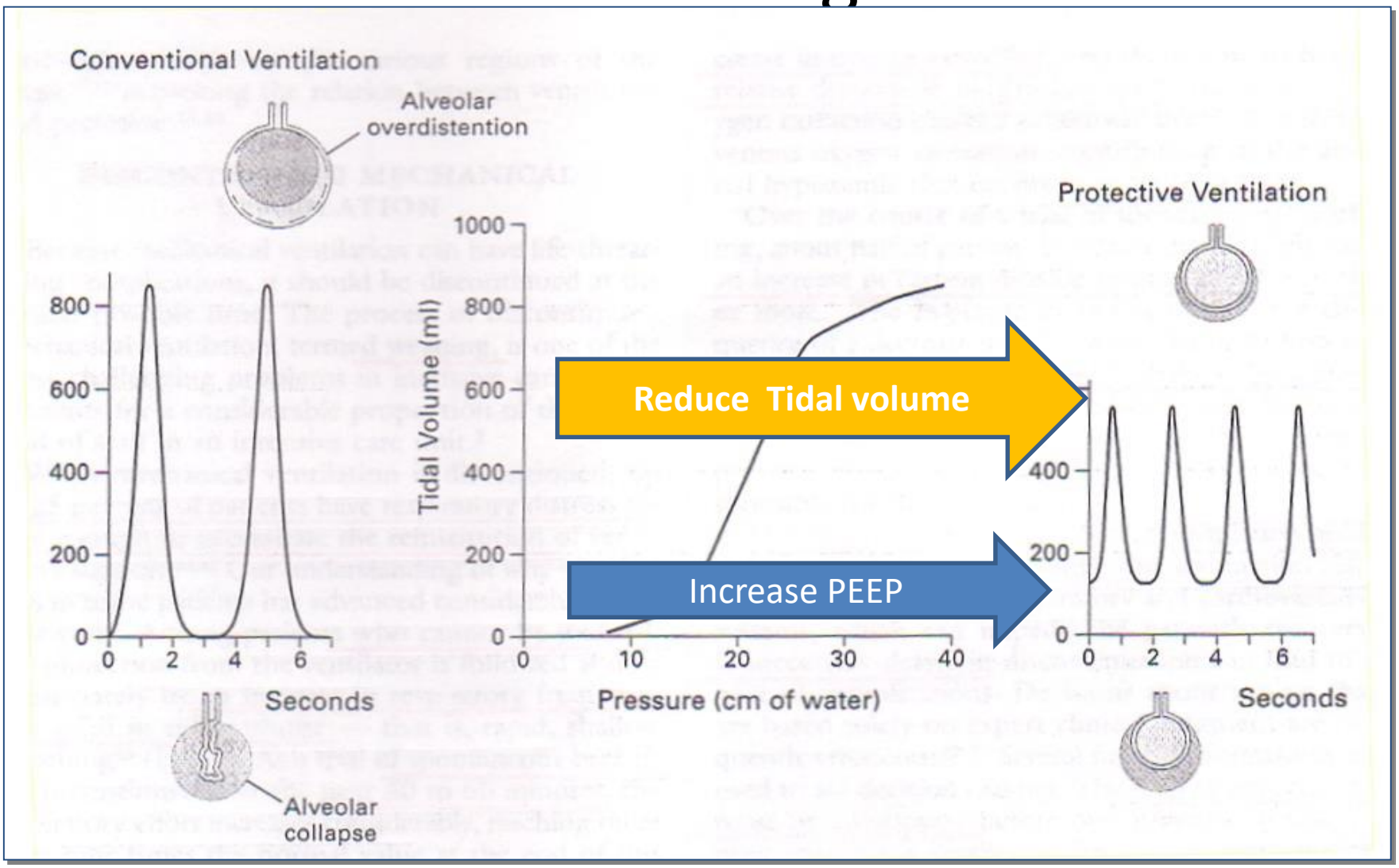


Figure 2. Postulated mechanisms whereby volutrauma, atelectrauma, and biotrauma caused by mechanical ventilation contribute to multiple organ dysfunction syndrome (*MODS*). The potential importance of biotrauma is not only that it can aggravate ongoing lung injury, but also that it can contribute to the development of MODS, possibly through the release of proinflammatory mediators from the lung. Adapted with permission from Slutsky and Tremblay (2).

Lung protective strategy:
lower TV and higher PEEP



NIH NHLBI ARDS Clinical Network
Mechanical Ventilation Protocol Summary

INCLUSION CRITERIA: Acute onset of

1. $PaO_2/FiO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW)
   Males = 50 + 2.3 [height (inches) - 60]
   Females = 45.5 + 2.3 [height (inches) -60]
2. Select any ventilator mode
3. Set ventilator settings to achieve initial V_T = 8 ml/kg PBW
4. Reduce V_T by 1 ml/kg at intervals ≤ 2 hours until V_T = 6ml/kg PBW.
5. Set initial rate to approximate baseline minute ventilation (not > 35 bpm).
6. Adjust V_T and RR to achieve pH and plateau pressure goals below.

OXYGENATION GOAL: PaO_2 55-80 mmHg or SpO_2 88-95%

Use a minimum PEEP of 5 cm H_2O. Consider use of incremental FiO_2/PEEP combinations such as shown below (not required) to achieve goal.

Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O

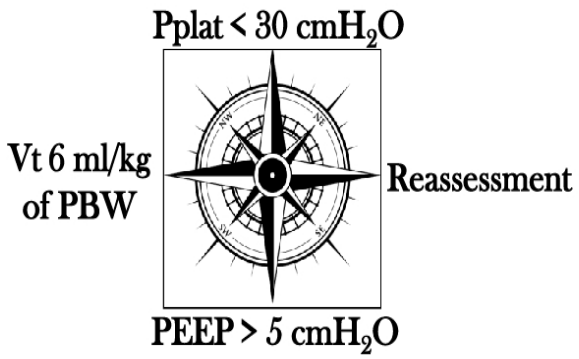
Check Pplat (0.5 second inspiratory pause), at least q 4h and after each change in PEEP or V_T.

If Pplat > 30 cm H_2O: decrease V_T by 1ml/kg steps (minimum = 4 ml/kg).

If Pplat < 25 cm H_2O and V_T< 6 ml/kg, increase V_T by 1 ml/kg until Pplat > 25 cm H_2O or V_T = 6 ml/kg.

If Pplat < 30 and breath stacking or dys-synchrony occurs: may increase V_T in 1ml/kg increments to 7 or 8 ml/kg if Pplat remains ≤ 30 cm H_2O.

Early management of ARDS in 2019



P/F < 80 — Discuss VV-ECMO

P/F < 150 — Neuromuscular blockers
Prone positioning

P/F < 200 — High level of PEEP if improves oxygenation

Tidal volume about 6 ml/kg of PBW
Plateau pressure < 30 cmH_2O
PEEP > 5 cmH_2O
Check for hypercapnia

Confirmed ARDS

Initiation of invasive mechanical ventilation with sedation in ICU

Tidal volume (Vt) about 6 ml/kg of PBW in the absence of severe metabolic acidosis

Systematic screening for ARDS diagnosis criteria

ARDS severity

Reassessment of ventilator settings and of the management strategy at least every 24h

Inclusion criteria

- PaO_2/FiO_2 < 50 mm HG with FiO_2 ≥80% for > 3 hours
- PaO_2/FiO_2 < 80 mm HG with FiO_2 ≥80% > 6 hours
- pH < 7.25 for > 6 hours with Pplat ≤ 32 cm H_2O

Despite optimal mechanical ventilation

Veno-venous ECMO
- ❑ In case of refractory hypoxemia or when protective ventilation can not be applied
- ❑ To be discussed with experienced ECMO centres

Neuromuscular blockers: continuous intravenous infusion
- ❑ Early initiation (within the first 48h of ARDS diagnosis)

Prone positioning methods :
- ❑ Applied for >16h a day, for several consecutive days

Moderate or severe ARDS -> High PEEP test (> 12 cmH_2O)
Use high levels if:
- ❑ Oxygenation improvement
- ❑ Without hemodynamic impairment or significant decrease in lung compliance
- ❑ Maintain Pplat < 30 cmH_2O, continuous monitoring

ARDS diagnosis criteria
- ❑ PaO_2/FiO_2 ≤ 300 mmHg
- ❑ PEEP ≥ 5 cmH_2O
- ❑ Bilateral opacities on chest imaging
- ❑ Not fully explained by cardiac failure or fluid overload
- ❑ Within a week of a known clinical insult

Might be applied
- ➢ Inhaled Nitric Oxide (iNO), when severe hypoxemia remains despite prone positioning and before considering VV-ECMO
- ➢ Partial ventilation support after early phase to generate tidal volume about 6 ml/kg and less than 8 ml/kg

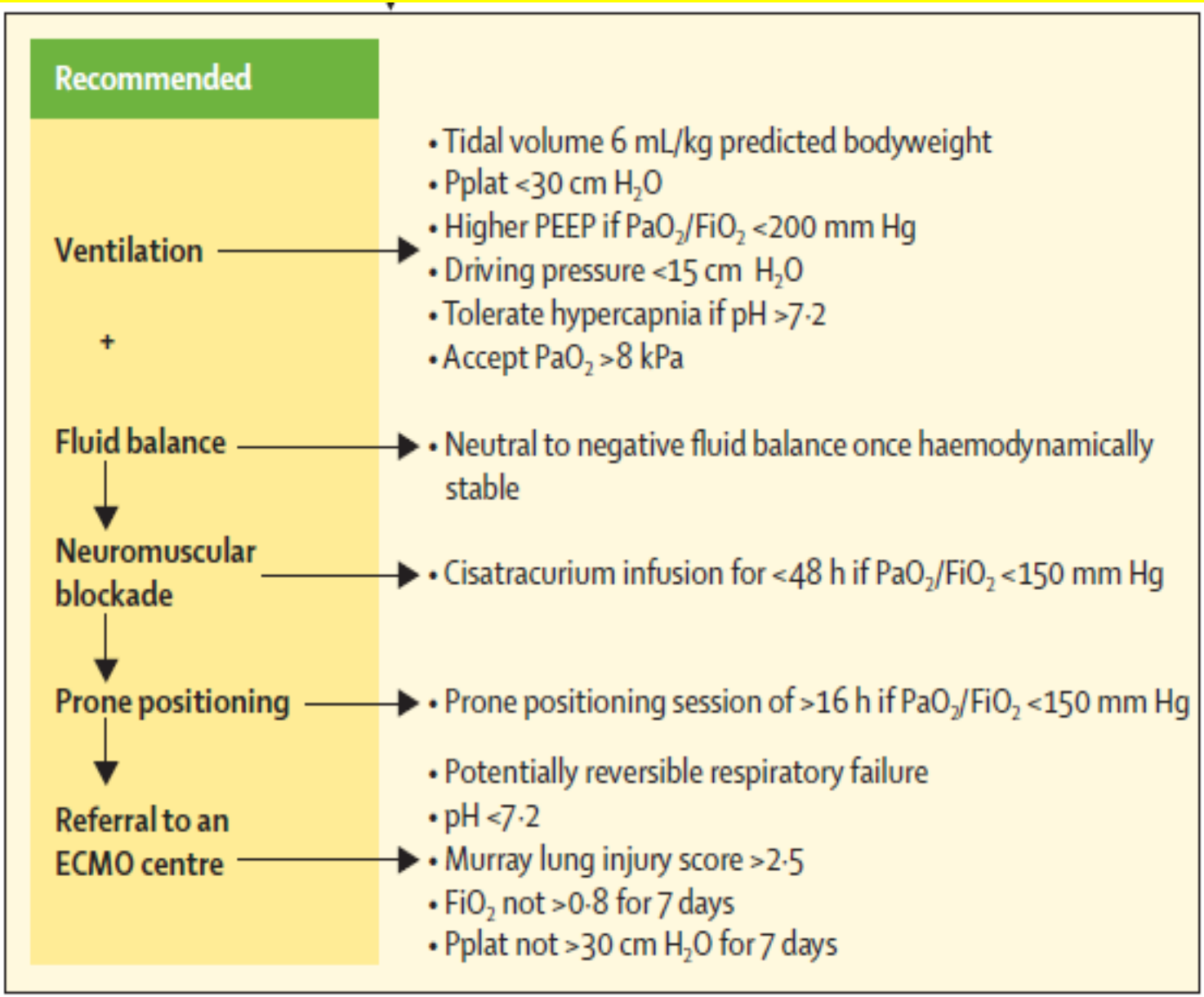
No recommendation could be made
- ➢ $ECCO_2R$
- ➢ Driving pressure
- ➢ Partial ventilation support at the early phase

Should probably not be done
- ➢ Systematic recruitment maneuvers

Should not be done
- ➢ HFOV

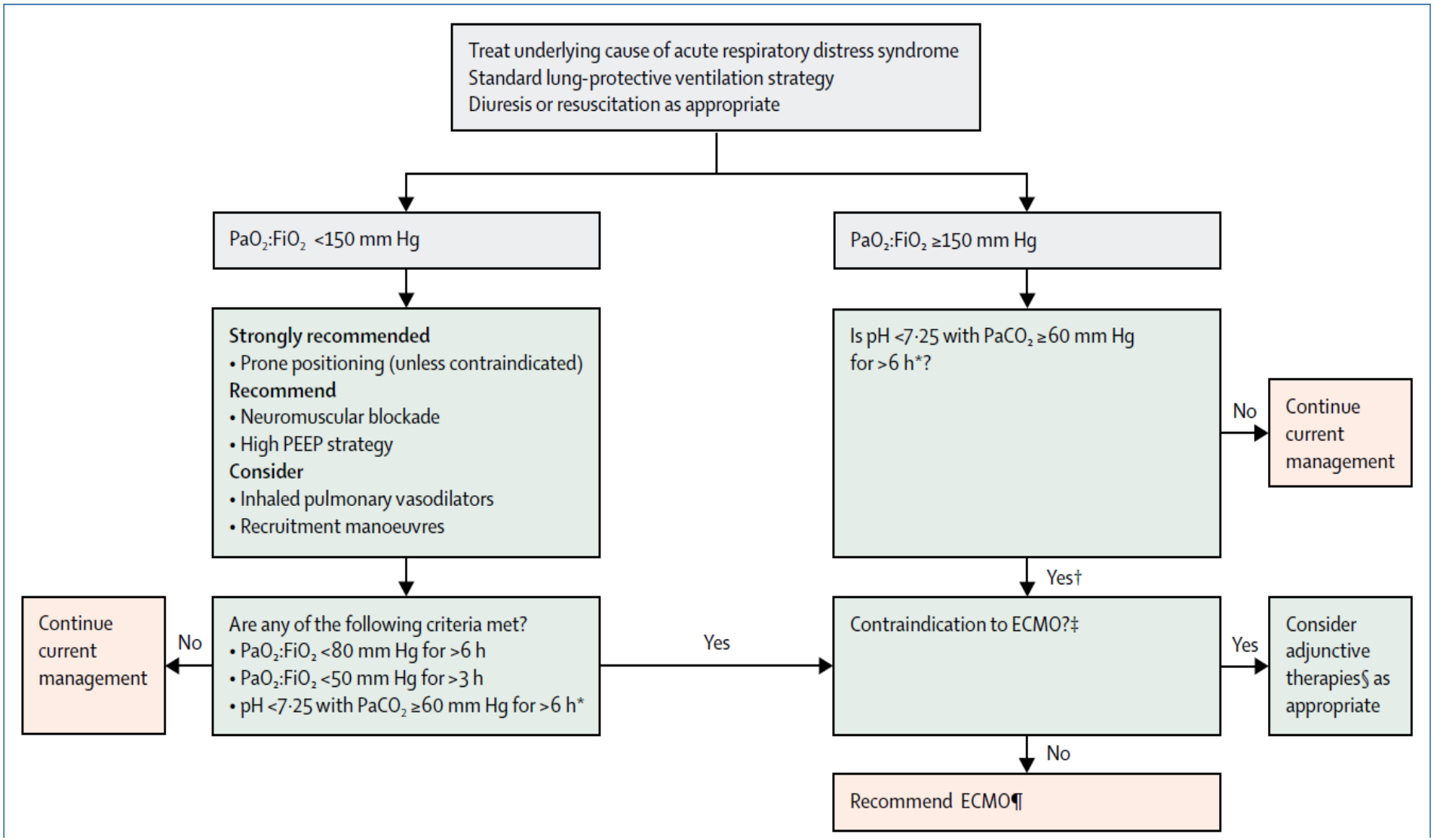
Ann Intensive Care. 2019 Jun 13;9(1):69

Algorithm of a suggested management of ARDS



Lancet 2016 April 28

Algorithm for management of ARDS



Lancet Respiratory Medicine January 29, 2019

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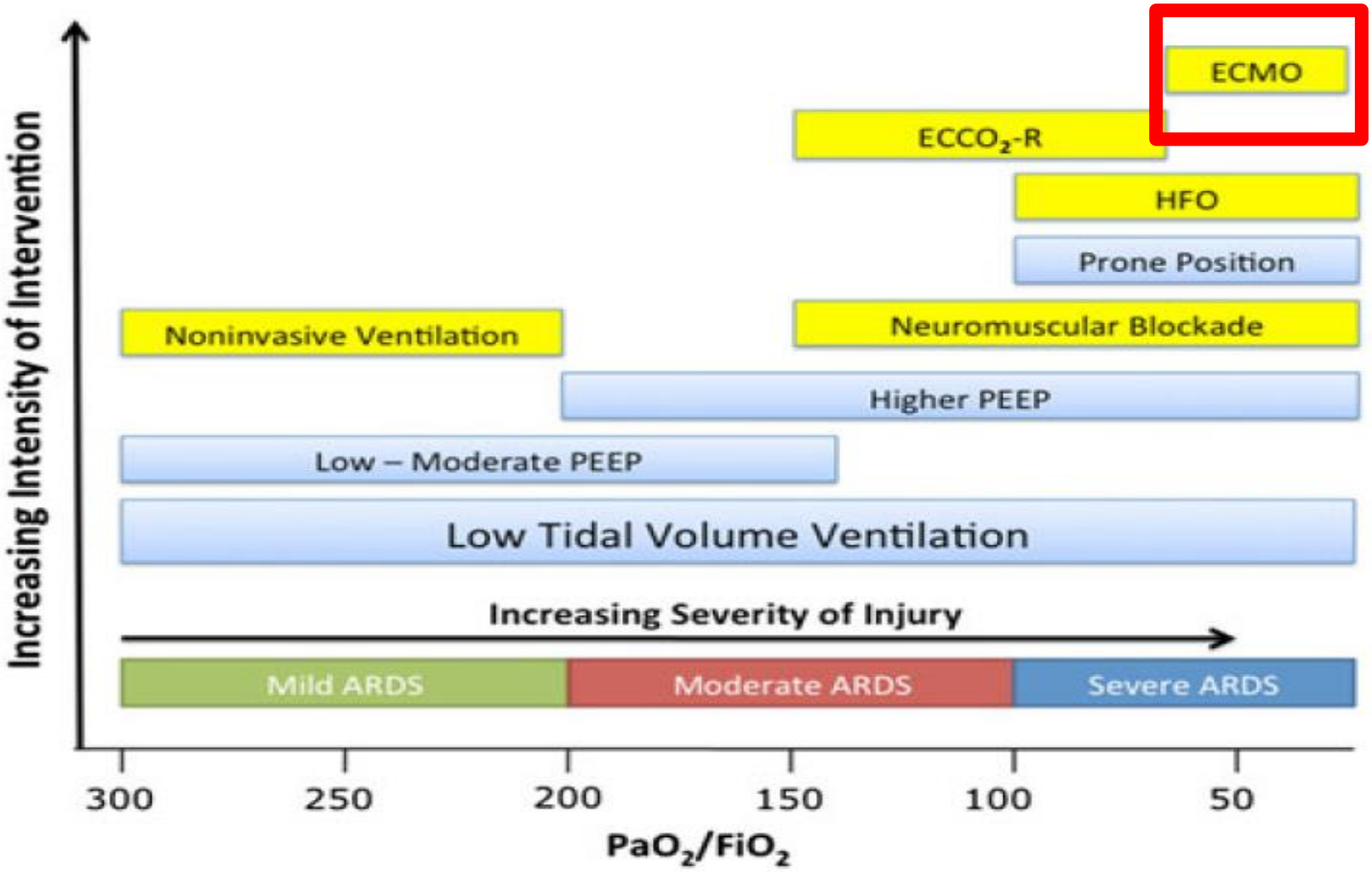
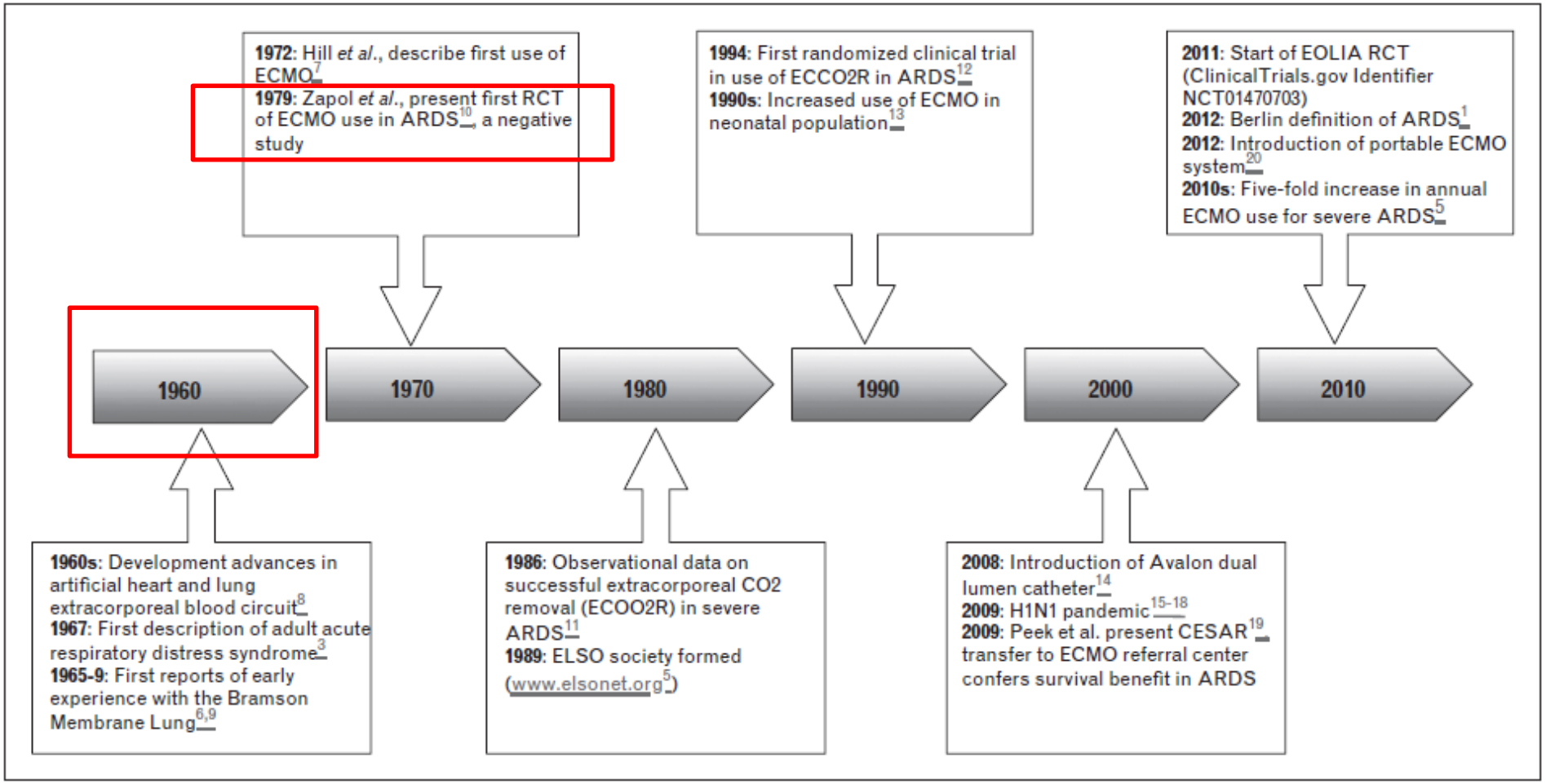
Therapeutic Options with Berlin Definition

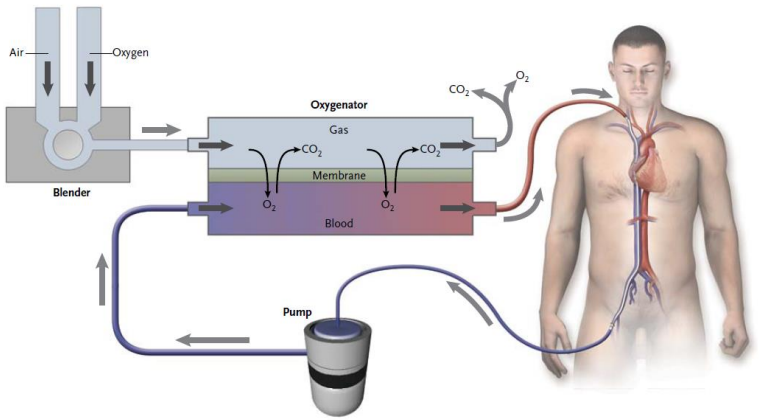


<Niall D. Ferguson et al,Intensive Care Med 2012;38:1573–82>

Timeline of ECMO in severe ARDS



Curr Opin Crit Care 2015, 21:13–19

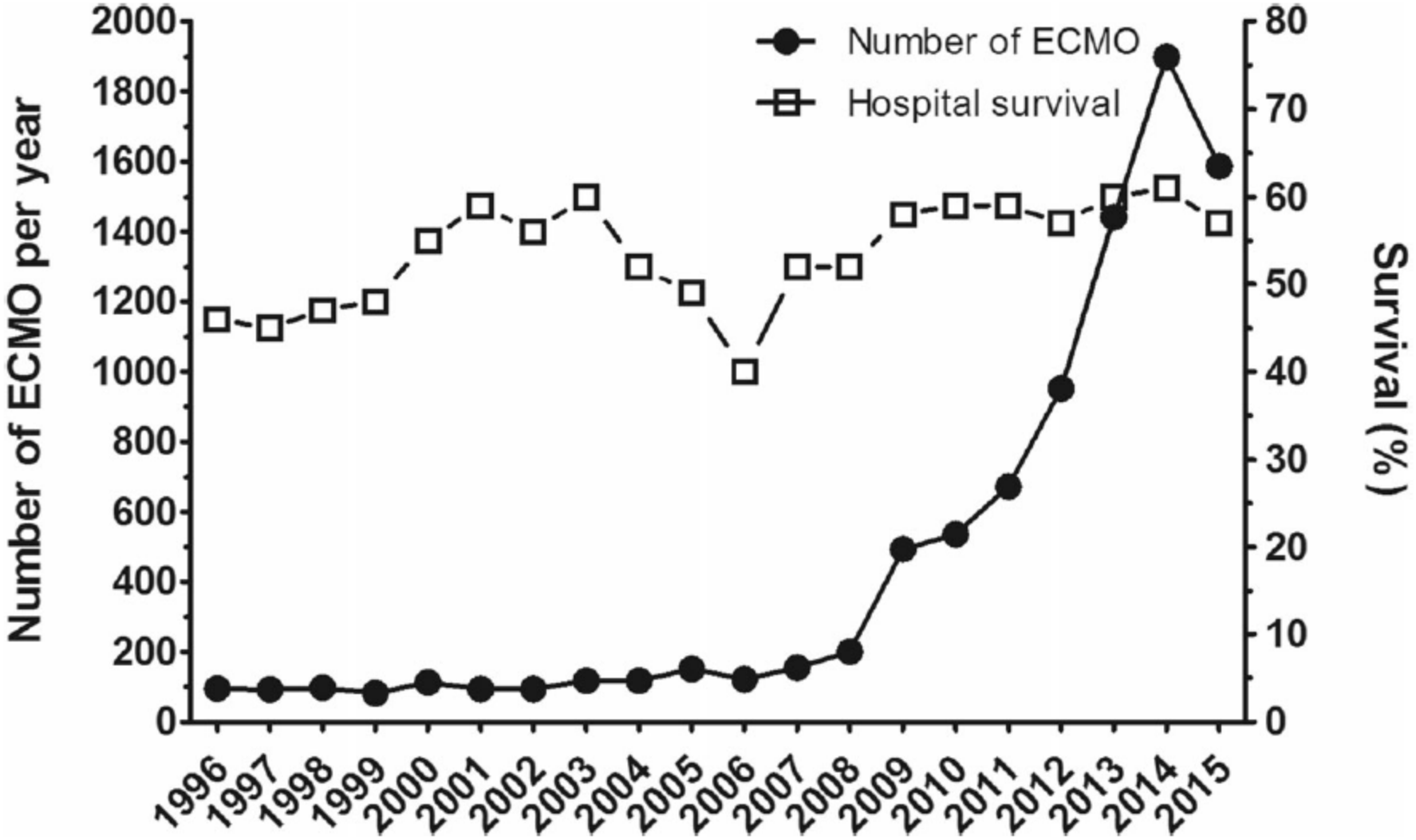


2011: Start of EOLIA RCT (ClinicalTrials.gov Identifier NCT01470703)
2012: Berlin definition of ARDS[1]
2012: Introduction of portable ECMO system[20]
2010s: Five-fold increase in annual ECMO use for severe ARDS[5]

2000 → 2010

2008: Introduction of Avalon dual lumen catheter[14]
2009: H1N1 pandemic[15–18]
2009: Peek et al. present CESAR[19] transfer to ECMO referral center confers survival benefit in ARDS

Curr Opin Crit Care 2015, 21:13–19



ELSO ECLS Registry Report. http://www.elso.org. Accessed 23 Aug 2016.

Rozencwajg *et al. Critical Care* (2016) 20:392

Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial

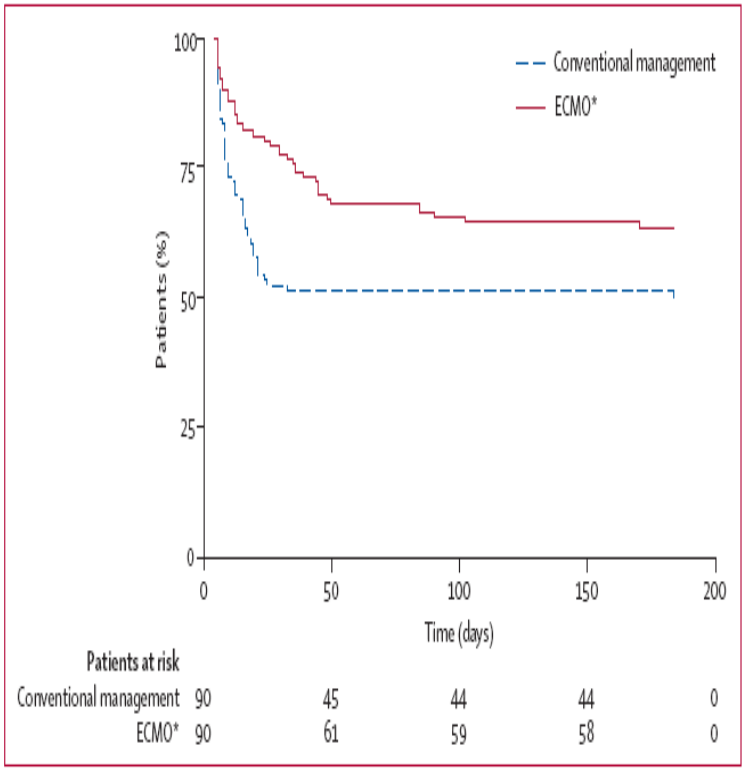
Giles J Peek, Miranda Mugford, Ravindranath Tiruvoipati, Andrew Wilson, Elizabeth Allen, Mariamma M Thalanany, Clare L Hibbert, Ann Truesdale, Felicity Clemens, Nicola Cooper, Richard K Firmin, Diana Elbourne, for the CESAR trial collaboration

- 766 were screened, 180 were enrolled (ECMO vs Conventional 90 : 90)
- Enrolled: LIS > 3, pH < 7.2
- Exclude: High pressure > 30 cmH2O or FiO2 > 0.8 for > 7 D

Lancet 2009; 374: 1351–63

Outcomes

	ECMO group (n=90)*	Conventional management group (n=90)	Relative risk (95% CI, p value)
Death or severe disability at 6 months	NA	NA	0·69 (0·05–0·97, 0·03)†
No	57 (63%)	41 (47%)‡	NA
Yes	33 (37%)	46 (53%)‡	NA
No information about severe disability	0	3 (3%)§	NA
Died at ≤6 months or before discharge	NA	NA	0·73 (0·52–1·03, 0·07)
No	57 (63%)	45 (50%)	NA
Yes	33 (37%)	45 (45%)	NA
Severe disability			
No	57 (63%)	41 (46%)	NA
Yes	0	1 (1%)	NA
Cause of death			
Respiratory failure	8 (9%)	24 (27%)	NA
Multiorgan failure	14 (16%)	15 (17%)	NA
Neurological disorder	4 (4%)	2 (2%)	NA
Cardiovascular disorder	1 (1%)	3 (3%)	NA
Related to ECMO	1 (1%)	0	NA



Interpretation We recommend transferring of adult patients with severe but potentially reversible respiratory failure, whose Murray score exceeds 3·0 or who have a pH of less than 7·20 on optimum conventional management, to a centre with an ECMO-based management protocol to significantly improve survival without severe disability. This strategy is also likely to be cost effective in settings with similar services to those in the UK.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 24, 2018 VOL. 378 NO. 21

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

EOLIA study

In an international clinical trial, we randomly assigned patients with very severe ARDS, as indicated by one of three criteria —

- P/F <50 mm Hg for more than 3 hours
- P/F <80 mm Hg for more than 6 hours
- pH <7.25 with a $PaCO_2$ >60 mm Hg for >6 hours

N Engl J Med 2018;378:1965-75.

249 Underwent randomization

124 Were assigned to receive ECMO
121 Received ECMO

125 Were assigned to receive conventional mechanical ventilation
35 Received rescue ECMO

124 Were included in the primary analysis

125 Were included in primary analysis

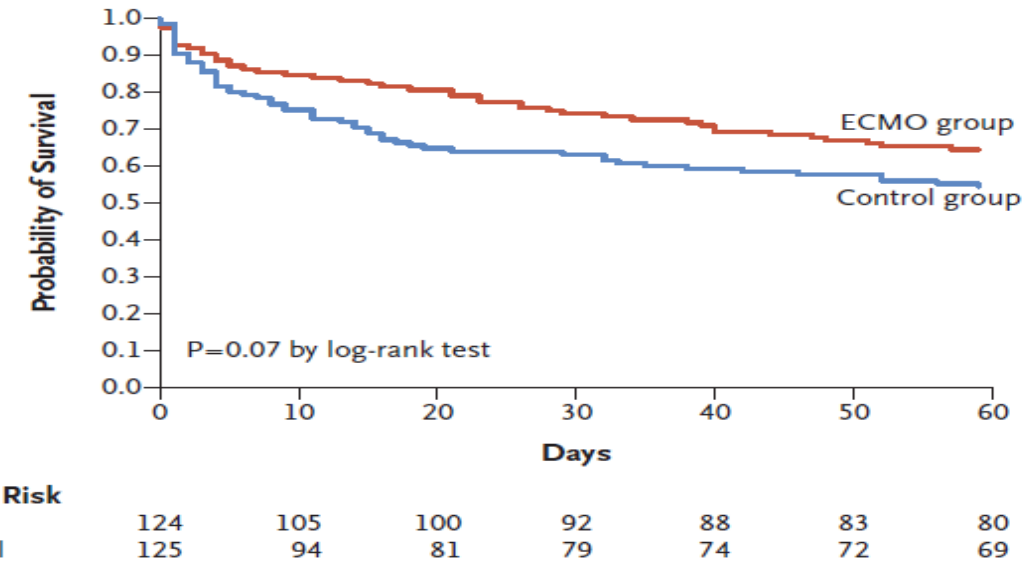


Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

N Engl J Med 2018;378:1965-75.

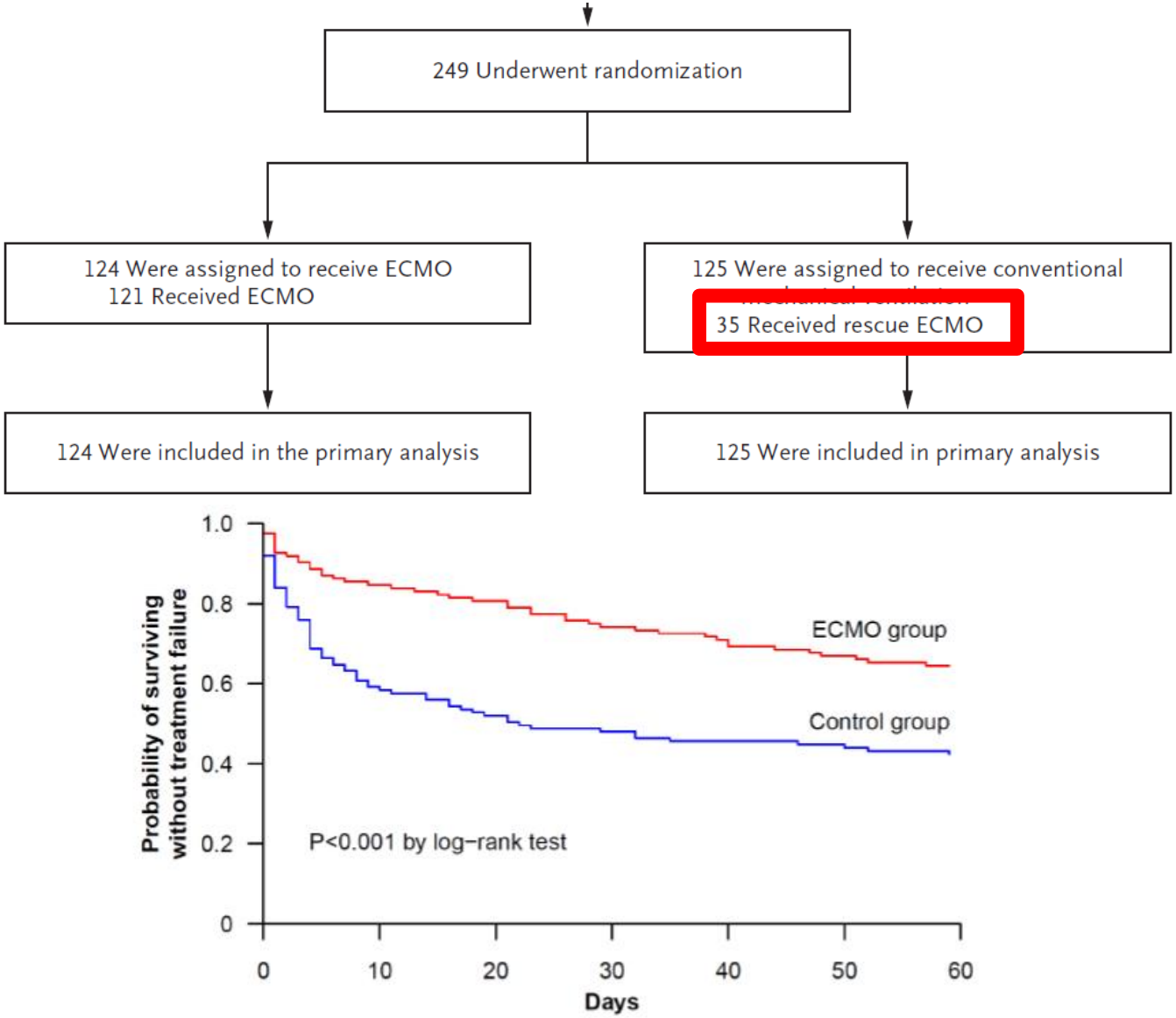


Figure S8. Kaplan–Meier Estimates of Survival Without Treatment Failure, Defined as Crossover to ECMO or Death for the Control Group and Death for the ECMO Group in the Intention-to-Treat Population During the First 60 Study Days.

N Engl J Med 2018;378:1965-75.

Conclusions

- 60 d mortality rate:
  - 35% in ECMO group and 46% in control group (P = 0.09).
    - In control group, crossover to ECMO in 35 patients (28%), with 57% dying.
- Complications did not differ significantly, except
  - More bleeding leading to transfusion (46% vs. 28%)
  - More severe thrombocytopenia (27% vs. 16%)

CONCLUSIONS

Among patients with very severe ARDS, 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy. (Funded by the Direction de la Recherche Clinique et du Développement and the French Ministry of Health; EOLIA ClinicalTrials.gov number, NCT01470703.)

Outlines

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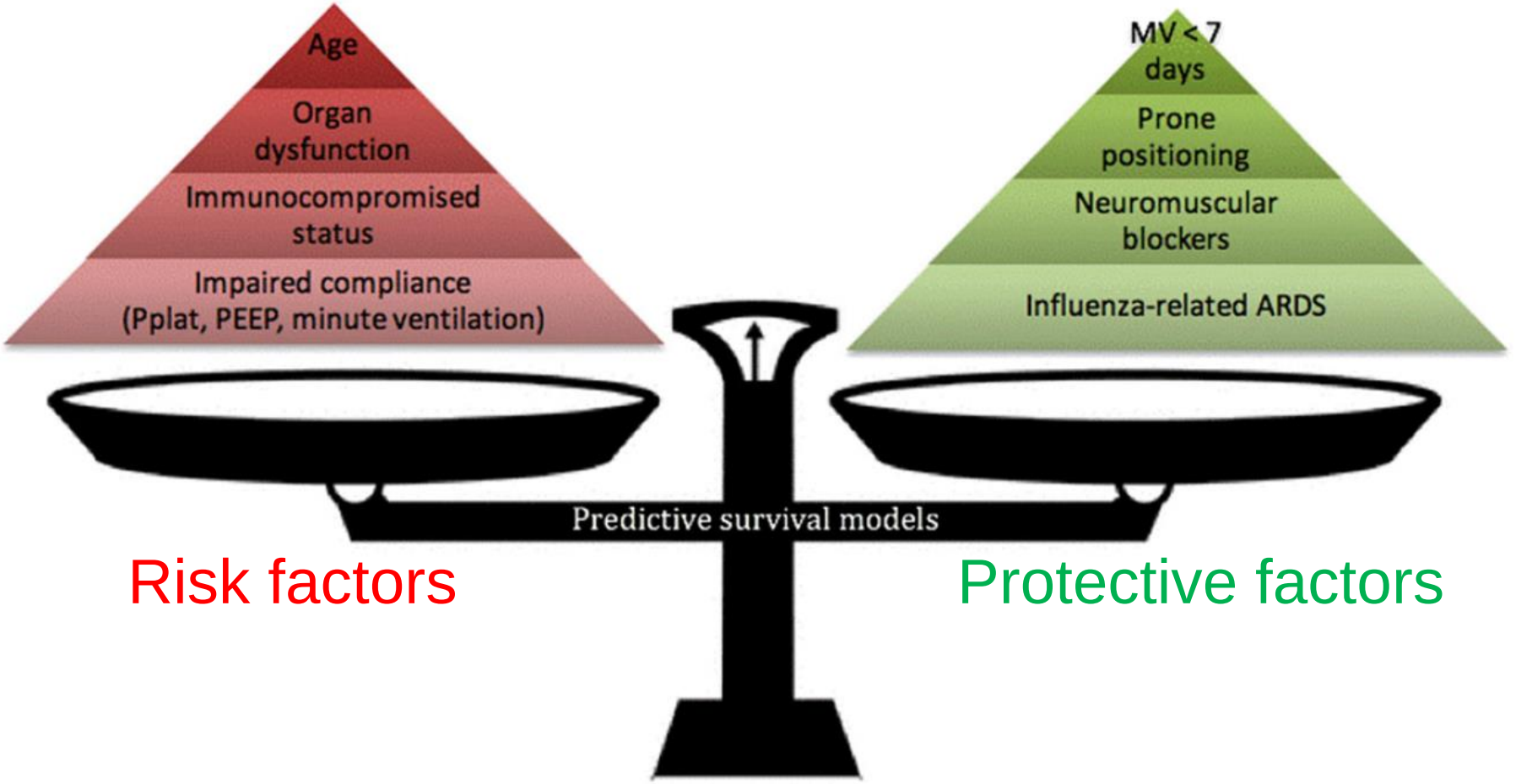
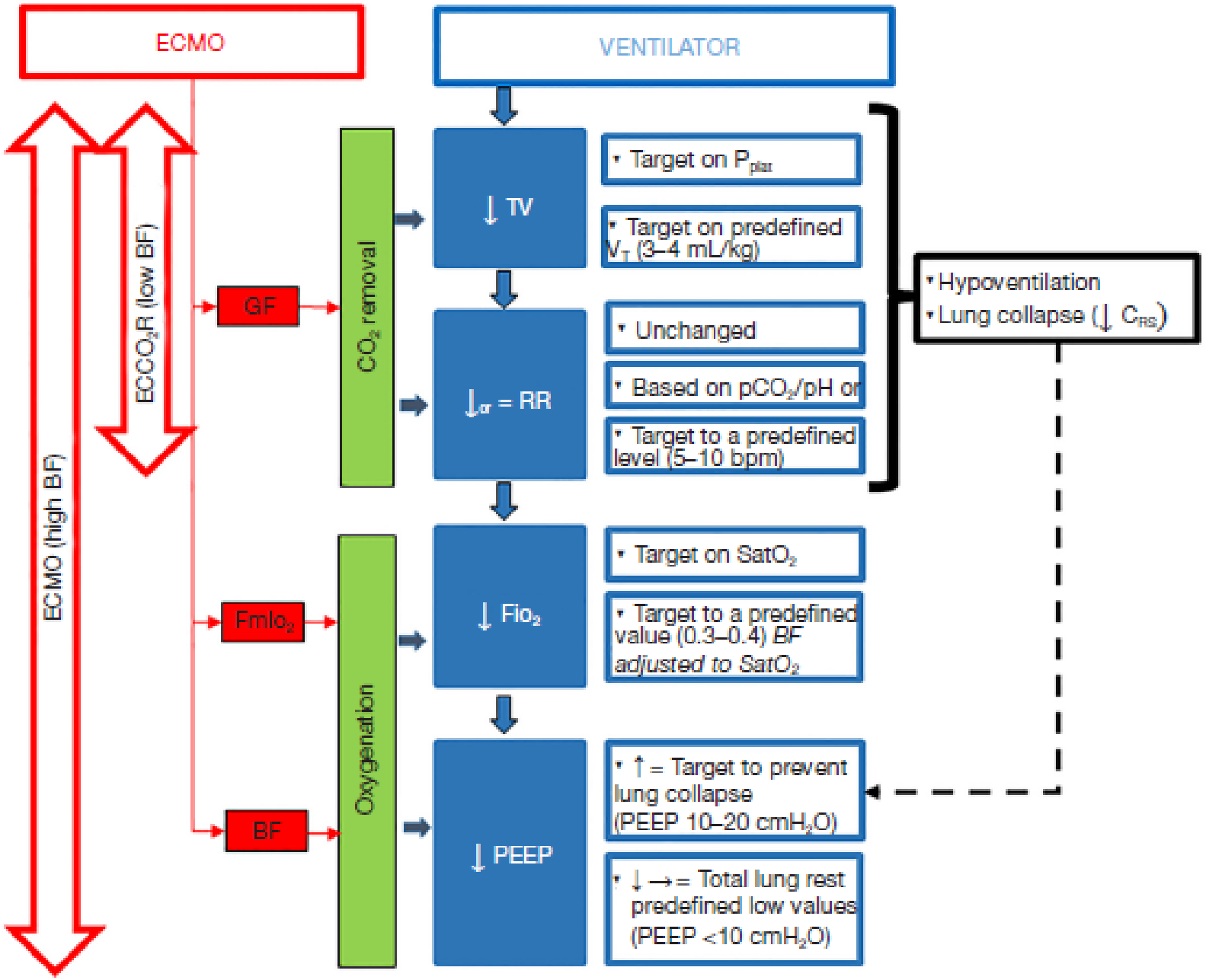
Mechanical Ventilator Settings during ECMO for ARDS

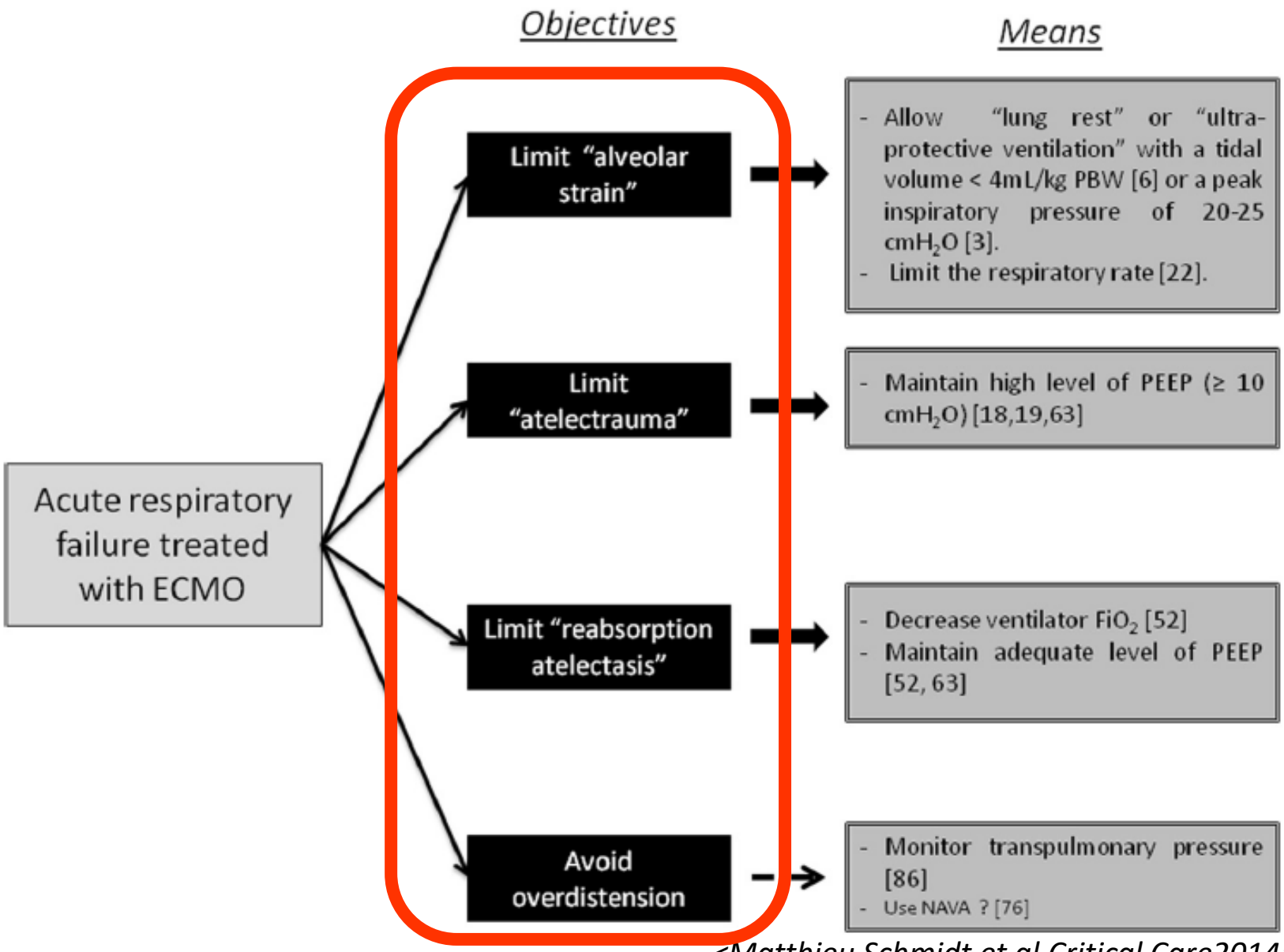
Pre-ECMO factors associated with mortality



Rozencwajg *et al. Critical Care* (2016) 20:392

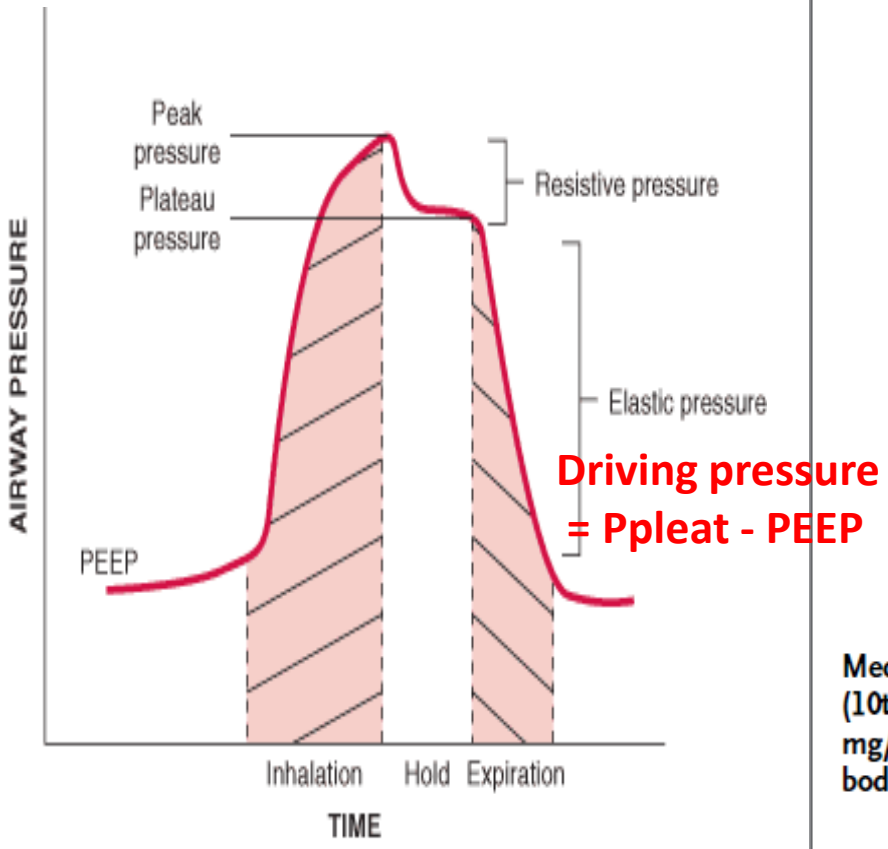

ECMO
VENTILATOR
ECMO (high BF)
ECCO2R (low BF)
GF
FmIo2
BF
CO2 removal
Oxygenation
↓ TV
↓α = RR
↓ Fio2
↓ PEEP
• Target on Pplat
• Target on predefined VT (3–4 mL/kg)
• Unchanged
• Based on pCO2/pH or
• Target to a predefined level (5–10 bpm)
• Target on SatO2
• Target to a predefined value (0.3–0.4) BF adjusted to SatO2
• ↑ = Target to prevent lung collapse (PEEP 10–20 cmH2O)
• ↓ → = Total lung rest predefined low values (PEEP <10 cmH2O)
• Hypoventilation
• Lung collapse (↓ CRS)

Objectives of ECMO for ARDS



<Matthieu Schmidt et al,Critical Care2014;18;203>

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome



Driving pressure = Ppleat - PEEP

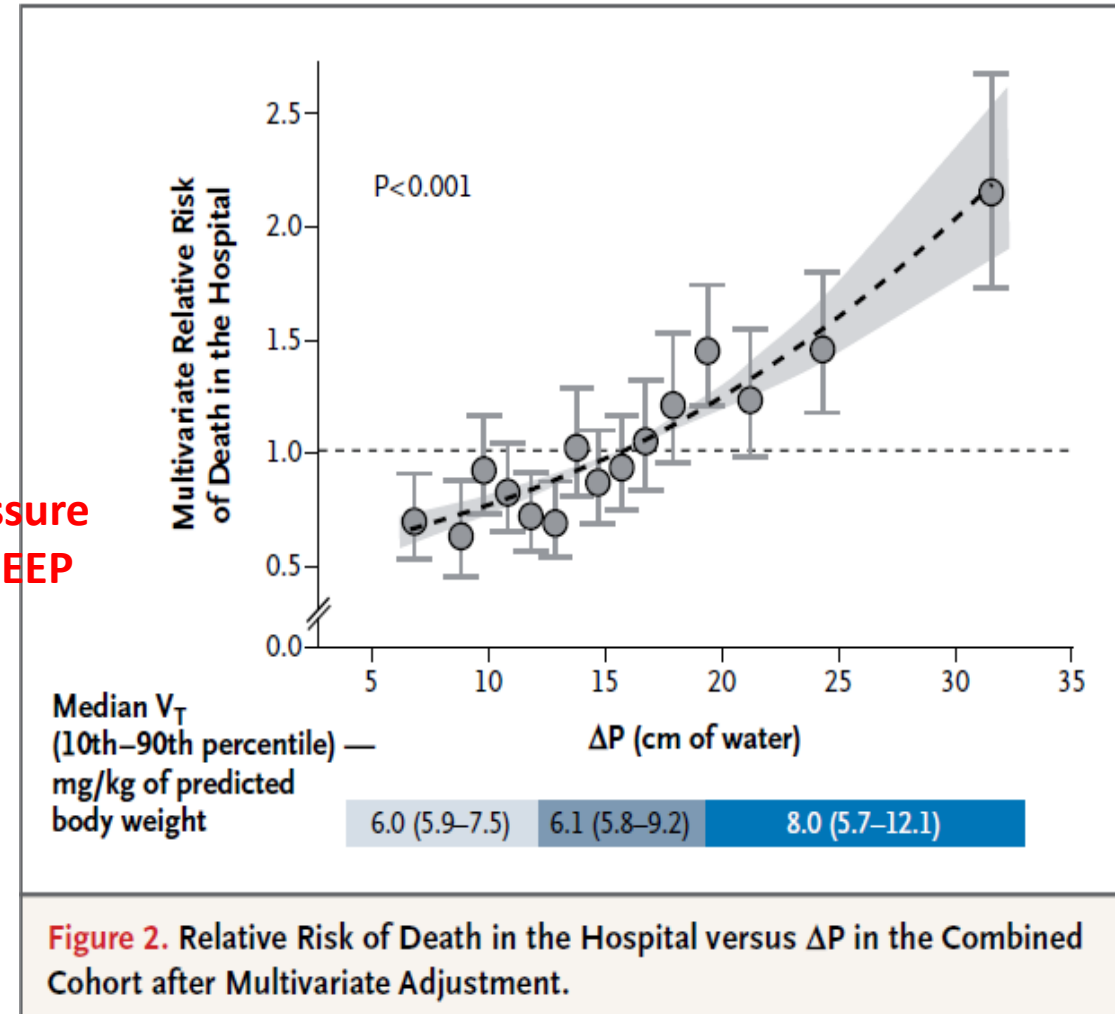
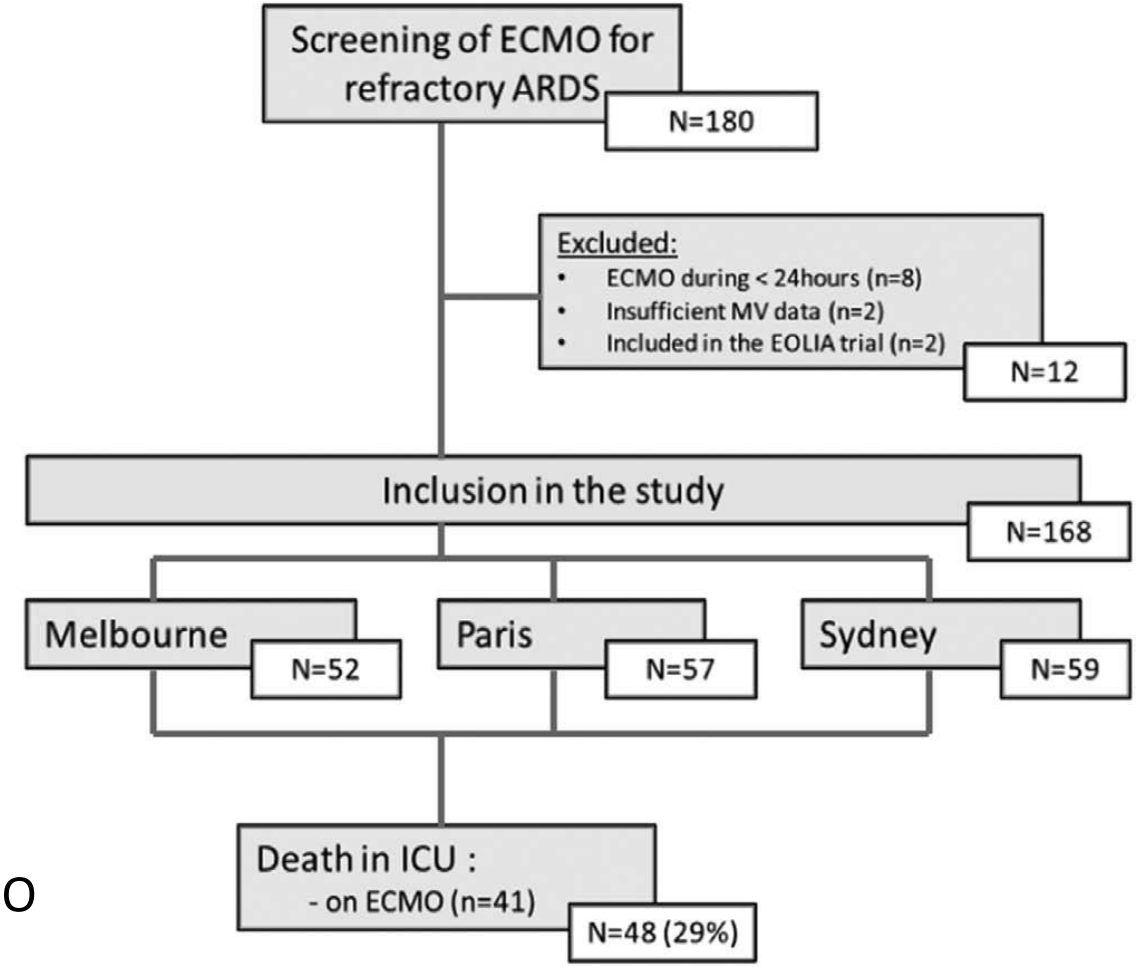


Figure 2. Relative Risk of Death in the Hospital versus ΔP in the Combined Cohort after Multivariate Adjustment.

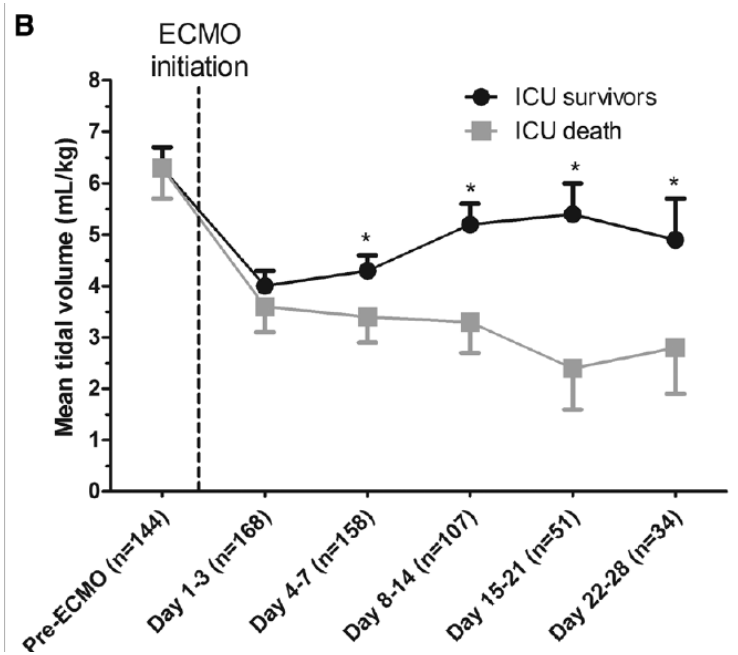
< NEJM 2015;372;8:747-55>

Mechanical Ventilation Management During Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: A Retrospective International Multicenter Study

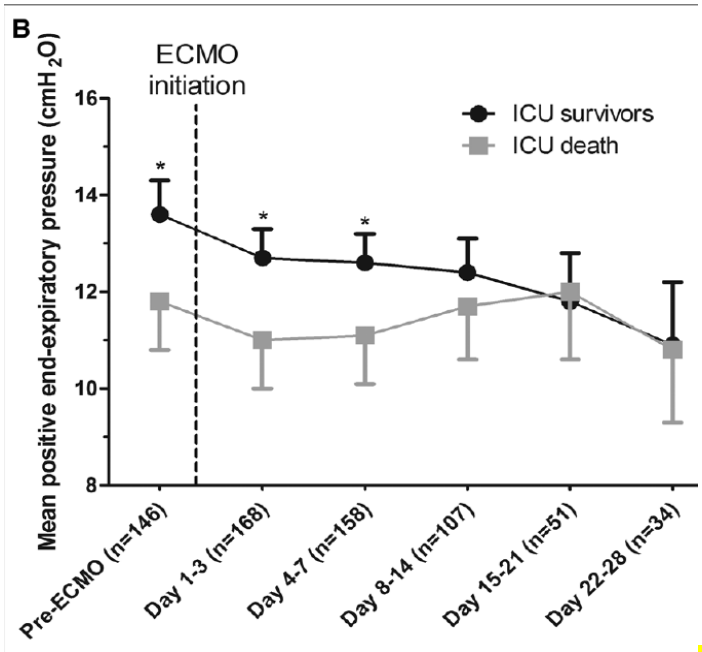


Retrospective
2007/01~2013/01
Australia & France
168 ARDS pts on ECMO
ICU mortality:29%

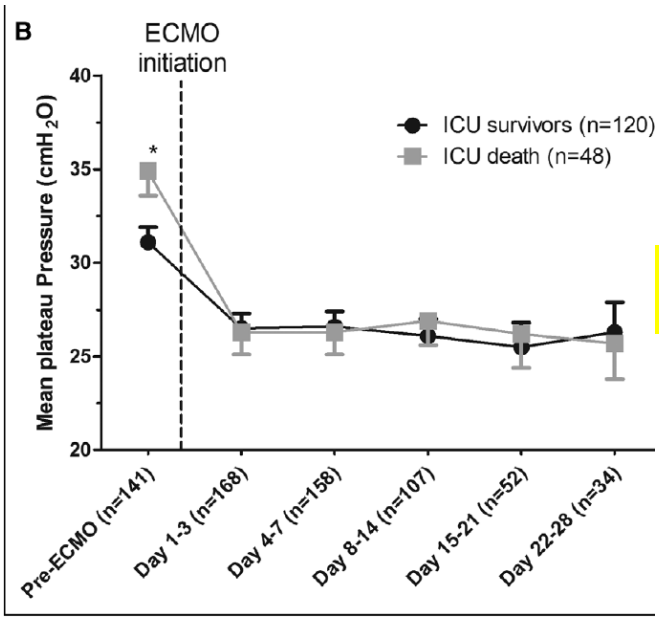
<Matthieu Schmidt et al,CCM2015>



TV during ECMO



PEEP during ECMO



Pplateau during ECMO

<Matthieu Schmidt et al,CCM2015>

Variables associated with ICU death

Variables	ICU Death		Time to ICU Death	
	OR (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
Country (France vs Australia)	0.56 (0.22–1.42)	0.56	0.39 (0.19–0.81)	0.01
Duration between ICU admission and ECMO initiation (d)	1.15 (1.06–1.26)	0.001	1.02 (0.97–1.07)	0.56
Plateau pressure before ECMO > 30 cm H_2O	5.18 (1.88–14.31)	0.02	3.31 (1.53–7.15)	0.002
Mean positive end-expiratory pressure from day 1 to 3 on ECMO	0.75 (0.64–0.88)	0.0006	0.78 (0.69–0.88)	< 0.0001
Lactate at day 3 (log transformed)	4.77 (2.12–10.73)	0.0002	3.64 (2.24–5.92)	< 0.0001

<Matthieu Schmidt et al,CCM2015>

ORIGINAL

Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis

Mechanical ventilation during ECMO

Abstract

Purpose: Extracorporeal membrane oxygenation (ECMO) is a rescue therapy for patients with acute respiratory distress syndrome (ARDS). The aim of this study was to evaluate associations between ventilatory settings during ECMO for refractory hypoxemia and outcome in ARDS patients.

Methods: In this individual patient data meta-analysis of observational studies in adult ARDS patients receiving ECMO for refractory hypoxemia, a time-dependent frailty model was used to determine which ventilator settings in the first 3 days of ECMO had an independent association with in-hospital mortality.

Meta analysis: 9 studies, 545 patients ; Hospital mortality: 35.2 %

<Serpa Meto A et al, Intensive Care Med 2016;42:1672-84>

Table 1 Baseline characteristics of the patients and ventilatory parameters before ECMO

	All ($n = 545$)	Survivors ($n = 353$)	Non-survivors ($n = 192$)	p value[a]
Ventilatory parameters				
Tidal volume, ml/kg PBW	6.0 ± 1.9	6.2 ± 1.8	5.8 ± 2.1	0.032
Tidal volume, ml/kg ABW	4.8 ± 1.8	4.8 ± 1.8	4.9 ± 1.8	0.840
PEEP, cmH_2O	13.7 ± 4.3	13.7 ± 4.0	13.6 ± 5.0	0.733
FiO_2, %	0.90 ± 0.17	0.91 ± 0.17	0.91 ± 0.16	0.944
Plateau pressure, cmH_2O	31.1 ± 5.7	30.7 ± 5.2	32.2 ± 6.3	0.032
Driving pressure, cmH_2O	17.7 ± 6.8	16.9 ± 6.4	19.4 ± 7.3	0.004
Respiratory rate, bpm	21.9 ± 7.9	21.2 ± 6.9	23.2 ± 9.4	0.012
Minute ventilation, l/min	9.1 ± 3.9	9.0 ± 3.7	9.2 ± 4.2	0.644
Static compliance[c]	26.8 ± 16.9	27.7 ± 17.6	24.8 ± 15.2	0.178
Laboratory parameters				
PaO_2, mmHg	64.8 ± 21.2	64.4 ± 23.2	65.2 ± 20.2	0.715
PaO_2/FiO_2, mmHg	72.6 ± 38.5	73.2 ± 38.6	71.3 ± 39.0	0.610
$PaCO_2$, mmHg	58.3 ± 22.7	57.3 ± 22.1	60.3 ± 23.8	0.206
pHa	7.27 ± 0.15	7.29 ± 0.14	7.24 ± 0.16	0.008
Lactate, mg/dL	33.5 ± 36.4	29.4 ± 23.6	42.1 ± 42.1	0.031

Before ECMO: associated with survival

TV(PBW); Pplateau; Driving pressure; RR

Ventilator parameters on First day of ECMO

	All ($n = 545$)	Survivors ($n = 353$)	Non-survivors ($n = 192$)	p value[a]
Ventilatory parameters				
Tidal volume, ml/kg PBW	4.0 ± 1.7	4.0 ± 1.6	4.0 ± 1.9	0.934
Tidal volume, ml/kg ABW	3.2 ± 1.6	3.1 ± 1.5	3.4 ± 1.8	0.075
PEEP, cmH_2O	12.9 ± 3.4	13.0 ± 3.3	12.5 ± 3.7	0.125
FiO_2	0.69 ± 0.24	0.67 ± 0.23	0.74 ± 0.23	0.005
Plateau pressure, cmH_2O	26.2 ± 4.6	26.0 ± 4.3	26.7 ± 5.1	0.205
Driving pressure, cmH_2O	13.7 ± 5.3	13.3 ± 4.8	14.5 ± 6.2	0.048
Respiratory rate, bpm	17.8 ± 8.0	17.4 ± 7.7	18.7 ± 8.7	0.105
Minute ventilation, l/min	5.0 ± 3.2	4.8 ± 2.9	5.3 ± 3.3	0.117
Static compliance[b]	23.2 ± 18.8	22.7 ± 16.9	24.1 ± 22.3	0.564

First day of ECMO: associated with survival

FiO2; Driving pressure

Table 3 Multivariable time-dependent frailty model with in-hospital mortality as the primary outcome

	HR (95 %CI), *p*
Age, years	1.01 (1.00–1.02), 0.006
Gender, male	1.63 (1.21–2.21), 0.001
BMI, kg/m^2	0.95 (0.93–0.97), <0.001
Risk of death, %[a]	1.01 (0.99–1.01), 0.063
SOFA	1.03 (0.98–1.07), 0.252
Time between MV-ECMO	
≤24 h	1.00 (Reference)
24–72 h	0.70 (0.45–1.09), 0.112
>72 h	0.78 (0.58–1.05), 0.103
Indication of ECMO	
Hypoxemia	0.96 (0.34–2.70), 0.935
Hypercapnia	1 (Reference)
Ventilatory parameters	
PEEP, cmH_2O	–
FiO_2, %	0.96 (0.40–2.30), 0.924
Driving pressure, cmH_2O	1.06 (1.03–1.10), <0.001
Respiratory rate, bpm	–
Laboratory parameters	
PaO_2/FiO_2, mmHg	1.00 (0.99–1.00), 0.431
$PaCO_2$, mmHg	0.99 (0.99–1.01), 0.891
Lactate, mg/dL	1.00 (1.00–1.01), 0.005
Hemodynamics (pre-ECMO)	
Norepinephrine, µg/kg/min[b]	1.07 (0.88–1.29), 0.518

Multivariable parameter associated with hospital mortality:

Age; Gender; BMI;

Driving pressure; Lactate

<Serpa Neto A et al, Intensive Care Med 2016;42:1672-84>

RESEARCH Open Access

Dynamic driving pressure associated mortality in acute respiratory distress syndrome with extracorporeal membrane oxygenation

Li-Chung Chiu[1*], Han-Chung Hu[1,2,3], Chen-Yiu Hung[1], Chih-Hao Chang[1], Feng-Chun Tsai[4], Cheng-Ta Yang[1,2], Chung-Chi Huang[1,2,3], Huang-Pin Wu[5] and Kuo-Chin Kao[1,2,3]

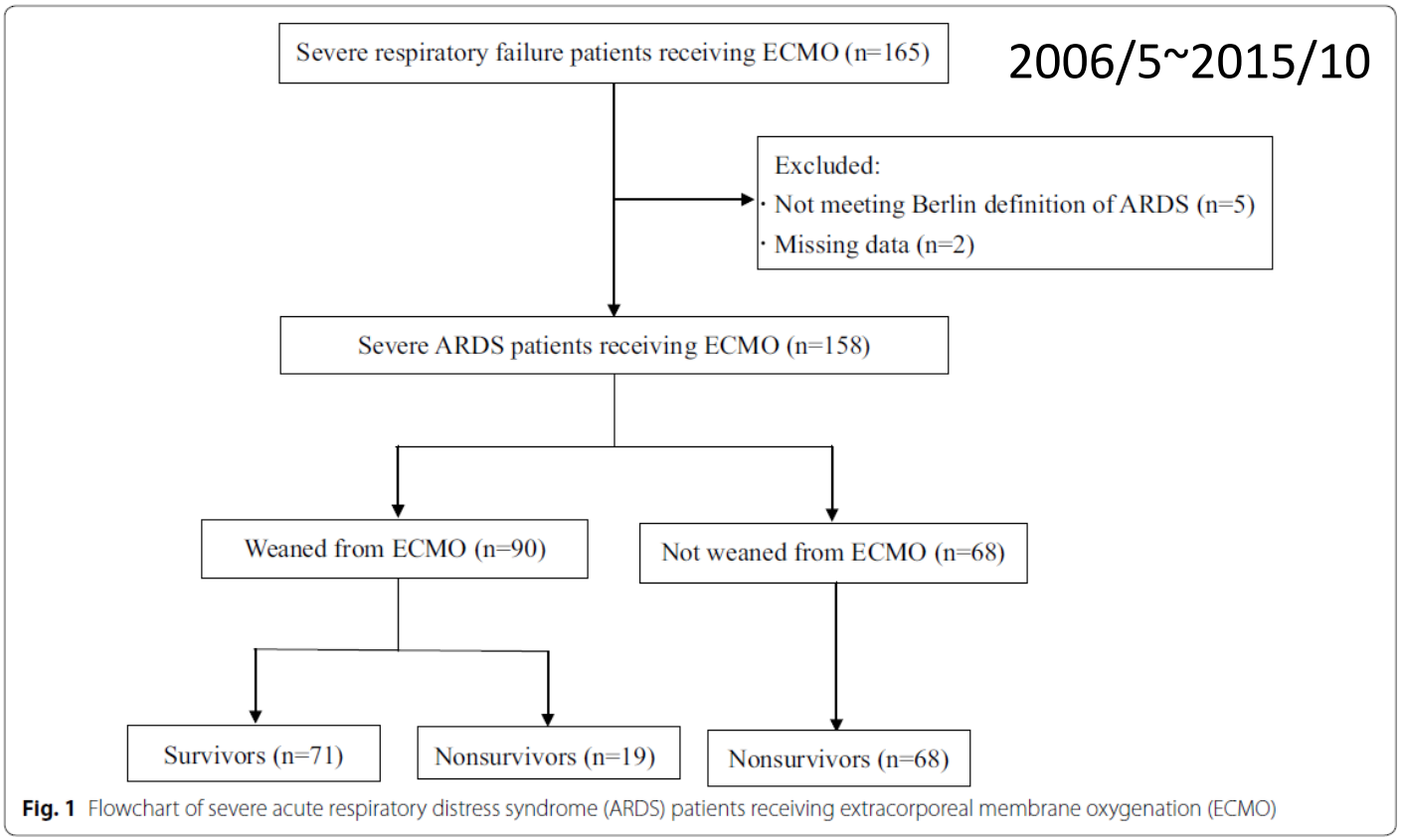


Fig. 1 Flowchart of severe acute respiratory distress syndrome (ARDS) patients receiving extracorporeal membrane oxygenation (ECMO)

<LC Chiu et al, Ann. Intensive Care 2017;7:12>

Table 2 Cox proportional hazards regression model with ICU mortality as outcome

Factors	Hazard ratio (95% CI)	*p* value
Univariate analysis		
Age	1.011 (0.998–1.025)	0.108
Pulmonary contusion	0.417 (0.181–0.958)	0.039
Aspiration pneumonia	0.405 (0.128–1.285)	0.125
Diabetes mellitus	0.635 (0.373–1.083)	0.096
Chronic liver disease	1.611 (0.931–2.788)	0.088
Immunocompromised	1.731 (1.115–2.689)	0.015
APACHE II score	1.032 (1.004–1.062)	0.027
Lung injury score	0.596 (0.374–0.951)	0.030
ARDS duration before ECMO	1.002 (1.001–1.003)	0.001
Mean PEEP from day 1 to 3 on ECMO	0.942 (0.877–1.013)	0.106
Mean dynamic driving pressure from day 1 to 3 on ECMO	1.052 (1.015–1.090)	0.005
Mean dynamic compliance from day 1 to 3 on ECMO	0.971 (0.941–1.002)	0.069
Multivariate analysis		
Immunocompromised	1.957 (1.216–3.147)	0.006
APACHE II score	1.039 (1.005–1.073)	0.023
ARDS duration before ECMO	1.002 (1.000–1.003)	0.029
Mean dynamic driving pressure from day 1 to 3 on ECMO	1.070 (1.026–1.116)	0.002

Multivariable parameter associated with ICU mortality:
Immunocompromise; APACHE II score; ARDS duration before ECMO;
Dynamic Driving Pressure from D 1-3

<LC Chiu et al, Ann. Intensive Care 2017;7:12>

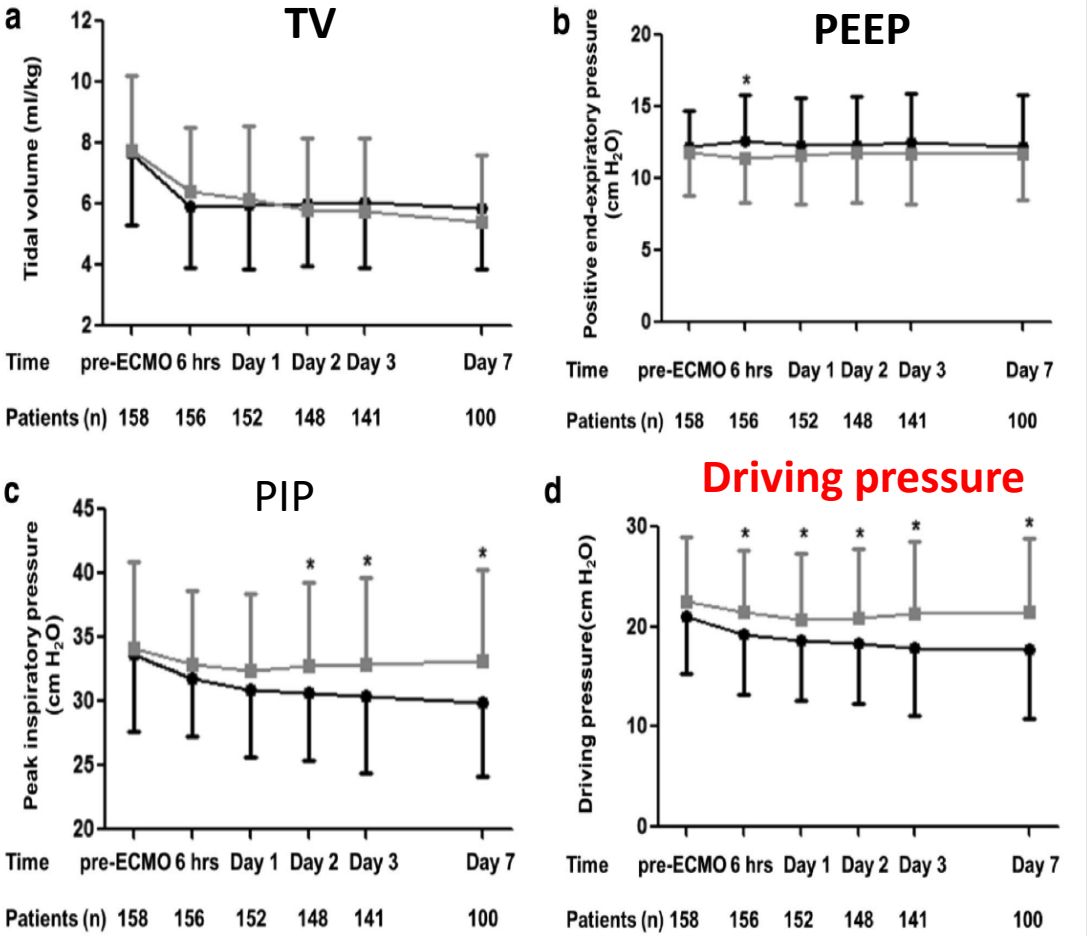


Fig. 2 Serial changes in **a** tidal volume, **b** positive end-expiratory pressure (PEEP), **c** peak inspiratory pressure and **d** dynamic driving pressure before and after extracorporeal membrane oxygenation (ECMO). *Error bars* represent the mean ± standard error. *Dark line* denotes survivors and *gray line* denotes nonsurvivors. *A value of *p* less than 0.05 compared between survivors and nonsurvivors

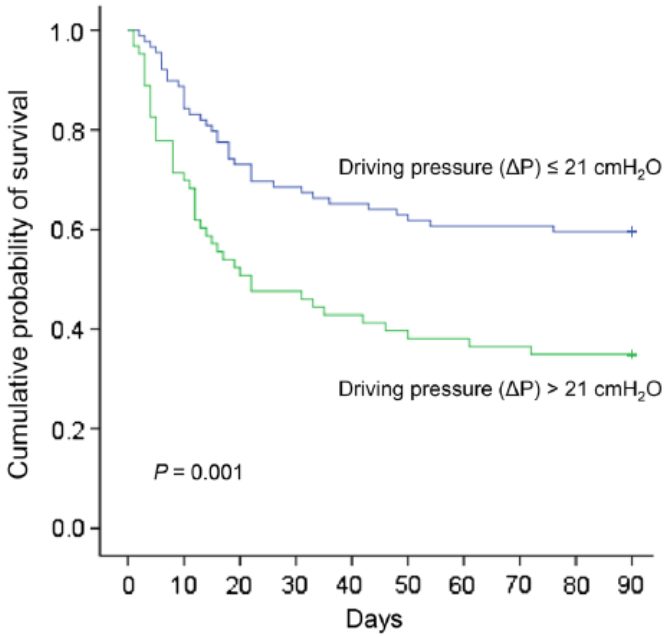
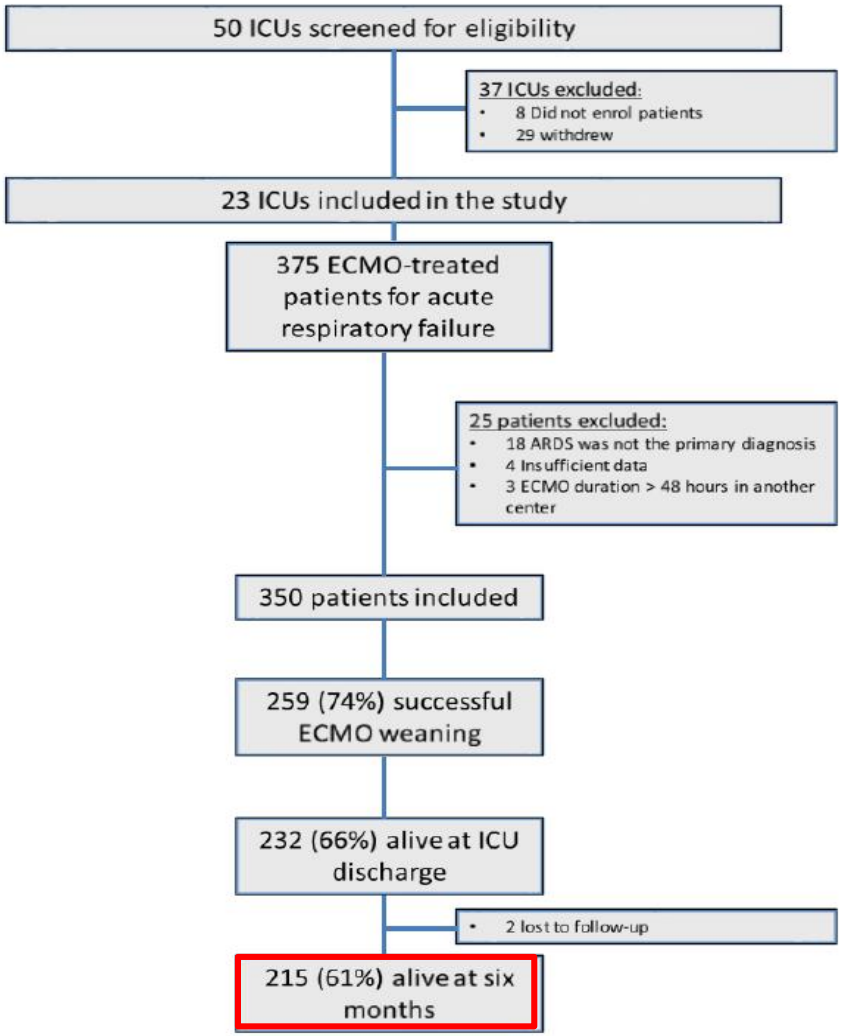


Fig. 4 Kaplan–Meier survival curves in patients with severe acute respiratory distress syndrome (ARDS) on extracorporeal membrane oxygenation (ECMO). *Blue line* denotes patients with mean dynamic driving pressure ≦21 cm H_2O, and *green line* denotes patients with mean dynamic driving pressure >21 cm H_2O from day 1 to 3 on ECMO. The overall survival rate of patients with dynamic driving pressure ≦21 cm H_2O was significantly higher than those with dynamic driving pressure >21 cm H_2O (56.1 vs. 33.3%, $p = 0.001$)

<LC Chiu et al, Ann. Intensive Care 2017;7:12>

Mechanical Ventilation Management during Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome

An International Multicenter Prospective Cohort



74% successful ECMO weaning

65% ICU survival

61% 6 months survival

<M Schmidt et al Am J Respir Crit Care Med, 2019; 200(8):1002-1012 >

Table 1. Baseline Characteristics and Clinical Biological Findings at the Time of ECMO Initiation according to 6-Month Survival Status

Characteristics	All Patients (*n* = 350)	Status 6 Months after ICU Admission		*P* Value
		Nonsurvivors (*n* = 133)	Survivors (*n* = 215)	
Sex, M	227 (65)	89 (67)	136 (63)	0.56
Age, yr	46 ± 17	52 ± 18	43 ± 15	<0.001
APACHE II score	24 ± 11	27 ± 12	22 ± 10	<0.001
SOFA score at ICU admission	7.8 ± 4.1	7.8 ± 4.4	7.9 ± 3.8	0.90
Body mass index, kg/m^2	28.7 ± 8.5	27.0 ± 7.4	29.8 ± 9.2	0.002
Immunodeficiency	79 (23)	50 (38)	29 (13)	<0.001
ARDS etiologies				0.02
Bacterial pneumonia	116 (33)	49 (37)	65 (30)	
Viral pneumonia*	90 (26)	21 (16)	69 (32)	
Aspiration pn				
Trauma/burns				
Post–lung tra				
Pancreatitis				
Pulmonary vasculitis	4 (1)	2 (1)	2 (1)	
Miscellaneous	65 (19)	32 (24)	33 (15)	
Pre-ECMO ventilation parameters				
$F_{I_{O_2}}$, %	100 (100–100)	100 (100–100)	100 (100–100)	0.91
Mechanical power, J/min*	26.1 ± 12.7	25.9 ± 13.1	26.1 ± 12.5	0.91
V_T, ml/kg IBW	6.4 ± 2.0	6.2 ± 1.8	6.5 ± 2.1	0.16
Respiratory rate, breaths/min	26 ± 8	27 ± 8	25 ± 7	0.02
Spontaneous respiratory rate, breaths/min	9 ± 13	10 ± 14	7 ± 13	0.06
Plateau pressure, cm H_2O†	32 ± 7	32 ± 8	32 ± 7	0.77
PEEP, cm H_2O	12 ± 4	12 ± 4	13 ± 4	0.01
Driving pressure, cm H_2O‡	20 ± 7	20 ± 7	19 ± 8	0.28
Static compliance, ml/cm H_2O§	24 ± 12	22 ± 11	25 ± 12	0.01
V_D/V_T ratio	0.70 (0.59–0.77)	0.73 (0.62–0.80)	0.67 (0.58–0.75)	0.001
Ventilatory ratio	2.7 ± 1.3	2.8 ± 1.3	2.6 ± 1.3	0.09
Pre-ECMO blood gases				
pH	7.24 ± 0.15	7.22 ± 0.15	7.26 ± 0.14	0.01
Pa_{CO_2}, mm Hg	68 ± 27	66 ± 26	62 ± 27	0.17
HCO_3^-, mmol/				0.54
Sa_{O_2}, %				0.62
Arterial lactate				0.66
$Pa_{O_2}/F_{I_{O_2}}$, mm				0.48

Better 6-month survival :
Young Age; Low APACHE II score; High BMI; Non Immunodeficiency

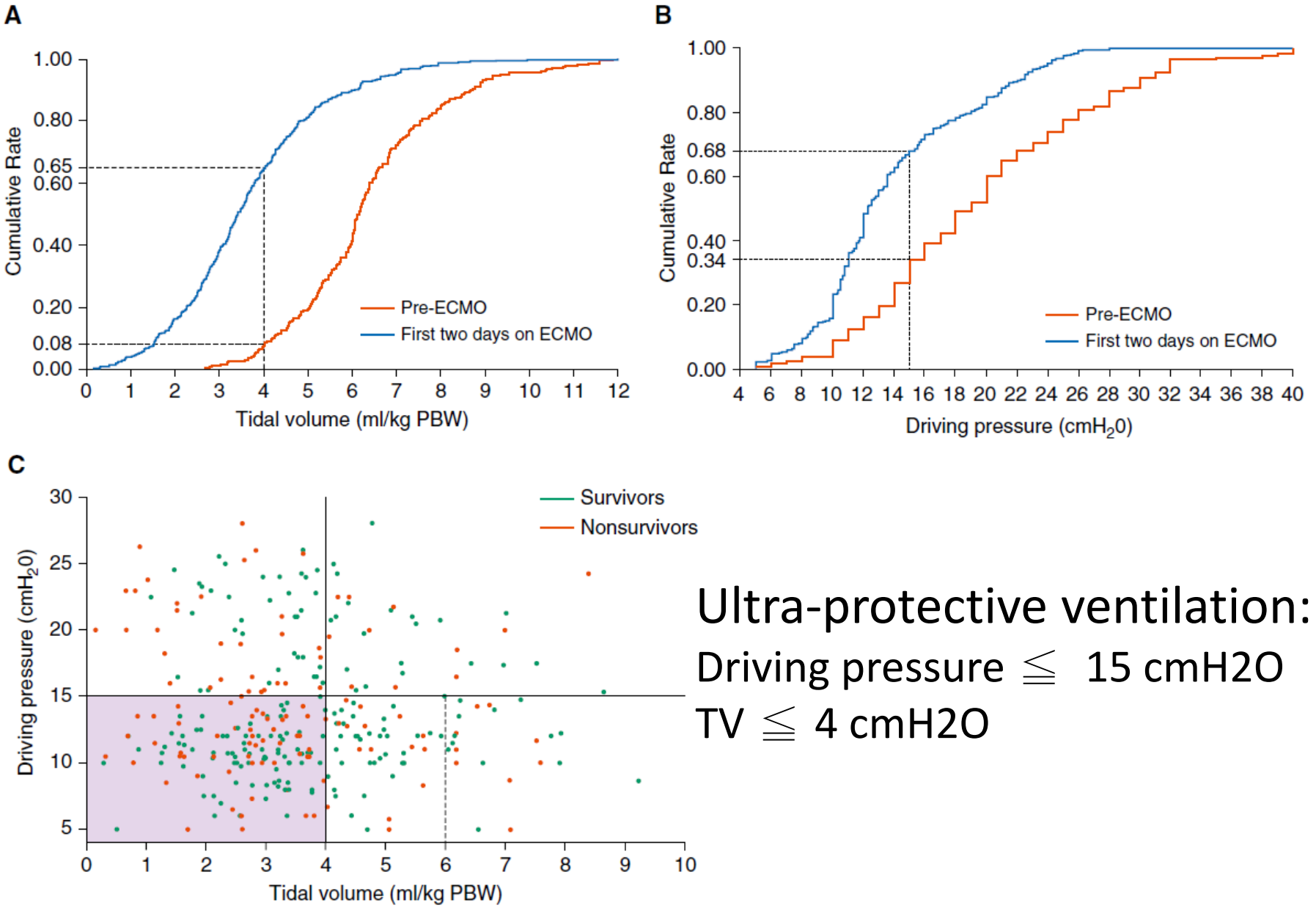
Better 6-month survival :
Lower RR; Higher PEEP; Higher compliance; Lower Vd/Vt; Higher pH

<M Schmidt et al Am J Respir Crit Care Med, 2019; 200(8):1002-1012 >

Table 2. ECMO Management and ECMO-related Complications during the First 2 Days according to 6-Month Survival Status

Parameter	All Patients (*n* = 350)	Status 6 Months after ICU Admission		*P* Value
		Nonsurvivors (*n* = 133)	Survivors (*n* = 215)	
Fluid balance, ml	1,191 ± 2,184	1,857 ± 2,477	783 ± 1,879	<0.001
Ventilation settings				
F_{IO_2}, %	50 (40–68)	54 (40–66)	54 (40–67)	0.79
Mechanical power, J/min*	6.6 ± 4.8	6.7 ± 5.0	6.5 ± 4.5	0.77
V_T, ml/kg IBW	3.7 ± 2.0	3.5 ± 1.8	3.8 ± 2.0	0.17
Total respiratory rate, breaths/min	14 ± 6	14 ± 6	13 ± 5	0.17
Spontaneous respiratory rate, breaths/min†	8 ± 11	10 ± 13	6 ± 10	0.01
Plateau pressure, cm H_2O‡	24 ± 7	24 ± 7	25 ± 6	0.30
Static compliance, ml/cm H_2O§	19 ± 12	18 ± 12	20 ± 11	0.25
PEEP, cm H_2O	11 ± 3	11 ± 3	11 ± 3	0.04
Driving pressure, cm H_2O‖	14 ± 4	14 ± 5	14 ± 5	0.64
ECMO settings				
Blood flow, L/min	4.2 ± 1.0	4.1 ± 1.1	4.2 ± 1.0	0.27
Sweep gas flow, L/min	5.2 ± 2.3	5.4 ± 2.2	5.1 ± 2.3	0.25
FdO_2, %	100 (100–100)	100 (100–100)	100 (100–100)	0.77
Blood gas				
pH	7.40 ± 0.07	7.38 ± 0.09	7.41 ± 0.06	0.004
Pa_{CO_2}, mm Hg	42 ± 7	41 ± 8	42 ± 6	0.16
Pa_{O_2}, mm Hg	93 ± 33	94 ± 36	92 ± 31	0.57
HCO_3^-, mmol/L	26 ± 5	24 ± 6	26 ± 5	0.003
Sa_{O_2}, %	95 (93–97)	95 (93–97)	95 (93–97)	0.84
Arterial lactate, mmol/L	2.5 ± 2.5	3.3 ± 3.3	2.1 ± 1.6	<0.001
Neuromuscular blockers	142 (41)	56 (42)	85 (39)	0.72
Prone positioning	20 (6)	8 (6)	12 (6)	0.85
Renal-replacement therapy	113 (32)	55 (41)	57 (26)	0.006
ECMO-related major bleeding	29 (8)	15 (11)	14 (6)	0.17
Major hemolysis	5 (1)	4 (3)	13 (6)	0.07

<*M Schmidt et al Am J Respir Crit Care Med, 2019; 200(8):1002-1012* >



Ultra-protective ventilation:

Driving pressure ≦ 15 cmH2O

TV ≦ 4 cmH2O

Figure 2. Mechanical ventilation during the first 2 days on extracorporeal membrane oxygenation (ECMO). Shown is the cumulative frequency distribution of (*A*) V_T and (*B*) driving pressure before ECMO and during the first 2 days on ECMO. (*C*) Distribution of Day 1 and Day 2 V_T versus driving pressure for each patient for which these data are available. One hundred forty patients (mortality 39%) fell within the limits for ultraprotective ventilation, defined as driving pressure ≤15 cm H_2O and V_T of ≤4 ml/kg of predicted body weight. PBW = predicted body weight.

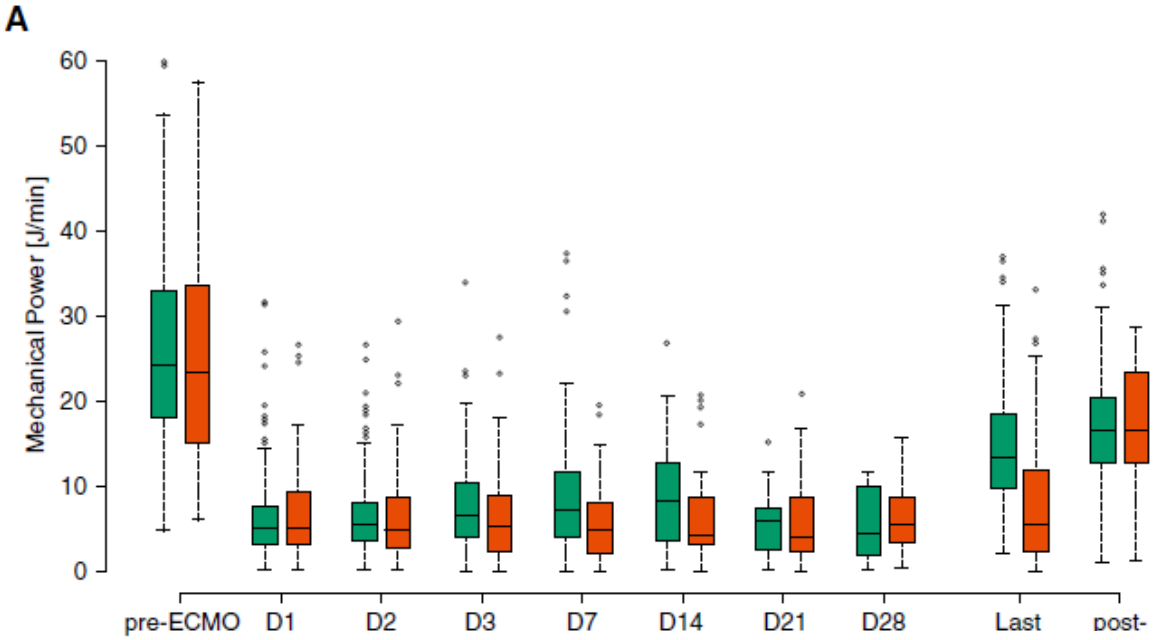
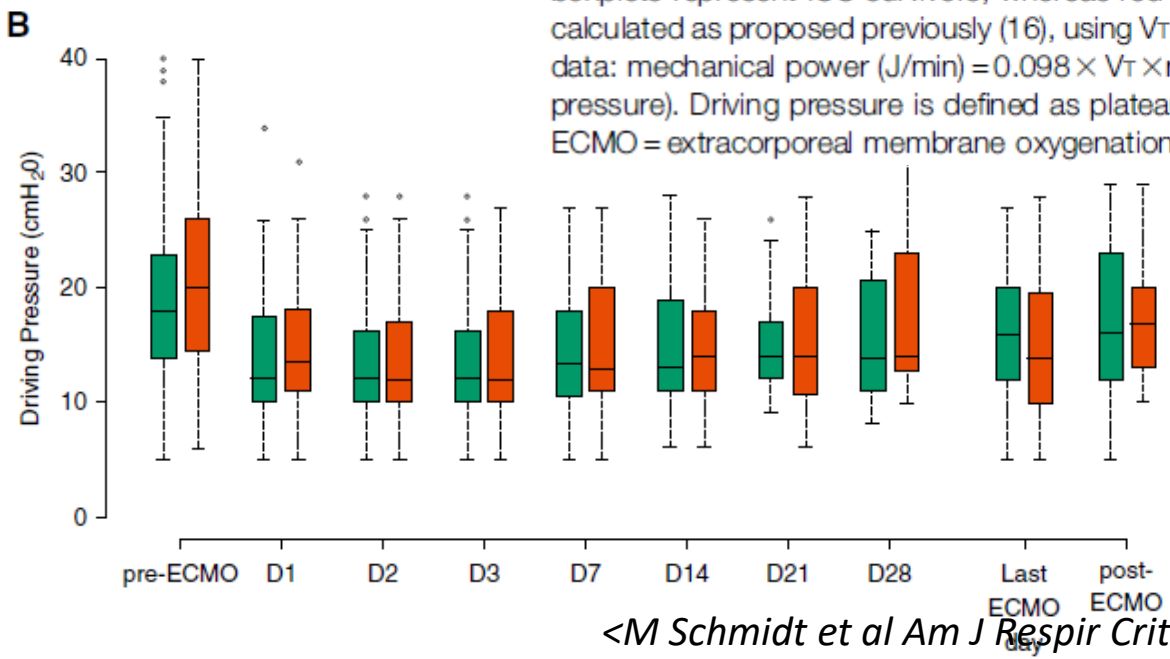


Figure 3. Median and interquartile range of the mechanical power (*A*) and the driving pressure (*B*) during the extracorporeal membrane oxygenation course according to time and ICU outcome. Green boxplots represent ICU survivors, whereas red boxplots are nonsurvivors. Mechanical power was calculated as proposed previously (16), using V_T, peak pressure, respiratory rate, and driving pressure data: mechanical power (J/min) = 0.098 × V_T × respiratory rate × (peak pressure − 1/2 × driving pressure). Driving pressure is defined as plateau pressure – positive end-expiratory pressure. ECMO = extracorporeal membrane oxygenation.



<M Schmidt et al Am J Respir Crit Care Med, 2019; 200(8):1002-1012 >

Table 3. Ventilatory Adjuvant Therapies on ECMO and ECMO-related Complications according to 6-Month Survival Status

Parameter	All Patients (*n* = 350)	Status 6 Months after ICU Admission		*P* Value
		Nonsurvivors (*n* = 133)	Survivors (*n* = 215)	
Ventilatory adjuvant therapies on ECMO				
Neuromuscular blockers	179 (51)	77 (58)	101 (47)	0.06
Prone positioning	53 (15)	17 (13)	36 (17)	0.40
First day of proning	4 (2–6)	4 (2–6)	4 (2–7)	0.956
Prone within 3 d of ECMO	25 (7)	9 (7)	16 (7)	0.900
Nitric oxide/prostacyclin	53 (15)	20 (15)	33 (15)	1.00
Refractory hypoxemia within 7 d of ECMO*	49 (14)	31 (14)	17 (13)	0.78
Renal-replacement therapy on ECMO	177 (51)	84 (63)	92 (43)	<0.001
Tracheotomy on ECMO	162 (46)	58 (44)	103 (48)	0.54
ECMO-related major bleeding	87 (25)	44 (33)	43 (20)	0.009
Transfused RBC units	5 (2–11)	8 (4–20)	4 (1–7)	<0.001
Transfused platelet units	0 (0–5)	1 (0–12)	0 (0–2)	<0.001
Fibrinogen transfusion on ECMO	28 (8)	9 (7)	19 (9)	0.63
Others complications on ECMO				
Major hemolysis	34 (10)	19 (14)	15 (7)	0.04
Cardiac arrest	37 (11)	29 (22)	8 (4)	<0.001
Pneumothorax	33 (9)	19 (14)	14 (6)	0.03
Outcomes				
ECMO duration, d	10 (6–18)	14 (6–28)	9 (6–14)	<0.001
Successful weaning	259 (74)	42 (32)	215 (100)	<0.0001
Mechanical ventilation duration, d	18 (11–34)	21 (10–36)	17 (11–32)	0.25
Alive at ICU discharge	232 (66)	15 (11)	215 (100)	<0.0001
ICU length of stay, d	24 (14–39)	24 (11–41)	24 (15–39)	0.39
Hospital length of stay, d	35 (20–55)	32 (14–50)	38 (22–57)	0.02

<M Schmidt et al Am J Respir Crit Care Med, 2019; 200(8):1002-1012 >

Table 4. Predictors of 6-Month Mortality of Patients with Severe ARDS Rescued by ECMO

Variable	OR (95% CI)	*P* Value
Pre-ECMO		
Age, per additional year	1.03 (1.02–1.05)	<0.001
Immunocompromised condition	3.85 (2.11–7.17)	<0.001
Extrapulmonary sepsis	2.32 (1.18–4.56)	0.014
Delay from intubation to the initiation of ECMO, for each day	1.08 (1.03–1.14)	0.004
pH, for 0.01 unit	0.98 (0.96–0.99)	0.004
Pre- and early post-ECMO		
Age, per additional year	1.03 (1.01–1.05)	<0.001
Immunocompromised condition	3.81 (2.10–7.02)	<0.001
Extrapulmonary sepsis	2.61 (1.30–5.30)	0.007
Delay from intubation to the initiation of ECMO, for each day	1.11 (1.05–1.18)	<0.001
Lactate in the first 2 d on ECMO, for 1 mmol/L	1.15 (1.01–1.33)	0.043
Fluid balance in the first 2 d on ECMO, for 1 L	1.28 (1.11–1.50)	0.001

No association found between MV settings during the first 2 days of ECMO and survival in the multivariable analysis

<M Schmidt et al Am J Respir Crit Care Med, 2019; 200(8):1002-1012 >

Table 5. Multivariable Cox Model with Time-fixed and Time-Dependent Covariates

Variable	HR (95% CI)	*P* Value
Time fixed		
Age, per additional year	1.01 (1.01–1.03)	0.003
Immunocompromised condition	1.43 (0.94–1.02)	0.09
Time from intubation to the initiation of ECMO, for each day	0.99 (0.96–1.01)	0.343
APACHE II score	1.00 (0.98–1.02)	0.828
Time dependent		
Driving pressure, for 1 cm H_2O	1.03 (1.01–1.07)	0.03
V_T, for 1 ml/kg PBW	0.71 (0.65–0.78)	<0.001
Fluid balance, for 1 L	1.11 (1.04–1.18)	0.003
Lactate, for 1 mmol	1.30 (1.24–1.37)	<0.001
Renal-replacement therapy	1.64 (1.21–2.48)	0.003

The Cox model with time-fixed and time-dependent covariates retained older age, higher fluid balance, higher lactate, and more use of RRT along the ECMO course as being associated with an increased hazard of death

<M Schmidt et al Am J Respir Crit Care Med, 2019; 200(8):1002-1012 >

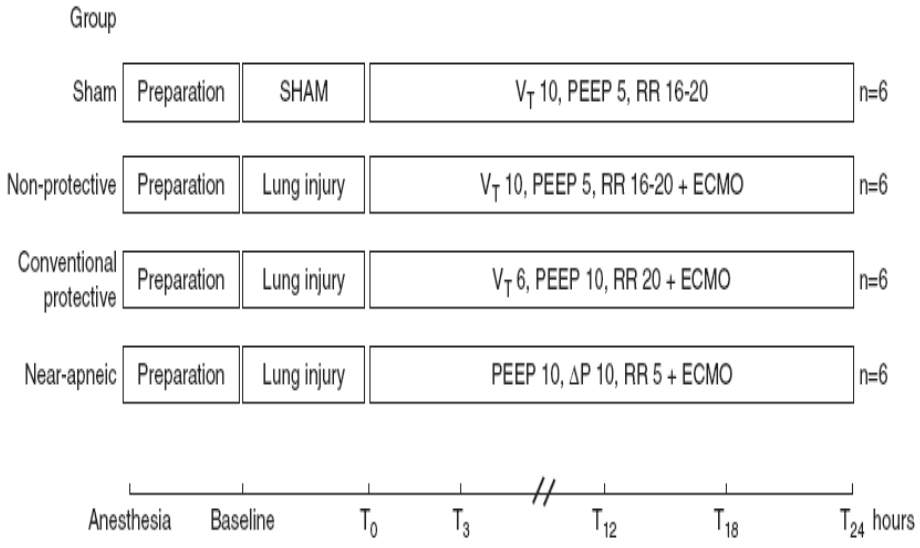
May MV settings impact on Survival?

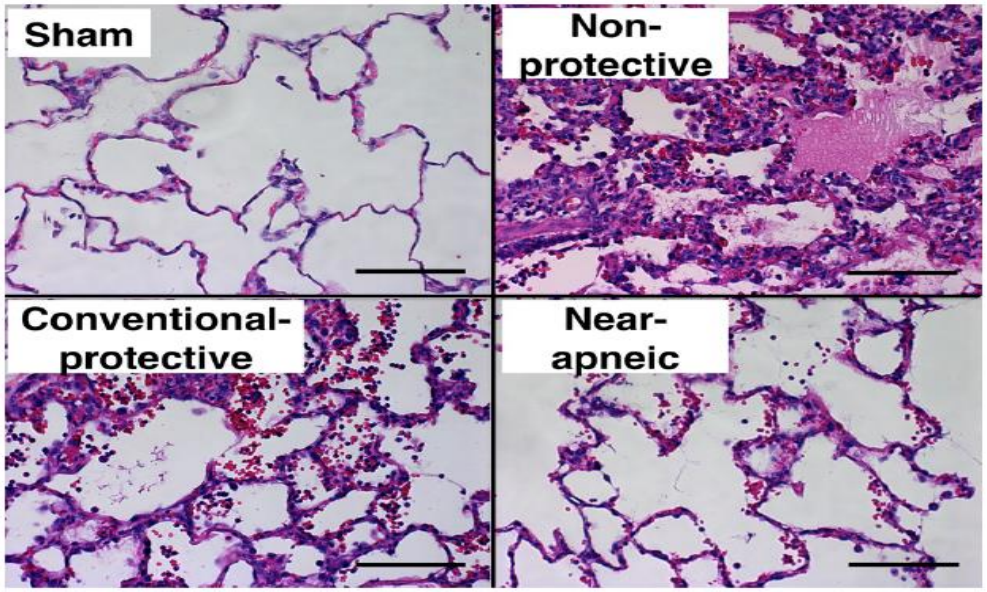
- Ultra-protective lung ventilation on ECMO was largely adopted across medium– to high–case volume ECMO centers.
- In contrast with previous observations, mechanical ventilation settings during ECMO did not impact patients' prognosis in this context.
- Homogeneous "ultra-protective" ventilation strategy with optimized ECMO settings in the experienced centers

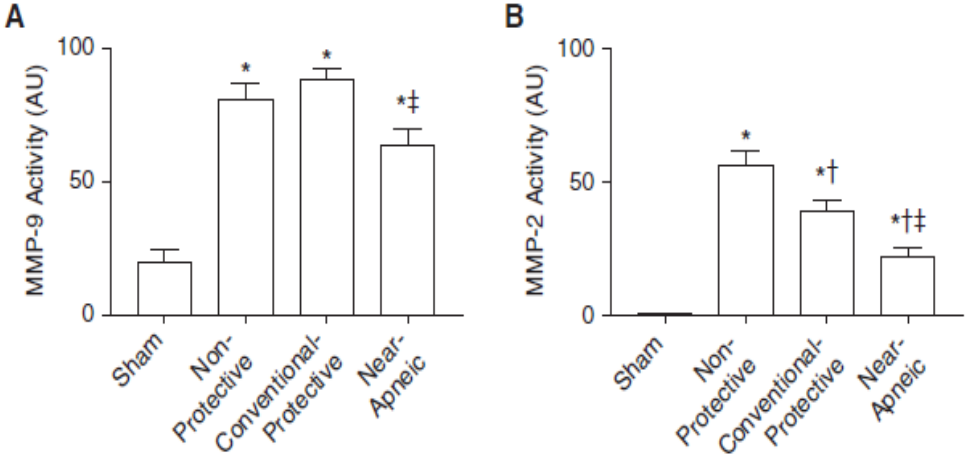
→ Lower driving pressure was set so unlikely to be prognostic factor

<M Schmidt et al Am J Respir Crit Care Med, 2019; 200(8):1002-1012 >

Near-Apneic Ventilation Decreases Lung Injury and Fibroproliferation in an Acute Respiratory Distress Syndrome Model with Extracorporeal Membrane Oxygenation







Am J Respir Crit Care Med Vol 199, Iss 5, pp 603–612, Mar 1, 2019

Conclusion

- "Ultra-protective ventilation" strategy

  (significantly lower plateau pressure, Vt and DP)

→ significantly reduced pulmonary biotrauma

- Plasma cytokine and bronchoalveolar lavage sRAGE levels did not differ among the different mechanical ventilation settings tested during ECMO
  - But all under ultra-protective ventilation

<S Rozencwajg et al Crit Care Med, 2019; Epub>

Outlines

- Introduction of ARDS
  - Lung protective strategy in ARDS
- ECMO in ARDS
- MV setting in ARDS with ECMO
- Summary

In conclusions

Experts' Opinion regarding MV in ECMO for ARDS

Source	Mechanical ventilation settings	Notes
ECMO for severe ARDS		
ELSO guidelines [22]	Reasonable initial ventilator settings during ECMO could be:	'These guidelines describe useful and safe practice, but these are not necessarily consensus recommendations. These guidelines are not intended as a standard of care …
	• decelerating flow (pressure control)	Once patients stabilize and sedation can be lightened, spontaneous ventilation with pressure support ventilation can be considered
	• modest PEEP (for example, 10 cmH_2O)	
	• low inflation pressure (for example, 10 cmH_2O above PEEP)	
	• respiratory frequency 4 to 5 breaths per minute	
European Network of Mechanical Ventilation (REVA) [24]	Volume assist control mode with:	These recommendations were done specifically for patients with H1N1 influenza-induced ARDS
	• PEEP ≥10 cmH_2O	
	• tidal volume reduced to obtain plateau pressure ≤20 to 25 cmH_2O	
	• respiratory rate 6 to 20 cycles/minute	
	• FiO_2 between 30 and 50%	
CESAR trial [3]	Lung rest settings with:	
	• peak inspiratory pressure 20 to 25 cmH_2O	
	• PEEP between 10 and 15 cmH_2O	
	• respiratory rate 10 cycles/minute	
	• FiO_2 30%	

<Matthieu Schmidt et al,Critical Care2014;18;203>

Experts' Opinion regarding MV in ECMO for ARDS

Source	Mechanical ventilation settings	Notes
EOLIA trial [72]	Assisted control mode with: • PEEP ≥10 cmH_2O • tidal volume reduced to obtain plateau pressure ≤20 cmH_2O • respiratory rate 10 to 30 cycles/minute • or APRV with: • high pressure ≤20 cmH_2O • PEEP ≥10 cmH_2O	Multicenter, international, randomized, open trial that will evaluate the impact on the morbidity and mortality of ECMO, early instituted after the diagnosis of ARDS with an unfavorable outcome after 3 to 6 hours despite optimal ventilatory management and maximum medical treatment. The trial is still in progress
ECMO for cardiac failure (VA-ECMO)		
ELSO guidelines [22]	'Whether the patient is on either venovenous or venoarterial mode, the ventilator should be managed at low settings to allow lung rest'	

<Matthieu Schmidt et al,Critical Care2014;18;203>

Table 2. Possible ventilatory scenarios in a representative acute respiratory distress syndrome patient before and during extracorporeal membrane lung oxygenation

	Pre-ECMO baseline	Usual treatment during ECMO	ELSO recommendation	Physiology-based limits
Weight (kg)	70	70	70	70
Vt/PBW (ml/kg)	6	4	3.5	Apneic oxygenation + 3.6 (sighs)
Vt (ml)	420	280	245	250
I:E ratio	1:1[b]	1:1[b]	2:1	2:1
PEEP (cmH_2O)	13.5	12.0	15.0	22.0
Driving pressure (cmH_2O)	17.0	13.5	10.0	10.0
Plateau pressure (cmH_2O)	30.5	25.5	25.0	32.0
Mean airway pressure (cmH_2O)	21.9	18.8	18.3	23.1
Respiratory rate (bpm)	22	16	5	2
Mechanical power (J/min)[a]	22.7	8.4	2.4	1.3
FiO_2 natural lung	0.9	0.7	0.5	0.5
FiO_2 membrane lung	–	1.0	1.0	0.5

ECMO, extracorporeal membrane lung oxygenation; ELSO, Extracorporeal Life Support Organization; FiO_2, fraction of inspired oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; Vt, tidal volume.
[a]Assuming airway resistance of 10 cmH_2O/l/s.
[b]Assumed value.

Gattinoni L et al; Curr Opin Crit Care 2017, 23:66–72

Table 1 Setting of PEEP, V_T, respiratory rate and FiO_2 before and 24 hours after VV-ECMO

Study	Type of study	N	PEEP (cmH_2O)		TV/PBW (mL/kg) or TV (mL)		RR (bpm)		FiO_2	
			Pre ECMO	During ECMO	Pre ECMO	During ECMO	Pre ECMO	During ECMO	Pre ECMO	During ECMO
Combes *et al.* (6)	Multi-center randomized trial	124	11.7 [3.9]	11.2 [3.9]	6.0 [1.3]	*3.4*	30.7 [3.4]	*23*	NR	NR
Bein *et al.* (17)	Multicenter randomized trial [av $ECCO_2$-R]	40	16.1 [3]	NR	5.9 [1.2]	*3*	22.4 [3]	*10–25*	0.62 [0.2]	NR
CESAR trial (5)	Multicenter randomized trial	68	13.7 [9.6]	*10–15*	NR	NR	NR	*10*	NR	*0.3*
Brogan *et al.* (18)	ELSO registry report	600	12 [10–17]	10 [8–14]	NR	NR	20 [15.25]	*10*	NR	0.5 [0.4–0.51]
Schmidt *et al.* (15)	Retrospective analysis of a multicenter registry	168	13.6 [4.0]	12.7 [2.9]	6.3 [1.5]	3.9 [1.5]	22 [18–30]	15 [10–25]	NR	NR
Serpa Neto *et al.* (10)	Individual patient data meta-analysis of observational studies	545	13.7 [4.0]	12.9 [3.4]	6.0 [1.9]	4.0 [1.7]	21.9 [7.9]	17.8 [8]	0.90 [0.17]	0.69 [0.24]
Pham *et al.* (8)	Retrospective multicenter cohort analysis	123	13 [4]	13 [4]	6.7 [1.6]	3.9 [1.4]	27 [6]	19 [8]	NR	NR
Patroniti *et al.* (19)	Retrospective multicenter cohort analysis	60	16 [14–19]	16 [14–19]	6.2 [4.7–7.7]	4.6 [3–6.3]	25 [22–28]	10 [8–12]	1 [1–1]	0.6 [0.4–0.8]

Study	Type of study	N	PEEP (cmH_2O)		TV/PBW (mL/kg) or TV (mL)		RR (bpm)		FiO_2	
			Pre ECMO	During ECMO	Pre ECMO	During ECMO	Pre ECMO	During ECMO	Pre ECMO	During ECMO
Marhong *et al.* (13)	Systematic review	2,042	14 [12.3–16.1]	12 [9.2–14]	6.1 [5.9–6.6]	3.9 [3–5]	NR	NR	0.99 [0.89–1]	0.4 [0.3–0.5]
Frenckner *et al.* (11)	Single center observational study	38	13 [0–20]	NR	610 [280–950]	NR	NR	*10*	> 0.9	0.4
Holzgraefe *et al.* (20)	Single center observational study	13	17 [15–20]	<5 (from chart)	545 [408–617]	<200 (from chart)	NR	NR	1	0.6 [0.46–0.63]
Kipping *et al.* (21)	Retrospective single center analysis	18	18 [14.5–24.5]	18 [16–24.5]	5.4 [3.2–7]	3.2 [2.4–4.7]	NR	NR	NR	NR
Bonacchi *et al.* (22)	Randomized single center analysis	30	13.2 [3.5]	*10–15*	NR	NR	NR	*4–10*	0.99 [0.07]	≤0.5

Data are expressed as mean [standard deviation] or median [interquartile range]. Italic data are predefined protocol targets. PEEP, positive end expiratory pressure; TV, tidal volume; RR, respiratory rate; FiO_2, fraction of inspired oxygen; NR, not reported.

Optimal MV management in ARDS with vv ECMO

- Remain undefined
- Ultra-lung Protective Ventilation: reasonable
  - Tidal volume (3-4 ml/kgw PBW)
  - Higher PEEP (10-15 cmH2O)
  - Driving pressure (14 cm H2O)
  - Plateau pressure (24-28 cm H2O)
- One size did not fit all:
  - Individualize
  - EIT, Transplumonary pressure, Recruitability, …

Thank you for your attention !