

VENTILATION ULTRA-PROTECTIVE À MOINS DE 6 ML/KG

PR JEAN-CHRISTOPHE RICHARD
SERVICE DE MEDECINE INTENSIVE REANIMATION
HOPITAL DE LA CROIX-ROUSSE
LYON

HCL
HOSPICES CIVILS
DE LYON

CONFLICT OF INTEREST

- Grants: HAMILTON MEDICAL
- Congress attendance
 - GILEAD
 - PFIZER

INTRODUCTION

Protective ventilation

Pressure- and volume-limited ventilation :
- $P_{plat} < 28-30 \text{ cmH}_2\text{O}$
- AND $VT \leq 4-8 \text{ mL/kg PBW}$
- And sufficient amount of PEEP

Ultraprotective ventilation

→ $VT \leq 4 \text{ mL/kg PBW}$

No extracorporeal technique

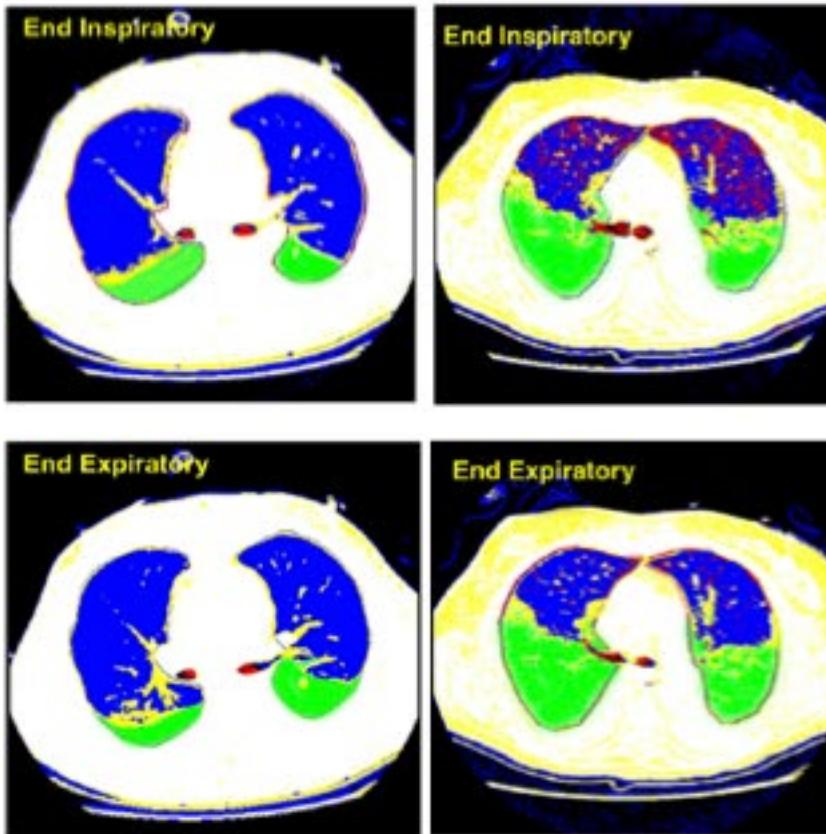
ECCO₂R

ECMO (severe hypoxemia)

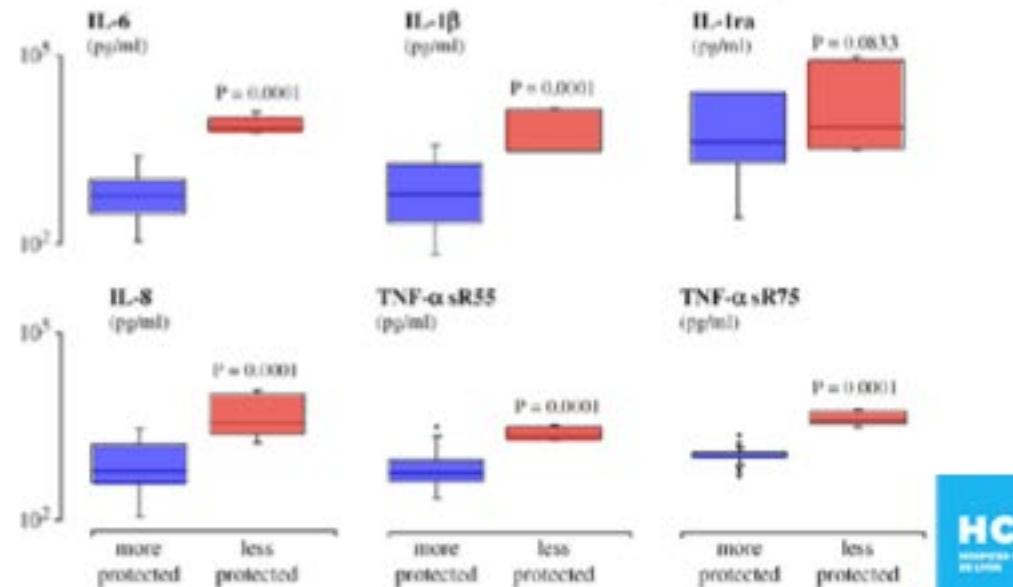
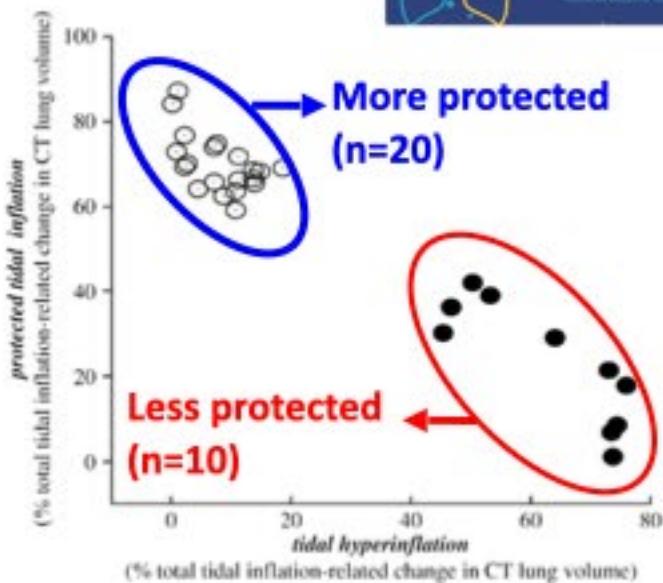
POURQUOI VENTILER DE FAÇON ULTRAPROTECTRICE ?

IS PROTECTIVE VENTILATION PROTECTIVE ?

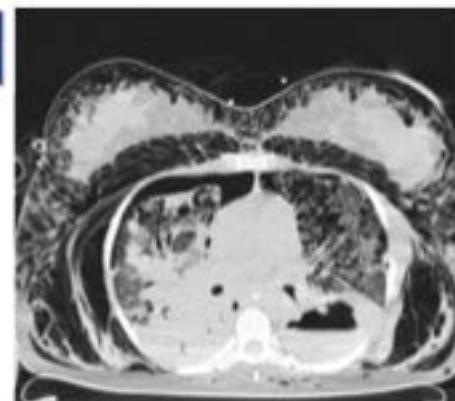
30 ARDS patients under protective MV



Excessive VT in 30% of the patients under protective ventilation?



IS PROTECTIVE VENTILATION PROTECTIVE ?



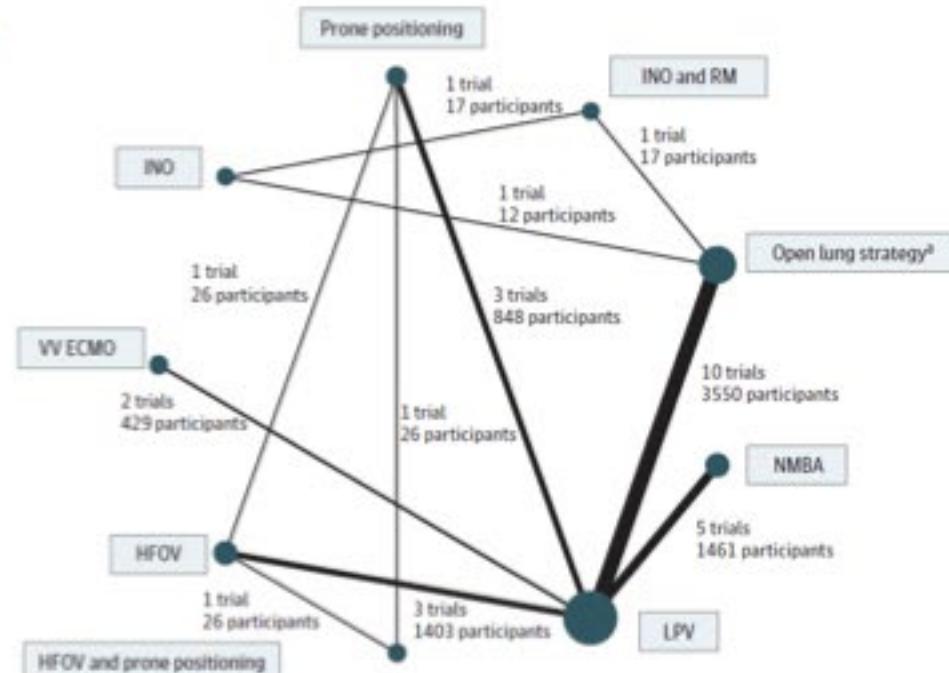
JAMA
Network Open™

Original Investigation | Critical Care Medicine

Assessment of Therapeutic Interventions and Lung Protective Ventilation in Patients With Moderate to Severe Acute Respiratory Distress Syndrome A Systematic Review and Network Meta-analysis

Editorial: Aoyama H, Uchida K, Aoyama K, et al. Assessment of Therapeutic Interventions and Lung Protective Ventilation in Patients With Moderate to Severe Acute Respiratory Distress Syndrome: A Systematic Review and Network Meta-analysis. JAMA Netw Open 2019;2(7):e198116.

Incidence of barotrauma: 7.2% from 17 trials evaluating 6 interventions



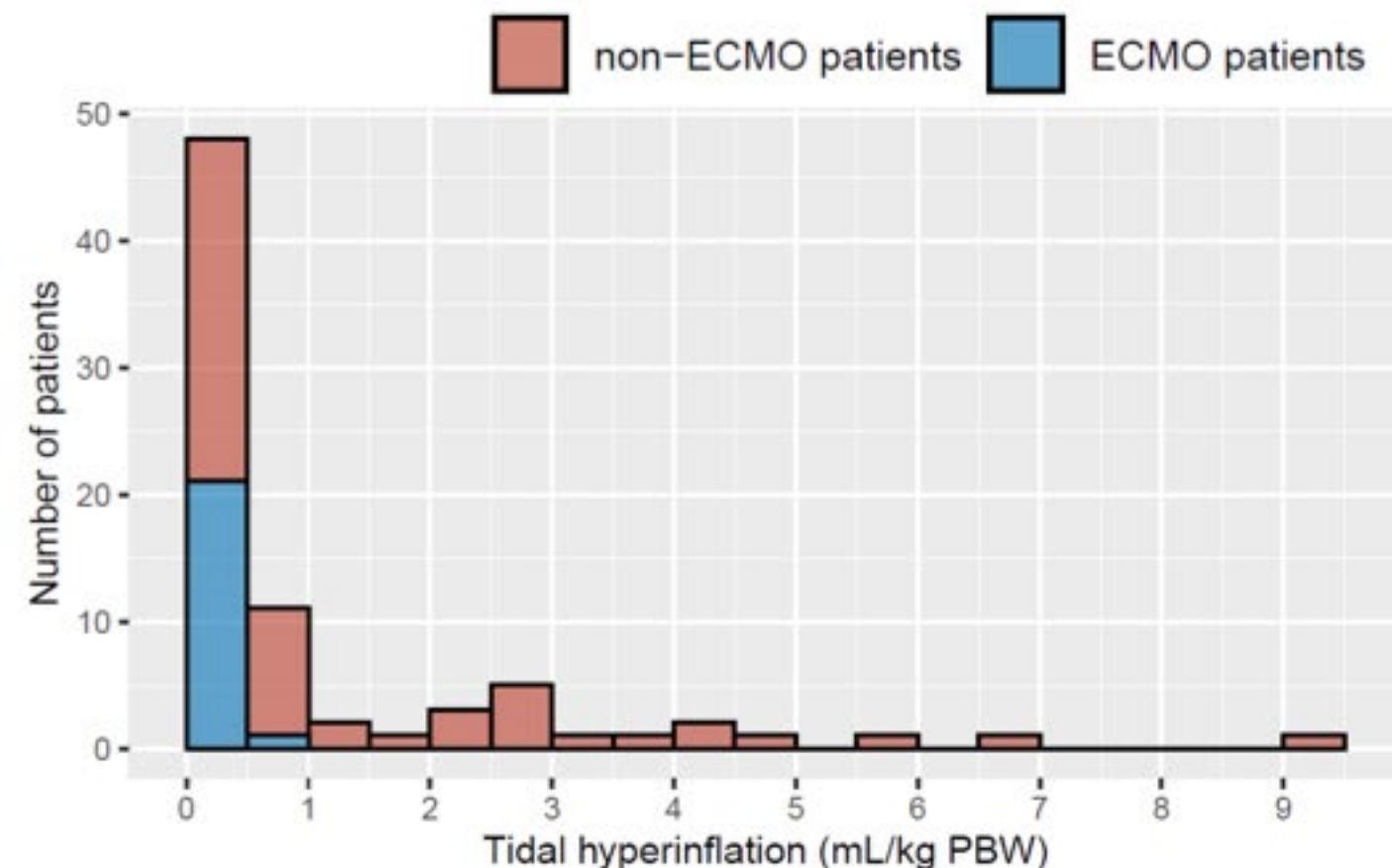
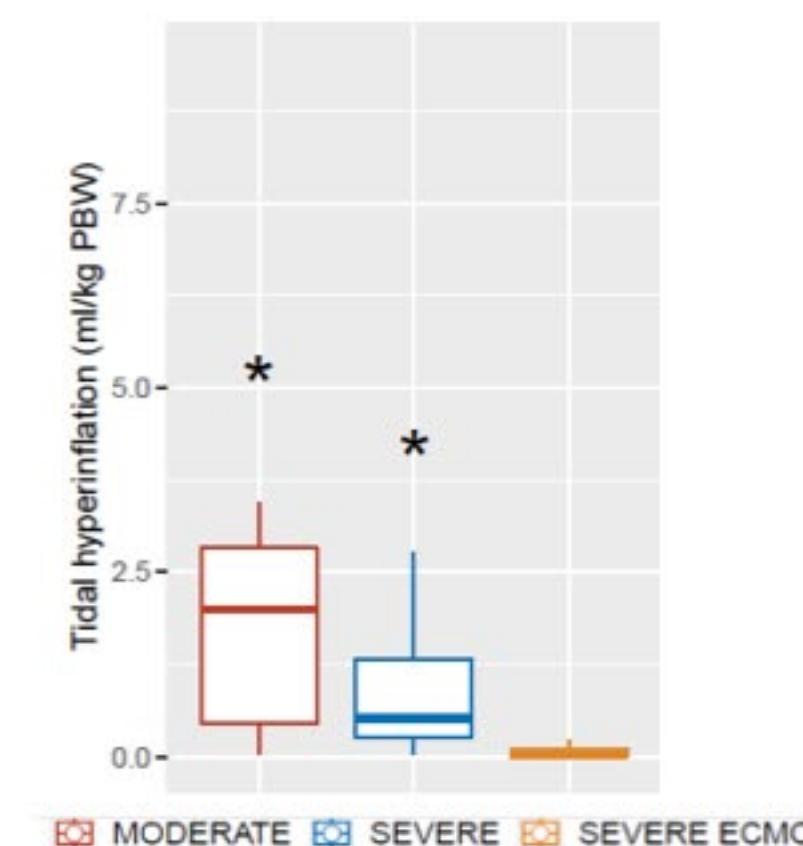
No intervention was superior to any other in reducing barotrauma, and each represented low to very low quality of evidence.

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IS PROTECTIVE VENTILATION REALLY PROTECTIVE DURING COVID-19 ARDS?

2-centers study

99 COVID-19 ARDS (moderate n=16, severe n=59, severe ECMO n=24)



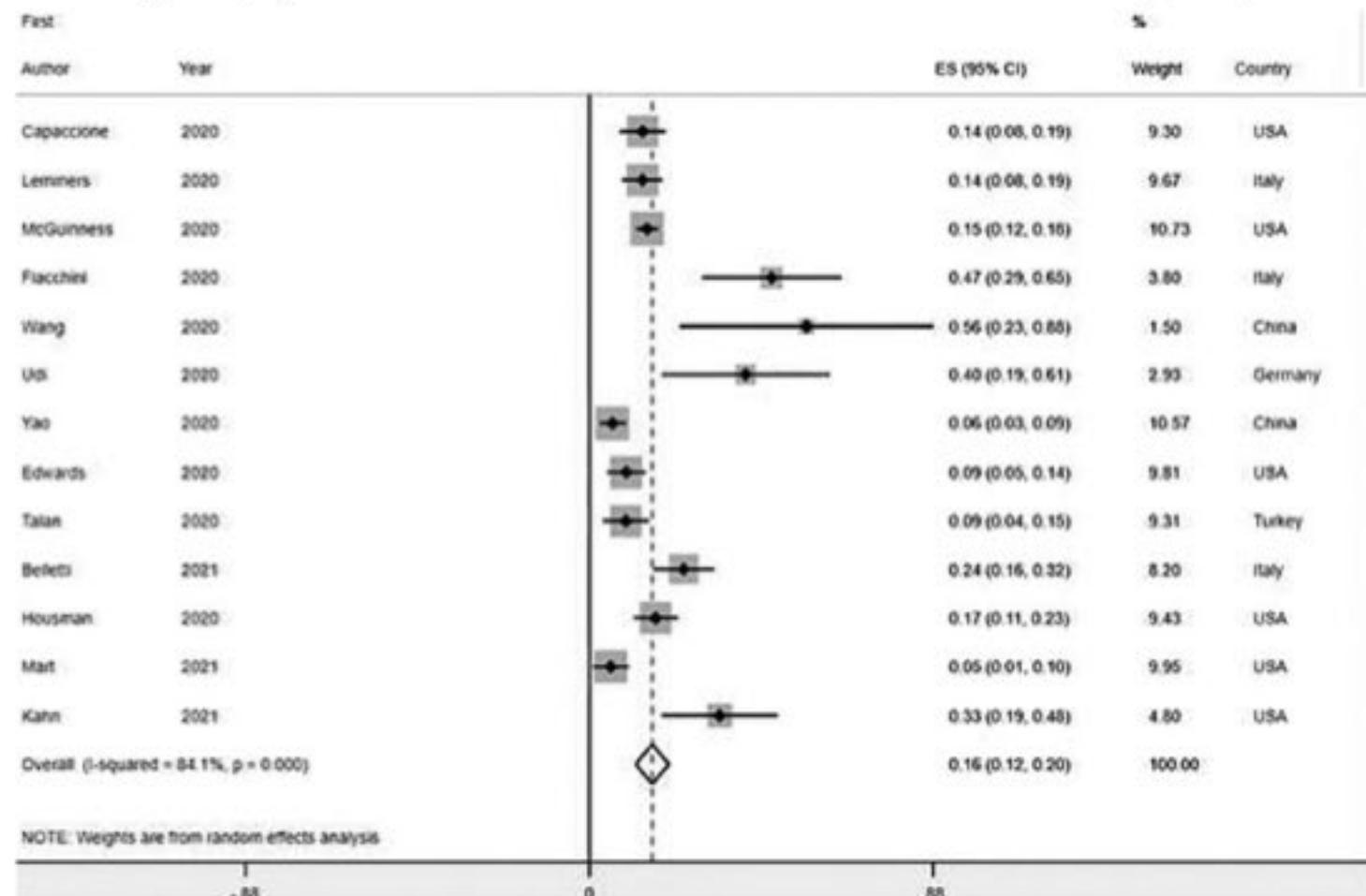
Tidal hyperinflation > 1 ml/kg in 19% of non-ECMO patients

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Hôpitaux Civils de Lyon

Richard JC, Sigaud F, Gaillet M, et al. Response to PEEP in COVID-19 ARDS patients with and without extracorporeal membrane oxygenation. A multicenter case-control computed tomography study. Crit Care 2022;26(1):195.

IS PROTECTIVE VENTILATION REALLY PROTECTIVE DURING COVID-19 ARDS?

Meta-analysis (random-effect) of studies with COVID-19 ARDS -13 studies with 1,814 patients



Rate: of barotrauma 16% ($CI_{95\%}$: 12-20%) - Rate of pneumothorax (11%; $CI_{95\%}$: , 7-15%),

Time from intubation
to barotrauma :3.7 ($CI_{95\%}$:
2-5) days after intubation

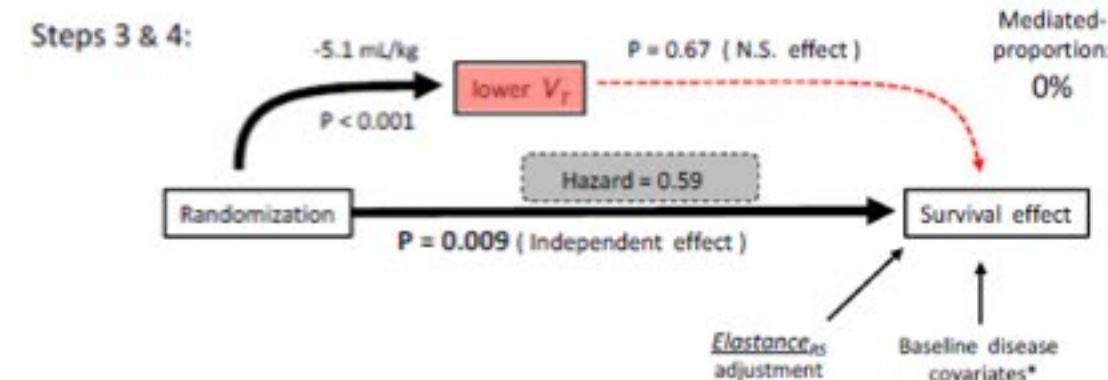
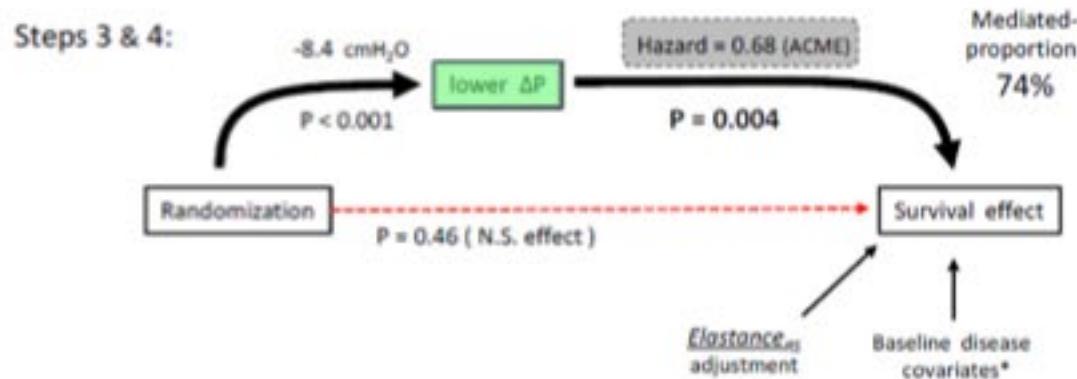
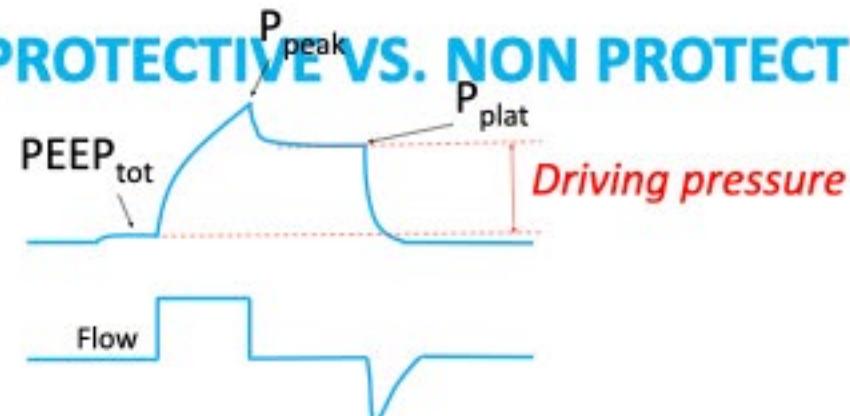
Mortality COVID-19ARDS
barotrauma: 62% ($CI_{95\%}$:
50-73%)



MEDIATION ANALYSIS OF RCT TESTING PROTECTIVE VS. NON PROTECTIVE VENTILATION

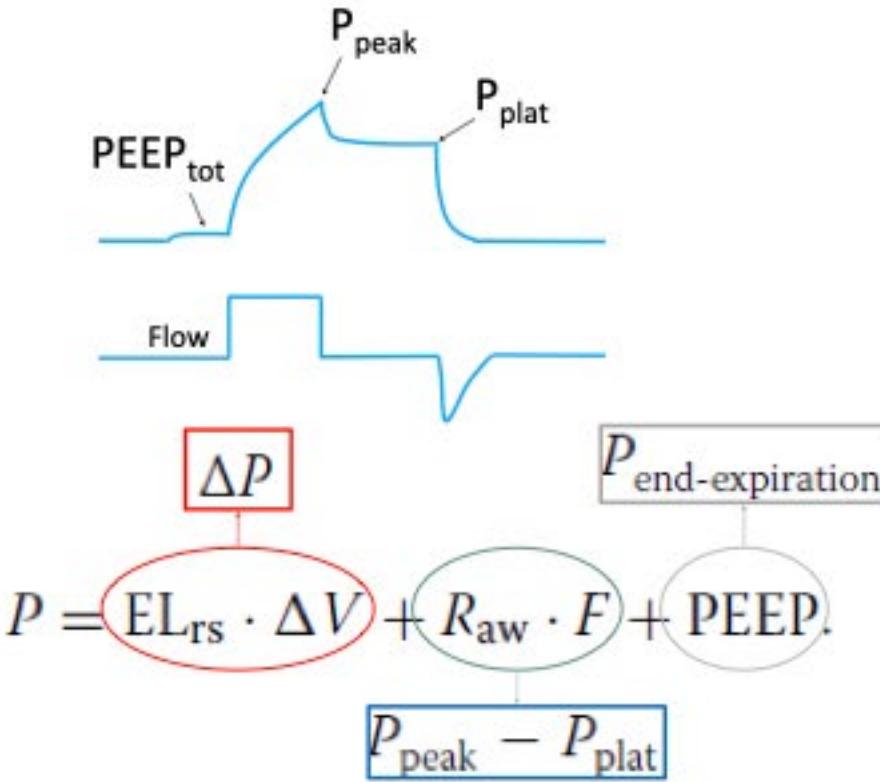
1147 ARDS patients

5 RCT of lower vs higher VT strategies



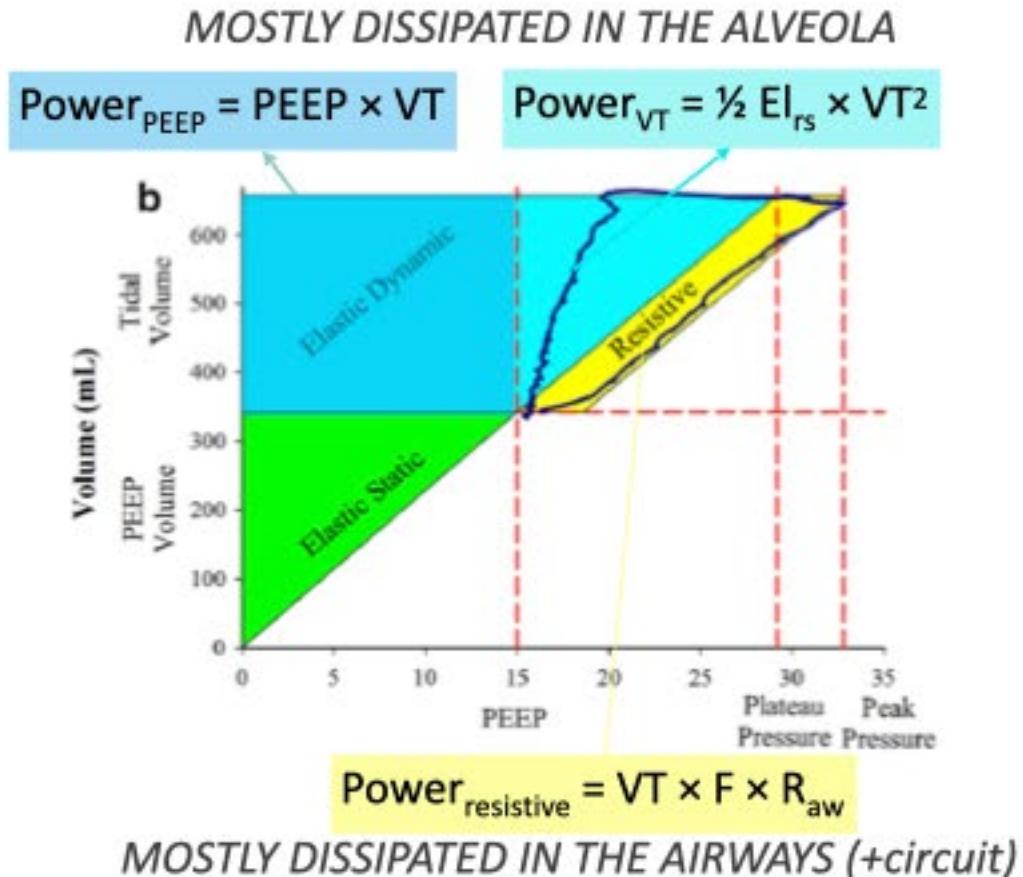
Driving pressure decrease (rather than VT decrease per se) is responsible for the decrease in mortality in RCT comparing protective vs. Non protective ventilation

MECHANICAL POWER

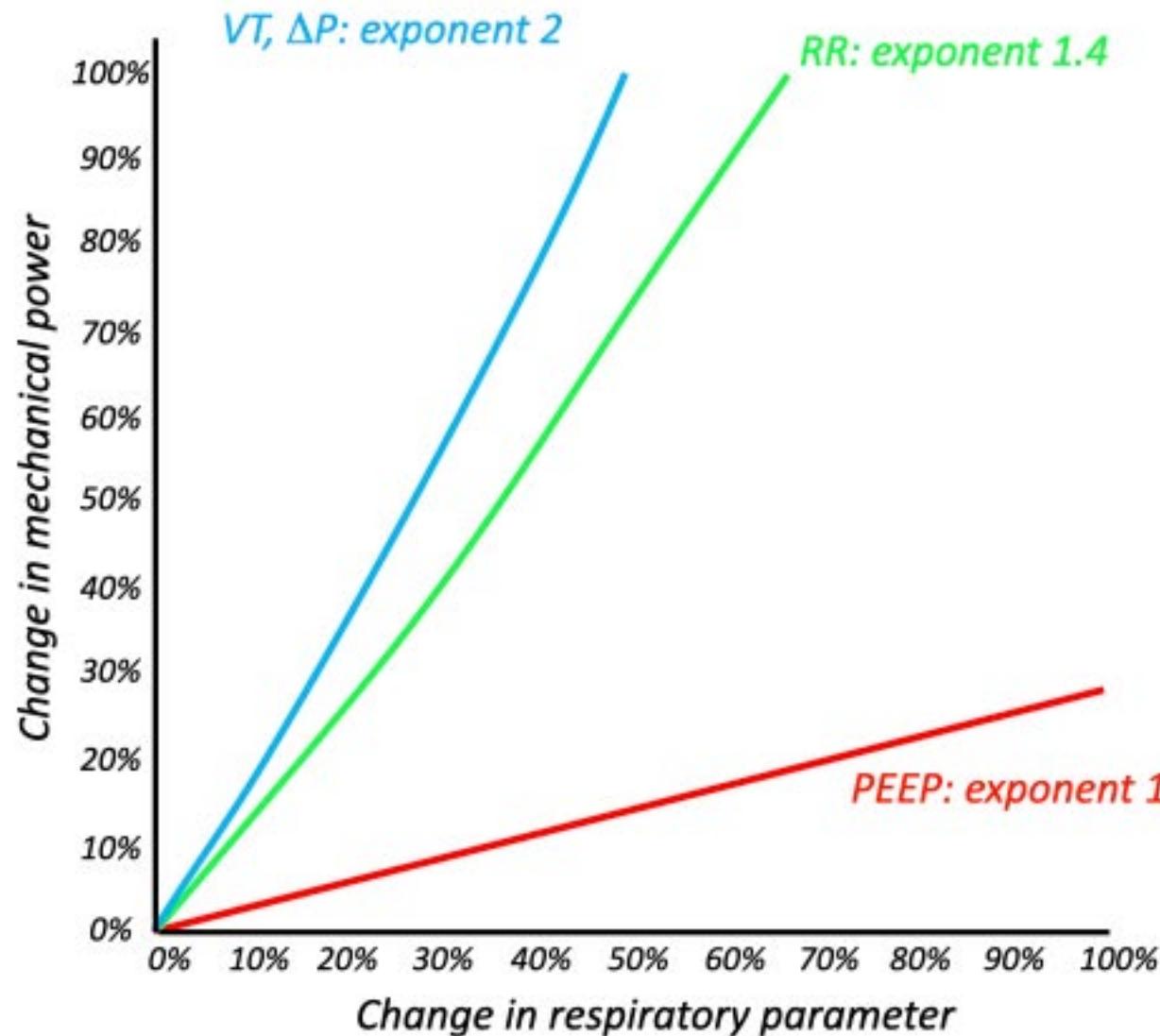


$$\text{Energy}_{\text{Breath}} = P \times \Delta V = \text{EL}_{rs} \times \Delta V^2 + R_{aw} \times F \times \Delta V + \text{PEEP} \times \Delta V$$

$$\text{POWER} = \text{Energy}/\text{min} = \text{Energy}_{\text{Breath}} \times \text{RR}$$



MECHANICAL POWER



Limitations and unanswered questions

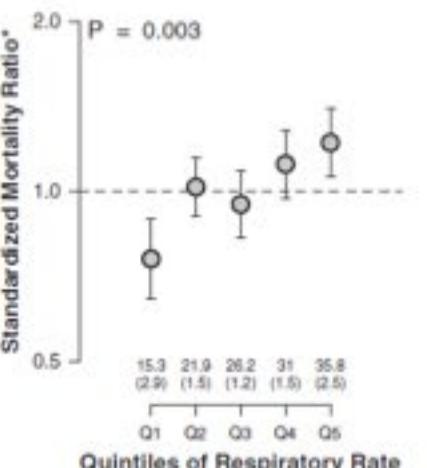
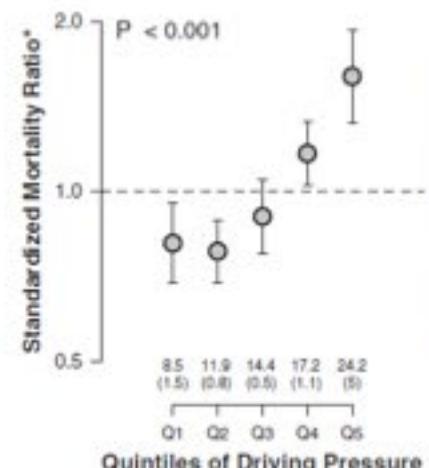
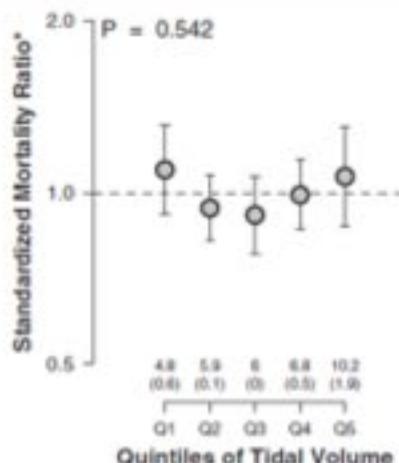
- Unknown/unidentified safety threshold
- MP is impacted by chest wall characteristics, ET size
- MP component dissipates energy in different zones
- Normalization to open lung units probably required (specific power)

MECHANICAL POWER COMPONENTS IN THE REAL LIFE

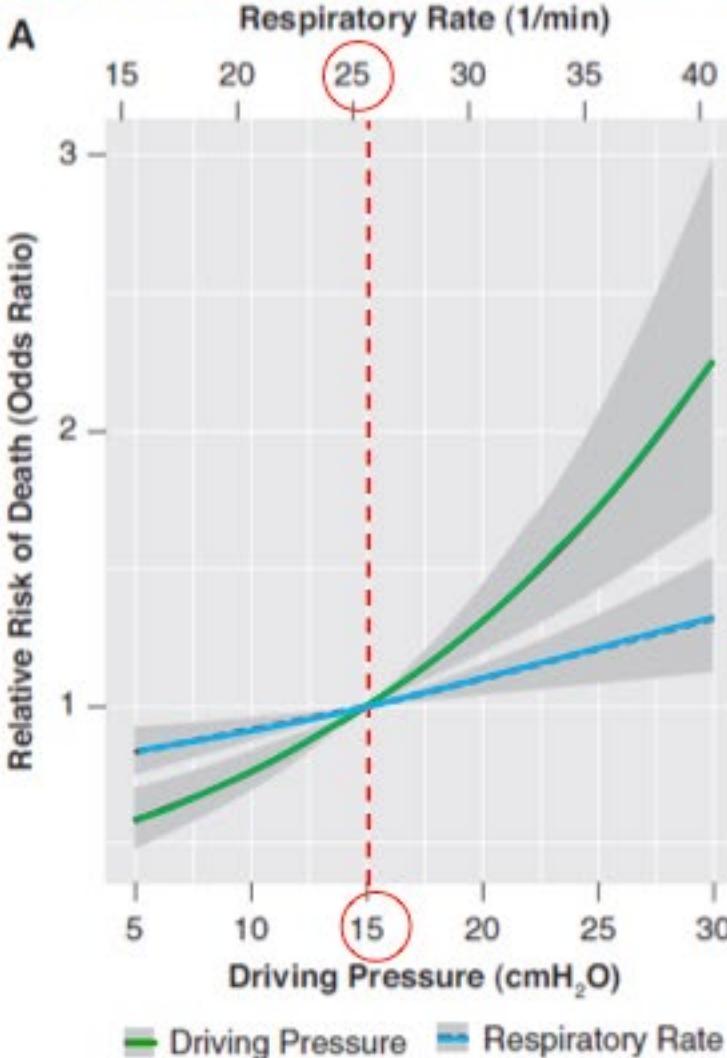
Patient-level data of 4,549 ARDS patients

- 693 pts from MIMIC-III observational database
- 3856 pts from RCT 1998-2017 (VT or PEEP intervention)

No independent association of VT with mortality



* Mortality adjusted with the following variables: trial, study arm, respiratory system compliance, ventilatory ratio, arterial pH, PaCO_2 , and $\text{PaO}_2/\text{FIO}_2$



Driving Pressure Respiratory Rate

The effect size of each 1 $\text{cm H}_2\text{O}$ increase in ΔP is 4.0 times that of each 1-breath/min increase in RR

VENTILATION ULTRAPROTECTRICE AVEC CEC

Feasibility and safety of extracorporeal CO₂ removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study

95 **MODERATE ARDS patients under UPV and ECCO,R-23 ICU**

Patients matching entry criteria (October 2015-June 2017):

- Moderate ARDS
- ≥ 18 years
- Expected to receive invasive mechanical ventilation for >24 hours

N= 755

Exclusion criteria: **87%**

- Pregnancy = 2
- Decompensated heart insufficiency or acute coronary syndrome = 45
- Severe Chronic Obstructive Pulmonary Disease = 56
- Major respiratory acidosis with PaCO₂ >60 mmHg = 74 **10%**
- Acute brain injury = 86
- Severe liver insufficiency (Child-Pugh scores >7) or fulminant hepatic failure = 42
- Heparin-induced thrombocytopenia = 4
- Contraindication for systemic anticoagulation = 186 **25%**
- Platelet <50 G/l = 36 **5%**
- Patient moribund, decision to limit therapeutic interventions = 45
- Catheter access to femoral vein or jugular vein impossible = 3
- Pneumothorax = 9
- Refused consent = 52
- Included in other trials = 20

N= 660

Protocol description

- ↘ VT to 4 mL/kg PBW in three steps
- PEEP titrated to a target **PPLAT 23–25 cmH₂O**.
- Sweep gas and blood flow set to keep PaCO₂ between 80% and 120% of baseline.
- If PaCO₂ > 75 mmHg and/or pH < 7.30 despite respiratory rate 35 breaths/min → ↑ VT was increased to the last previously tolerated.

Included in the trial and treated with ECCO2R:

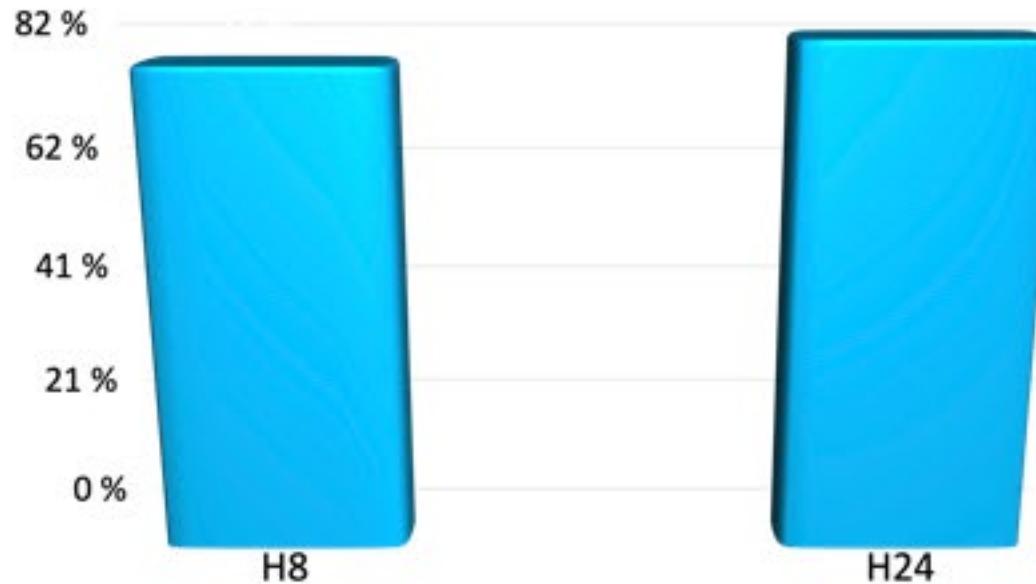
- Hemolung = 33
- iLAACIVVE = 34
- Cardiohelp® = 28

N= 95

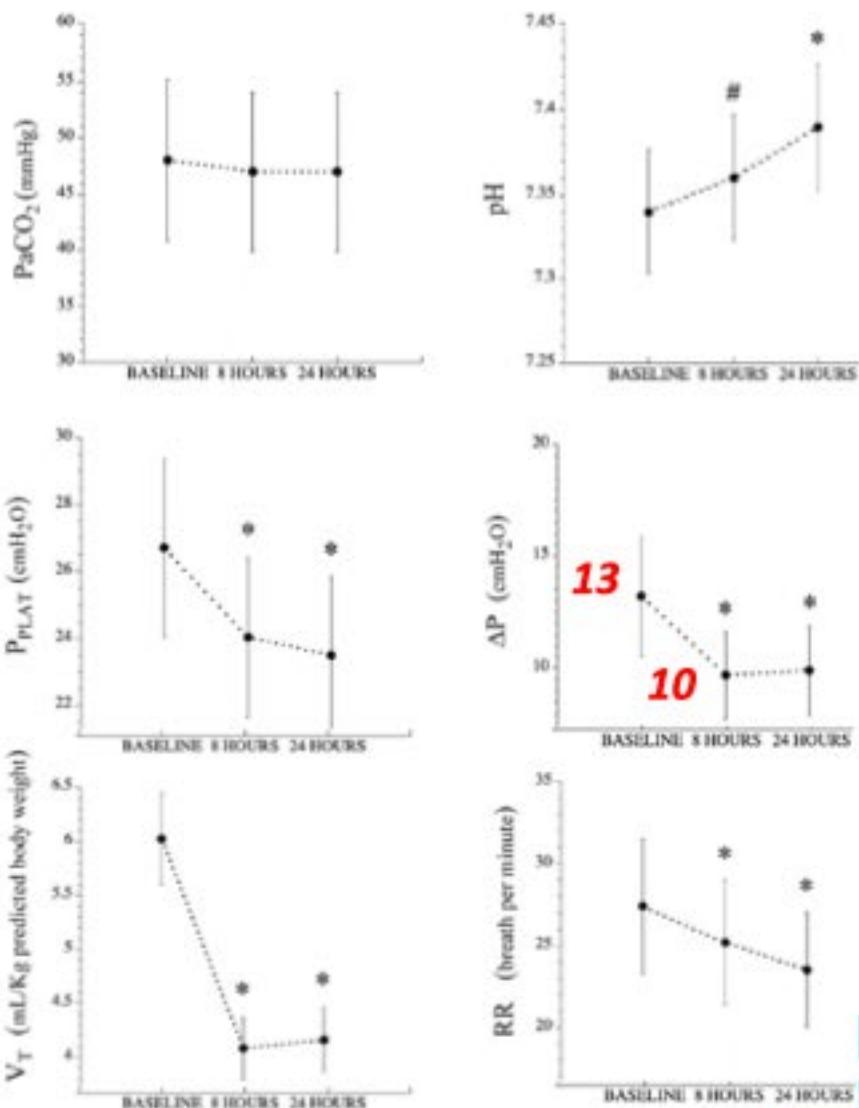
Feasibility and safety of extracorporeal CO₂ removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study

95 MODERATE ARDS patients under UPV and ECCO₂R in ICU

Jugular canulation 57%, femoral canulation 43%

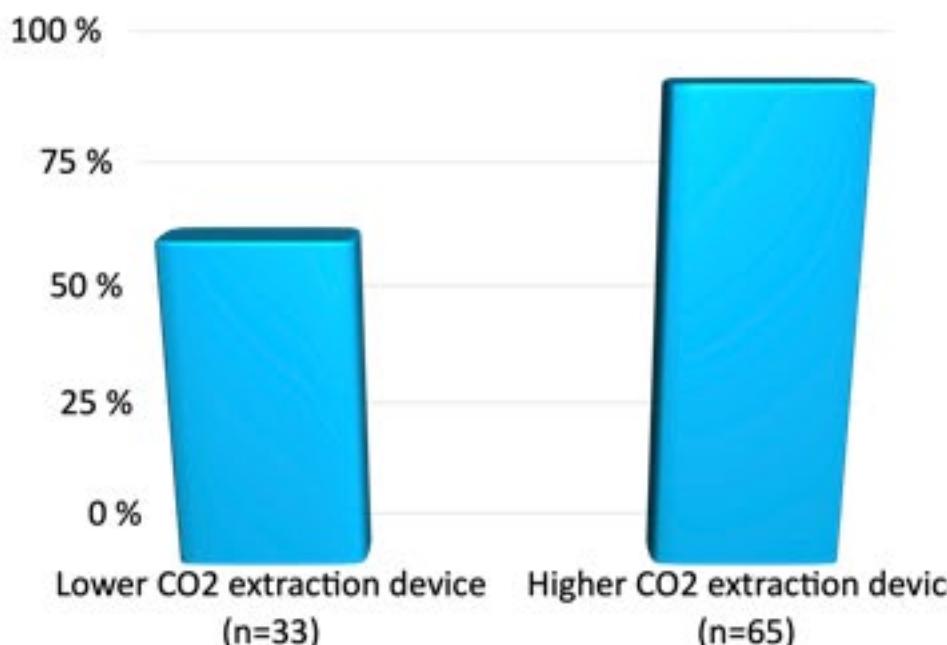


UPV is feasible in 80% of ARDS patients under ECCO₂R

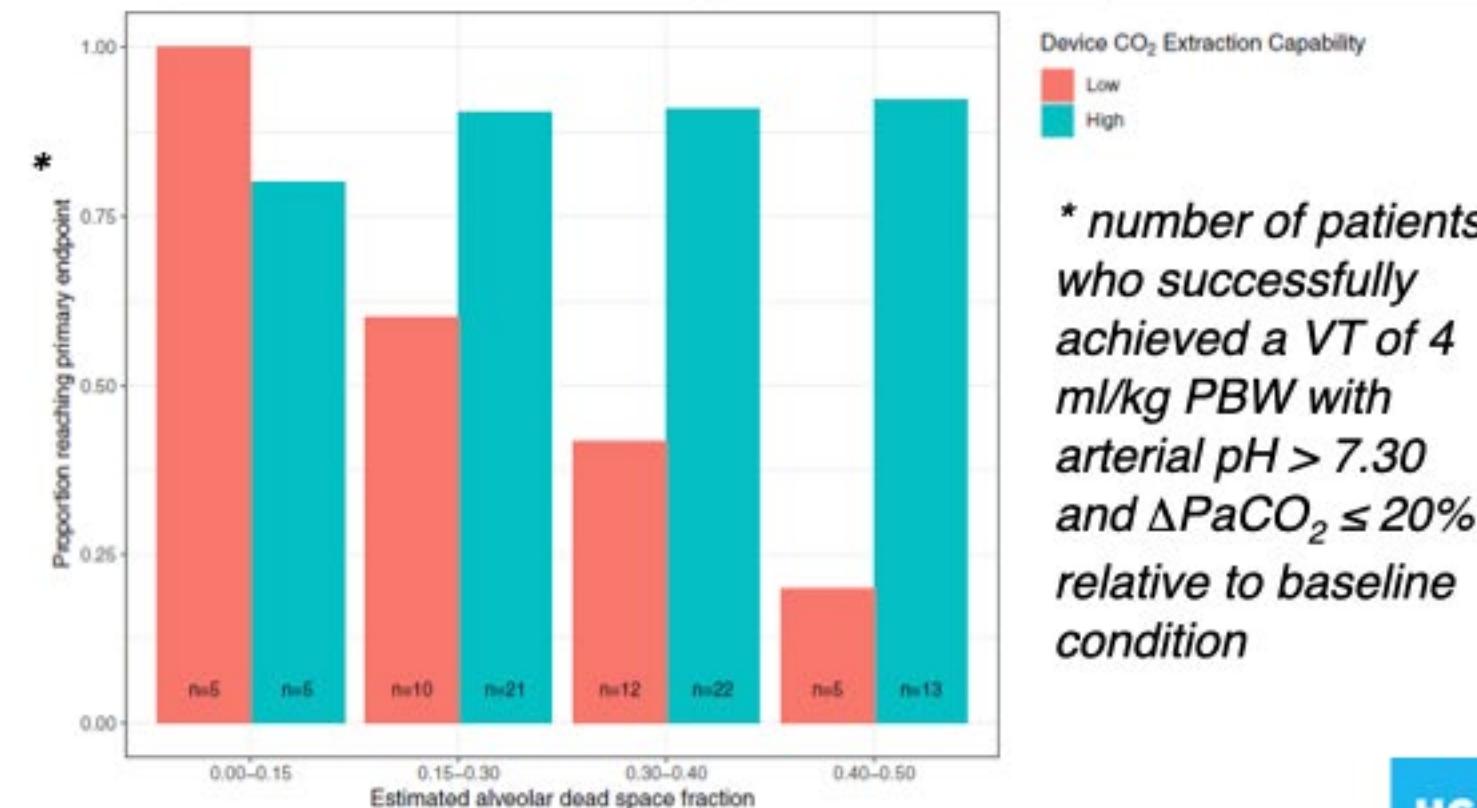


Combes A et al. Feasibility and safety of extracorporeal CO₂ removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. *Intensive Care Med* 2019;45(5):592–600.

95 ARDS patients under UPV and ECCO₂R
 Percentage of patients ventilated with VT 4 ml/kg PBW
 33 with lower ECCO₂R rate device (Hemolung)
 62 with higher ECCO₂R rate device (iLA active or Cardiohelp)



| Variable | Lower CO ₂ extraction device | Higher CO ₂ extraction device |
|------------------------------------|---|--|
| Catheter size (F) | 15.5 | 18 |
| Membrane surface (m ²) | 0.59 | 1.3 |
| Blood flow (mL·min ⁻¹) | 300-500 | 800-1000 |



Combes A, Tonetti T, Fanelli V, et al. Efficacy and safety of lower versus higher CO₂ extraction devices to allow ultraprotective ventilation: secondary analysis of the SUPERNOVA study. Thorax 2019;74(12):1179–81.

Goligher EC, Combes A, Brodie D, et al. Determinants of the effect of extracorporeal carbon dioxide removal in the SUPERNOVA trial: implications for trial design. Intensive Care Med 2019;45(9):1219–30.

Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure

The REST Randomized Clinical Trial

Large RCT – 51 centers

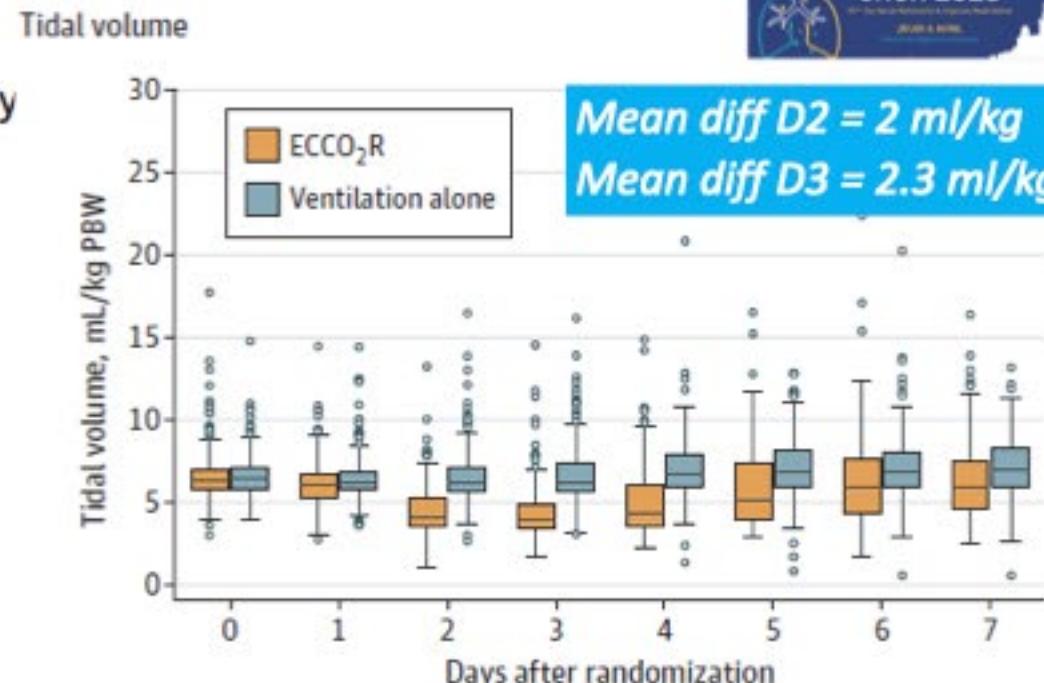
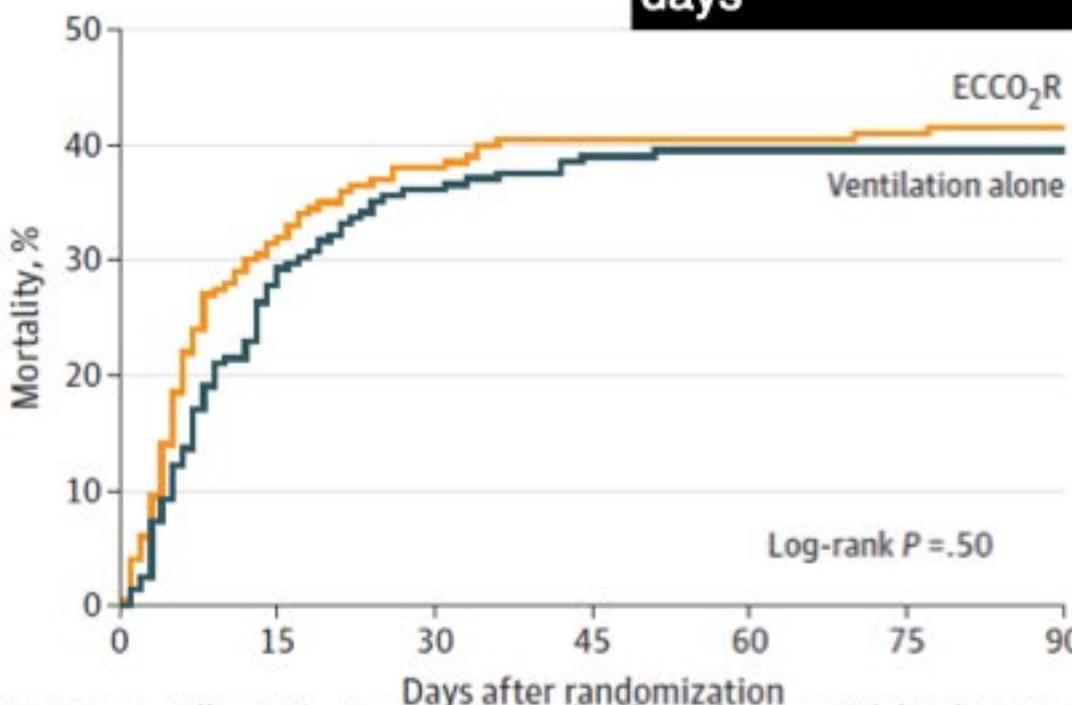
412 pts with hypoxemic ARF

Lower VT ($\leq 3 \text{ ml/kg PBW}$) + ECCO₂R (HEMOLUNG-7 days max) (n=202)

Standard of care (n=210)

Premature stop for futility

Duration of ECCO₂R: 4±2 days



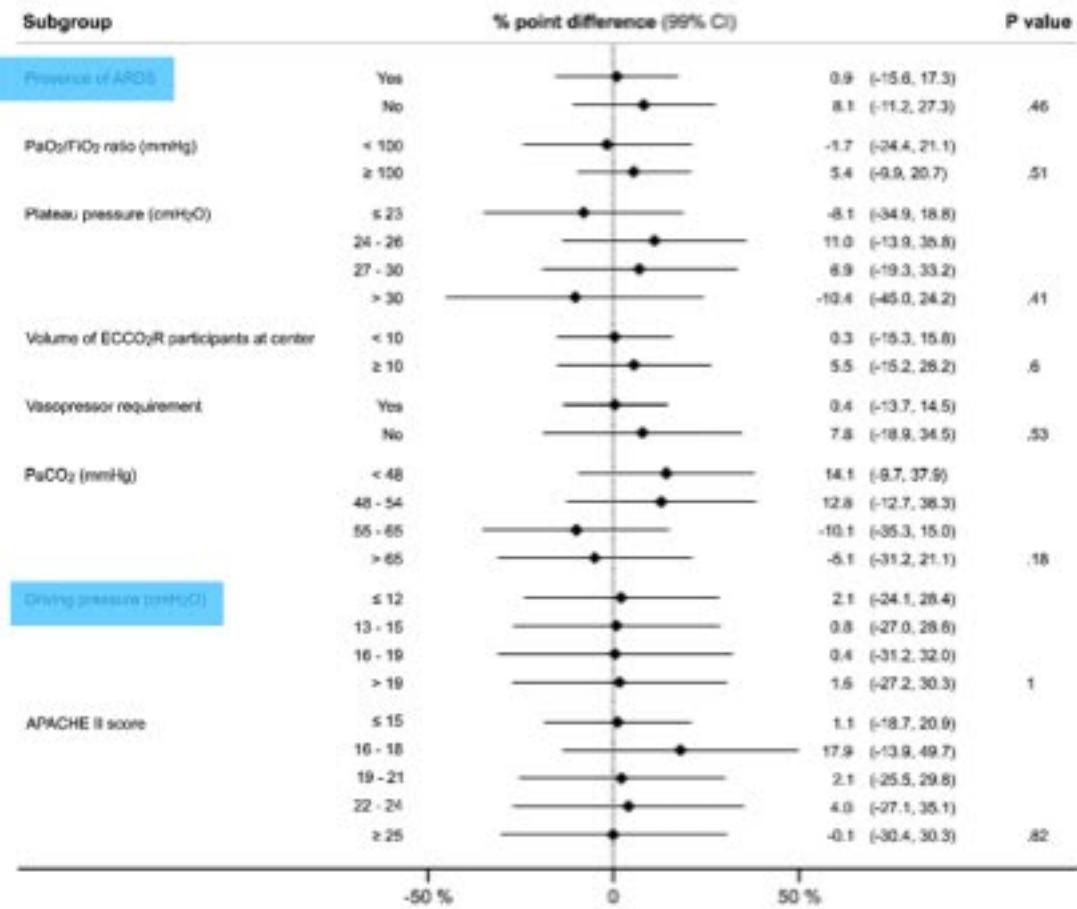
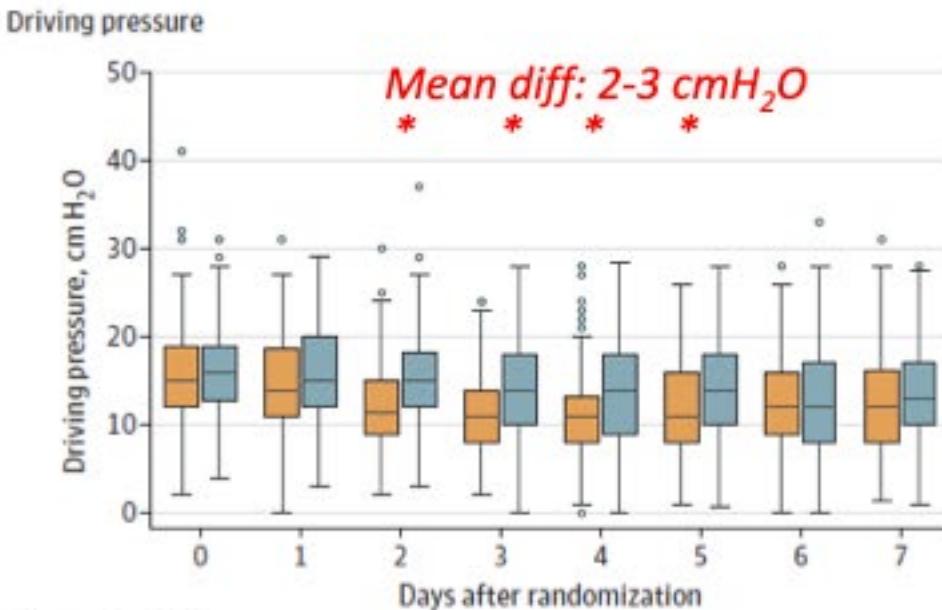
Mean diff D2 = 2 ml/kg
Mean diff D3 = 2.3 ml/kg

Limitations:

- CI to anticoagulation = most common reason for exclusion (22%)
- 60% ARDS
- Most of the sites naïve to the intervention before the study commenced
- Lower blood flow ECCO₂R system (350-550 ml/min)

Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure

The REST Randomized Clinical Trial



Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure
The REST Randomized Clinical Trial



Table 3. Adverse Events in a Study of Lower Tidal Volume Facilitated by Extracorporeal Carbon Dioxide Removal in Patients With Acute Hypoxemic Respiratory Failure

| Adverse event | ECCO ₂ R (n = 202) | | Ventilation alone (n = 210) | |
|--|-------------------------------|---------------------|-----------------------------|---------------------|
| | No. of events | No. (%) of patients | No. of events | No. (%) of patients |
| Adverse events ^a | 168 | 106 (52.5) | 61 | 48 (22.9) |
| Related to study intervention ^{a,b} | 65 | 51 (25.3) | 0 | 0 |
| Serious adverse events ^{c,d} | 70 | 62 (30.7) | 20 | 18 (8.6) |
| Related to study intervention ^b | 22 | 21 (10.4) | 0 | 0 |
| Adverse events of specific interest | | | | |
| Bleeding at other site (excluding intracranial hemorrhage) | 18 | 17 (8.4) | 3 | 3 (1.4) |
| Intracranial hemorrhage | 10 | 10 (5.0) | 2 | 2 (1.0) |
| Device failure causing adverse event | 9 | 9 (4.5) | 0 | 0 |
| Bleeding at cannula site | 8 | 8 (4.0) | 0 | 0 |
| Infectious complications ^e | 7 | 7 (3.5) | 1 | 1 (0.5) |
| Heparin-induced thrombocytopenia | 4 | 4 (2.0) | 0 | 0 |
| Hemolysis | 3 | 3 (1.5) | 0 | 0 |
| Ischemic stroke | 1 | 1 (0.5) | 3 | 3 (1.4) |
| Serious adverse events of specific interest^f | | | | |
| Bleeding at other site (excluding intracranial hemorrhage) | 6 | 6 (3.0) | 1 | 1 (0.5) |
| Intracranial hemorrhage | 9 | 9 (4.5) | 0 | 0 |
| Infectious complications ^e | 5 | 5 (2.5) | 0 | 0 |
| Device failure causing serious adverse event | 2 | 2 (1.0) | 0 | 0 |
| Heparin-induced thrombocytopenia | 1 | 1 (0.5) | 0 | 0 |
| Ischemic stroke | 1 | 1 (0.5) | 3 | 3 (1.4) |

Bleeding event: 17%

Serious bleeding: 8%

Does the adverse event rate related to ECCO₂R outweigh the benefit of reducing VILI?



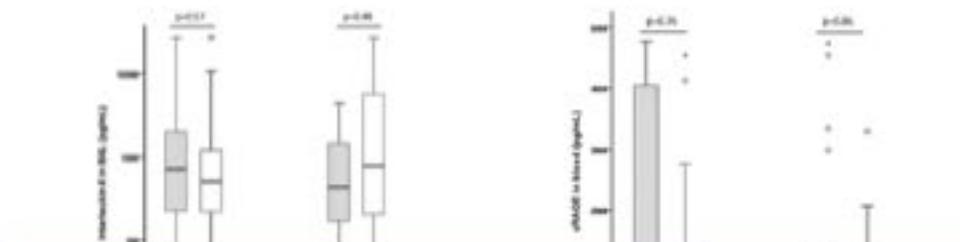
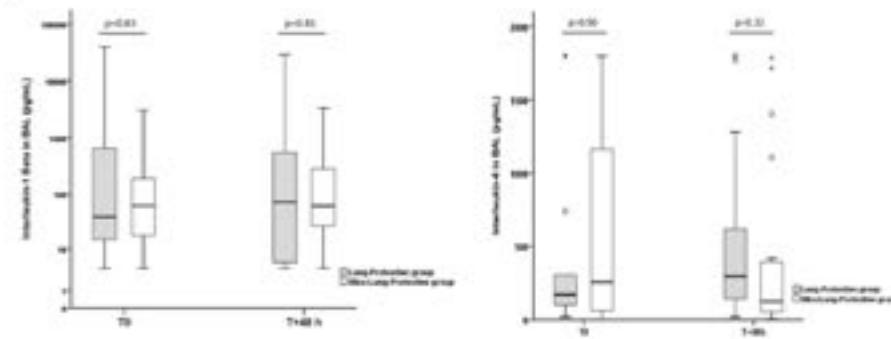
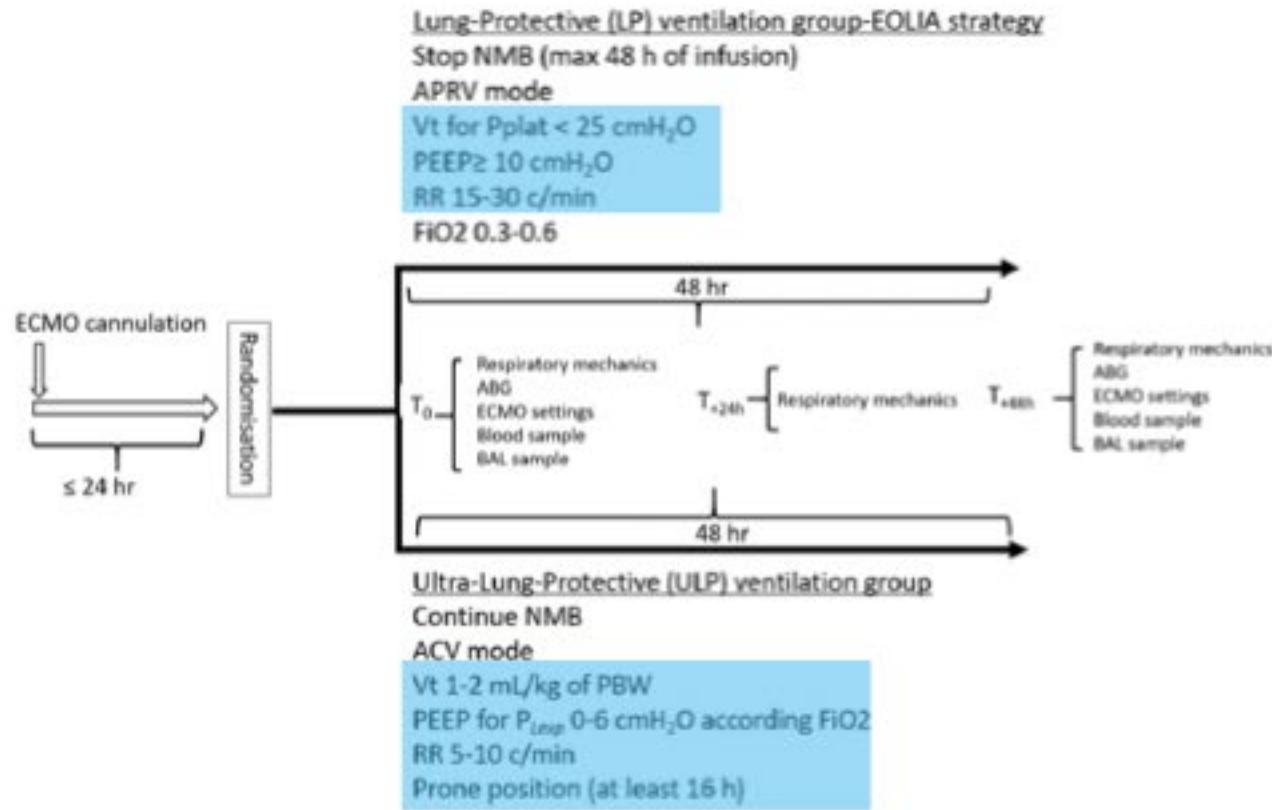
ULTRA-ULTRA PROTECTIVE VENTILATION UNDER ECMO

2 center Randomized controlled trial

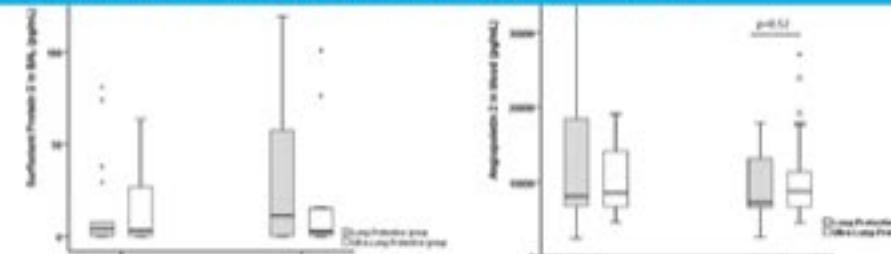
20 patients UPV+ECMO vs 19 patients PV+ECMO (50% COVID)

Primary judgment criterion: decrease in biomarkers in BAL and blood.

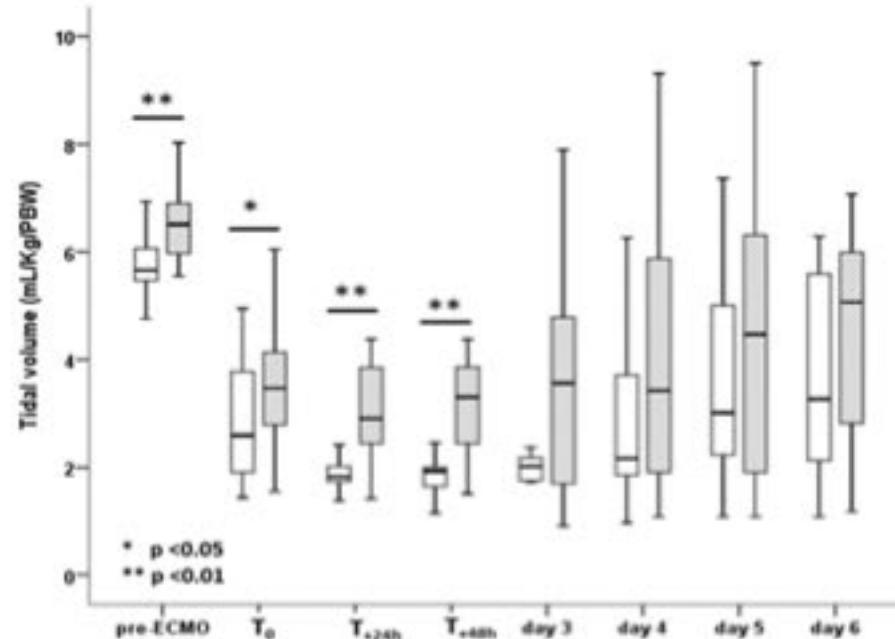
Premature termination for futility



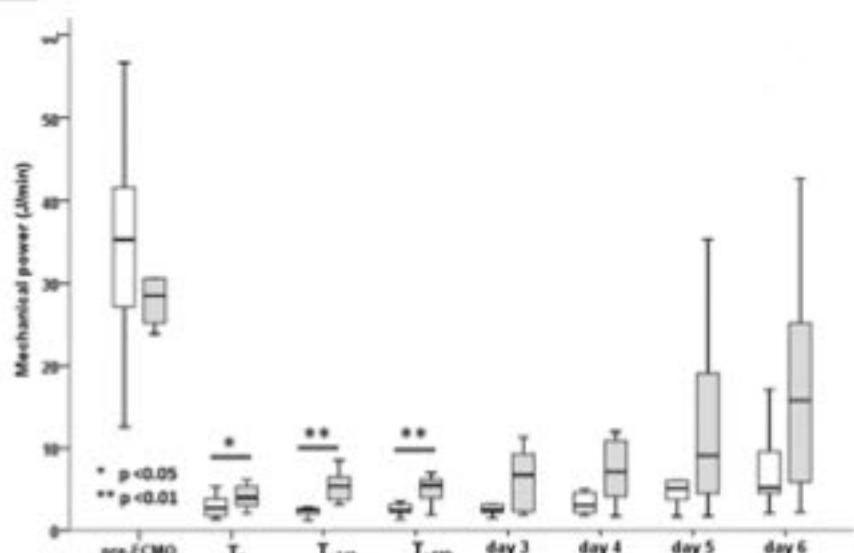
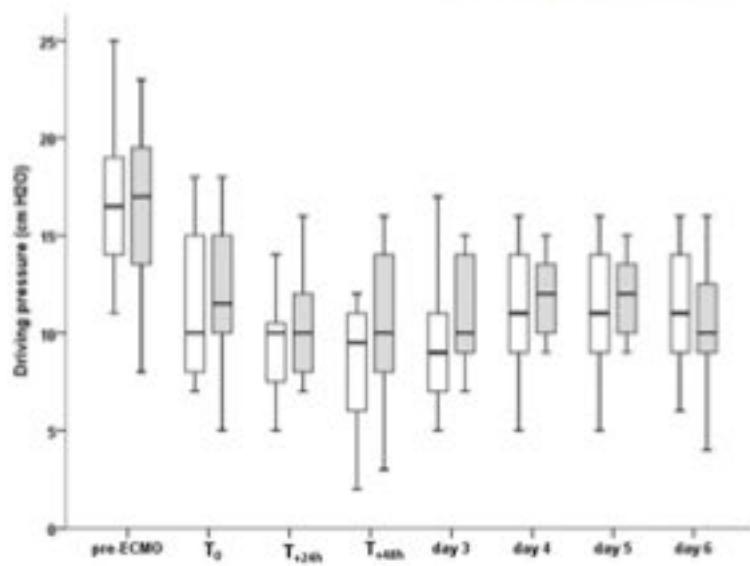
BAL concentrations of IL-1 β IL-6, IL-8, SP-D and blood concentrations of sRAGE not different between groups at T+ 48 h



ULTRAPROTECTIVE VENTILATION UNDER ECMO



Ultra-Lung-Protective group
Lung-Protective group



*Relevance of decreasing VT
below 3-4 ml/kg ?*

Guervilly C, Fournier T, Chommeloux J, et al. Ultra-lung-protective ventilation and disconnection in severe ARDS patients on veno-venous extracorporeal membrane oxygenation: a randomized controlled study. Crit Care. 2022;26:383.

VENTILATION ULTRAPROTECTRICE SANS CEC



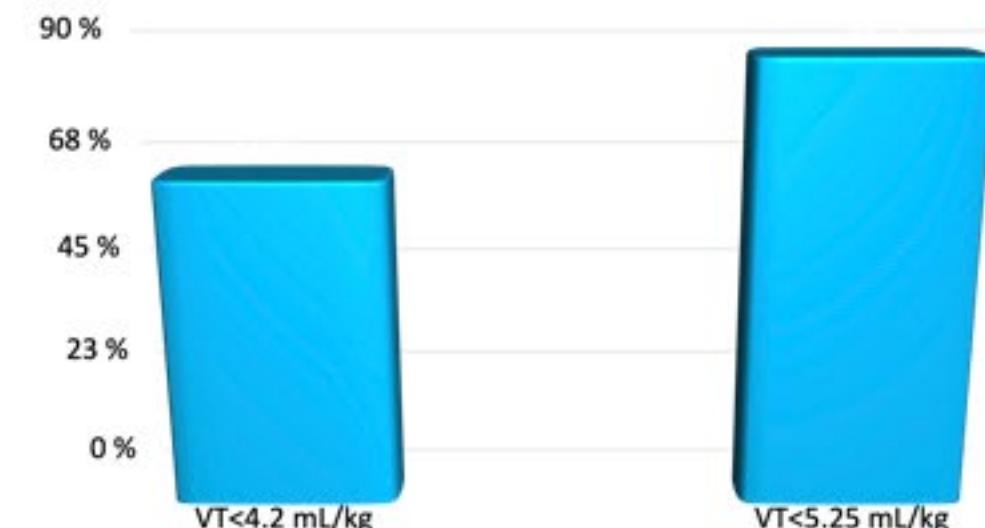
Feasibility and safety of ultra-low tidal volume ventilation without extracorporeal circulation in moderately severe and severe ARDS patients

Before-and-after multicenter study

35 ARDS patients with $\text{PaO}_2/\text{FiO}_2 \leq 150$ mmHg, within 24 h of ARDS diagnosis.

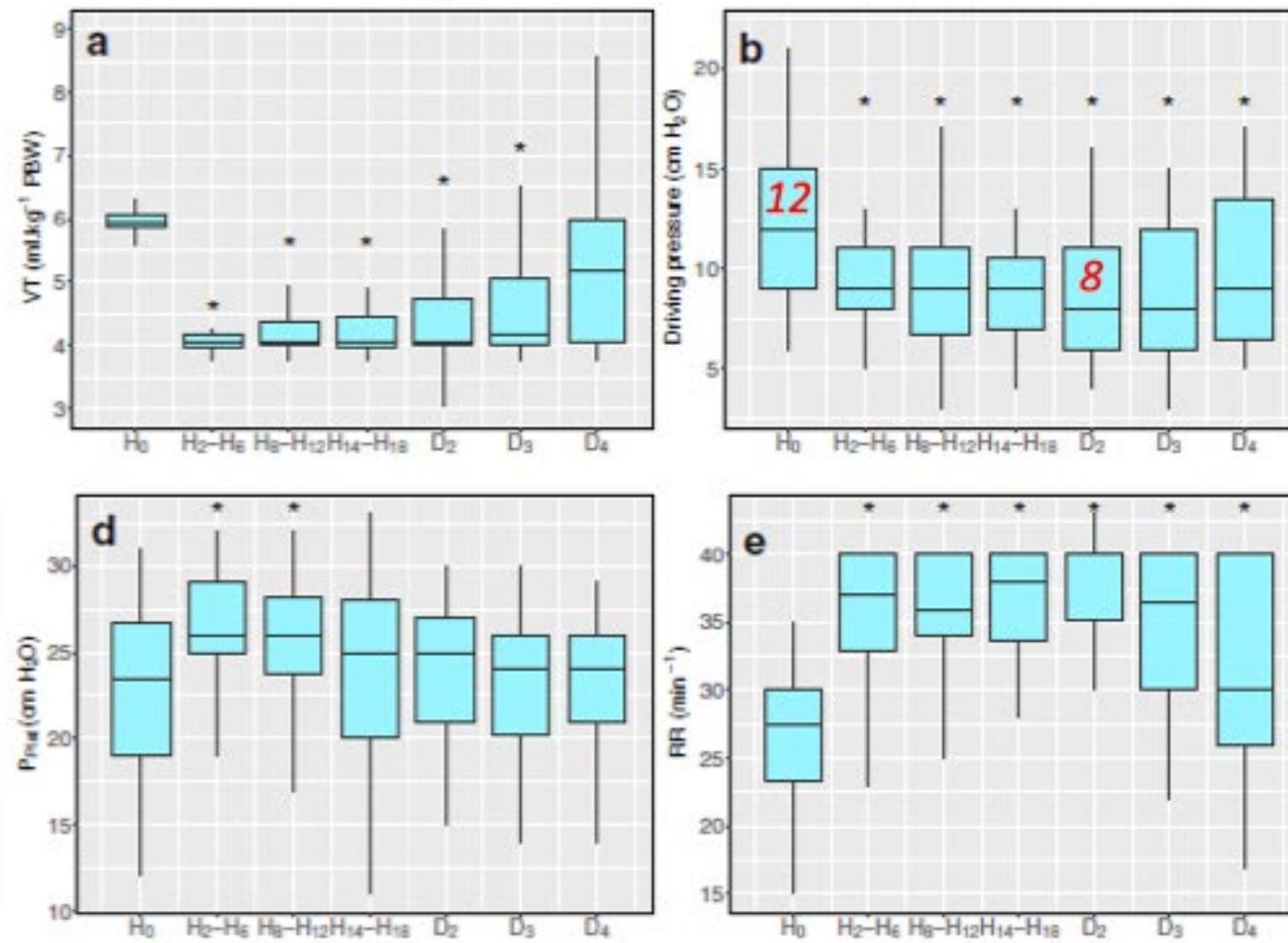
Day 2

1. Minimization of instrumental dead space
2. VT stepwise reduction by $1 \text{ mL} \cdot \text{kg}^{-1}$ PBW
3. RR increase up to 40 min^{-1} to maintain MV constant
4. Ventilatory goals:
 - plateau pressure $\leq 30 \text{ cm H}_2\text{O}$;
 - $55 \leq \text{PaO}_2 \leq 80 \text{ mm Hg}$ or $88\% \leq \text{SpO}_2 \leq 95\%$;
 - $7.20 \leq \text{pH} \leq 7.45$
5. Reevaluate PEEP level (PEEP- FiO_2 table, high PEEP arm)
6. Reapply usual VT after successful PEEP weaning trial



Feasibility and safety of ultra-low tidal volume ventilation without extracorporeal circulation in moderately severe and severe ARDS patients

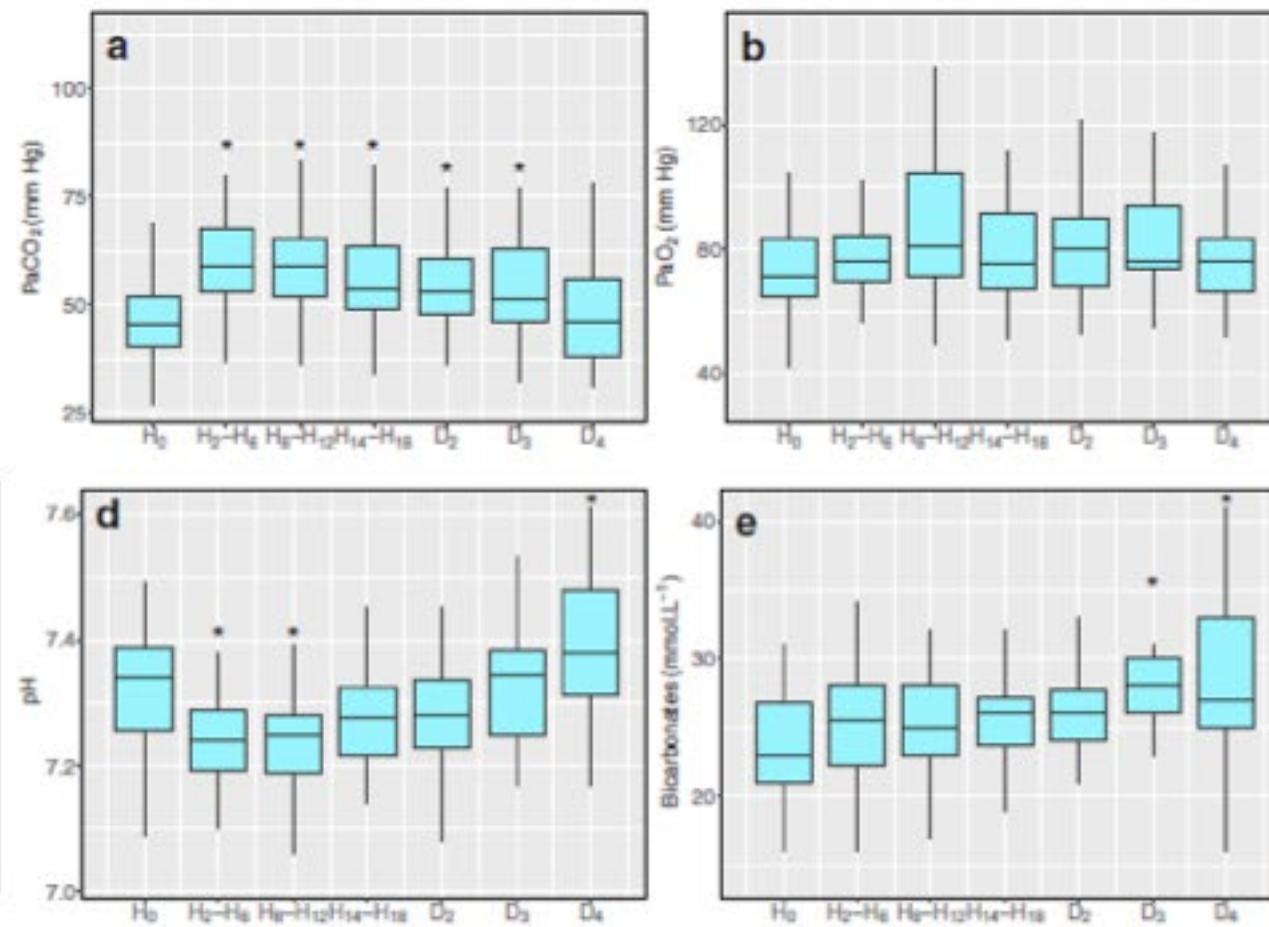
Before-and-after multicenter study
 35 ARDS patients with $\text{PaO}_2/\text{FiO}_2 \leq 150$ mmHg, within 24 h of ARDS diagnosis.



Richard JC, Marque S, Gros A, et al. Feasibility and safety of ultra-low tidal volume ventilation without extracorporeal circulation in moderately severe and severe ARDS patients. *Intensive Care Med* 2019;45(11):1590–8.

Feasibility and safety of ultra-low tidal volume ventilation without extracorporeal circulation in moderately severe and severe ARDS patients

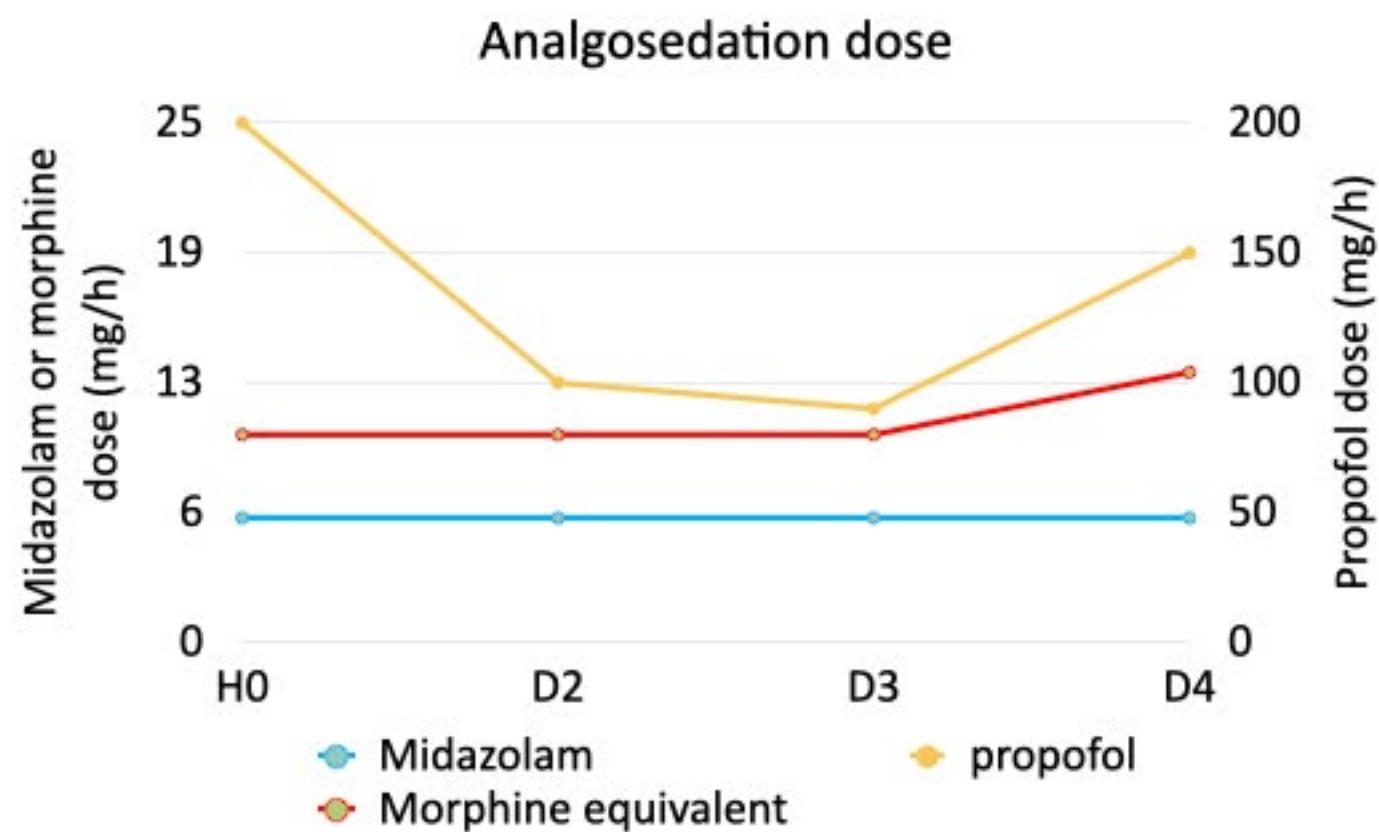
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Feasibility and safety of ultra-low tidal volume ventilation without extracorporeal circulation in moderately severe and severe ARDS patients

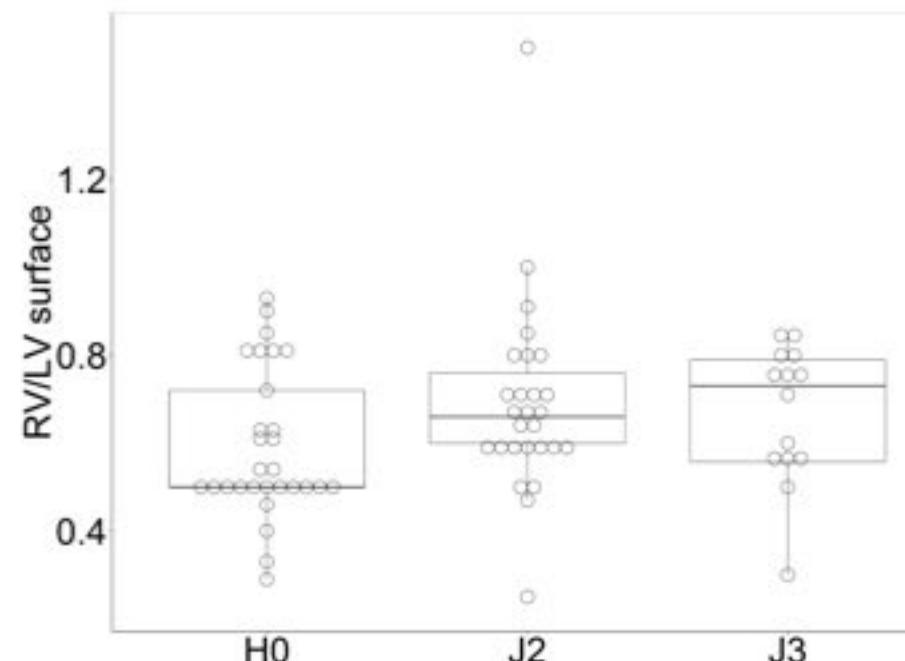
IMPACT OF UTV ON SEDATION DOSE



No detectable variation during the first 4 days of the study

ADVERSE EVENTS

| | J1 (H0) n=31 | J2 n=28 | J3 n=18 |
|---------------------|-----------------|------------|------------|
| Acute cor pulmonale | 2 (6%) | 3 (11%) | 1 (6%) |



| Adverse events | Number of episodes | Number of patients (%) | Delay of occurrence (day) |
|--------------------------------------|--------------------|------------------------|---------------------------|
| Metabolic events | | | |
| Severe mixed acidosis with pH < 7.15 | 16 | 11 (32%) | 0 [0-1] |
| Other metabolic events | 1 | 1 (3%) | 0 [0-0] |
| Respiratory events | | | |
| Pneumothorax | 2 | 2 (6%) | 6 [4-7] |
| Refractory hypoxemia requiring ECMO | 1 | 1 (3%) | 1 [1-1] |
| Other | 6 | 6 (18%) | 6 [3-14] |
| Infectious events | | | |
| Nosocomial pneumonia | 14 | 13 (38%) | 8 [6-14] |
| Non-respiratory infection site | 4 | 3 (9%) | 9 [8-11] |
| Bacteremia | 8 | 7 (21%) | 4 [2-6] |
| Cardiovascular events | | | |
| Shock | 5 | 5 (15%) | 13 [6-15] |
| Cardiac arrest | 3 | 3 (9%) | 13 [7-17] |
| Acute cor pulmonale | 2 | 2 (6%) | 1 [1-1] |
| Supraventricular tachycardia | 3 | 2 (6%) | 1 [1-6] |
| Neurological events | | | |
| ICU-acquired weakness | 5 | 5 (15%) | 11 [9-16] |
| Central nervous system disease | 5 | 5 (15%) | 7 [6-11] |
| Acute kidney injury | 8 | 8 (24%) | 3 [2-8] |
| Digestive events | | | |
| Acute liver failure | 3 | 3 (9%) | 5 [3-7] |
| Multi-organ failure | 2 | 2 (6%) | 14 [12-15] |
| Hemorrhage | 3 | 3 (9%) | 15 [14-15] |

Multivariate analysis of variables associated with severe mixed acidosis

| Variables | OR [CI _{95%}] |
|---|-------------------------|
| Renal SOFA sub-score at inclusion (per 1 unit increase) | 1.91 [1.08-3.71] |
| pH at inclusion (per 0.01 unit increase) | 0.91 [0.80-0.99] |

ULTRAPROTECTIVE VENTILATION WITHOUT EC TECHNIQUE → IMPACT ON COVID-19 ARDS PROGNOSIS???

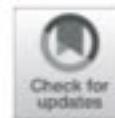
Richard et al. Trials (2021) 22:692
https://doi.org/10.1186/s13063-021-05665-z

Trials

STUDY PROTOCOL

Open Access

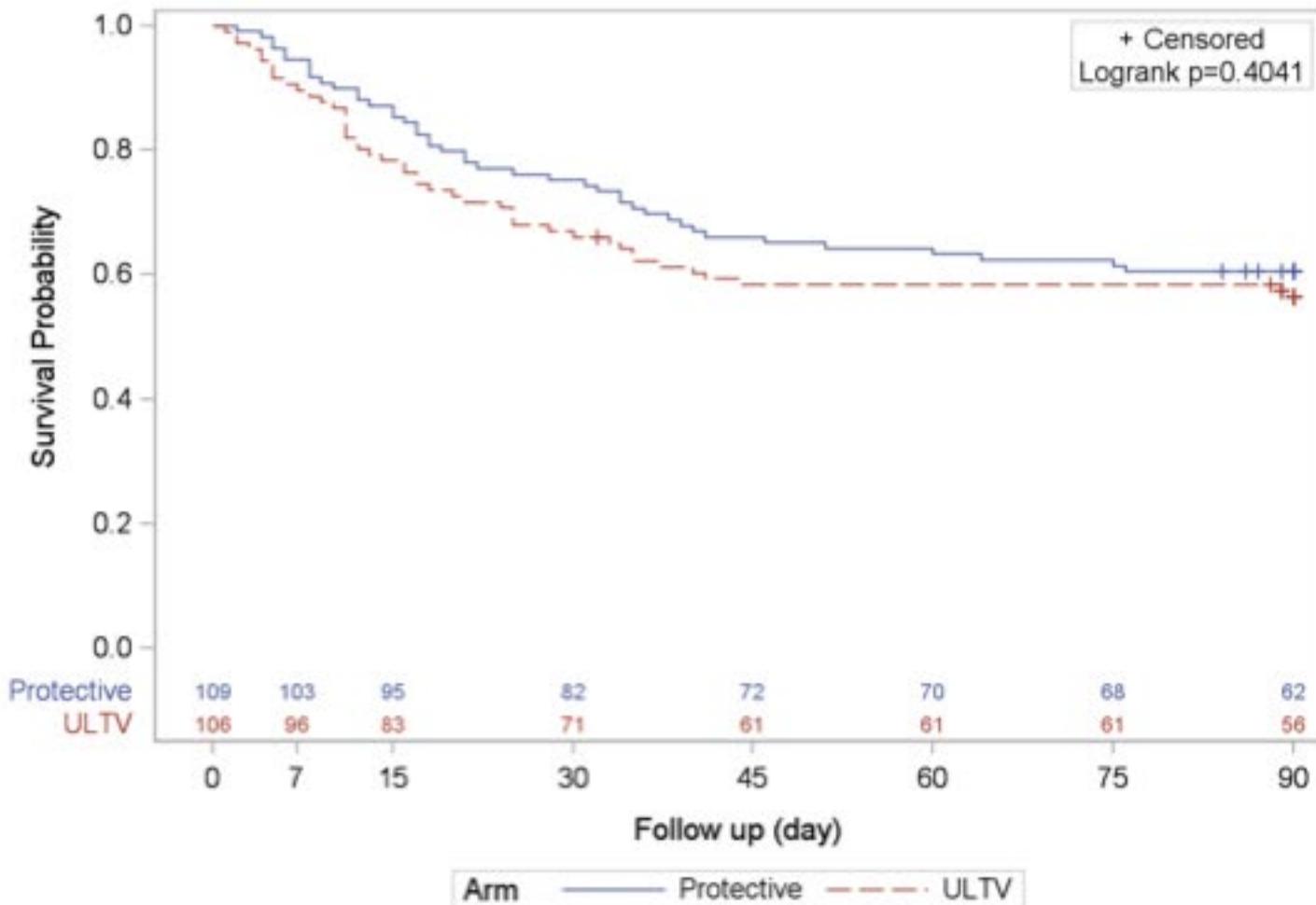
Open-label randomized controlled trial of ultra-low tidal ventilation without extracorporeal circulation in patients with COVID-19 pneumonia and moderate to severe ARDS: study protocol for the VT4COVID trial



- 215 patients included - End of inclusion : 2021
- Primary judgment criterion: composite score based on 90-day mortality as the first criterion and VFD at day 60 after inclusion as the second criterion.

HCL
HOSPITAL CLINIC LIMA

ULTRAPROTECTIVE VENTILATION WITHOUT EC TECHNIQUE → IMPACT ON COVID-19 ARDS PROGNOSIS???

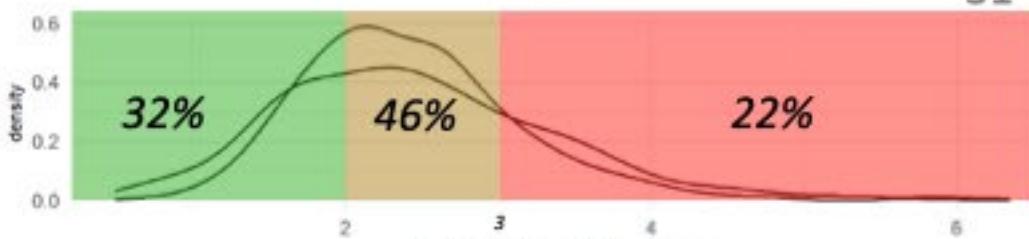
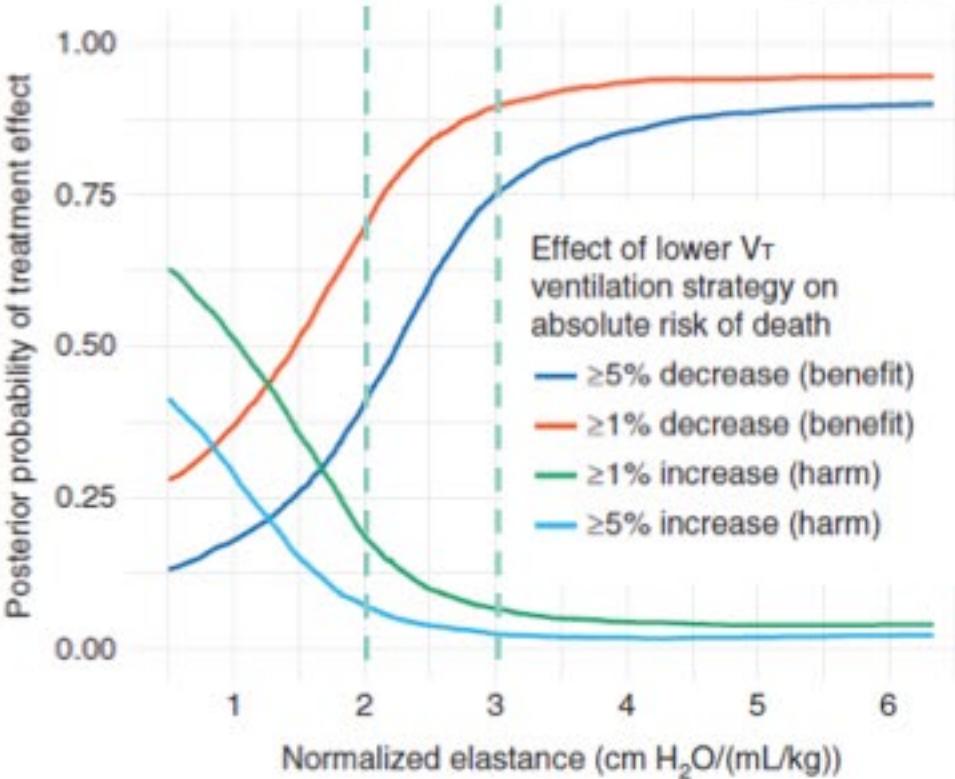
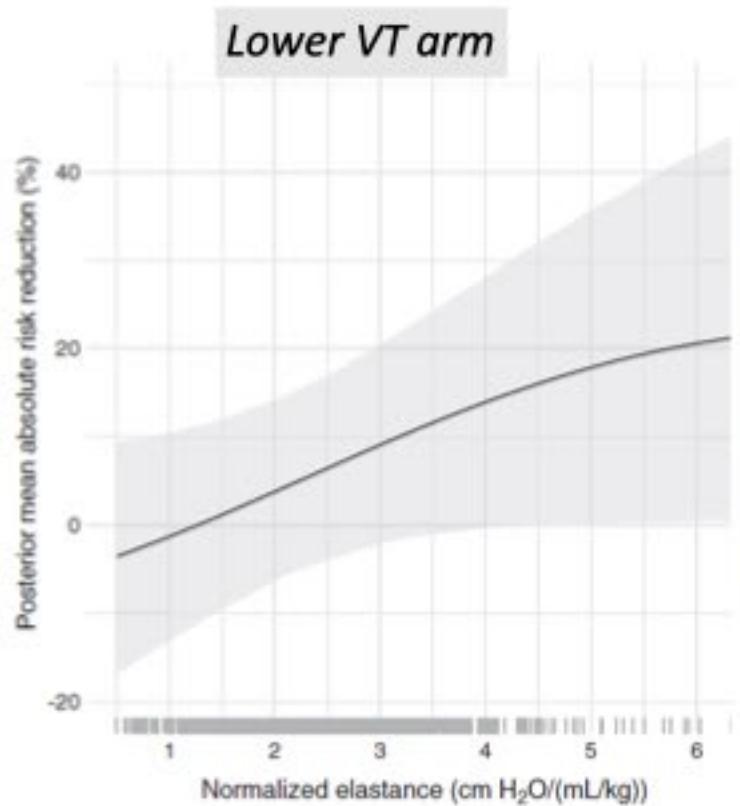


VENTILATION ULTRAPROTECTRICE POUR QUELS PATIENTS?

HIGH NORMALIZED ELASTANCE?

31

Meta-analysis of 5 RCT testing lower vs. higher VT
1202 ARDS patients

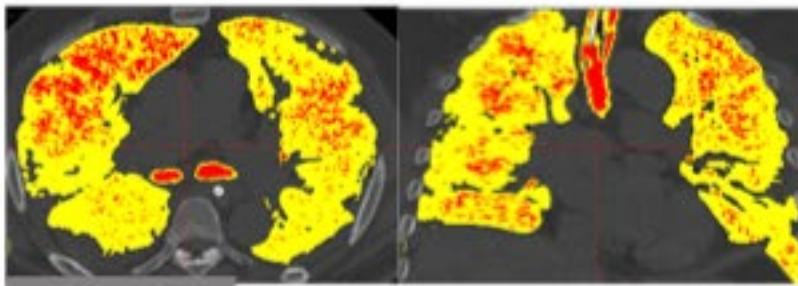
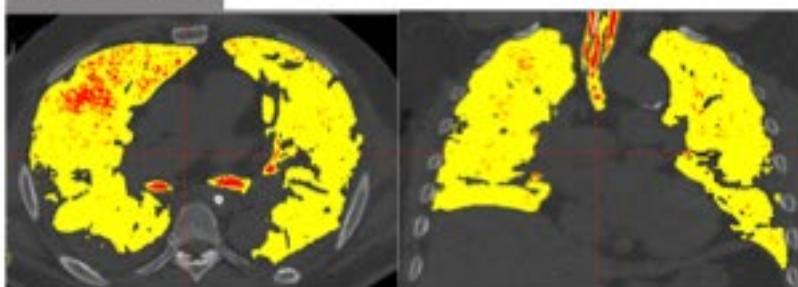


Goligher EC, Costa ELV, Yarnell CJ, et al. Effect of Lowering V_t on Mortality in Acute Respiratory Distress Syndrome Varies with Respiratory System Elastance. Am J Respir Crit Care Med 2021;203(11):1378–85.

HIGH TIDAL HYPERINFLATION (REAL-TIME QUANTITATIVE ANALYSIS OF CT)

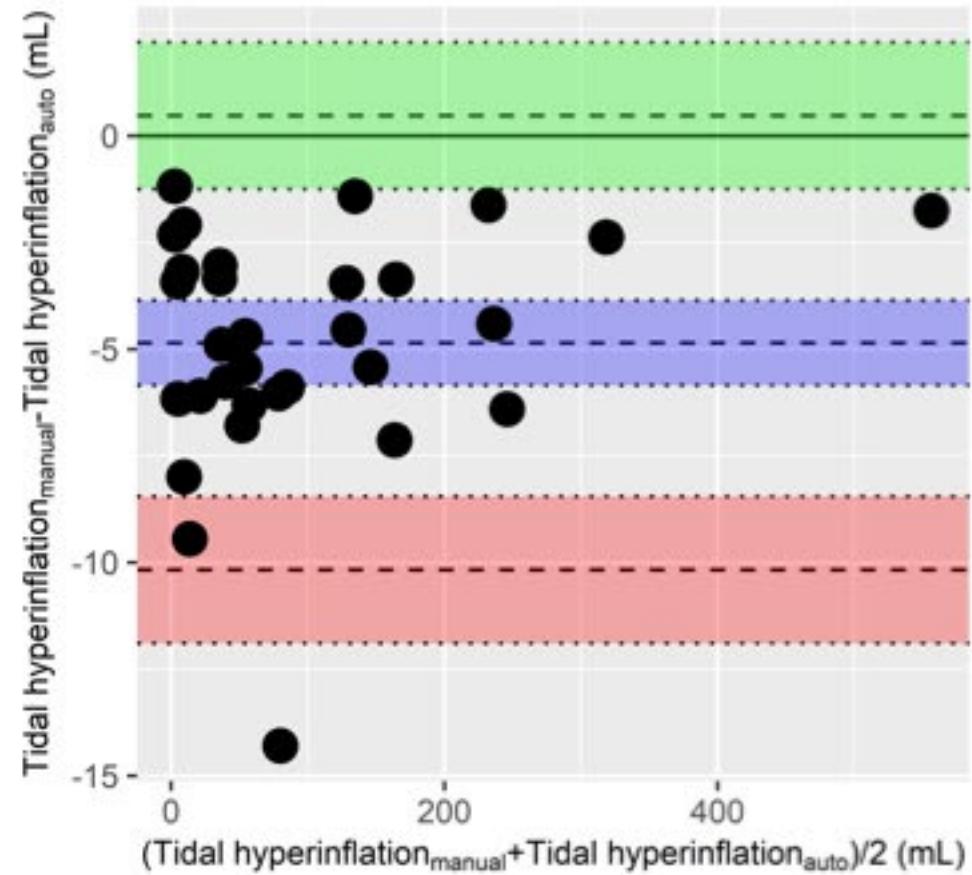
Tidal hyperinflation = 4ml/kg PBW = 74% of VT

Expiration



Inpiration

■ Hyperinflated voxels (<-900HU)



Dávila Serrano E, Dhelft F, Bitker L, Richard J-C, Orkisz M. Software for CT-image Analysis to Assist the Choice of Mechanical-Ventilation Settings in Acute Respiratory Distress Syndrome. In: International Conference on Computer Vision and Graphics. ICCVG 2020. Lecture Notes in Computer Science. Warsaw, Poland: Springer; 2020. p. 48–58.

LOW ELASTANCE AND HIGH VD/VT?

Prediction with the physiological equations defining alveolar ventilation

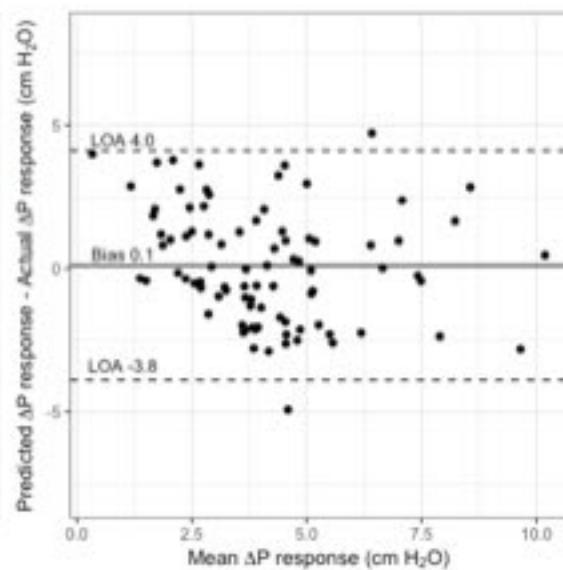
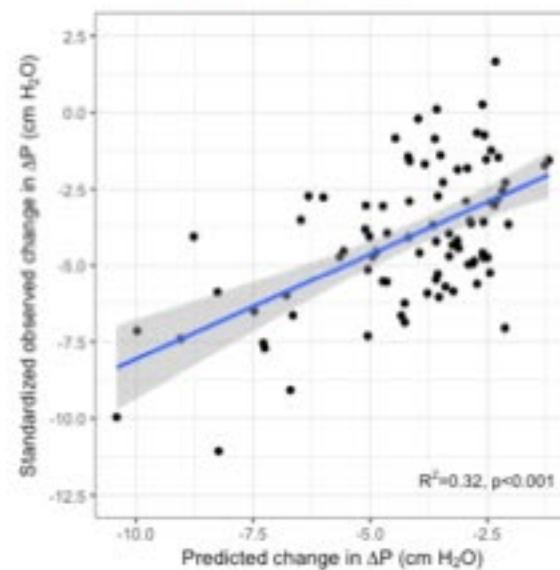
$$\Delta P_{aw,2} - \Delta P_{aw,1} = C_{RS} \cdot \left(1 - \frac{V_{d,alv}}{V_t} \right) \cdot RR \times P_{aCO_2}$$

↑ CO₂,ECML,

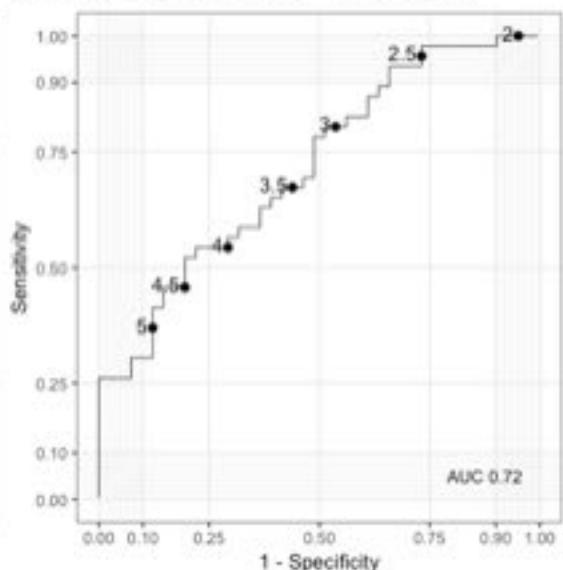
Low Crs patients

High VD/VT patients

Higher ECCO₂R rate (150ml/min)



Capacity to discriminate between high responders and minimal responders (cutoff: ΔP change: -4 cm H₂O)



Goligher EC, Combes A, Brodie D, et al. Determinants of the effect of extracorporeal carbon dioxide removal in the SUPERNOVA trial: implications for trial design. Intensive Care Med 2019;45(9):1219–30.

CONCLUSION

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