Developing Precision Medicine with ICU Subphenotypes

Precision medicine of respiratory support in ARDS patients

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Outline : Precision medicine of respiratory support in ARDS patients

- **Non intubated ARDS**
  - New ARDS definitions : non-intubated, SpO2/FiO2, sen↑spe↓*(ACRCCM. 2024 1;209(1):37-47)*
  - Nasal high flow or BIPAP *(JAMA. 2025;333(10):875-890)*
  - Better usage of nasal high flow : PSILI and lung protective sedation *(ICM. 2020; 46:2314–2326)*
  - Better usage of NIV *(JAMA. 2024 ;26;332(20):1709-1722.)*
- **Oxygen target (FiO2)**
  - Who benefit from higher FiO2 ? Who benefit from lower FiO2? *(JAMA. 2024;331(14):1195-1204)*
- **ARDS severity and treatment strategies**
  - Categorized by PF ratio or Compliance? *(ICM. 2025; 51(1):62-71)*
  - Treatment strategies based on compliance? *(AJRCCM 2025 Jun;211(6):966-974)*
  - Minimized driving pressure in
    - older patient *(AJRCCM 2024 Dec;210(11):1329-1337)*
    - acute brain injury patients *(AJRCCM 2024 Nov;210(9):1123-1131)*

American Journal of Respiratory and Critical Care Medicine

A New Global Definition of Acute Respiratory Distress Syndrome

Michael A. Matthay[1,2,3], Yaseen Arabi[5], Alejandro C. Arroliga[6], Gordon Bernard[7], Andrew D. Bersten[9], Laurent J. Brochard[10], Carolyn S. Calfee[1,2,3], Alain Combes[11], Brian M. Daniel[4], Niall D. Ferguson[12,13], Michelle N. Gong[14], Jeffrey E. Gotts[15], Margaret S. Herridge[16], John G. Laffey[17], Kathleen D. Liu[1,2], Flavia R. Machado[18], Thomas R. Martin[19], Danny F. McAuley[20], Alain Mercat[21], Marc Moss[22], Richard A. Mularski[23], Antonio Pesenti[24,25], Haibo Qiu[26], Nagarajan Ramakrishnan[27], V. Marco Ranieri[28], Elisabeth D. Riviello[29], Eileen Rubin[30], Arthur S. Slutsky[10], B. Taylor Thompson[31], Theogene Twagirumugabe[32], Lorraine B. Ware[8], and Katherine D. Wick[33]

Matthay MA et al. A New Global Definition of Acute Respiratory Distress Syndrome.
Am J Respir Crit Care Med. 2024 Jan 1;209(1):37-47. PMID: 37487152

Ongoing challenges to define ARDS

1994 — AECC
- Onset not clear
- ALI category
- No minimal PEEP
- PAWP requirement
- Risk factors not defined

2012 — Berlin definition
- Onset clarified
- Removed ALI
- Categorized severity
- Minimum PEEP
- Defined CXR criteria
- Removed PAWP
- Define risk factors

2016 — Kigali modification
- SpO2/FiO2
- No minimum PEEP
- CXR or LUS

2024 — Proposed global definition
Goals:
- Address rise in HFNC use
- Limitations of Berlin definition in resource-limited settings
- Include LUS and non-invasive pulse ox methods

ACRCCM. 2024 1;209(1):37-47

	Berlin criteria	Proposed definition
Chest imaging	Bilateral opacities on CXR or CT	Addition of bilateral B lines and/or consolidations on lung ultrasound
Categories of ARDS	PaO2/FIO2 ≤300 mm Hg on a PEEP≥ 5 or CPAP≥ 5 (mild) <u>Mild</u> 200 to ≤300 <u>Moderate</u> 100 to ≤200 <u>Severe</u> ≤100	**Non-intubated ARDS**: PaO2:FIO2 ≤300mmHg or SpO2:FIO2 ≤315 on HFNO with flow of >30 L/min or NIV/CPAP ≥ 5 H2O PEEP **Intubated ARDS**: <u>Mild:</u> 200 < PaO2:FIO2 ≤ 300 mm Hg OR 235 ≤ SpO2:FIO2 ≤ 315 <u>Moderate</u>: 100 <PaO2:FIO2 ≤ 200 mm Hg OR 148 < SpO2:FIO2 ≤235 <u>Severe:</u> PaO2:FIO2 ≤100 mm Hg OR SpO2:FIO2 ≤148 **Resource limited setting**: SpO2:FIO2 ≤315

SpO2: FiO2 is meaningful when the SpO2 is< 97%

ACRCCM. 2024 1;209(1):37-47

Bottom line

- Definition is more sensitive and less specific
- Not formally endorsed by scientific societies
- Concern of racial bias in pulse oximetry measurements among patients with dark skin tones
- Predictive validity of various SpO2: FiO2 thresholds and proposed categories of ARDS?
- Formal radiographic scoring system for LUS use and increasing training of operators?

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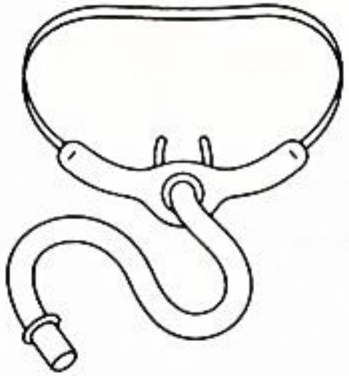
High-Flow Nasal Oxygen vs Noninvasive Ventilation in Patients with Acute Respiratory Failure: RENOVATE RCT

Citation: RENOVATE Investigators and the BRICNet Authors; Maia IS, Kawano-Dourado L, Tramujas L, et al. JAMA. 2025 Mar 11;333(10):875-890. doi: 10.1001/jama.2024.26244. PMID: 39657981.

Rationale

Uncertainty remains regarding comparative effectiveness of high-flow nasal oxygen vs noninvasive ventilation



Easier to use and more comfortable

May be more effective in reducing workload on respiratory muscles

JAMA. 2025;333(10):875-890

Objective

To assess whether HFNO is **noninferior** to NIV on rates of endotracheal intubation or death at 7 days in 5 patient groups with acute respiratory failure

JAMA. 2025;333(10):875-890

Methods

- Multicenter, adaptive, noninferiority randomized clinical trial
- 33 hospitals in Brazil
- Frequent interim analyses that allowed for stopping of individual patient groups with acute respiratory failure based on futility, noninferiority, superiority

JAMA. 2025;333(10):875-890

Acute Respiratory Failure Groups

- Non-immunocompromised with hypoxemia
- Immunocompromised with hypoxemia
- COPD exacerbation with respiratory acidosis
- Acute cardiogenic pulmonary edema
- Hypoxemic COVID-19

JAMA. 2025;333(10):875-890

Statistical Analysis

- Primary Outcome: Endotracheal intubation or death within 7 days
- Bayesian hierarchical model with dynamic borrowing across patient groups
- For each patient group, noninferiority was declared if the posterior probability was greater than 0.992

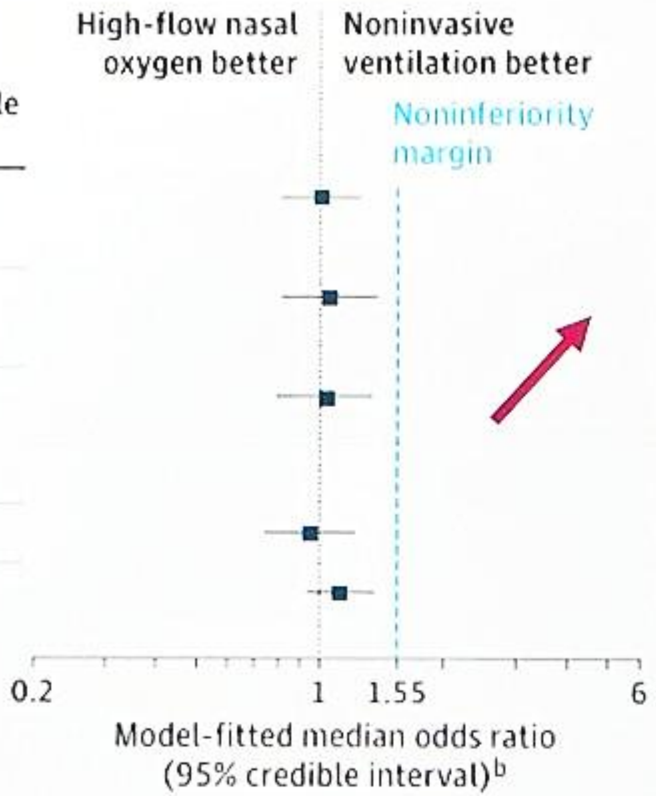
JAMA. 2025;333(10):875-890

Analysis of Primary Outcome

A Analysis of the primary outcome[a]

Patients with acute respiratory failure	No./total (%) High-flow nasal oxygen	No./total (%) Noninvasive ventilation	Model-fitted median odds ratio (95% credible interval)[b]	Posterior probability[c] Noninferiority[d]	Posterior probability[c] Superiority[e]
Nonimmunocompromised with hypoxemia	81/249 (32.5)	78/236 (33.1)	1.02 (0.81-1.26)	0.999	0.433
Immunocompromised with hypoxemia	16/28 (57.1)	8/22 (36.4)	1.07 (0.81-1.39)	0.989	0.334
Chronic obstructive pulmonary disease exacerbation with respiratory acidosis	10/35 (28.6)	11/42 (26.2)	1.05 (0.79-1.36)	0.992	0.375
Acute cardiogenic pulmonary edema	14/136 (10.3)	29/136 (21.3)	0.97 (0.73-1.23)	0.997	0.575
Hypoxemic COVID-19	223/435 (51.3)	210/447 (47.0)	1.13 (0.94-1.38)	0.997	0.136

用NHF未達Noninferiority (插管機率稍高)



四個族群 NHF 達到Noninferiority

Conclusions

- High-flow nasal oxygen was noninferior to noninvasive ventilation in the following patient groups
  - Non-immunocompromised with hypoxemia
  - COPD exacerbation with respiratory acidosis
  - Acute cardiogenic pulmonary edema
  - Hypoxemic COVID-19
- High-flow nasal cannula was <u>**not**</u> found to be <u>**noninferior**</u> compared with noninvasive ventilation among immunocompromised patients with hypoxemia.

JAMA. 2025;333(10):875-890

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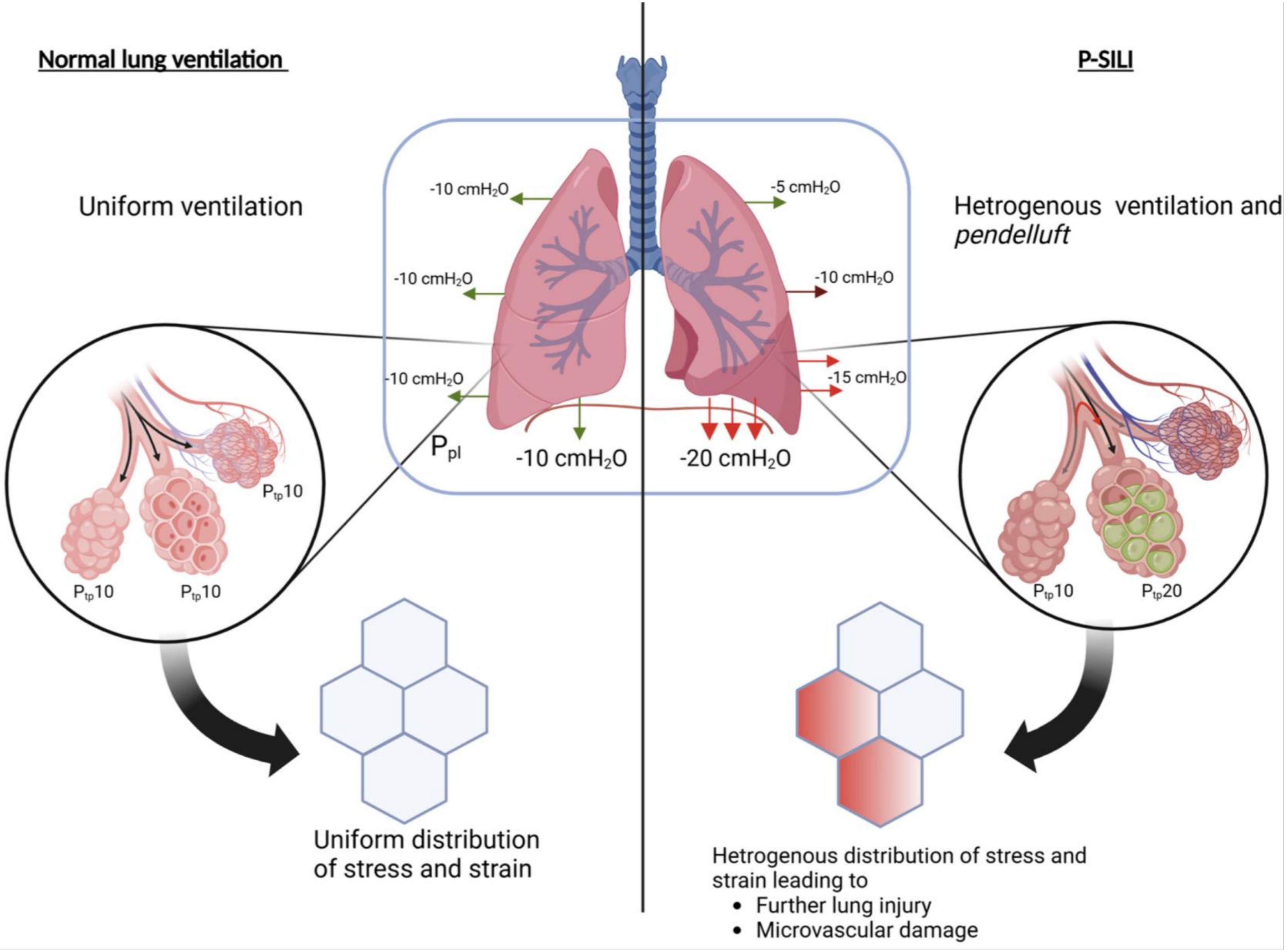
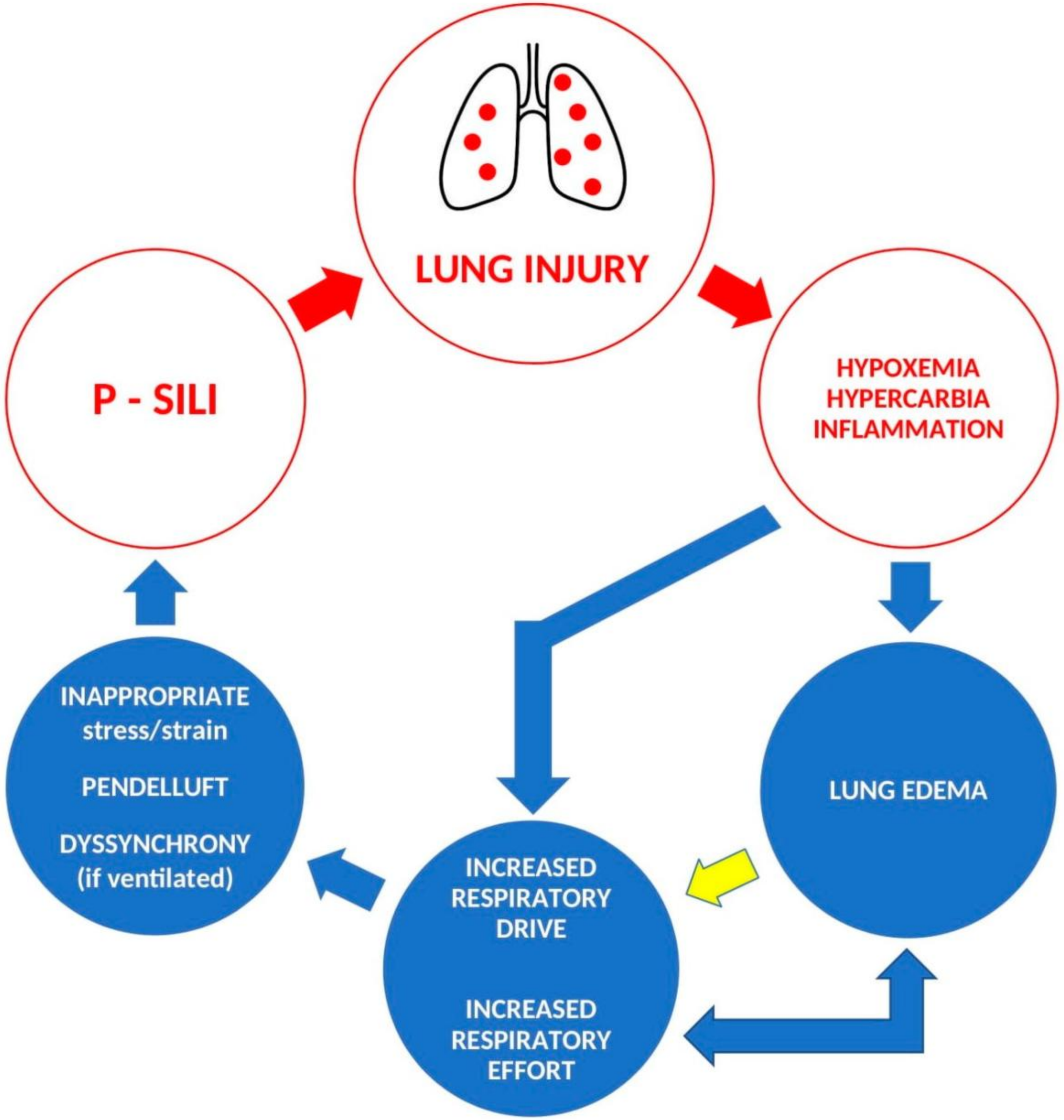
Patient Self-Inflicted Lung Injury (P-SILI)



J. Clin. Med. **2025**, *14*(5), 1632;

Patient Self-Inflicted Lung Injury

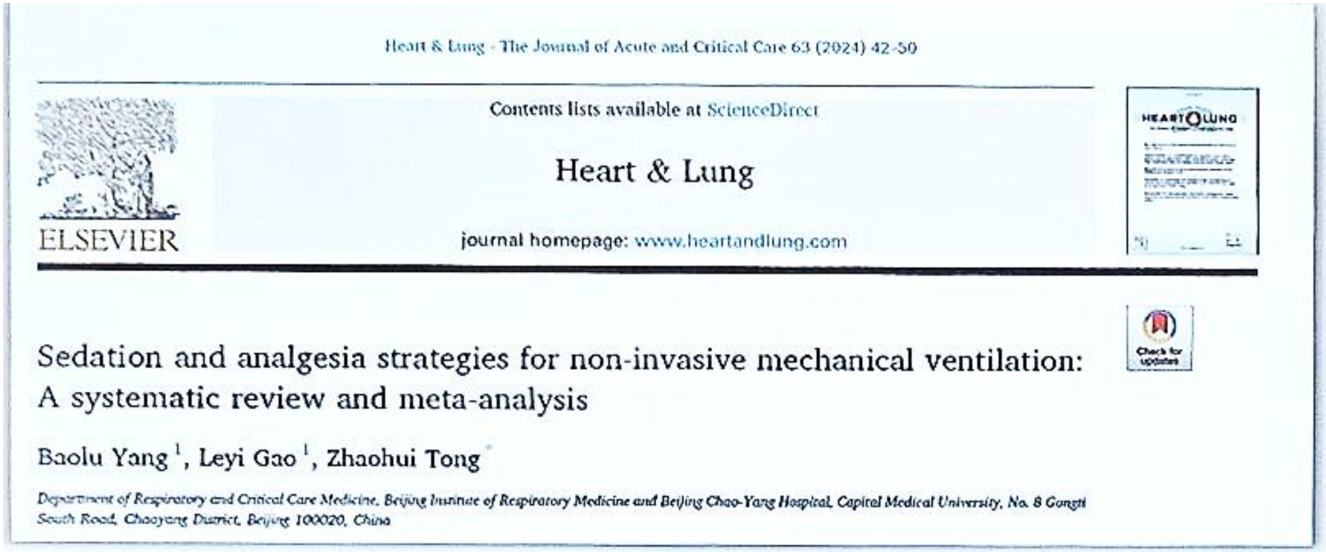


J. Pers. Med. **2023**, *13*(4), 593;

Lung protective sedation

Drug class	Inspiratory effort and tidal volume	Respiratory rate	Ventilatory response to hypercapnia and hypoxemia	Effect on diaphragm function and patient-ventilator interaction
Benzodiazepines	↓	⟷ or ↑ ↓ at high doses	↓	Delay restoration of diaphragm activity
Propofol	↓	⟷ or ↑ ↓ at high doses	↓	May ↑ dyssynchrony (i.e., ineffective efforts because of lower respiratory effort)
Opioids	⟷ or ↑	↓	↓	May ↓ dyssynchrony (i.e., fewer ineffective efforts because of slower, deeper respiratory efforts)
Dexmedetomidine	⟷	⟷	⟷	↓ dyssynchrony by decreasing agitation/delirium

Intensive Care Med (2020) 46:2314–2326


Heart & Lung - The Journal of Acute and Critical Care 63 (2024) 42–50

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Heart & Lung

journal homepage: www.heartandlung.com

Sedation and analgesia strategies for non-invasive mechanical ventilation: A systematic review and meta-analysis

Baolu Yang [1], Leyi Gao [1], Zhaohui Tong [*]

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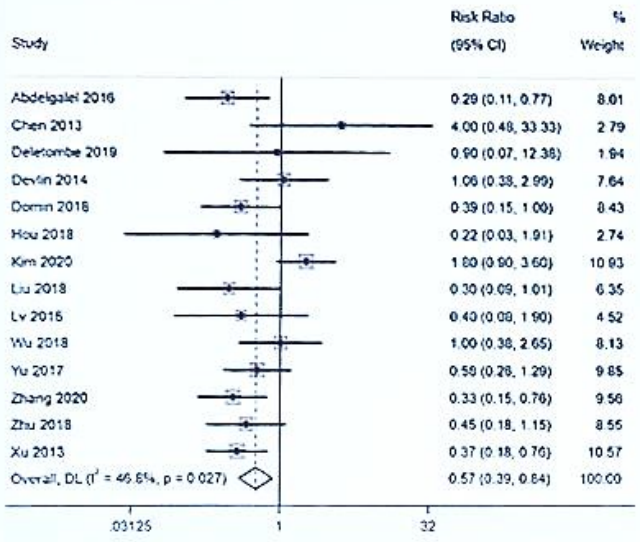
Lung Protective Sedation



21 RCTs

Any sedative/analgesia vs. none showed lower intubation rates on NIV.

Dexmedetomidine vs other medications reduced intubation

INDEX trial currently underway to evaluate dexmedetomidine and NIV

Dr.Kim Lewis, McMaster, Canada

Administering sedative and analgesic medications during NIV can reduce the risk of tracheal intubation and delirium. Dexmedetomidine outperformed other sedative medications in terms of these clinical outcomes.

HFNC with lung protective sedation, if fail, try NIV

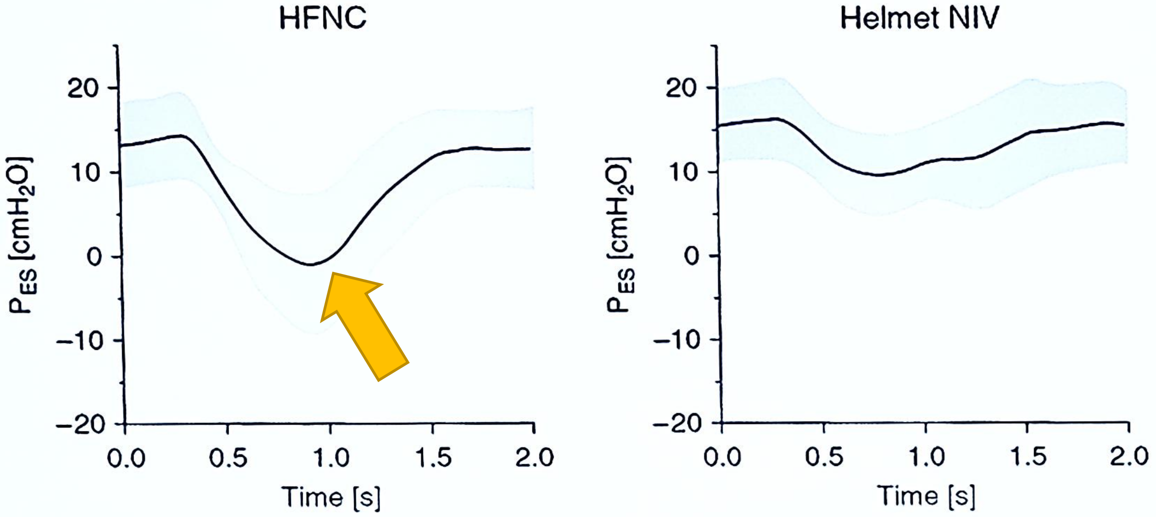
Check for updates

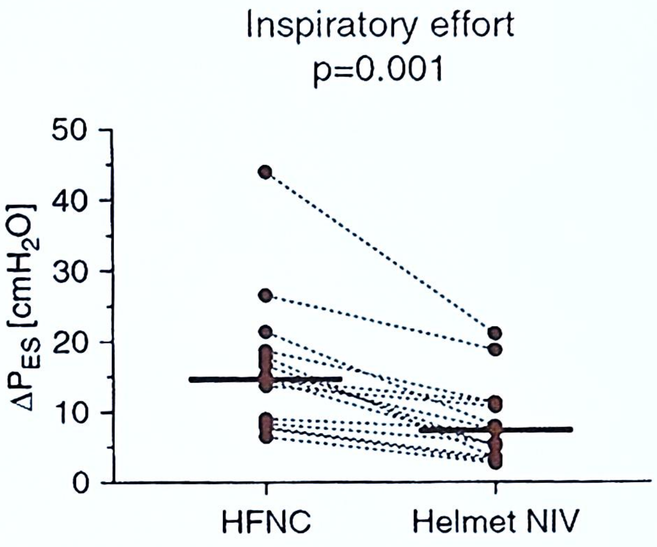
ORIGINAL ARTICLE

Physiological Comparison of High-Flow Nasal Cannula and Helmet Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure

Domenico Luca Grieco[1,2], Luca S. Menga[1,2], Valeria Raggi[1,2], Filippo Bongiovanni[1,2], Gian Marco Anzellotti[1,2], Eloisa S. Tanzarella[1,2], Maria Grazia Bocci[1,2], Giovanna Mercurio[1,2], Antonio M. Dell'Anna[1,2], Davide Eleuteri[1,2], Giuseppe Bello[1,2], Riccardo Maviglia[1,2], Giorgio Conti[1,2], Salvatore Maurizio Maggiore[3], and Massimo Antonelli[1,2]

[1]Dipartimento di Scienze dell'Emergenza, Anestesiologiche e della Rianimazione, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [2]Department of Anesthesiology and Intensive Care Medicine, Catholic University of the Sacred Heart, Rome, Italy; and [3]Department of Medical, Oral and Biotechnological Sciences, School of Medicine and Health Sciences, Section of Anesthesia, Analgesia, Perioperative and Intensive Care, SS. Annunziata Hospital, Gabriele d'Annunzio University of Chieti-Pescara, Chieti, Italy

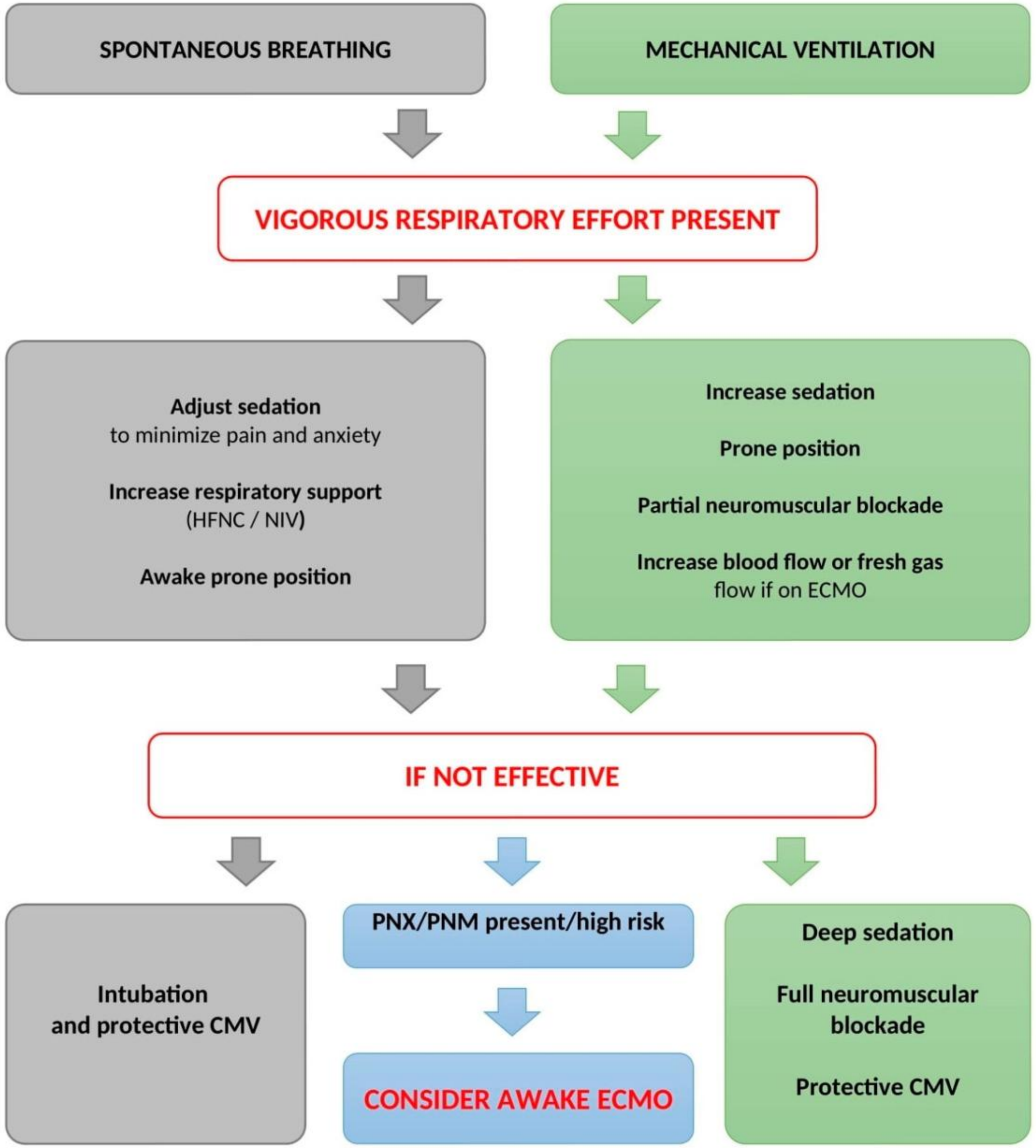




Physiology study alternating HFNC and Helmet NIV

Helmet (more effective PEEP) yielded a reduction in negative inspiratory swings (surrogate for inspiratory effort) measured by esophageal balloon

HFNC with lung protective sedation, if fail, try NIV



J. Pers. Med. **2023**, *13*(4), 593;

HAPPEN trial

Research

JAMA | Original Investigation

Effect of High-Intensity vs Low-Intensity Noninvasive Positive Pressure Ventilation on the Need for Endotracheal Intubation in Patients With an Acute Exacerbation of Chronic Obstructive Pulmonary Disease

The HAPPEN Randomized Clinical Trial

Zujin Luo, MD; Yichong Li, PhD; Wenjun Li, MD; Ying Li, MD; Qingrong Nie, MD; Yu Shi, PhD; Juan Wang, BSN; Qiuling Ji, MD; Xuefeng Han, MD; Sijie Liu, MD; Dongmei Li, MD; ShaSha Wang, MD; Zhijun Li, MD; Dong Jia, MD; Huiqing Ge, MD; Peifeng Xu, BSc; Zhijun Feng, MD; Fengjie Li, MD; Fucheng An, MD; Na Tai, MD; Lili Yue, MD; Hongwei Xie, MD; Xiuhong Jin, MD; Hongru Liu, MD; Qiang Dang, MD; Yongxiang Zhang, MD; Li Sun, MD; Jinxiang Wang, MD; He Huang, MD; Liang Chen, MD; Yingmin Ma, MD; Zhixin Cao, MD; Chen Wang, MD, PhD; for the HAPPEN Investigators

Title adapted from Z Luo et al, *JAMA*, Sept 2024

Non invasive ventilation for COPD exacerbations

- Hypothesis:
  - High intensity non-invasive ventilation superior to low intensity ventilation to prevent intubation for hypercapnic COPD exacerbations
- Patients:
  - Chinese adults with type 2 respiratory failure due to COPD exacerbation
- Interventions:
  - Low intensity - Tidal volume 6 to 10ml/kg with max IPAP 20cm H_2O
  - High intensity - Tidal volume 10 to 15ml/kg with max IPAP 30cm H_2O
- Primary outcome – Pre-determined intubation criteria of pH <7.25, increase in PaCO2 and clinical signs of worsening hypercapnia

JAMA. 2024 ;26;332(20):1709-1722.

Non invasive ventilation for COPD exacerbations

Table 2. Primary and Secondary Outcomes

	Noninvasive positive pressure ventilation (NPPV)			
	High intensity (n = 147)	Low intensity (n = 153)	Unadjusted absolute difference (95% CI)[a]	*P* value
Primary outcome[d]				
Need for endotracheal intubation during hospitalization, No. (%)	7 (4.8)	21 (13.7)	−9.0 (−15.4 to −2.5)	.004[e]
Secondary outcomes[d]				
Endotracheal intubation during hospitalization, No. (%)	5 (3.4)	6 (3.9)	−0.5 (−4.8 to 3.7)	.81
Endotracheal intubation at 28 d, No. (%)				
Met prespecified criteria for the need for intubation	7 (4.8)	21 (13.7)	−9.0 (−15.4 to −2.5)	.008
Intubated	5 (3.4)	6 (3.9)	−0.5 (−4.8 to 3.7)	.81
Composite of endotracheal intubation or avoiding intubation, No. (%)[f]	5 (3.4)	17 (11.1)	−7.7 (−13.5 to −1.9)	.01

Adapted from Z Luo et al, *JAMA*, Sept 2024

Non invasive ventilation for COPD exacerbations

- High intensity ventilation prevents meeting pre-specified criteria for intubation
- But trialling low intensity ventilation first, then moving to high intensity in the 13% of patients who need it, is safe
- No difference in intubation or mortality
- Patients allocated high intensity more likely to have abdominal distension

JAMA. 2024 ;26;332(20):1709-1722.

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  - Better usage of nasal high flow: PSILI and **lung protective sedation** *(ICM. 2020; 46:2314–2326)*
  - Better usage of NIV: **higher intensity (IPAP=30, TV=10-15)>**lower intensity (IPAP=30, TV=6-10) *(JAMA. 2024 ;26;332(20):1709-1722.)*
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Individualized Treatment Effects of Oxygen Targets in Mechanically Ventilated Critically Ill Adults

Citation: Buell KG, Spicer AB, Casey JD, et al. JAMA. 2024 Apr 9;331(14):1195-1204. doi: 10.1001/jama.2024.2933. PMID: 38501205.

Rationale

- Randomized trials have reported similar outcomes for patients allocated to lower oxygenation compared to higher oxygenation targets

- This may be because patients have multiple characteristics that influence the effect of a lower versus higher oxygenation targets on mortality not accounted for in traditional analyses of randomized trials (i.e., **heterogeneity of treatment effect**)

JAMA. 2024;331(14):1195-1204

Objective

To test the hypothesis that the effect of Spo_2 targets on mortality would differ based on individual patient characteristics

JAMA. 2024;331(14):1195-1204

Study Population and Outcomes

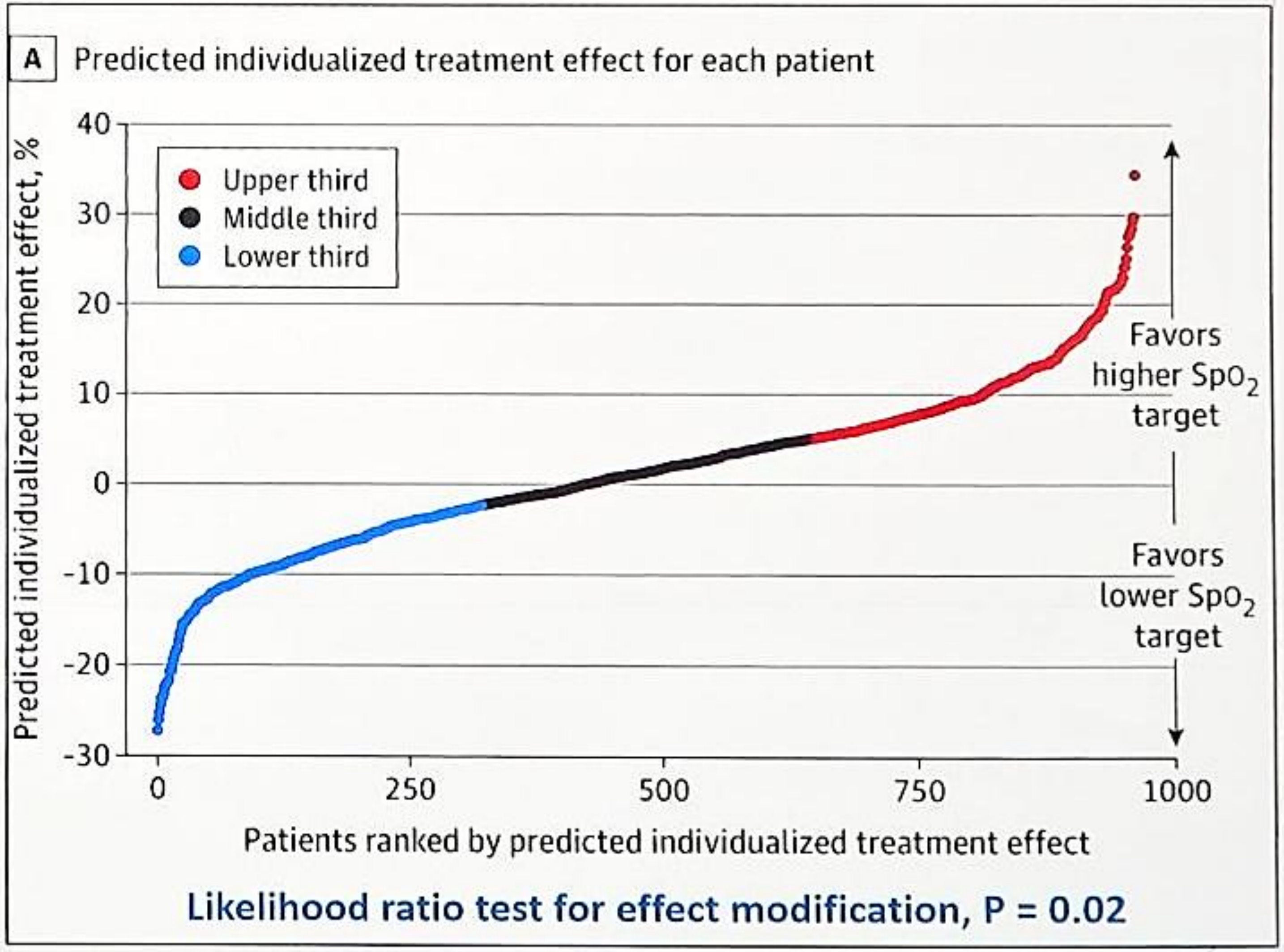
Trial Characteristics	PILOT (n=2541)	ICU-ROX (n=965)
	Derivation Model	External Validation Model
Randomization	Cluster-randomized, cluster crossover	Individual patient, parallel group
Interventions and Groups	Lower Spo2 target: 90% (range 88-92%) Intermediate: 94% (92-96%) Higher: 98% (96-100%)	Lower Spo2 target: 91-96% Higher: 91-100%
Location	1 center in US	21 centers in Australia and New Zealand
Primary Outcome	VFD (ventilator-free days)	VFD (ventilator-free days)
Result of trial	No between-group difference in outcomes	No between-group difference in outcomes

JAMA. 2024;331(14):1195-1204

Results

- Original trials demonstrated no significant **average** treatment effect of lower vs higher Spo_2 groups on mortality

- ITE in the ICU-ROX cohort ranged from 27.2% absolute reduction in mortality with use of **lower** SpO_2 target to 34.4% absolute risk reduction in mortality with use of **higher** target



JAMA. 2024;331(14):1195-1204

Table 2. Baseline Characteristics of Patients in the ICU-ROX Validation Cohort by Predicted Individualized Treatment Effect

Characteristic	No. (%) of participants: Lower third: predicted to benefit from lower Spo_2 target (n = 322)	Middle third: predicted to have similar outcomes with either target (n = 322)	Upper third: predicted to benefit from higher Spo_2 target (n = 321)	*P* value[a]
Demographics				
Age, median (IQR), y	67 (55 to 74)	58 (45 to 68)	57 (49 to 65)	<.001
Sex				
Female	89 (27.6)	128 (39.8)	140 (43.6)	<.001
Male	233 (72.4)	194 (60.2)	181 (56.4)	<.001
Source of admission to ICU				
Hospital ward	44 (13.7)	58 (18.0)	87 (27.1)	<.001
Emergency department	155 (48.1)	120 (37.3)	124 (38.6)	.01
Operating room or postanesthesia care unit	101 (31.4)	109 (33.9)	85 (26.5)	.12
Transfer from another ICU or another hospital	22 (6.8)	35 (10.9)	25 (7.8)	.16
Time from initiation of mechanical ventilation to enrollment, median (IQR), h	3.6 (1.9 to 5.9)	3.2 (1.6 to 5.7)	2.6 (1.2 to 4.3)	<.001
ICU admitting diagnosis[b]				
Cardiovascular disease	94 (29.2)	63 (19.6)	48 (15.0)	<.001
Acute nonhypoxic brain injury	90 (28.0)	86 (26.7)	41 (12.8)	<.001
Acute hypoxic brain injury	84 (26.1)	46 (14.3)	36 (11.2)	<.001
Respiratory disease	25 (7.8)	46 (14.3)	67 (20.9)	<.001
Sepsis	20 (6.2)	33 (10.2)	43 (13.4)	<.001
Baseline physiology[c]				
Heart rate, median (IQR), beats/min	80 (66 to 100)	92 (80 to 106)	102 (88 to 122)	<.001
>80	160 (49.8)	228 (71.0)	277 (86.3)	<.001

較多病人
在低血氧目標組

較多病人
在高血氧目標組

JAMA. 2024;331(14):1195-1204

Table 3. Primary Outcome of 28-Day Mortality

Outcome	No. (%) of participants			P value
	Lower third: predicted to benefit from lower SpO_2 target (n = 322)	Middle third: predicted to have similar outcomes with either target (n = 322)	Upper third: predicted to benefit from higher SpO_2 target (n = 321)	
Overall	115 (35.7)	92 (28.6)	84 (26.2)	
Randomized to lower SpO_2 group	54 (32.7)	47 (28.7)	51 (32.9)	
Randomized to higher SpO_2 group	61 (38.9)	45 (28.5)	33 (19.9)	
Treatment effect (difference in incidence in 28-d mortality between lower vs higher SpO_2 groups), % (95% CI)	−6.1 (−16.5 to 4.3)	0.2 (−9.6 to 10.0)	13.0 (3.5 to 22.6)	.02[a]

Abbreviation: SpO_2, peripheral oxygenation-saturation by pulse oximetry.

[a] Likelihood ratio test P value for interaction term between the thirds of predicted individualized treatment effect and the randomized SpO_2 group assignment.

JAMA. 2024;331(14):1195-1204

Conclusions

- In 2 RCTS, patients' individual characteristics modified the effect of lower vs higher Spo_2 targets on 28-day mortality
  - For example: Use of lower target may decrease mortality for patients with acute brain injury and use of higher target may decrease mortality for patients with sepsis and abnormal vital signs

- Heterogeneity of treatment effect may explain findings, on average, of no difference between groups in prior RCTs of Spo_2 targets

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  - Better usage of NIV: **higher intensity (IPAP=30, TV=10-15)>**lower intensity (IPAP=30, TV=6-10) *(JAMA. 2024 ;26;332(20):1709-1722.)*
- **Oxygen target (FiO_2)**
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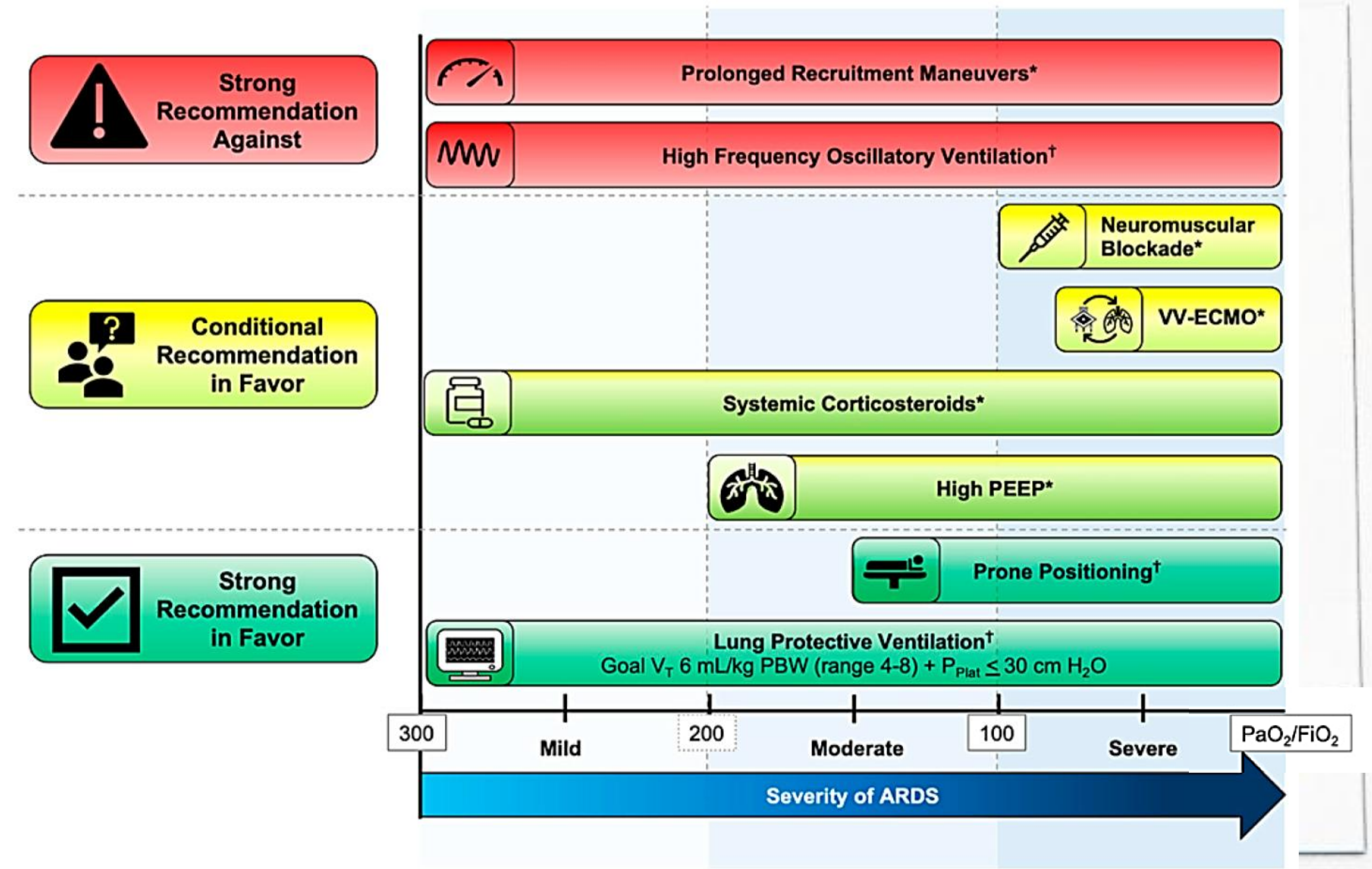
- **ARDS severity and treatment strategies**
  - Categorized by PF ratio or Compliance? *(ICM. 2025; 51(1):62-71)*
  - Treatment strategies based on compliance? *(AJRCCM 2025 Jun;211(6):966-974)*
  - Minimized driving pressure in
    - older patient *(AJRCCM 2024 Dec;210(11):1329-1337)*
    - acute brain injury patients *(AJRCCM 2024 Nov;210(9):1123-1131)*

Rethinking ARDS Classification: Oxygenation Impairment Fails to Predict VILI Risk

Citation: Catozzi G, Pozzi T, Nocera D, et al. Intensive Care Med. 2025 Jan;51(1):62-71. doi: 10.1007/s00134-024-07712-0. PMID: 39661133

Rationale

Current ARDS clinical practice guidelines recommend management based on severity of P:F ratio impairment



Update on Management of Adult Patients with ARDS: Official ATS Clinical Practice Guideline
Qadir et al. AJRCCM. 2024

(ICM. 2025; 51(1):62-71)

Objective

Evaluate whether oxygenation and mechanical variables are sufficiently correlated to justify the current guidance of basing therapy intensity on oxygenation criteria

Methods & Study Population

- 228 patients with ARDS enrolled between 2003 and 2024 (Italy, Germany, Chile)
- Population stratified into 3 groups

ARDS P:F severity groups	Mechanical Power Ratio* groups	Driving Pressure groups
1. Mild-Moderate (200-151 mmHg) 1. Moderate-Severe (150-101 mmHg) 2. Severe (< 100 mmHg)	1. Low 2. Middle 3. High	1. Low 2. Middle 3. High

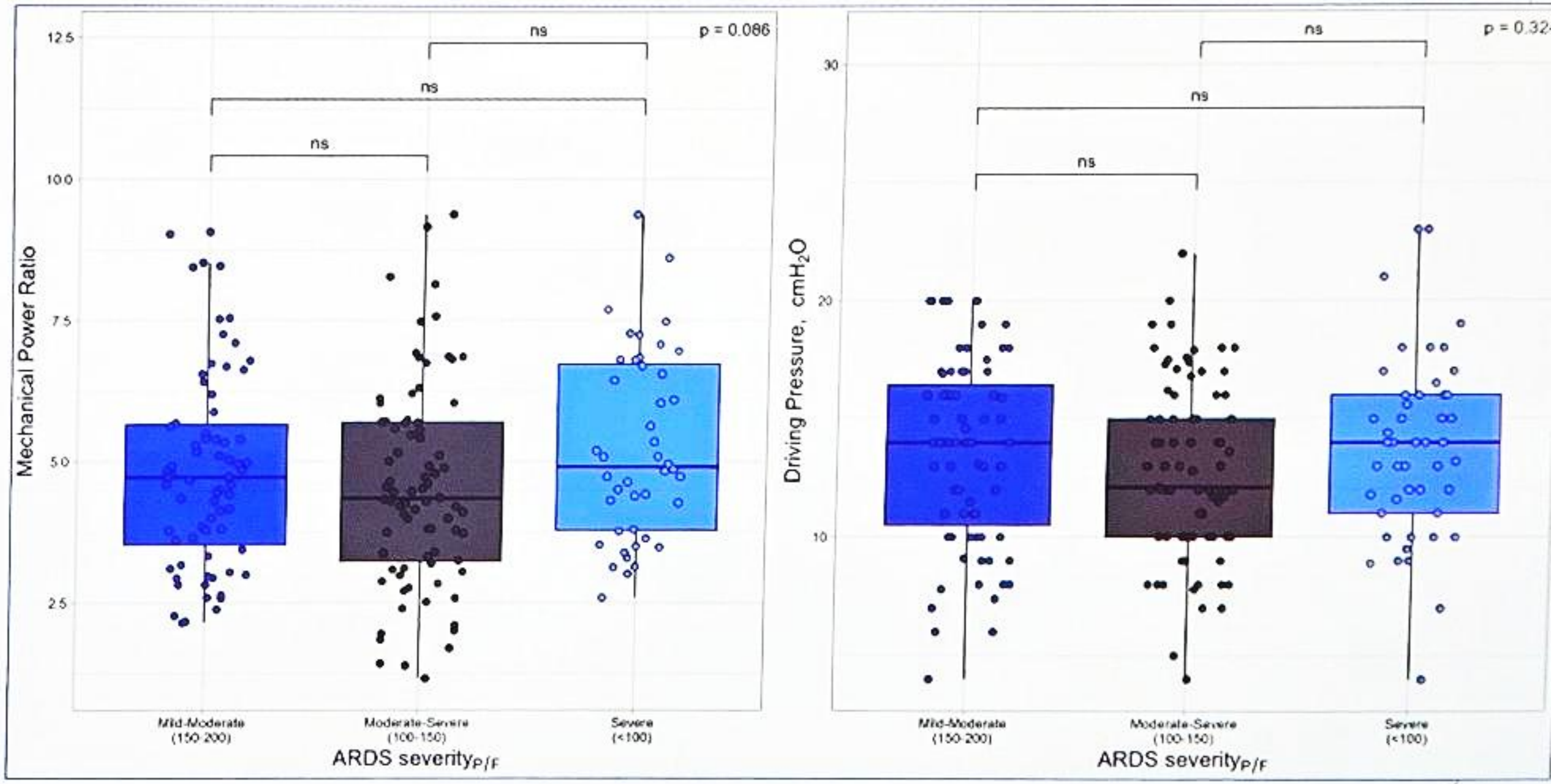
*Compares actual mechanical power delivered during mechanical ventilation to expected mechanical power for normal breathing

(ICM. 2025; 51(1):62-71)

Results

Fig 1:
MPR and ΔP
as function of P:F
severity classes

Result:
MPR and ΔP
were similar
across ARDS P:F
severity groups



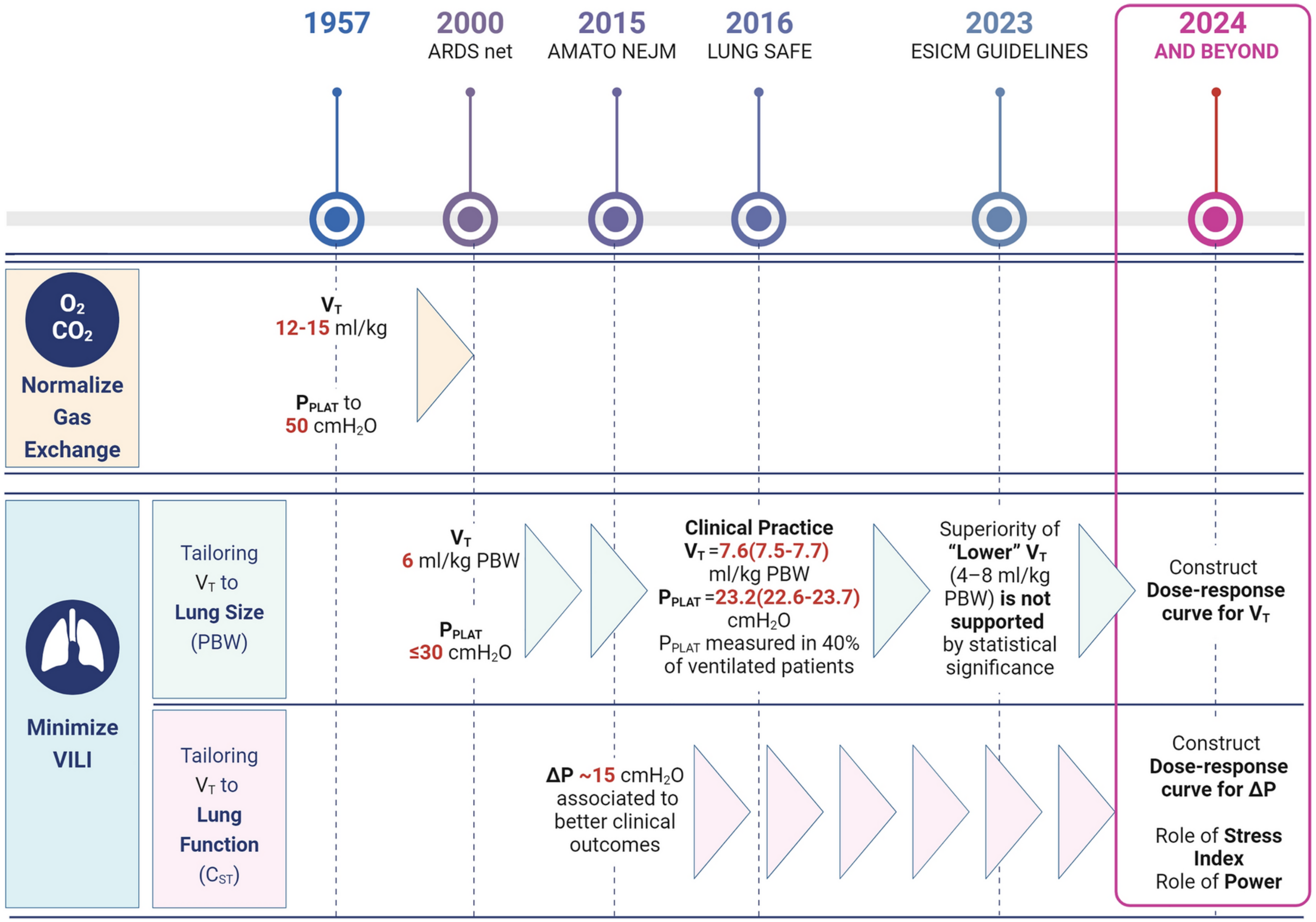
(ICM. 2025; 51(1):62-71)

Conclusions

- Mechanical ventilation intensity increased across MPR and ΔP tertiles
- ARDS severity based on oxygenation impairment did not reflect prerequisites and determinants of VILI

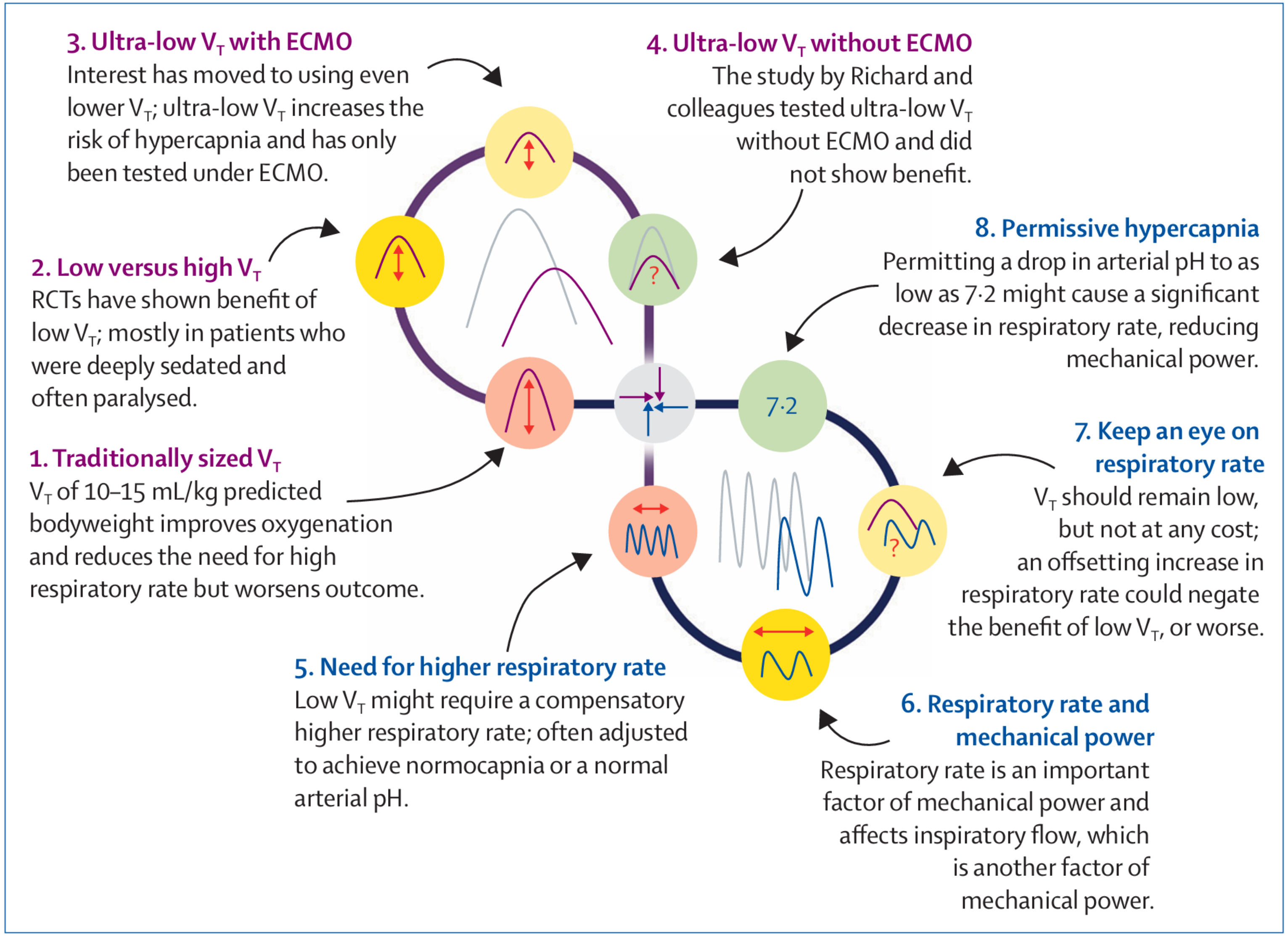
(ICM. 2025; 51(1):62-71)

Finding the optimal tidal volume in ARDS



Ref. Pellegrini, M., Del Sorbo, L. & Ranieri, V.M. Finding the optimal tidal volume in acute respiratory distress syndrome. *Intensive Care Med* (2024).

The interplay between Vt and Resp. rate



Ref. *Lancet Respir Med* 2023; 11: 950

ICM

ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies

American Journal of Respiratory and Critical Care Medicine

An Update on Management of Adult Patients with Acute Respiratory Distress Syndrome

An Official American Thoracic Society Clinical Practice Guideline

Scientific symposium: Contrasting concurrent guidelines and making sense of their differences- ATS and ESCIM ARDS guidelines
Today: 12 -1 pm in 6B

ATS 2024

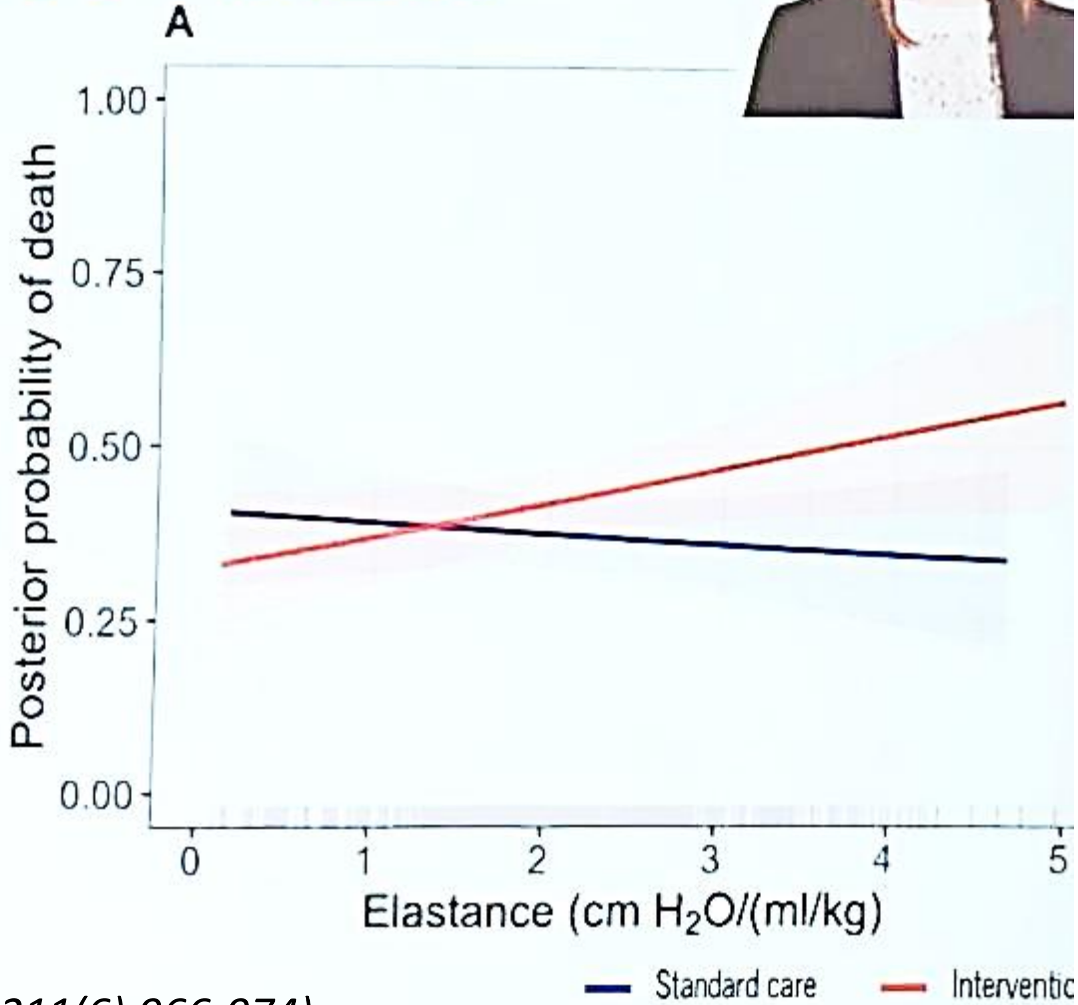
Grasselli et al. European Society of Intensive Care Medicine Taskforce on ARDS. ESICM guidelines on acute respiratory distress syndrome definition, phenotyping and respiratory support strategies. Intensive Care Med. 2023 Jul;49(7):727-759. PMID: 3732664

Qadir et al. An Update on Management of Adult Patients with Acute Respiratory Distress Syndrome: An Official American Thoracic Societ Clinical Practice Guideline. Am J Respir Crit Care Med. 2024 Jan 1;209(1):24-36. PMID: 3803268

ATS		ESCIM
Strong recommendation for	Lung protective ventilation	Strong recommendation for
Strong recommendation for	Early prone positioning in mod-severe ARDS	Strong recommendation for
Conditional recommendation in favor of	VV-ECMO in severe ARDS	Suggestion for
Conditional recommendation in favor of High PEEP vs. low PEEP in moderate to severe ARDS	PEEP titration strategy	No recommendation
Conditional recommendation in favor of	Corticosteroids	Do not address
Conditional recommendation in favor of use in moderate to severe ARDS	Neuromuscular blockade	Strongly recommendation against
Strongly recommendation against	Prolonged recruitment maneuvers	Strong recommendation against
Strongly recommendation against	HFOV	No recommendation
Do not address	HFNO	Strong recommendation for in AHRF
Do not address	Awake prone positioning in non-intubated patients with AHRF due to COVID-19	Suggestion for
Do not address	NIV to reduce intubation in COVID-19	Weak recommendation for
Do not address	$ECCO_2R$	Strong recommendation against

Phenotyping by Elastance: NMBA

- Re-analysis of ROSE trial
- Moderate-severe ARDS
- 92% probability that effect of NMB on mortality varies with baseline elastance
- Benefit greatest if baseline E_{RS} > 2 cmH2O/(mL/kg)
- No difference if E_{RS} < 2 cmH2O/(mL/kg)
- No HTE by VR, IL6, IL8, TNF1
- Unique phenotype from inflammatory subphenotype



(AJRCCM 2025 Jun;211(6):966-974)

Zalucky et al, AJRCCM accepted

Outline : Precision medicine of respiratory support in ARDS patients

- **Non intubated ARDS**
  - New ARDS definitions : **non-intubated, SpO_2/FiO_2,** sen↑spe↓*(ACRCCM. 2024 1;209(1):37-47)*
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  - Minimized driving pressure in
    - older patient? *(AJRCCM 2024 Dec;210(11):1329-1337)*
    - acute brain injury patients? *(AJRCCM 2024 Nov;210(9):1123-1131)*

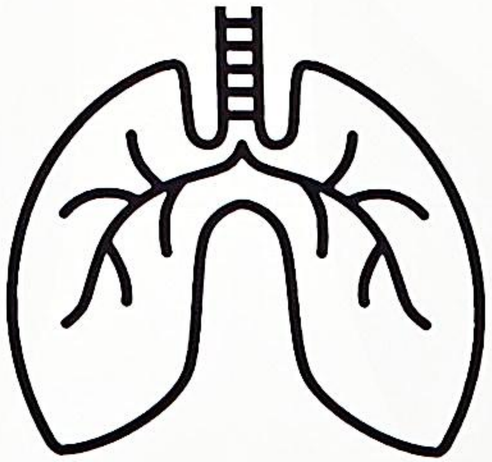
Association Between Baseline Driving Pressure and Mortality in Very Old Patients with ARDS

Citation: Papoutsi E, Gkirgkiris K, Tsolaki V et al.. *Am J Respir Crit Care Med*. 2024 Dec 1;210(11):1329-1337.
doi: 10.1164/rccm.202401-0049OC. PMID: 39388641.

Rationale

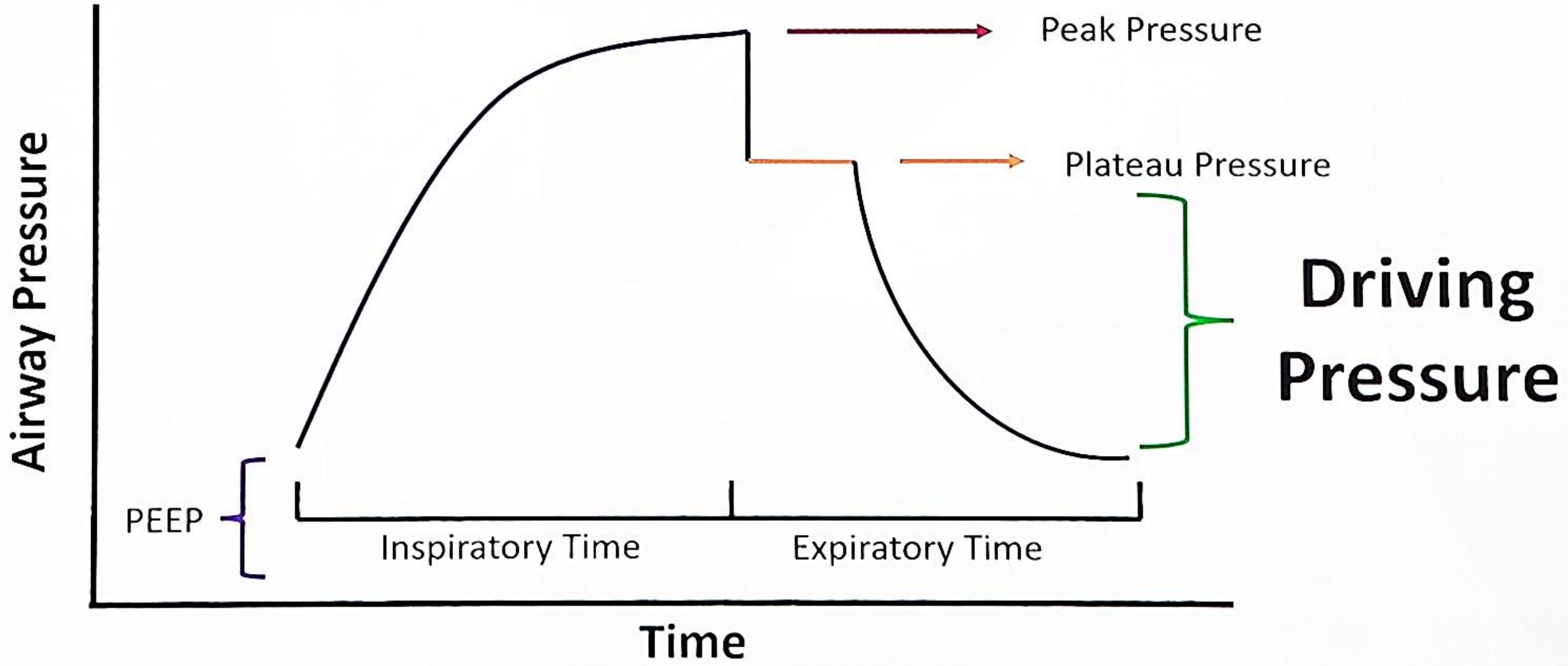
- Older patients may be more susceptible to VILI

- Aging effects the respiratory system
  - Decrease in chest wall compliance
  - Loss of alveolar elastic recoil
  - More prone to atelectasis



AJRCCM 2024 Dec;210(11):1329-1337

Driving Pressure (ΔP) = Pplat - PEEP



AJRCCM 2024 Dec;210(11):1329-1337

Objective

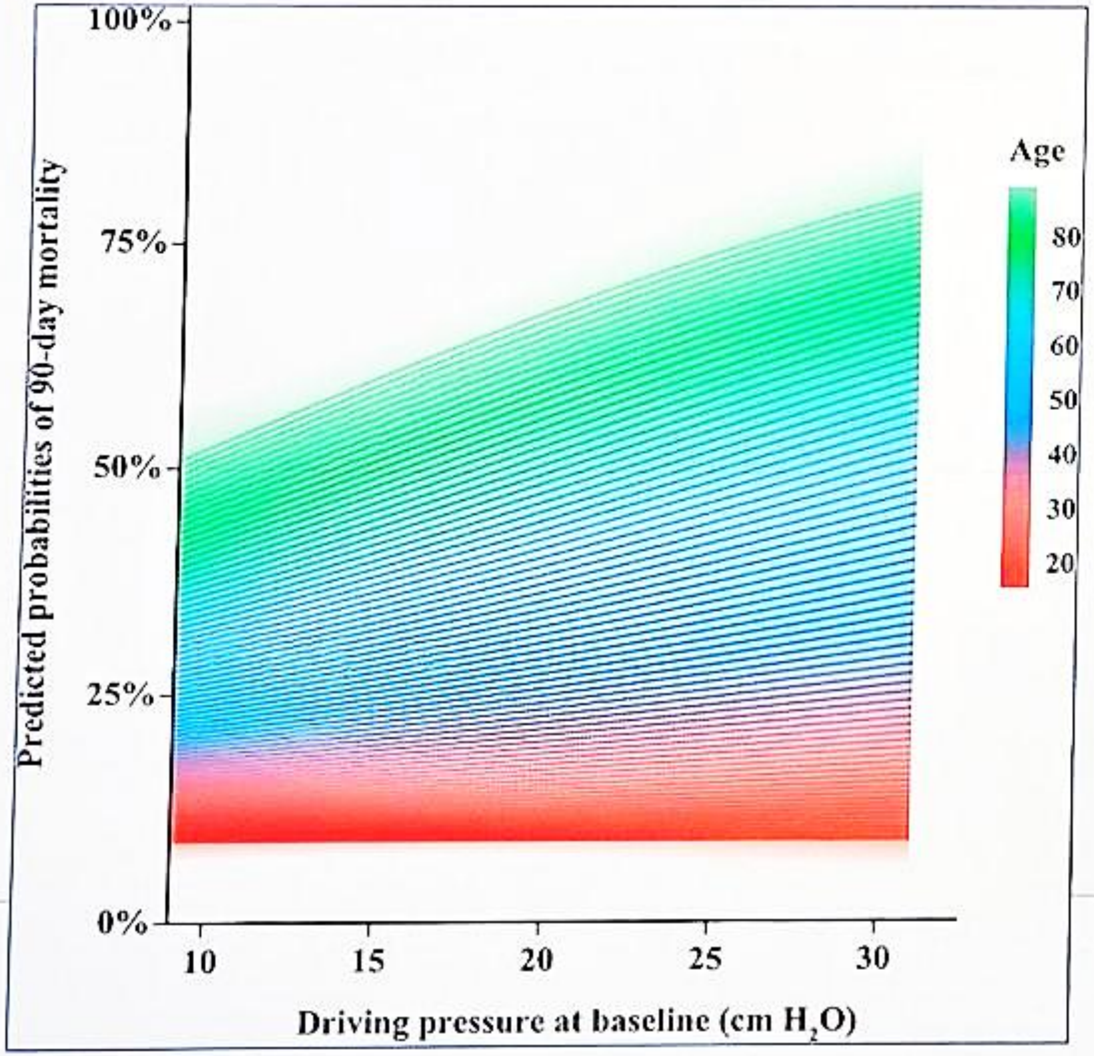
Evaluate whether the association between driving pressure and mortality is stronger in older patients with ARDS

AJRCCM 2024 Dec;210(11):1329-1337

Study Design

- Secondary analysis of individual patient-level data from 7 ARDS and PETAL Network RCTs
- 4,567 total patients with baseline driving pressure data
- Tested findings in independent cohort of patients with COVID-19 related ARDS

Does effect of driving pressure on mortality depend on age?



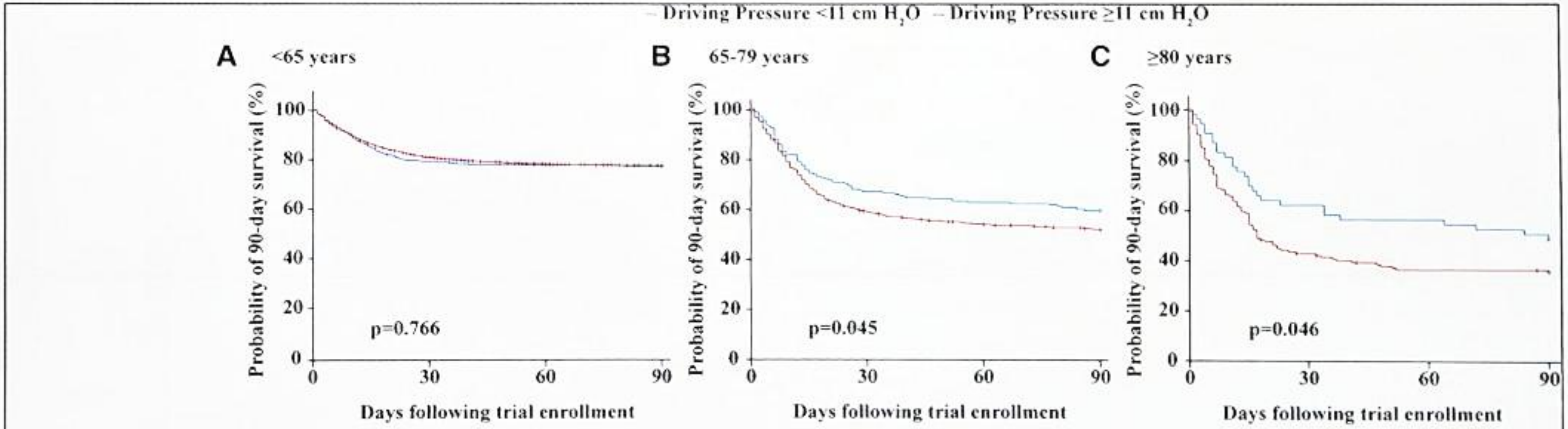
Binary logistic and Cox regression unadjusted analyses

- **Predictor**: Interaction term between age and driving pressure
- **Dependent variable**: 90-day mortality

Figure 1. Interaction plot showing that the effect of driving pressure on 90-day mortality depended on age ($P = 0.01$ for the interaction between age as a continuous variable and driving pressure).

AJRCCM 2024 Dec;210(11):1329-1337

Does threshold of ΔP associated with mortality depend on age?



No. at risk

Driving Pressure <11 cmH_2O	577	451	442	434	214	142	133	126	52	32	29	26
Driving Pressure ≥11 cmH_2O	2872	2283	2169	2118	703	407	365	342	149	61	50	49

Figure 3. Kaplan-Meier curves of mortality for patients with **driving pressure <11 cm H_2O** compared with patients with driving pressure ≥11 cm H_2O across the three age groups

AJRCCM 2024 Dec;210(11):1329-1337

Conclusions

- Effect of driving pressure on mortality depended on age
- Very old patients may be more vulnerable to high driving pressure
- Driving pressure threshold of 11 cm H_20 might be appropriate for very old patients

AJRCCM 2024 Dec;210(11):1329-1337

Lung-Protective Mechanical Ventilation in Patients with Severe Acute Brain Injury: PROLABI

Citation: Mascia L, Fanelli V, Mistretta A et al. Am J Respir Crit Care Med. 2024 Nov 1;210(9):1123-1131. PMID: 39288368

Rationale

- Possible benefits to lung protective ventilation in patients with acute brain injury
  - Increased susceptibility to VILI
  - ARDS may occur in 10-15% of these patients

- Possible risks
  - Low V_T may increase risk of $PaCO_2$ and intracranial pressure
  - PEEP may decrease cerebral venous drainage

AJRCCM 2024 Nov;210(9):1123-1131

Objective

Determine if ventilation with lower V_T and higher PEEP compared with conventional ventilation would improve clinical outcomes in patients with acute brain injury

AJRCCM 2024 Nov;210(9):1123-1131

Study Design

- Multicenter, open-label, controlled clinical trial conducted over 5-year period with 1 year follow-up
- <u>Participants</u>: Severe acute brain injury secondary to TBI, SAH, intracerebral hemorrhage or ischemic stroke. **Excluded if ARDS at admission** or mechanically ventilated > 24 hours
- Target sample size: 524 participants

AJRCCM 2024 Nov;210(9):1123-1131

Group Assignments

Lung Protective Strategy	Conventional Strategy
• V_T 6 ml/kg PBW	• $V_T \geq$ 8 ml/kg PBW
• PEEP 8 cm H_20	• PEEP 4 cm H_20
• Volume-assist mode	• Volume-assist mode
• RR adjusted to maintain $PaCO_2$ between 35 and 38 mmHg	• RR adjusted to maintain $PaCO_2$ between 35 and 38 mmHg
• Oxygenation target: $80 < PaO_2 < 100$ mmHg	• Oxygenation target: $80 < PaO_2 < 100$ mmHg

AJRCCM 2024 Nov;210(9):1123-1131

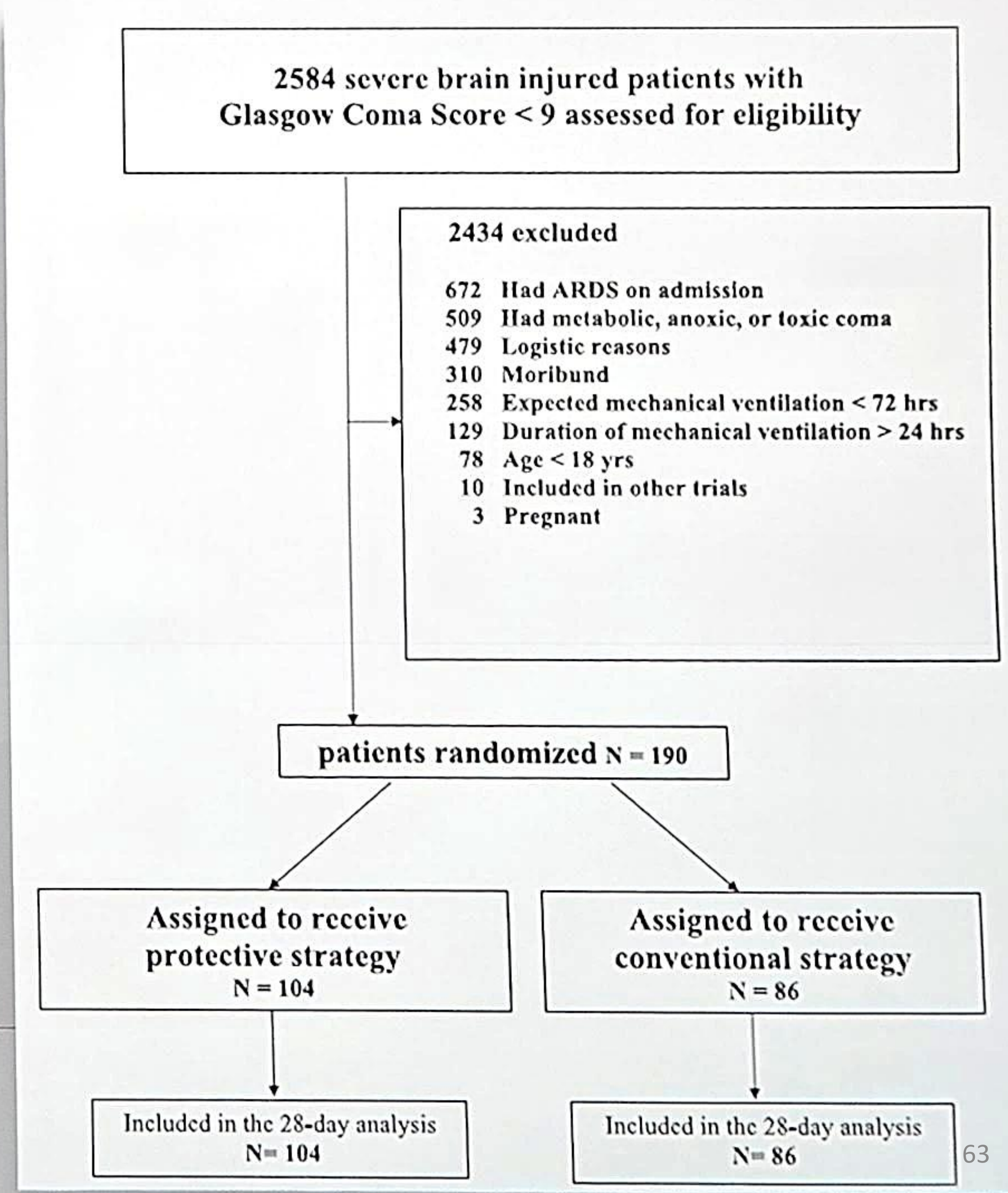
Outcomes

- Primary Outcome: Composite endpoint for death, ventilatory dependence, or ARDS at day 28 after randomization
- Secondary Outcomes:
  - Modified Oxford Handicap Scale (MOHS) at ICU discharge
  - Glasgow Outcome Scale extended (GOSe) at 6 months
  - ICU and hospital length of stay
  - Ventilator-free days

AJRCCM 2024 Nov;210(9):1123-1131

Results

Enrollment stopped after 190 patients due to termination of funding



AJRCCM 2024 Nov;210(9):1123-1131

Selected Results

	Protective Strategy (n = 104)	Conventional Strategy (n = 86)	RR (95% CI)	P Value
Primary Composite Outcome (n, %)	64 (61.5)	39 (45.7)	1.35 (1.03; 1.79)	**0.0258**
Mortality at 28d, n (%)	30 (28.9)	13 (15.1)	1.91 (1.06; 3.42)	**0.0244**
Ventilatory dependency at 28 d, n (%)	44 (42.3)	24 (27.9)	1.52 (1.01; 2.28)	**0.0393**
Incidence of ARDS at 28 d, n (%)	32 (30.8)	19 (22.1)	1.39 (0.85; 2.27)	0.179
Secondary Outcomes				
MOHS at ICU discharge, n (%)				
Independent	29 (28.4)	22 (25.6)	1.34 (0.85-2.09)	0.201
Dependent	43 (42.2)	51 (59.3)	REF	N/A
Death	30 (29.4)	13 (15.1)	2.02 (1.16; 3.53)	**< 0.001**
GOSe at 6 months, n (%)				
Death/vegetative state	36 (45.0)	20 (29.0)	1.55 (1.00; 2.42)	**0.0442**
Severe/moderate/good recovery	44 (55.0)	49 (71.0)	REF	

- Modified Oxford Handicap Scale (MOHS) at ICU discharge
- Glasgow Outcome Scale extended (GOSe) at 6 months

AJRCCM 2024 Nov;210(9):1123-1131

Conclusions

- Protective strategy (V_T, 6 ml/kg PBW, 8 cm H_20 PEEP) **did not** reduce mortality, ventilatory dependence, and ARDS compared to conventional strategy ($\geq$ 8 ml/kg PBW, 4 cm H_20 PEEP)
- Small difference in $PaCO_2$ (~ 2mmHg) may have resulted in a small increase in cerebral blood flow in protective group
- Driving pressure and mechanical power at upper limit of safe range in both groups
- Results require confirmation in larger trials

AJRCCM 2024 Nov;210(9):1123-1131

Outline : Precision medicine of respiratory support in ARDS patients

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  - **Sepsis, Resp dz. benefit from higher FiO2.** Brain injury, CV dz. Favor lower. *(JAMA. 2024;331(14):1195-1204)*
- **ARDS severity and treatment strategies : 用順從性分類，順從差給予NMBA更有好處；降低driving pressure需考慮病患特質**
  - Categorized by **Compliance**. *(ICM. 2025; 51(1):62-71)*
  - Treatment strategies **(NMBA)** better survival in **poor compliance**. *(AJRCCM 2025 Jun;211(6):966-974)*
  - Minimized driving pressure in
    - older patient, **driving pressure < 11** *(AJRCCM 2024 Dec;210(11):1329-1337)*
    - **acute brain injury w/o ARDS** not benefit from lung protective strategies *(AJRCCM 2024 Nov;210(9):1123-1131)*