

Neuromuscular blocking agents in ARDS: do they really work?

Associate Professor

Su Hwan Lee, MD.

Division of Pulmonology and Critical Care Medicine , Department of Internal Medicine,
Severance Hospital, Yonsei University College of Medicine

Severance

NEUROMUSCULAR BLOCKING AGENTS

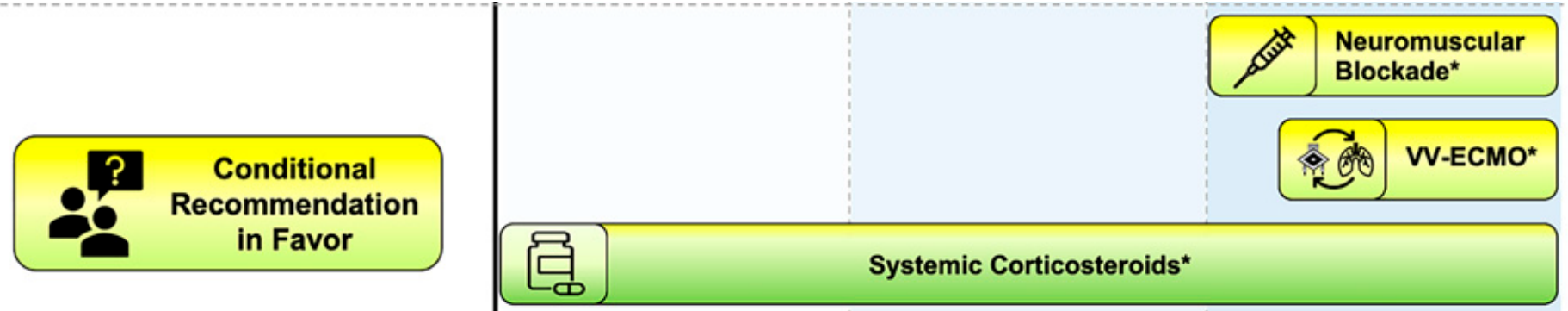
Q1 Does the *routine* use of a continuous infusion of neuromuscular blocking agents (NMBA) in patients with moderate to severe ARDS not due to COVID-19 or moderate to severe ARDS due to COVID-19 reduce mortality?

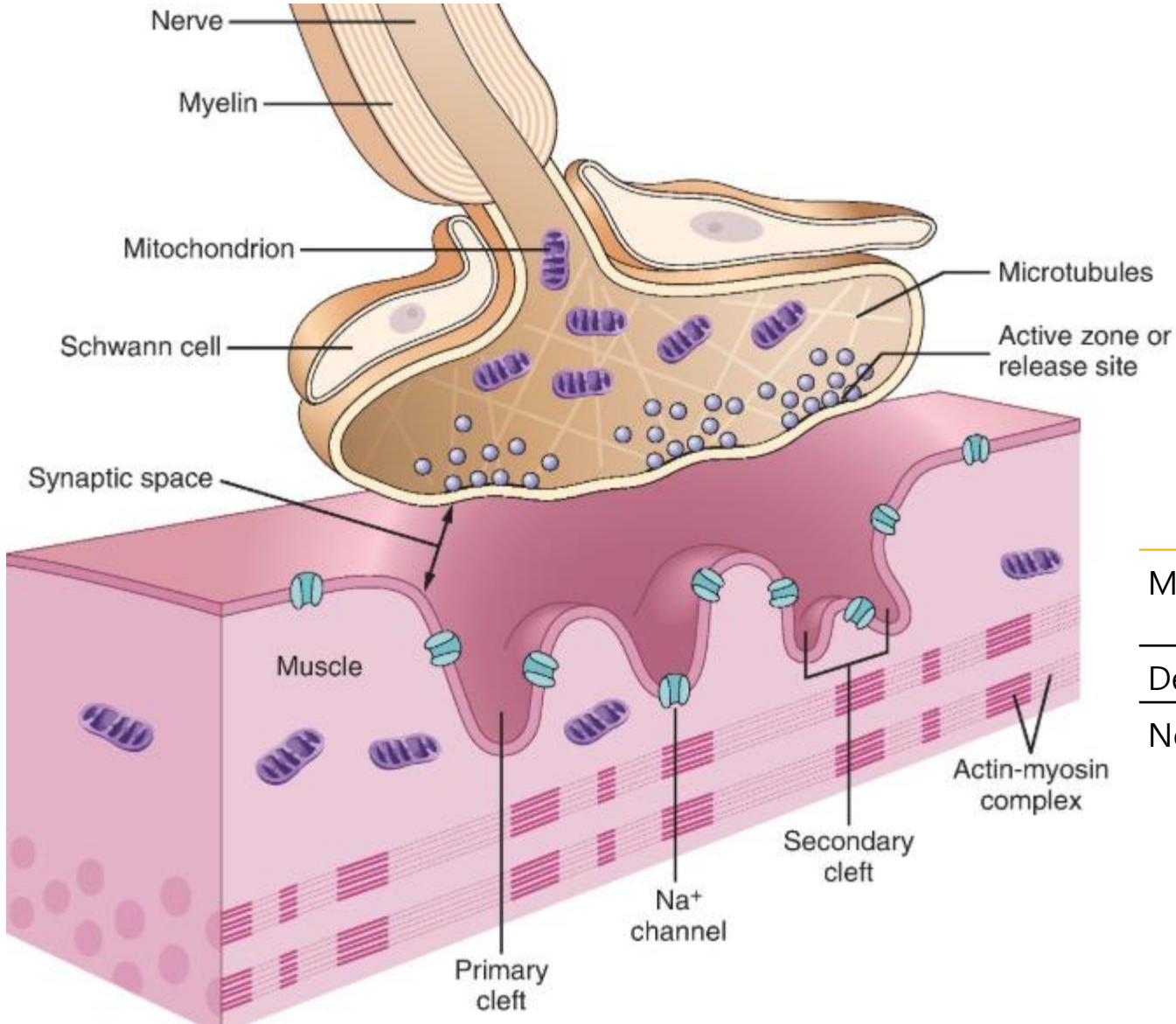
- 1 We **recommend against** the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate to severe ARDS not due to COVID-19.
- 2 We are **unable to make a recommendation** for or against the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate to severe ARDS due to COVID-19.

 MODERATE LEVEL OF EVIDENCE

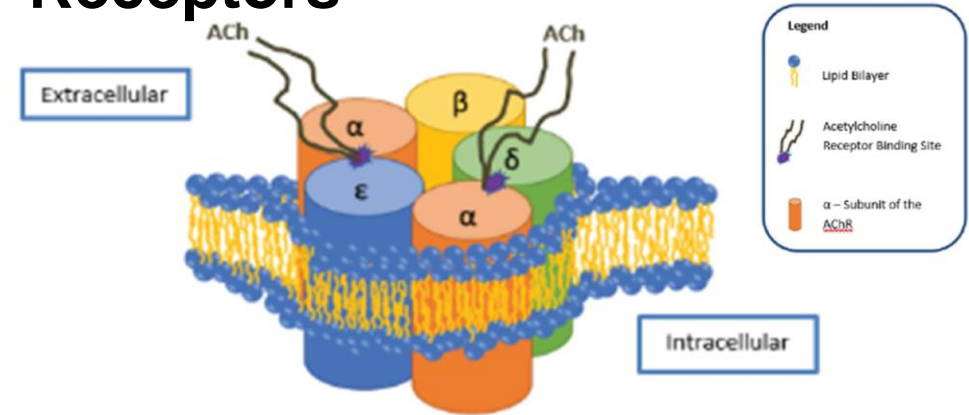
 NO EVIDENCE

VS.





Postjunctional Receptors

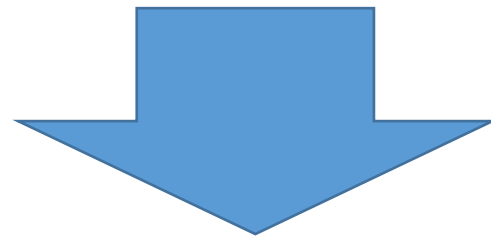


Mechanism of Action	Neuromuscular Blocking Agent	Duration of Action
Depolarizing	Succinylcholine	Ultrashort-acting
Nondepolarizing	Pancuronium	Long-acting
	Vecuronium	Intermediate-acting
	Rocuronium	Intermediate-acting
	Atracurium	Intermediate-acting
	Cisatracurium	Intermediate-acting
	Mivacurium	Short-acting

- Extra junctional Receptors

- Whereas postjunctional receptors are confined to the area of the end plate of skeletal muscle that is opposite the prejunctional motor neurons (as a component of the motor end plate), extrajunctional receptors are present throughout skeletal muscles.

- **Prolonged inactivity, sepsis, skeletal muscle denervation, burn injury, or trauma may be associated with a proliferation of extrajunctional receptors.**



Critically ill patient

Pulmonary and serum concentration of IL-6, and IL-8 were lower in the NABA group improvement in PaO2/FiO2 ratio was observed and reinforced in the NMBA

Mortality rate at 90 days did not differ between groups (42.5% in the control group vs. 42.8% in the intervention group)

NM blockade in ARDS

Prone position



Evaluate the effects of a 48 h NMBAs infusion on gas exchange over a 120 h time period in patients with ARDS

Early administration of NMBAs for 48 h decreased 90-day mortality (31.6% with NMBAs vs. 40.7% in the placebo group) and risk of barotrauma in patients with moderate to severe ARDS

with an improvement in oxygenation (higher PaO2/FiO2) in moderate and severe ARDS, accompanied by a decrease in both Pplat and total PEEP; the mean inspiratory and expiratory P L were higher in the moderate ARDS group receiving NMBA than in the control group; no change driving pressure or ΔP L related to NMBA administration

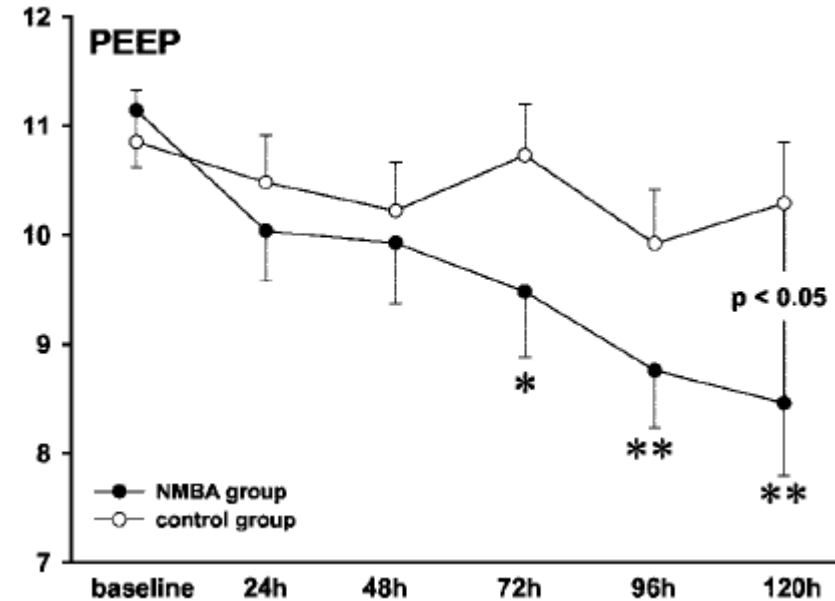
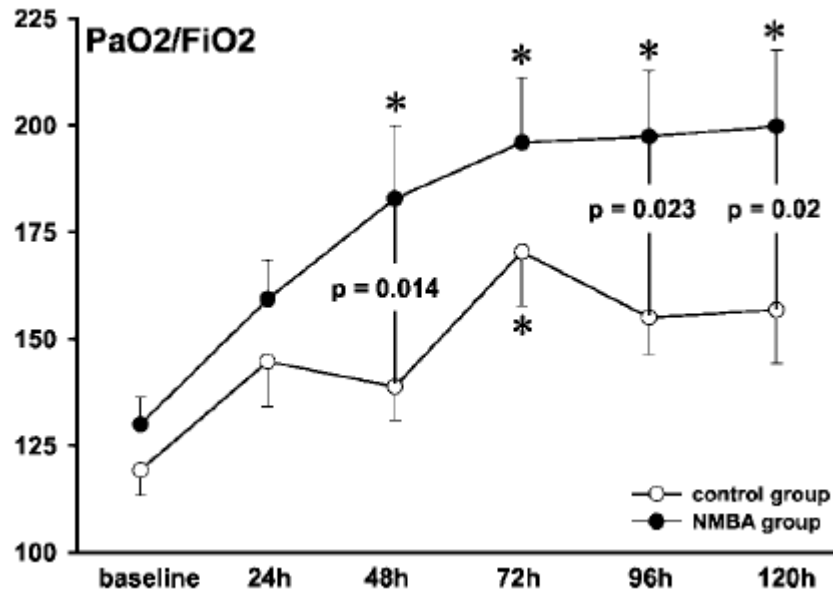
2000: ARDS network trial
Low tidal, plateau pressure

Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome*

Marc Gannier, MD; Antoine Roch, MD; Jean-Marie Forel, MD; Xavier Thirion, MD, PhD; Jean-Michel Arnal, MD; Stéphane Donati, MD; Laurent Papazian, MD, PhD

Multi-center, controlled, randomized trial
56 patients with $\text{PaO}_2/\text{FiO}_2 < 150$ with $\text{PEEP} \geq 5 \text{ cmH}_2\text{O}$
control (n = 28) vs. NMBA (n = 28) groups

Evaluate the effects of a 48 h NMBAs infusion on gas exchange over a 120 h time period in patients with ARDS

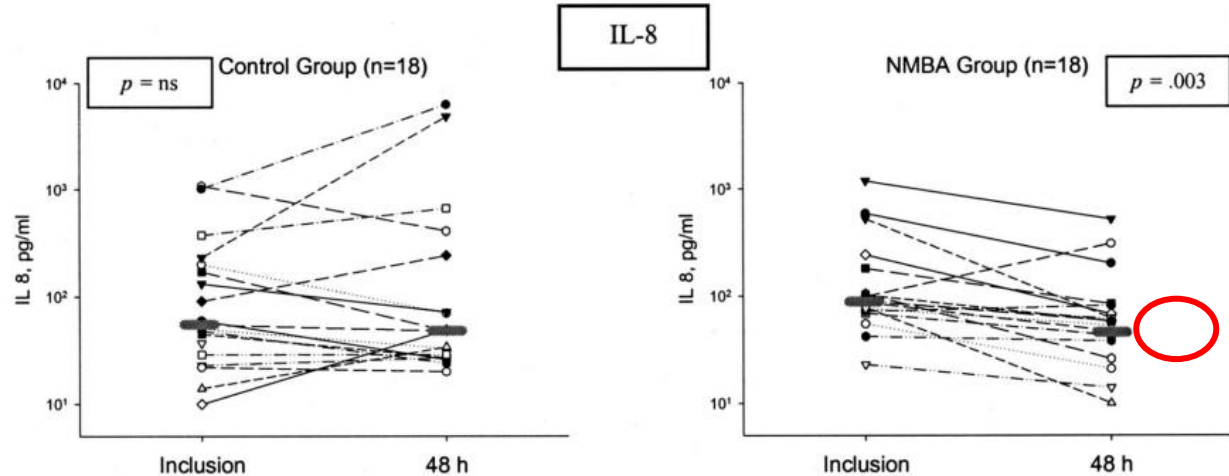
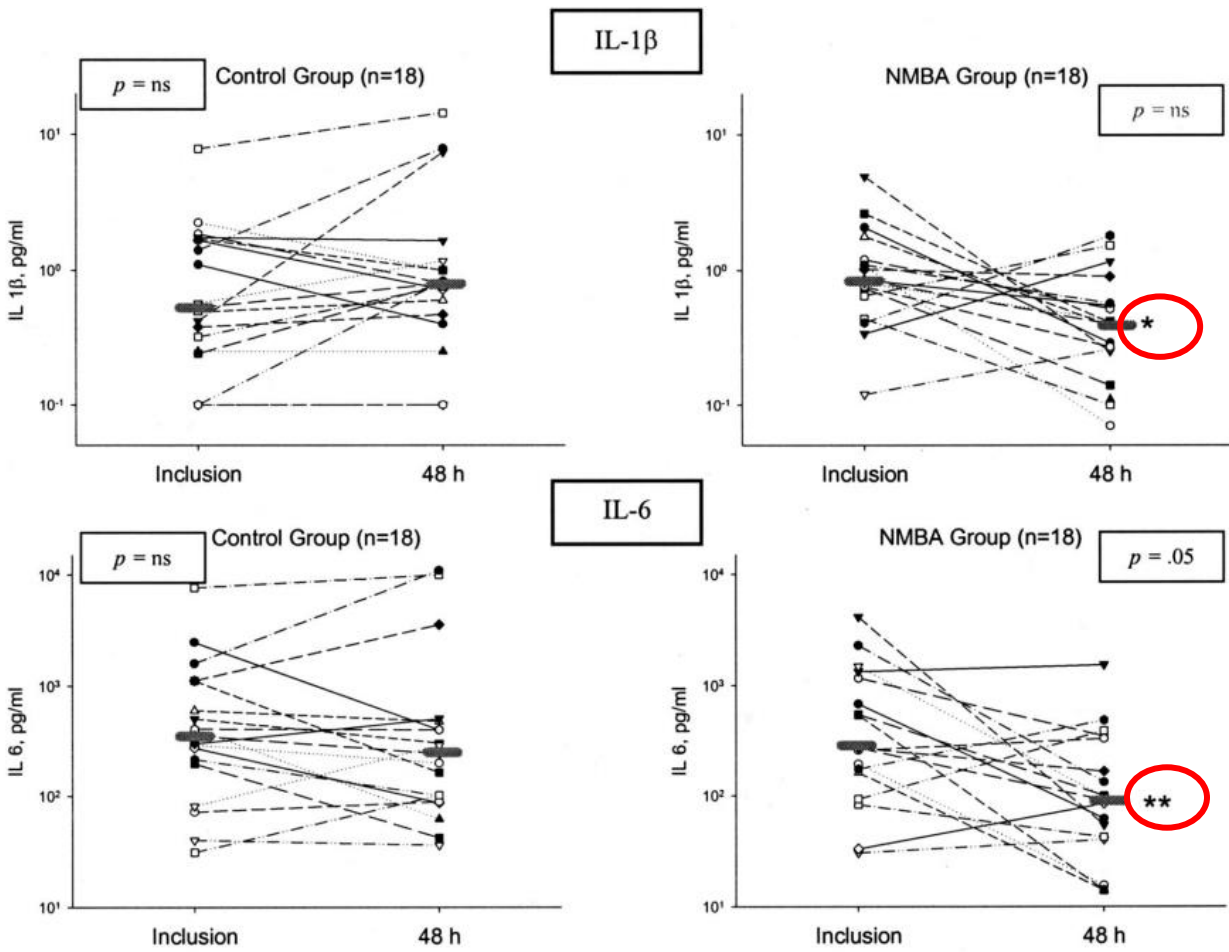


NMBAs were administered for 48 h; oxygenation ($\text{PaO}_2/\text{FiO}_2$ ratio) was better in NMBA compared to control group

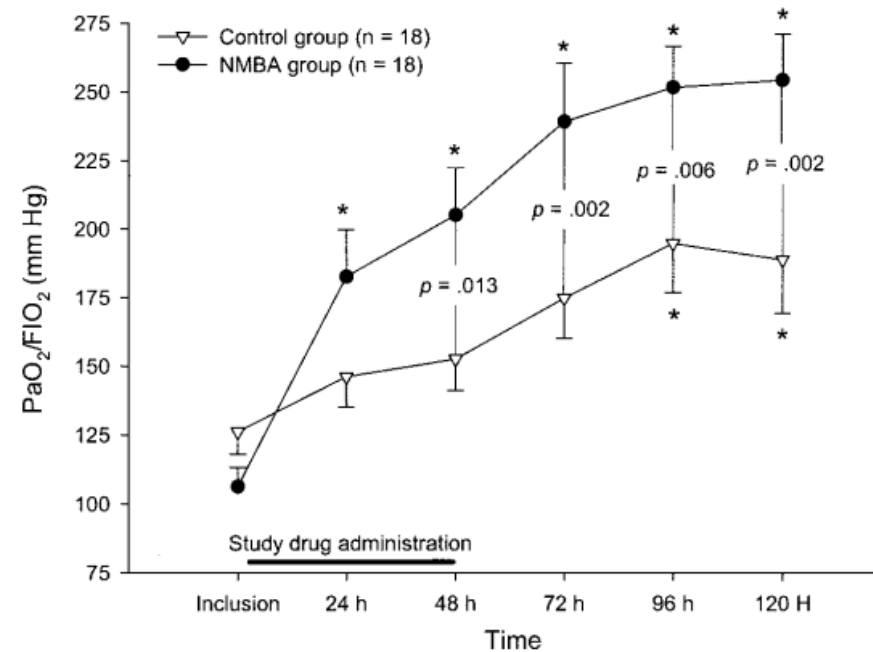
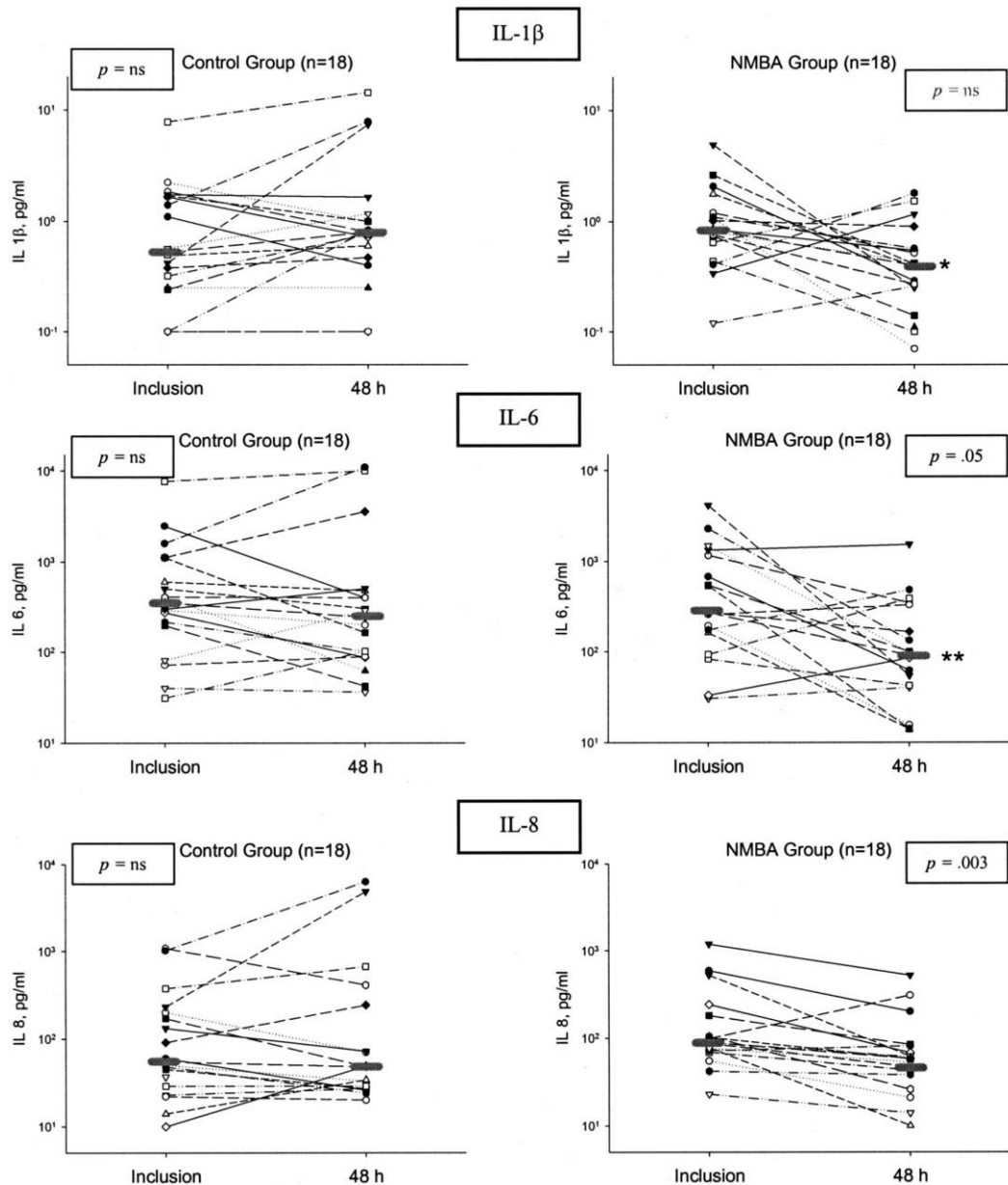
Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome*

Jean-Marie Forel, MD; Antoine Roch, MD, PhD; Valérie Marin, MD, PhD; Pierre Michelet, MD; Didier Demory, MD; Jean-Louis Blache, MD; Gilles Perrin, MD; Marc Gainnier, MD, PhD; Pierre Bongrand, MD, PhD; Laurent Papazian, MD, PhD

Multi-center, prospective, controlled, and randomized trial: patients with PaO₂/FiO₂ < 200 at a PEEP ≥ 5 cm H₂O placebo (n = 18) vs. NMBA (n = 18) groups



Concentrations of inflammatory mediators in pulmonary epithelial lining fluid.



At 48 h after randomization, pulmonary concentrations of IL-1β (p = 0.005), IL-6 (p = 0.038), and IL-8 (p = 0.017) and serum concentration of IL-6 (p = 0.05) and IL-8 (p = 0.003) were lower in the NMBA group as compared with the control group; improvement in PaO₂/FiO₂ ratio was observed and reinforced in the NMBA group (p < 0.001)

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Neuromuscular Blockers in Early Acute Respiratory
Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D., Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D., Claude Guérin, M.D., Ph.D., Gwenaél Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D., for the ACURASYS Study Investigators*

Evaluate clinical outcomes after 48 h of therapy with NMBAs in patients with early, severe ARDS

Primary outcome: the 90- day mortality

Secondary outcome:

the 28 day mortality

numbers of days outside the ICU

number of days without organ or system failure

barotrauma, ICU acquired paresis, MRC score

Etc..

Multicenter, prospective, double-blind controlled trial, patients with PF ratio < 150, total n= 340 randomized Cisatracurium n = 177 vs. Placebo n = 162 groups

Characteristic†	Cisatracurium (N=177)	Placebo N=162)	P Value
Age — yr	58±16	58±15	0.70
Tidal volume — ml/kg of predicted body weight	6.55±1.12	6.48±0.92	0.52
Minute ventilation — liters/min	10.0±2.5	10.1±2.2	0.83
PEEP applied — cm of water	9.2±3.2	9.2±3.5	0.87
Plateau pressure — cm of water	25.0±5.1	24.4±4.7	0.32
Respiratory-system compliance — ml/cm of water	31.5±11.6	31.9±10.7	0.71
F _I O ₂	0.79±0.19	0.77±0.20	0.33
PaO ₂ :F _I O ₂ ‡	106±36	115±41	0.03
pH	7.31±0.10	7.32±0.10	0.11
PaO ₂ — mm Hg	80±24	85±28	0.09
PaCO ₂ — mm Hg	47±11	47±11	0.62
Prone position or inhaled nitric oxide or almitrine mesylate — no. (%)	33 (18.6)	23 (14.2)	0.31
SAPS II§	50±16	47±14	0.15
Nonfatal condition according to McCabe–Jackson score — no. (%)¶	133 (75.1)	125 (77.2)	0.66
Main reason for ICU admission — no. (%)			
Medical	129 (72.9)	113 (69.8)	0.52
Surgical, emergency	27 (15.3)	31 (19.1)	0.34
Surgical, scheduled	21 (11.9)	18 (11.1)	0.83
Corticosteroids for septic shock — no. (%)	70 (39.5)	73 (45.1)	0.30
Direct lung injury — no. (%)	142 (80.2)	123 (75.9)	0.34

Outcome

Death — no. (%) [95% CI]

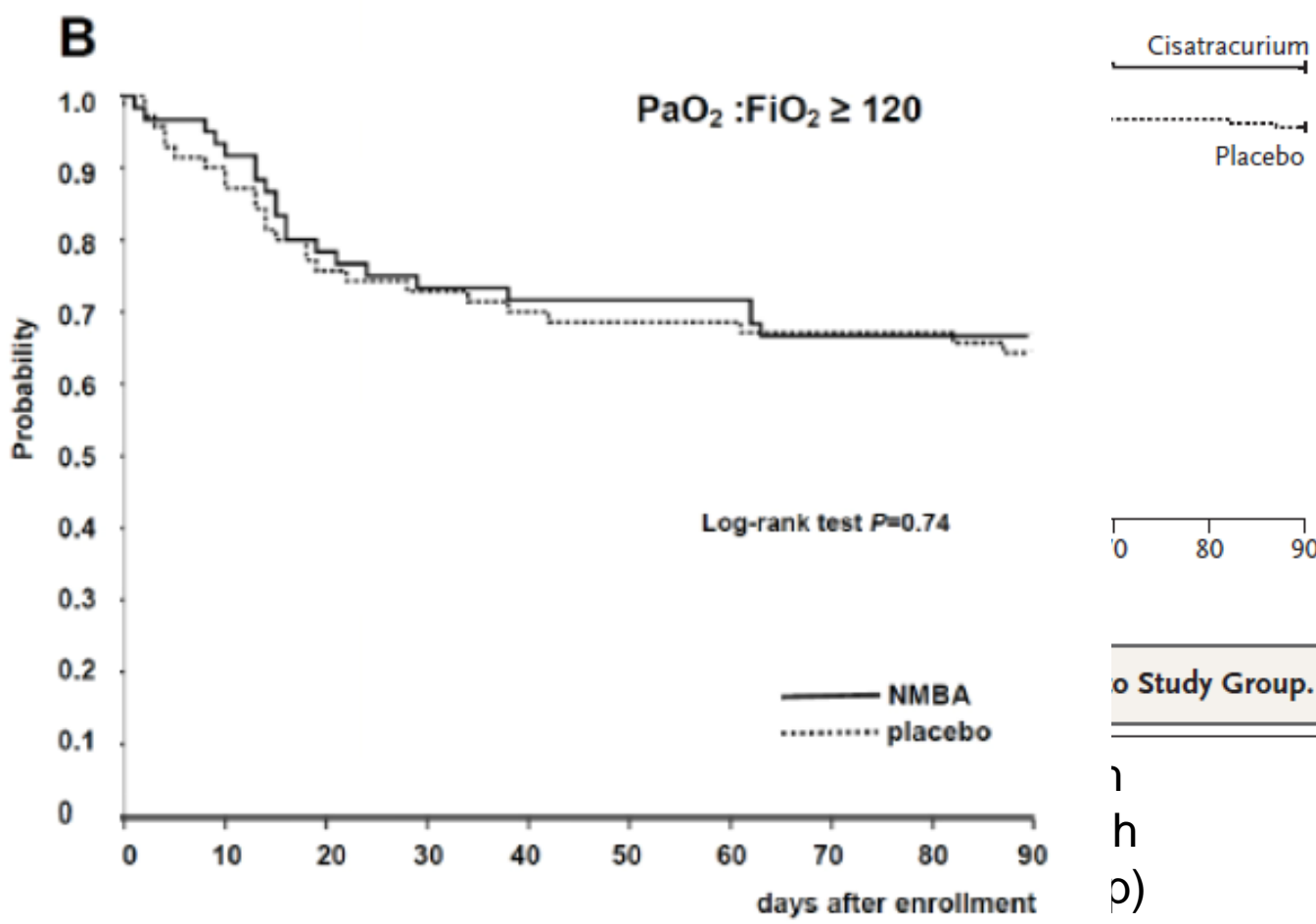
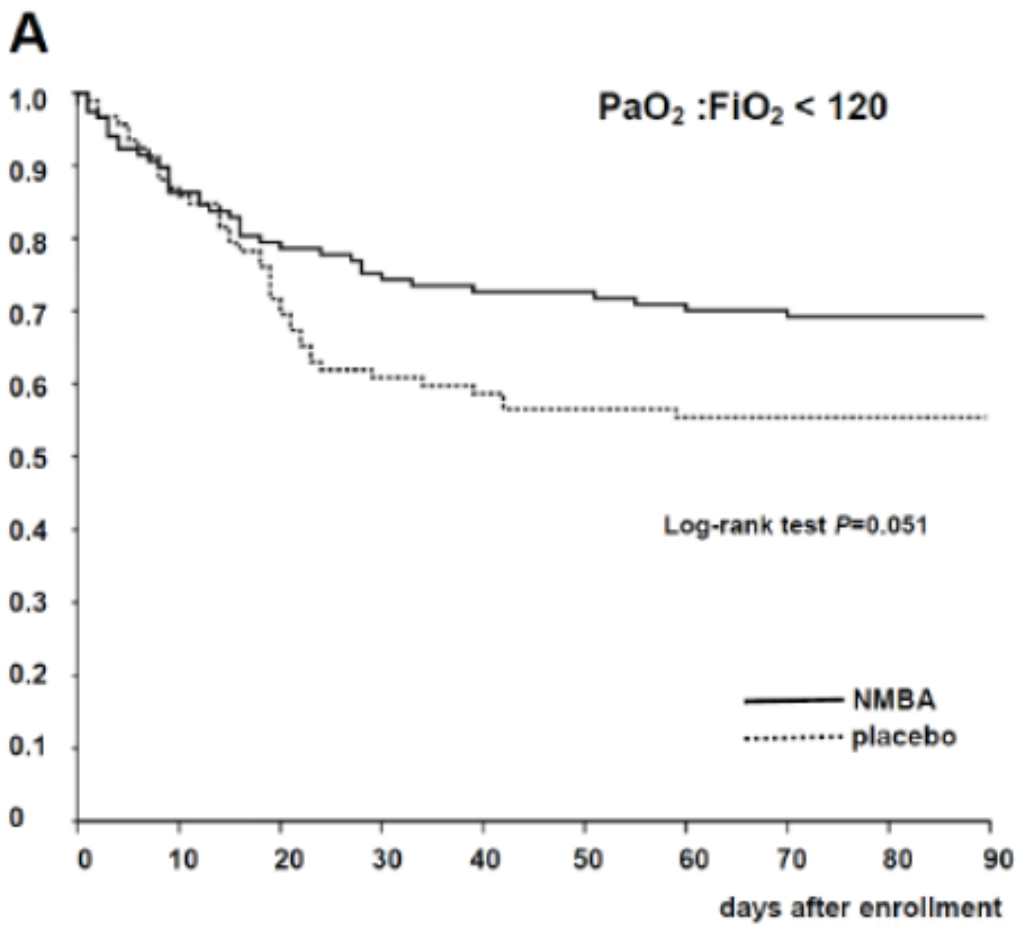
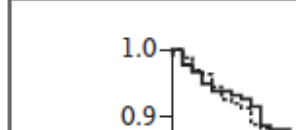
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Cisatracurium
(N=177)

Placebo
(N=162)

Relative Risk with
Cisatracurium
(95% CI)

P Value



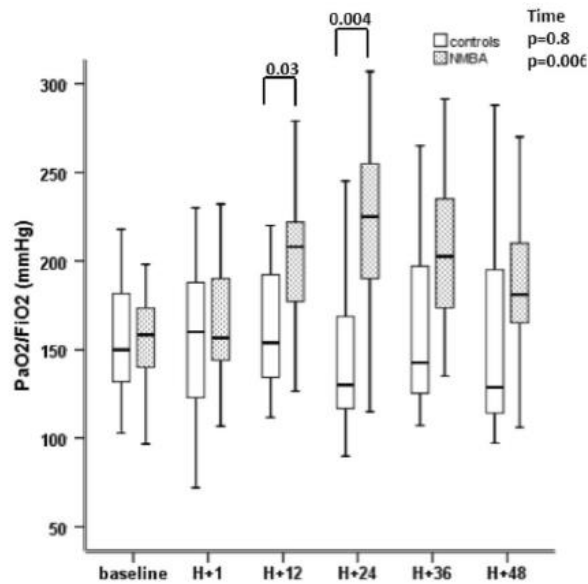
and risk of barotrauma in patients with moderate to severe ARDS

Effects of neuromuscular blockers on transpulmonary pressures in moderate to severe acute respiratory distress syndrome

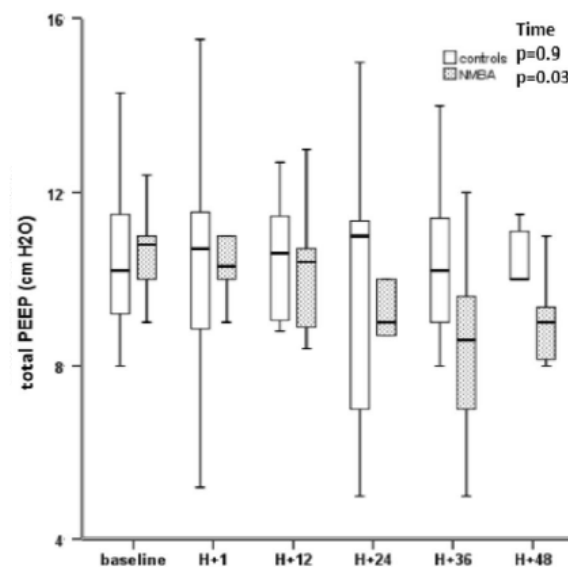
Christophe Guerville^{1*}, Magali Bisbal^{2,3}, Jean Marie Forel¹, Malika Mechat³, Samuel Lehingue¹, Jeremy Bourenne³, Gilles Perrin³, Romain Rambaud¹, Melanie Adda¹, Sami Hraiech¹, Elisa Marchi¹, Antoine Roch^{1,4}, Marc Gainnier³ and Laurent Papazian¹

Randomized controlled trial: 30 patients with moderate to severe ARDS; severe ARDS (n=6, treated with cisatracurium), moderate ARDS (n=24, 13/24 treated with cisatracurium; 11/24 not treated with NMBA)

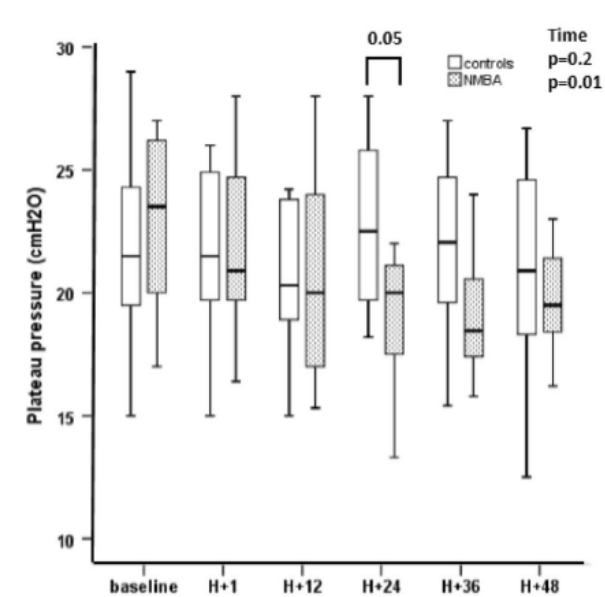
Investigate whether NMBA exert beneficial effects in ARDS by reason of their action on respiratory mechanics, particularly transpulmonary pressures (PL)



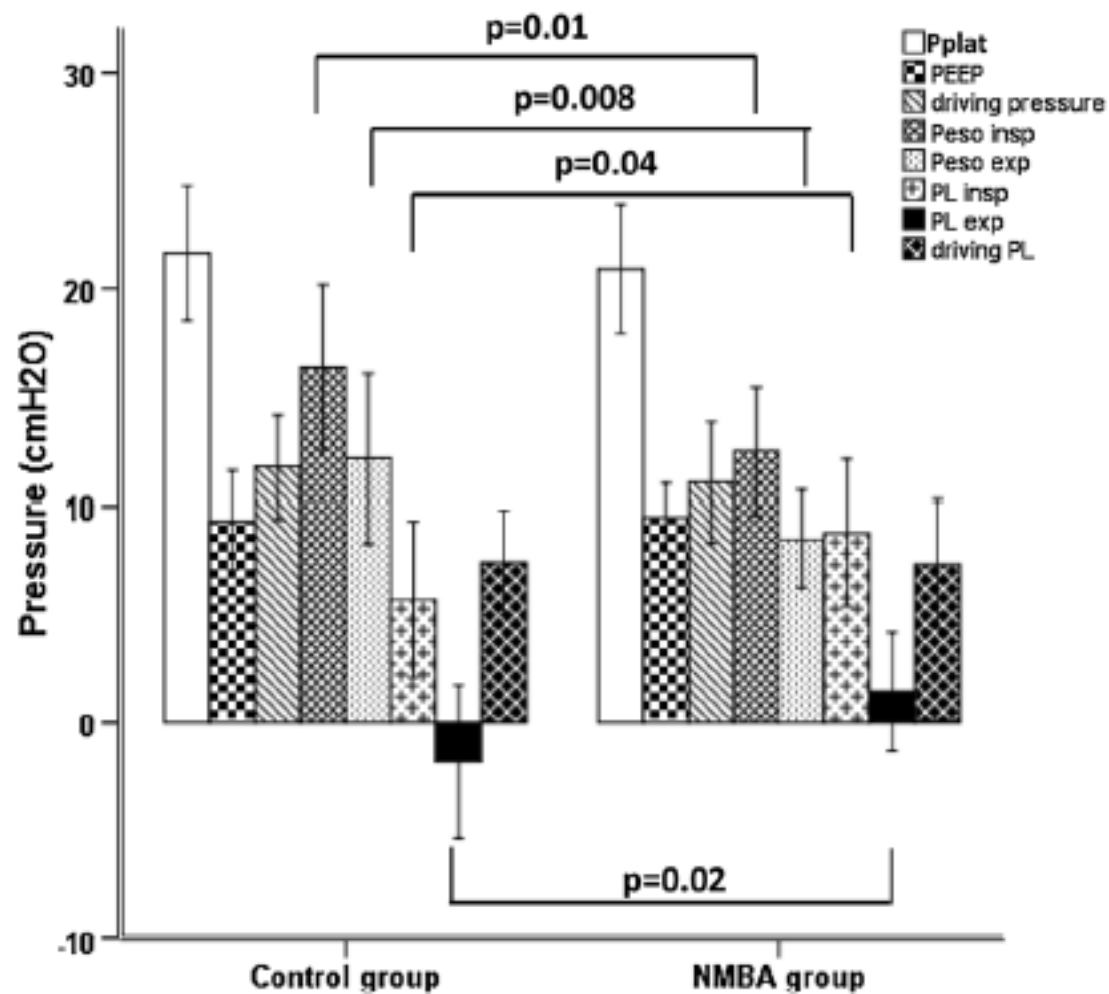
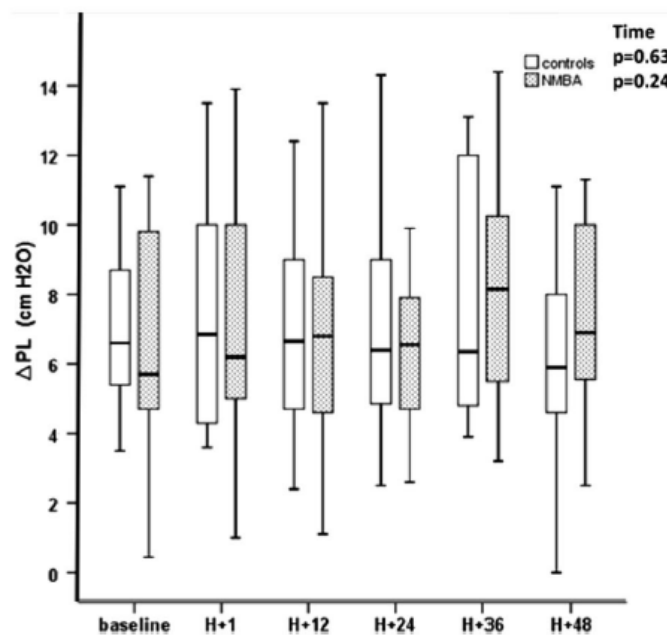
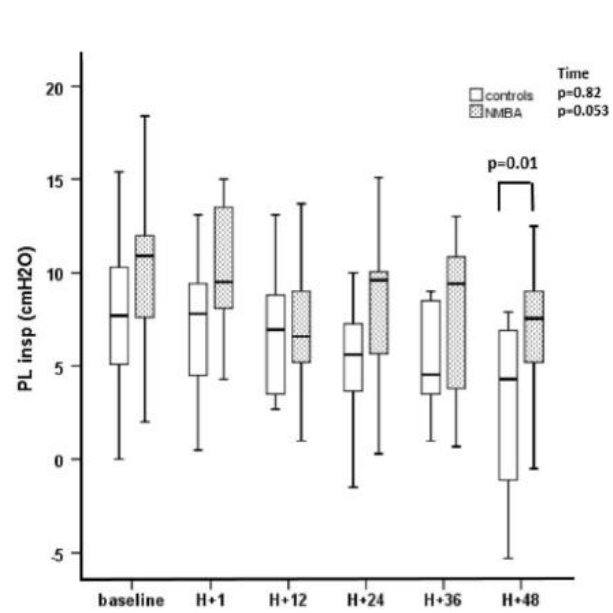
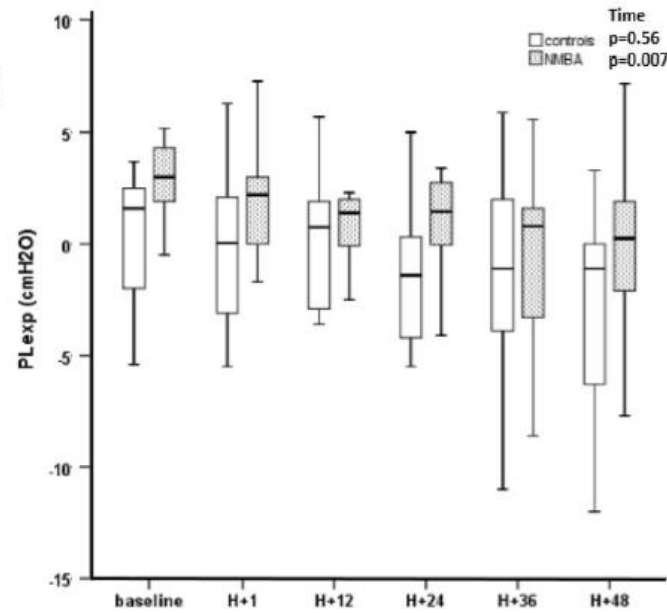
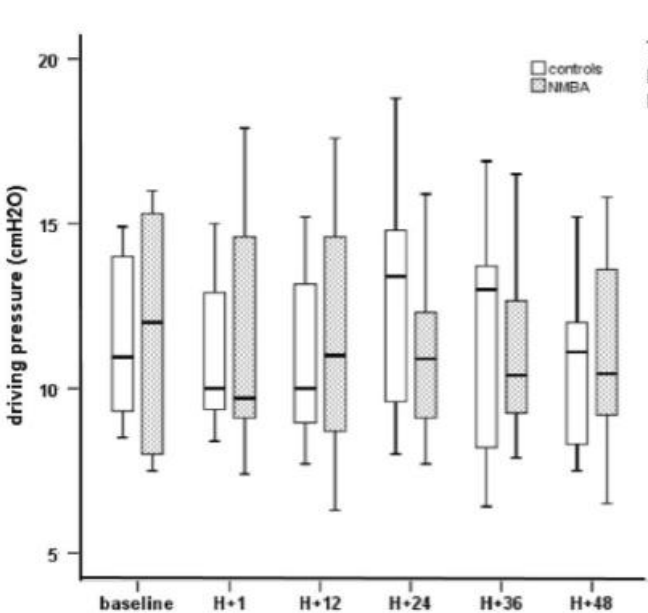
Improved oxygenation



Decreased peep

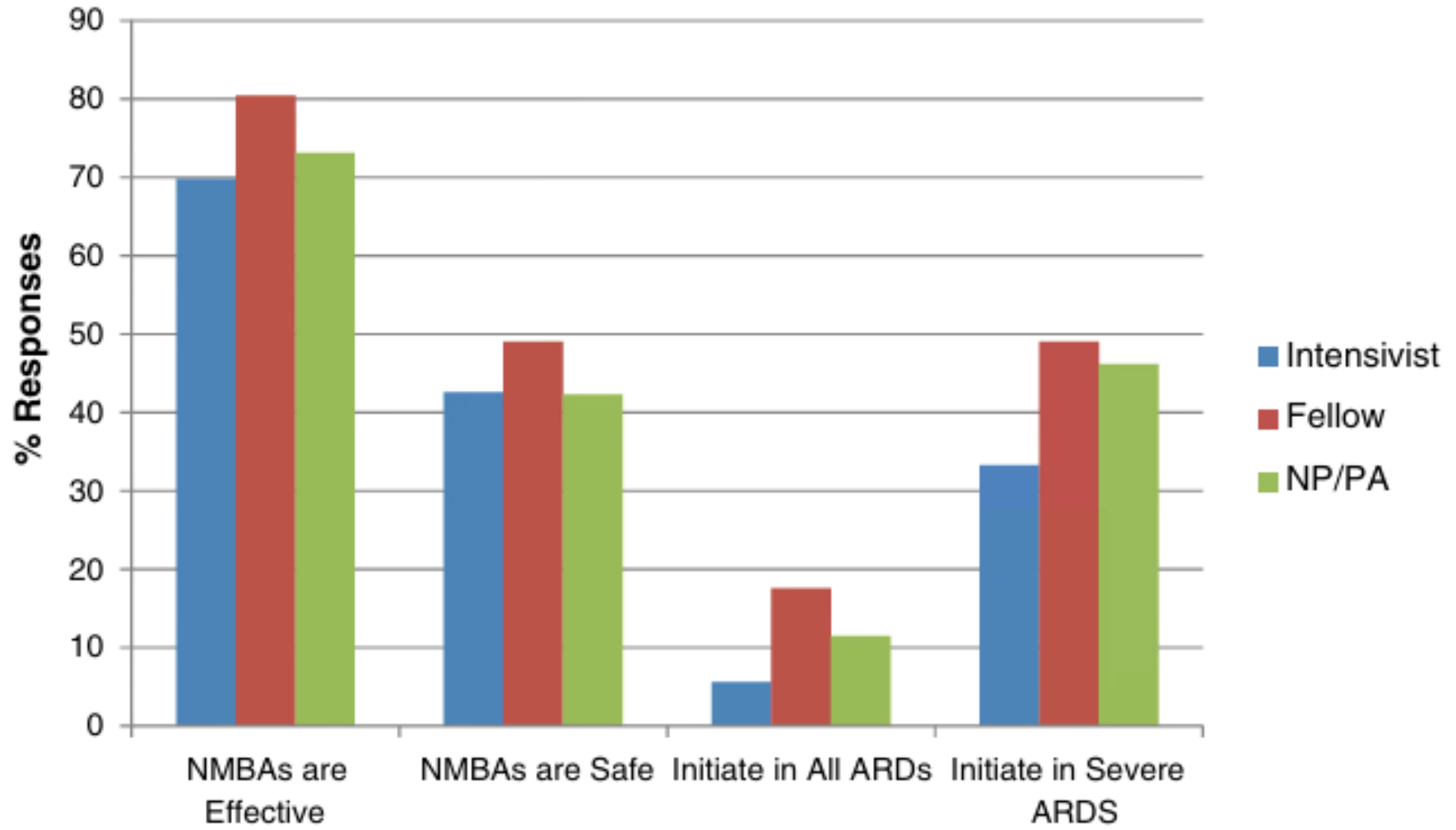


Decreased plateau pr



Benefit of neuromuscular blocking agent in ARDS

- Improved Oxygenation and Reduced Ventilator-Induced Lung Injury (VILI):
- Reduced Mortality and Morbidity:
- Decreased Organ Failure and ICU Stay:
- Anti-Inflammatory Effects:
- Simplified Ventilation Management:



- 5 tertiary care centers between July 2012 and May 2013
- Intensivist (n=54), fellow (n=51), NP/PA (n=26), pharmacist (n=20)

Controversy to the Use of NMBA in ARDS

NEUROMUSCULAR BLOCKING AGENTS

Q1 Does the *routine* use of a continuous infusion of neuromuscular blocking agents (NMBA) in patients with moderate to severe ARDS not due to COVID-19 or moderate to severe ARDS due to COVID-19 reduce mortality?

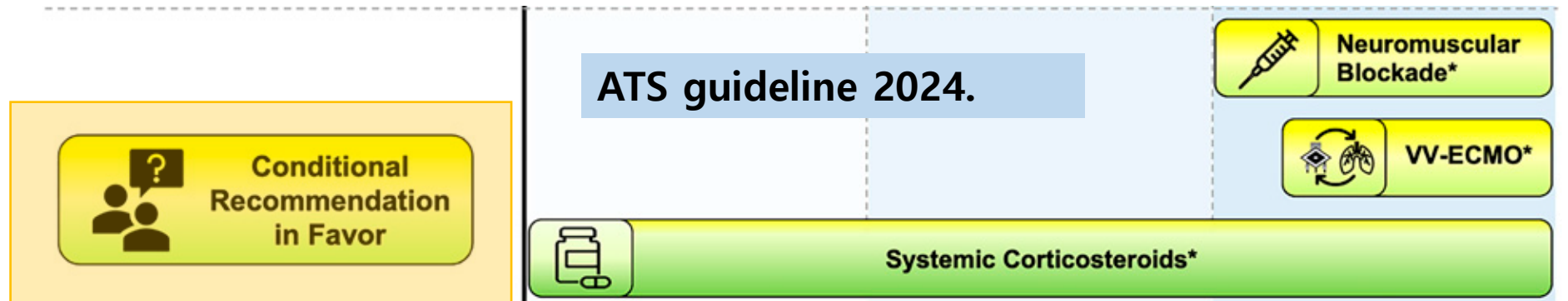
ESICM guideline 2023.

1 We **recommend against the routine use** of continuous infusions of NMBA to reduce mortality in patients with moderate to severe ARDS not due to COVID-19.

 MODERATE LEVEL OF EVIDENCE

2 We are **unable to make a recommendation for or against the routine use** of continuous infusions of NMBA to reduce mortality in patients with moderate to severe ARDS due to COVID-19.

 NO EVIDENCE



Mortality ?

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MAY 23, 2019

VOL. 380 NO. 21

Early Neuromuscular Blockade in the Acute Respiratory
Distress Syndrome

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

Primary outcome: the 90- day mortality

Secondary outcome:

In-hospital death at day 28,

Days free of mechanical ventilation,

Days not in the hospital at day 28

End points assessed at 3, 6, and 12 months were survival, disability, health-related quality of life, patient-reported health, pain interference, symptoms resembling those of post-traumatic stress, cognitive function, and return to work.

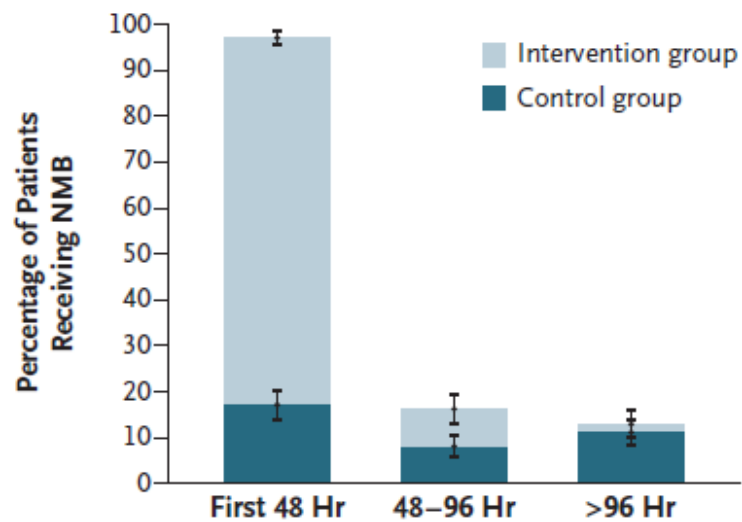
Multi center, prospective controlled randomized Patients with moderate to severe ARDS (PFio2 <150 mm Hg with a PEEP of 8 cm or more of water)

Intervention n =501, to receive 48 hours of continuous neuromuscular blockade with concomitant deep sedation

Control n=505, to receive usual care without routine neuromuscular blockade and with lighter sedation targets

Characteristic	Intervention Group (N = 501)	Control Group (N = 505)
Age — yr	56.6±14.7	55.1±15.9
Female sex — no. (%)†	210 (41.9)	236 (46.7)
White race — no. (%)†	361 (72.1)	344 (68.1)
Shock at baseline — no. (%)	276 (55.1)	309 (61.2)
Median time from eligibility to randomization (IQR) — hr	8.2 (4.0–16.4)	6.8 (3.3–14.5)
Neuromuscular blockade use between meeting inclusion criteria and randomization — no./total no. (%)	55/484 (11.4)	50/484 (10.3)
Primary cause of lung injury — no. (%)		
Pneumonia	292 (58.3)	301 (59.6)
Aspiration	91 (18.2)	75 (14.9)
Nonpulmonary sepsis	68 (13.6)	71 (14.1)
Other cause	50 (10.0)	58 (11.5)
Assessments and measurements		
APACHE III score‡	103.9±30.1	104.9±30.1
Total SOFA score§	8.7±3.6	8.8±3.6
Tidal volume — ml/kg of predicted body weight¶	6.3±0.9	6.3±0.9
Fio2	0.8±0.2	0.8±0.2
Inspiratory plateau pressure — cm of water**	25.5±6.0	25.7±6.1
PEEP — cm of water††	12.6±3.6	12.5±3.6
Pao2:Fio2 — mm Hg‡‡	98.7±27.9	99.5±27.9
Imputed Pao2:Fio2 — mm Hg§§	94.8±26.7	93.2±28.9

A NMB



B Light Sedation

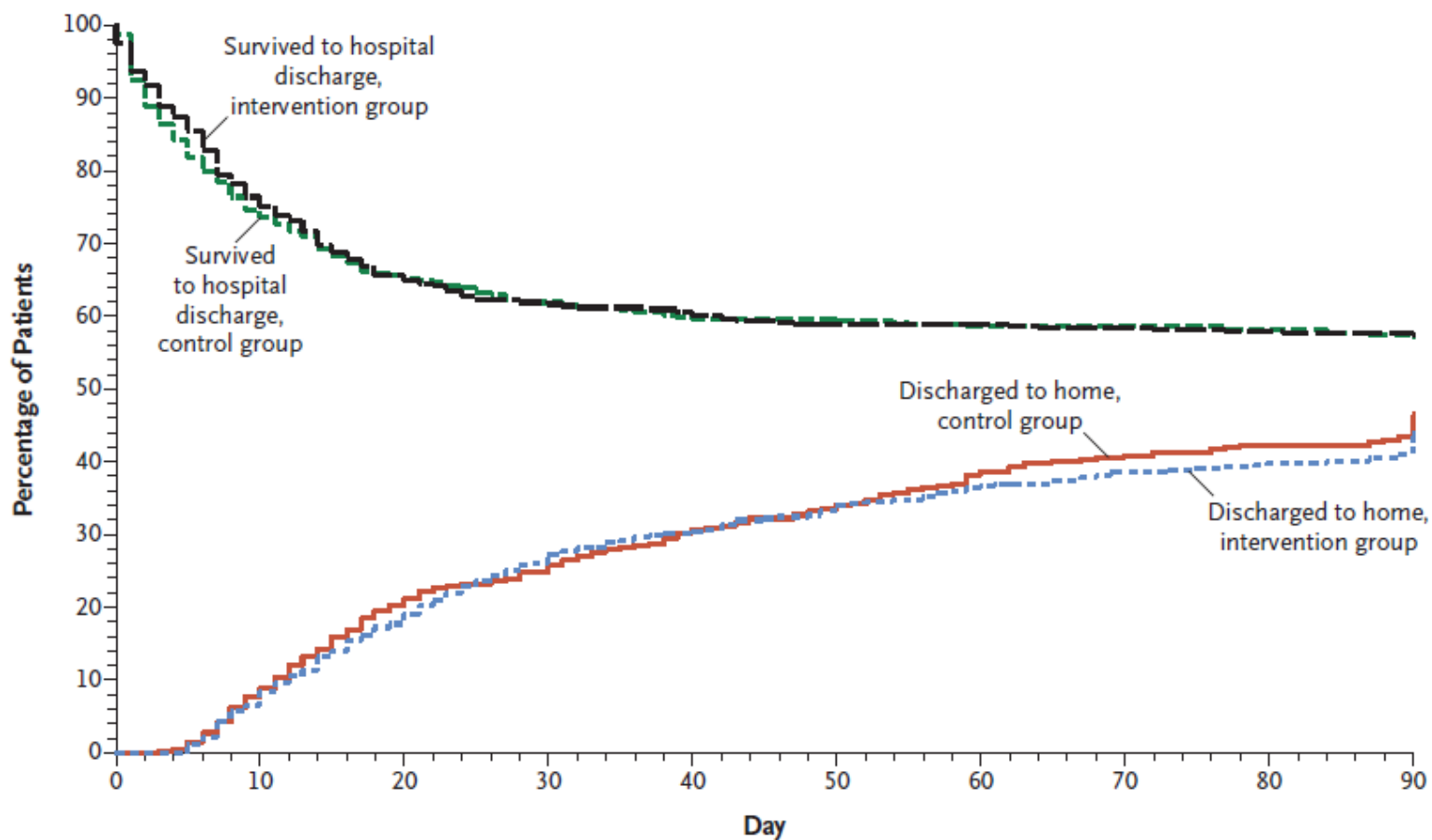
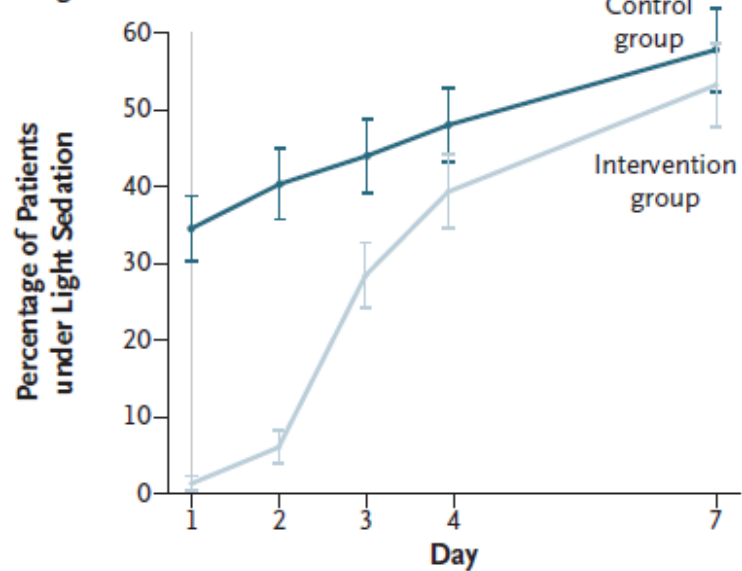


Figure 3. Patients Who Survived to Hospital Discharge and Were Discharged Home during the First 90 Days after Randomization.

Variable	Intervention Group (N = 501)	Control Group (N = 505)	Between-Group Difference (95% CI)	P Value
			<i>percentage points</i>	
Primary end point: in-hospital death by day 90 — no. (%) [†]	213 (42.5±2.2)	216 (42.8±2.2)	-0.3 (-6.4 to 5.9)	0.93
Secondary end points				
In-hospital death by day 28 — no. (%)	184 (36.7)	187 (37.0)	-0.3 (-6.3 to 5.7)	
Days free of ventilation at day 28 [‡]	9.6±10.4	9.9±10.9	-0.3 (-1.7 to 1.0)	
Days not in ICU at day 28	9.0±9.4	9.4±9.8	-0.4 (-1.6 to 0.8)	
Days not in hospital at day 28 [‡]	5.7±7.8	5.9±8.1	-0.2 (-1.1 to 0.8)	
Safety end points				
In-hospital recall of paralysis				
Total no. of patients (%)	9 (1.8)	10 (2.0)	-0.2 (-1.9 to 1.5)	
Among patients who received neuromuscular blockade — no./total no. (%)	9/487 (1.8)	2/129 (1.6)	0.3 (-2.1 to 2.7)	
MRC score [§]				
Day 7	46.7±14.4	49.5±12.3	-2.8 (-6.1 to 0.6) ¶	
Day 28	45.7±13.9	49.8±10.6	-4.1 (-9.0 to 0.9) ¶	
ICU-acquired weakness — no./total no. (%)				
Day 7	50/122 (41.0)	41/131 (31.3)	-9.7 (-21.5 to 2.1)	
Day 28	22/47 (46.8)	14/51 (27.5)	-19.4 (-38.2 to -0.6)	
Any time through day 28	107/226 (47.3)	89/228 (39.0)	-7.3 (-15.7 to 1.1)	
Serious adverse events — no. of events ^{**}	35	22		0.09
Serious cardiovascular adverse events — no. of events ^{**}	14	4		0.02
Atrial fibrillation or SVT during ICU stay — no. (%)	101 (20.2)	99 (19.6)		0.88
Barotrauma — no. (%)	20 (4.0)	32 (6.3)		0.12
Pneumothorax on days 0 through 2 — no. (%)	8 (1.6)	10 (2.0)		0.81
Pneumothorax on days 0 through 7 — no. (%)	14 (2.8)	25 (5.0)		0.10

항목	ROSE 연구 (2019)	ACURASYS 연구 (2010)
연구 기간	2016년 1월 ~ 2018년 4월	2006년 3월 ~ 2008년 3월
연구 장소	미국 48개 병원	유럽 20개 중환자실
환자 수	1,006명 (대조군 501명, NMB 505명)	340명 (대조군 177명, NMB 162명)
Blind	unblind (통계 분석 및 장기 결과 평가자만 blind)	Double blind
환기 전략	6 mL/kg , 폐보호적 환기	6-8 mL/kg, 폐보호적 환기
PEEP 전략	≥ 8 cmH ₂ O의 high PEEP	≥ 5 cmH ₂ O의 low PEEP
대조군 치료	경도 진정	깊은 진정
ARDS 정의	베를린 정의	AECC (American-European Consensus Conference) 정의
ARDS 진단 후 등록 median, hr	8 (4-16)	16 (6-29)

Deep sedation + NM blocker vs. deep sedation → mortality 이점
 Deep sedation + NM blocker vs. light sedation → mortality 차이 없음.



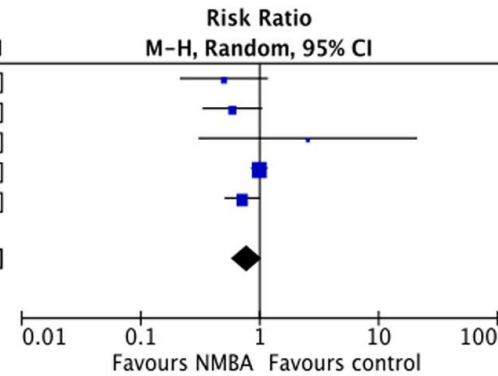
Neuromuscular blockade in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials

An Thi Nhat Ho^{1*}, Setu Patolia¹ and

Five randomized controlled trials (RCT) evaluating 28-day mortality in ARDS patients treated with NMBA within 48 h.

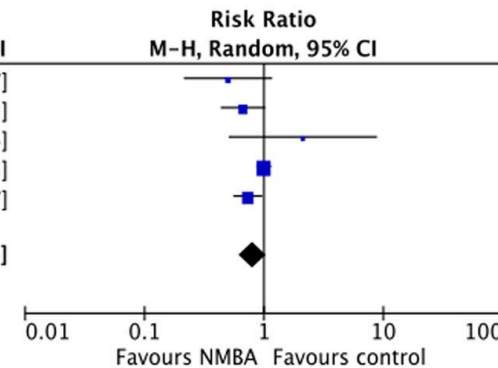
28-day mortality

Study or Subgroup	NBMA		Control		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Forel 2006	5	18	10	18	9.8%	0.50 [0.21, 1.17]
Gainnier 2004	10	28	17	28	17.1%	0.59 [0.33, 1.05]
Guervilly 2017	3	13	1	11	1.9%	2.54 [0.31, 21.06]
Moss 2019	184	501	187	505	41.8%	0.99 [0.84, 1.17]
Papazian 2010	42	177	54	162	29.4%	0.71 [0.51, 1.00]
Total (95% CI)		737		724	100.0%	0.78 [0.58, 1.06]
Total events	244		269			
Heterogeneity: Tau ² = 0.05; Chi ² = 8.01, df = 4 (P = 0.09); I ² = 50%						
Test for overall effect: Z = 1.60 (P = 0.11)						



90-day mortality

Study or Subgroup	NBMA		Control		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Forel 2006	5	18	10	18	7.9%	0.50 [0.21, 1.17]
Gainnier 2004	14	28	21	28	20.5%	0.67 [0.43, 1.02]
Guervilly 2017	5	13	2	11	3.2%	2.12 [0.51, 8.84]
Moss 2019	213	501	216	505	38.9%	0.99 [0.86, 1.15]
Papazian 2010	56	177	70	162	29.5%	0.73 [0.55, 0.97]
Total (95% CI)		737		724	100.0%	0.81 [0.62, 1.06]
Total events	293		319			
Heterogeneity: Tau ² = 0.04; Chi ² = 9.03, df = 4 (P = 0.06); I ² = 56%						
Test for overall effect: Z = 1.54 (P = 0.12)						



Trial auth

Year

Country

NBMA vs

PaO₂/FIO₂

inclusion

Importan

Ventilato
strategy

Cisatracu

Assessme

Sedation

E trial [19]

vs 505

0

ent continuous
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g protective high
strategy

s 15 mg, 37.5
hour

adjustment

5 - 4, - 5 in the
vention group
5 0 to - 1 in the
control group)^c



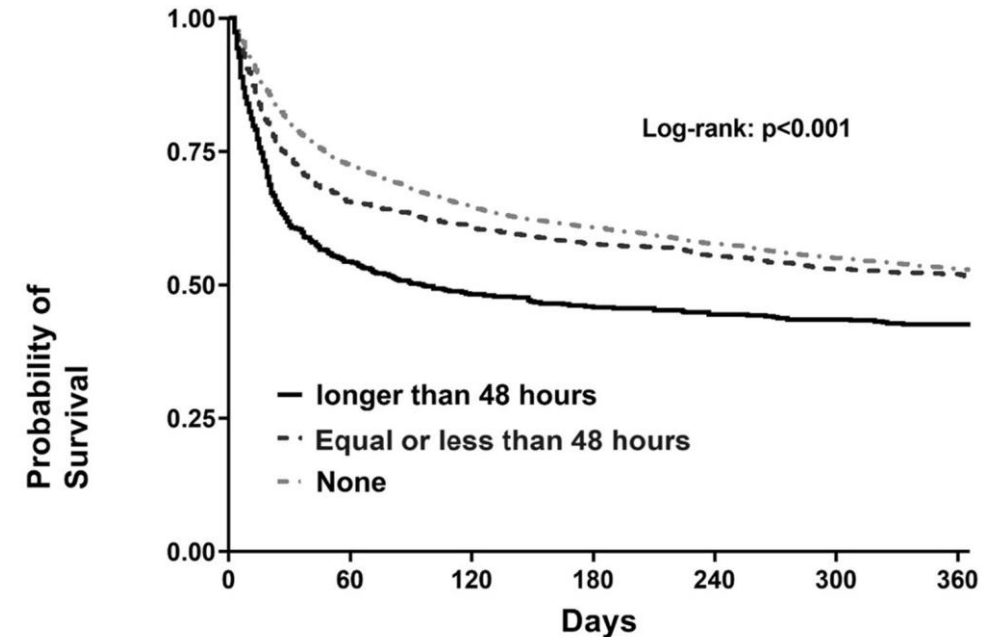
Prolonged use of neuromuscular blocking agents is associated with increased long-term mortality in mechanically ventilated medical ICU patients: a retrospective cohort study

Chun Lin¹, Wen-Cheng Chao^{2,3,4,5}, Kai-Chih Pai⁶, Tsung-Ying Yang^{1,7}, Chieh-Liang Wu^{2,3} and Ming-Cheng Chan^{2,3,8*}

Retrospective cohort study, 2015–2019 critical care databases at Taichung Veterans General Hospital (NHIRD)

MV Patients with using NMBA continuously for >8 hr within the first 72 h of ICU admission, Total n =5,709 survivors (n=2954) vs. non-survivors (n=2755)

Variables	Univariable		Multivariable	
	HR (95% C.I.)	p value ^a	HR (95% C.I.)	p value ^b
Age, per 1 year increment	1.013 (1.01–1.015 0)	<0.001	1.006 (1.002–1.009)	0.001
Male gender	1.160 (1.072–1.255)	<0.001	1.179 (1.066–1.303)	0.001
BMI, per 1 decrement	0.965 (0.957–0.973)	<0.001	0.966 (0.956–0.976)	<0.001
CCI, per 1 increment	1.165 (1.150–1.181)	<0.001	1.150 (1.131–1.170)	<0.001
APACHE II, per 1 increment	1.064 (1.057–1.071)	<0.001	1.023 (1.014–1.032)	<0.001
Platelet, per 1 × 10 ³ decrement	0.996 (0.995–0.996)	<0.001	0.997 (0.997–0.998)	<0.001
Lactate, per 1 increment	1.02 (1.019–1.0220)	<0.001	1.028 (1.025–1.030)	<0.001
Etiology for ICU admission				
Acute respiratory failure	1.201 (1.115–1.295)	<0.001	1.048 (0.932–1.177)	0.434
Pneumonia	1.298 (1.163–1.448)	<0.001	1.087 (0.941–1.256)	0.256
Sepsis (non-pneumonia)	1.289 (1.145–1.45)	<0.001	0.999 (0.854–1.168)	0.988
Acute cardiac conditions	0.727 (0.572–0.923)	0.009	0.681 (0.415–1.116)	0.128
Acute neurological conditions	0.809 (0.707–0.926)	0.002	1.055 (0.880–1.265)	0.560
Ventilatory parameters				
FIO ₂ ≥ 50%	1.384 (1.282–1.493)	<0.001	1.167 (1.050–1.297)	0.004
PEEP ≥ 8 cmH ₂ O	1.366 (1.267–1.472)	<0.001	0.939 (0.839–1.051)	0.275
PaO ₂ , per 10 decrement	0.999 (0.995–1.003)	0.677	0.998 (0.993–1.002)	0.320
Use of NMBAs				
None	[Reference]		[Reference]	
Use, equal or less than 48 h	1.092 (0.978–1.220)	0.118	0.962 (0.834–1.111)	0.602
Use, longer than 48 h	1.506 (1.336–1.697)	<0.001	1.261 (1.070–1.486)	0.006



	Number at risk						
	0	60	120	180	240	300	360
exceed 48hrs	535	291	258	246	238	233	228
Equal or less than 48 hrs	765	502	466	441	425	405	398
None	4409	3199	2854	2681	2546	2427	2337

After adjusting for age, sex, and relevant covariates

The use of early neuromuscular blockage in acute respiratory distress syndrome: A systematic review and meta-analyses of randomized clinical trials

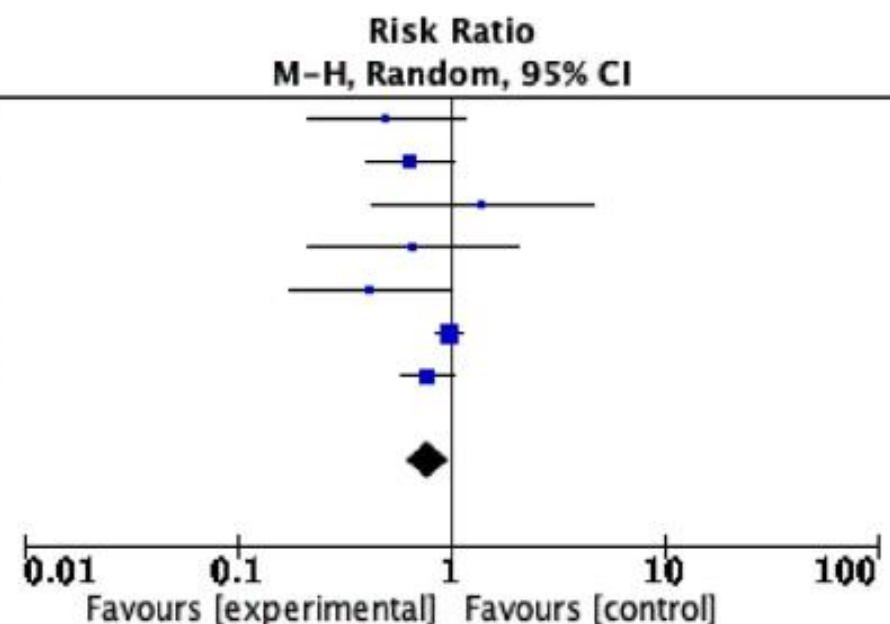
Félix H. Savoie-White^{a,b,e,*}, Laurence Tremblay^a, Charles Antoine Menier^a, Cécile Duval^b, Frédéric Bergeron^c, Mina Tadrous^d, Jade Tougas^a, Jason R. Guertin^{a,e}, Paula A. Ugalde^f

Trial	Year	Country	NMBA*	Treatment groups	Total (n), NMBA/Control
Forel	2006	France	Cisatracurium ¹	Cisatracurium + Heavy Sedation	18
Gainnier	2004	France	Cisatracurium ¹	Cisatracurium + Heavy Sedation	28
Guervilly	2016	France	Cisatracurium ³	Cisatracurium + Heavy Sedation	13
Lyu	2014	China	Vecuronium ³	Vecuronium + Heavy Sedation	48
Moss	2019	USA	Cisatracurium ⁴	Cisatracurium + Adequate Sedation	501
				Vecuronium + Adequate Sedation	505
				Vecuronium + Heavy Sedation	177
				Cisatracurium + Heavy Sedation	162

현재 까지 연구의 결과가 사망률의 이점이 명확치 않음.

Study or Subgroup	Experimental		Control		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Forel 2006	5	18	10	18	6.5%	0.50 [0.21, 1.17]
Gainnier 2004	13	28	20	28	16.2%	0.65 [0.41, 1.03]
Guervilly 2016	5	13	3	11	3.6%	1.41 [0.43, 4.61]
Lyu 2014 – Moderate	4	24	6	24	3.9%	0.67 [0.22, 2.07]
Lyu 2014 – Severe	5	24	12	24	6.2%	0.42 [0.17, 1.00]
Moss 2019	213	501	216	505	36.9%	0.99 [0.86, 1.15]
Papazian 2010	57	177	67	162	26.6%	0.78 [0.59, 1.03]
Total (95% CI)		785		772	100.0%	0.79 [0.62, 0.99]
Total events	302		334			

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 10.39$, $df = 6$ ($P = 0.11$); $I^2 = 42\%$
 Test for overall effect: $Z = 2.01$ ($P = 0.04$)



(Overall Survival RR 0.79 [95% CI, 0.62 to 0.99; I2 = 42%; 1557 patients, 6 trials])

- **Ventilator free day?**

N Engl J Med. 2010 Sep 16;363(12):1107-16

Outcome

No. of ventilator-free days†

Cisatracurium
(N=177)

Placebo
(N=162)

Relative Risk with
Cisatracurium
(95% CI)

P Value

From day 1 to day 28

10.6±9.7

8.5±9.4

0.04

J Intensive Care. 2020 Jan 28;8:12.

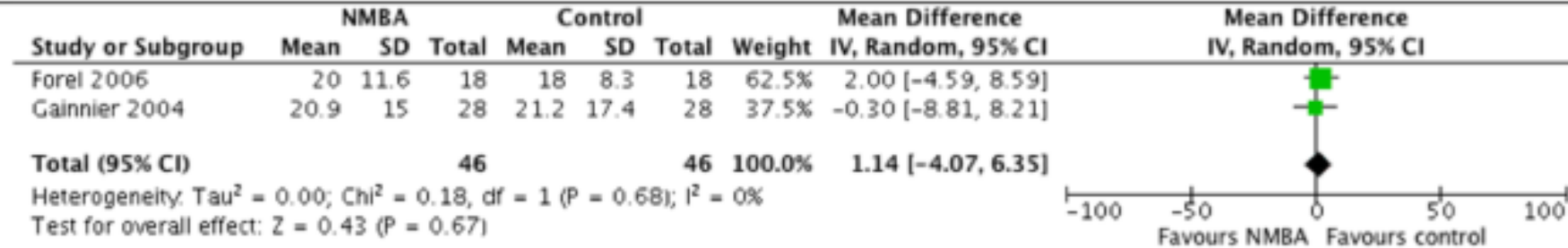
53.1±35.8

44.6±37.5

0.03

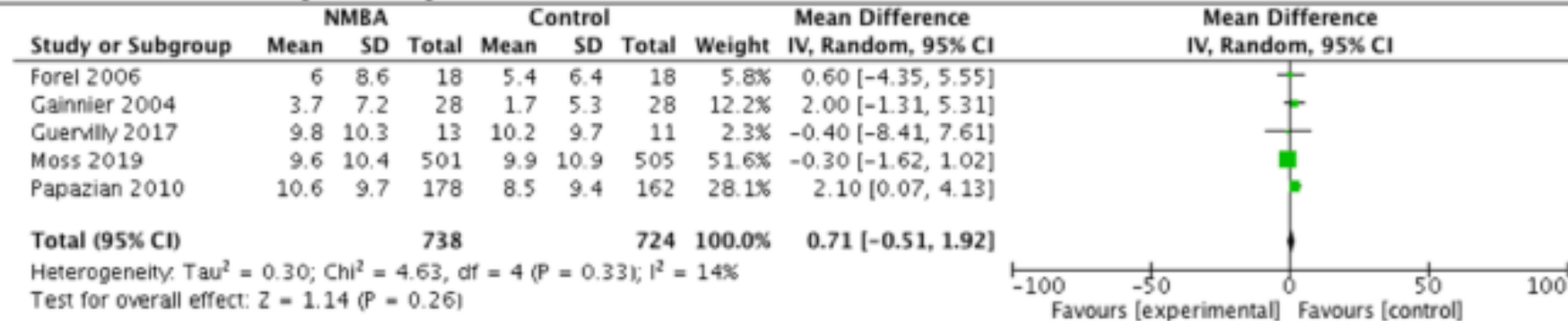
NM group 이득

Mechanical ventilation duration



차이없음

Ventilator free-days at day 28^a

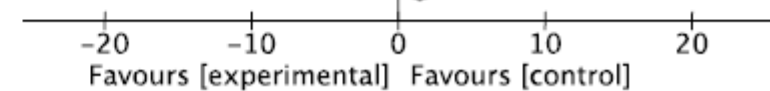


차이없음

Total (95% CI) 738 724 100.0% 1.00 [-1.53, 4.54]

Heterogeneity: Tau² = 5.14; Chi² = 8.16, df = 4 (P = 0.09); I² = 51%

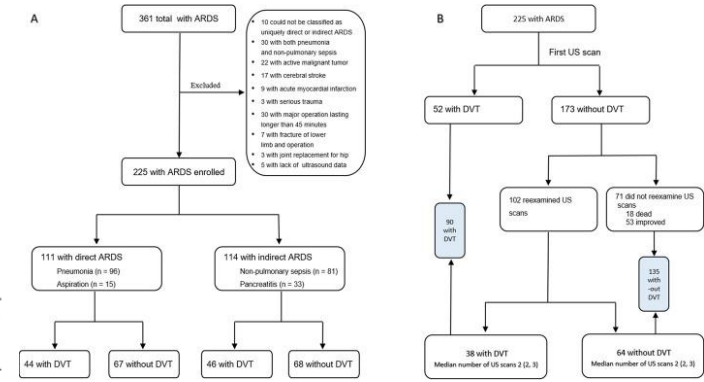
Test for overall effect: Z = 1.06 (P = 0.29)



Prevalence, risk, and outcome of deep vein thrombosis in acute respiratory distress syndrome

Na Cui^{1,2}, Chunguo Jiang^{1,2}, Hairong Chen³, Liming Zhang^{1,2*} and Xiaokai Feng^{1,2*}

Characteristic	Total (N = 225)	DVT (N = 90)	Non-DVT (N = 135)	P value
Age (years)	66 ± 17	70 ± 13	63 ± 18	< 0.001
Male, n (%)	144 (64.0)	52 (57.8)	92 (68.1)	0.112
Bedridden time (days)	8 (4, 15)	10 (5, 18)	7 (4, 15)	0.216
Caprini score	7 (5, 9)	7 (5, 10)	7 (5, 9)	0.135
Padua prediction score	6 (5, 6)	6 (5, 8)	5 (5, 6)	0.023
APACHE II score	23 (19, 28)	24 (20, 28)	23 (18, 29)	0.596
SOFA score	8 (5, 10)	7 (5, 9)	8 (5, 11)	0.622
Treatments				
Glucocorticoid therapy, n (%)	51 (22.7)	22 (24.4)	29 (21.5)	0.603
Immunoglobulin, n (%)	5 (2.2)	2 (2.2)	3 (2.2)	1.000
Sedative therapy, n (%)	96 (42.7)	50 (55.6)	46 (34.1)	0.001
Vasoactive agent therapy, n (%)	55 (24.4)	25 (27.8)	30 (22.2)	0.342
CRRT, n (%)	33 (14.7)	10 (11.1)	23 (17.0)	0.218
CVC, n (%)	125 (55.6)	55 (61.1)	70 (51.9)	0.171
IMV, n (%)	122 (54.2)	66 (73.3)	56 (41.5)	< 0.001
Length of IMV (days)	3 (2, 7)	3 (2, 6)	3 (2, 8)	0.543
LMWH + physical prophylaxis, n (%)	75 (33.3)	29 (32.2)	46 (34.1)	0.817
Physical prophylaxis only, n (%)	23 (10.3)	9 (10.1)	14 (10.4)	0.950
ICU length of stay (days)	11 (6, 24)	12 (5, 24)	11 (6, 26)	0.563
Hospital length of stay (days)	19 (12, 32)	20 (11, 32)	19 (12, 31)	0.816
Mortality, n (%)	77 (34.2)	45 (50.0)	32 (23.7)	< 0.001



DVT risk 높음

현재 까지 연구를 종합할 때 기계환기 기간에 영향은 ?

- **Weakness and critical illness myopathy**

ACURASYS 2010

Outcome	Cisatracurium (N=177)	Placebo (N=162)	Relative Risk with Cisatracurium (95% CI)	P Value
MRC score — median (IQR) [§]				
At day 28	55 (46–60)	55 (39–60)	1.07 (0.80–1.45)	0.49
At ICU discharge	55 (43–60)	55 (44–60)	0.92 (0.71–1.19)	0.94
Patients without ICU-acquired paresis [¶]				
By day 28 — no./total no. (% [95% CI])	68/96 (70.8 [61.1–79.0])	52/77 (67.5 [56.5–77.0])		0.64
By ICU discharge — no./total no. (% [95% CI])	72/112 (64.3 [55.1–72.6])	61/89 (68.5 [58.3–77.3])		0.51

ROSE 2019

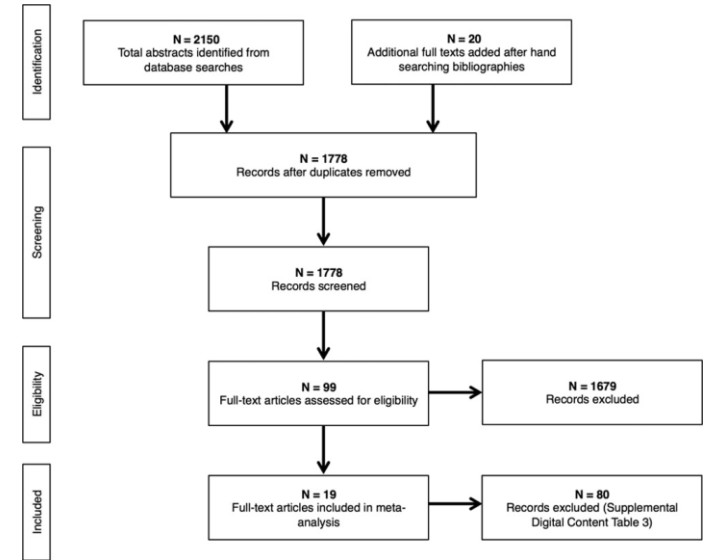
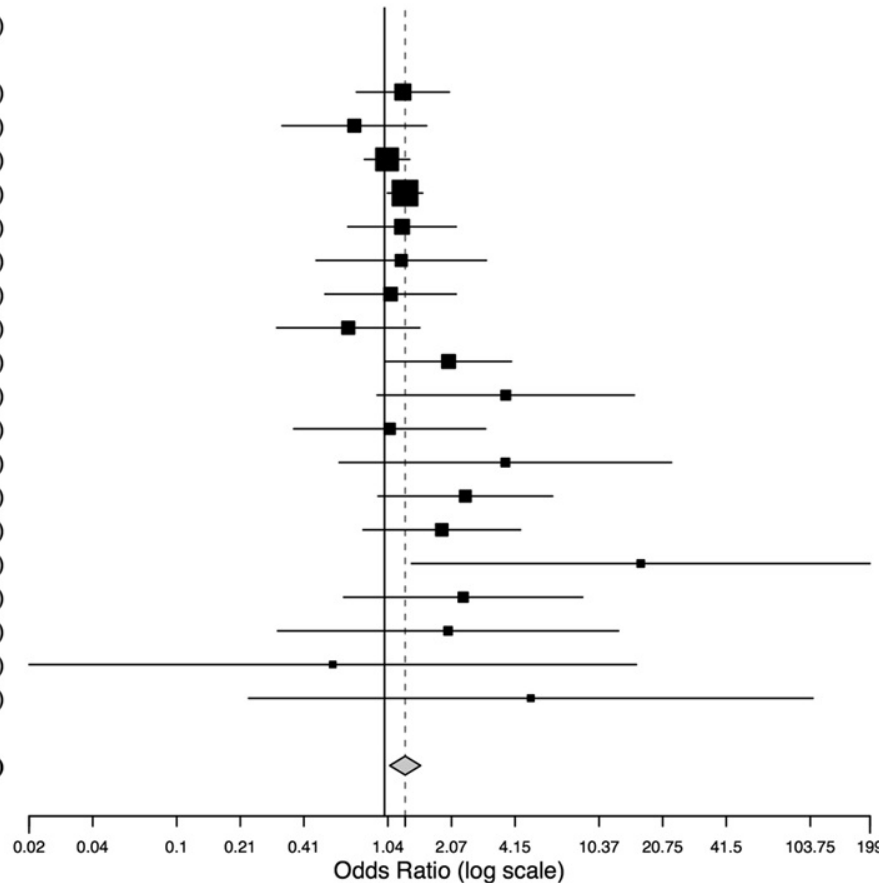
Variable	Intervention Group (N=501)	Control Group (N=505)	Between-Group Difference (95% CI)	P Value
MRC score [§]				
Day 7	46.7±14.4	49.5±12.3	-2.8 (-6.1 to 0.6) [¶]	
Day 28	45.7±13.9	49.8±10.6	-4.1 (-9.0 to 0.9) [¶]	
ICU-acquired weakness — no./total no. (%)				
Day 7	50/122 (41.0)	41/131 (31.3)	-9.7 (-21.5 to 2.1)	
Day 28	22/47 (46.8)	14/51 (27.5)	-19.4 (-38.2 to -0.6)	
Any time through day 28	107/226 (47.3)	89/228 (39.0)	-7.3 (-15.7 to 1.1)	

Neuromuscular Blocking Agents and Neuromuscular Dysfunction Acquired in Critical Illness: A Systematic Review and Meta-Analysis

Price, David R. MD^{1,3}; Mikkelsen, Mark E. MD, MSCE^{2,3}; Umscheid, Craig A. MD, MSCE^{1,3}; Armstrong, Ehrin J. MD, MSc^{4,5}

Primary Analysis: Forest plot of all included studies

Studies	Estimate (95% C.I.)
Hermans 2014	1.22 (0.74, 2.03)
Fan 2014	0.72 (0.33, 1.58)
Derde 2012	1.03 (0.80, 1.32)
Brunello 2010	1.25 (1.03, 1.52)
Papazian 2010	1.21 (0.67, 2.19)
Ali 2008	1.20 (0.47, 3.04)
Nanas 2008	1.07 (0.52, 2.19)
De Jonghe 2007	0.67 (0.31, 1.47)
Hermans 2007	2.01 (1.01, 3.99)
Garnacho–Montero 2005	3.75 (0.92, 15.24)
Bednarik 2005	1.06 (0.37, 3.01)
Amaya–Villar 2005	3.73 (0.61, 22.86)
De Jonghe 2002	2.41 (0.93, 6.26)
de Letter 2001	1.87 (0.79, 4.40)
Garnacho–Montero 2001	16.34 (1.34, 199.00)
Leijten 1996	2.36 (0.64, 8.68)
Verheul 1994	2.00 (0.31, 12.84)
Coakley 1993	0.57 (0.02, 15.58)
Douglass 1992	4.93 (0.23, 106.88)
Overall (I²=16%, P=0.26)	1.25 (1.06, 1.48)

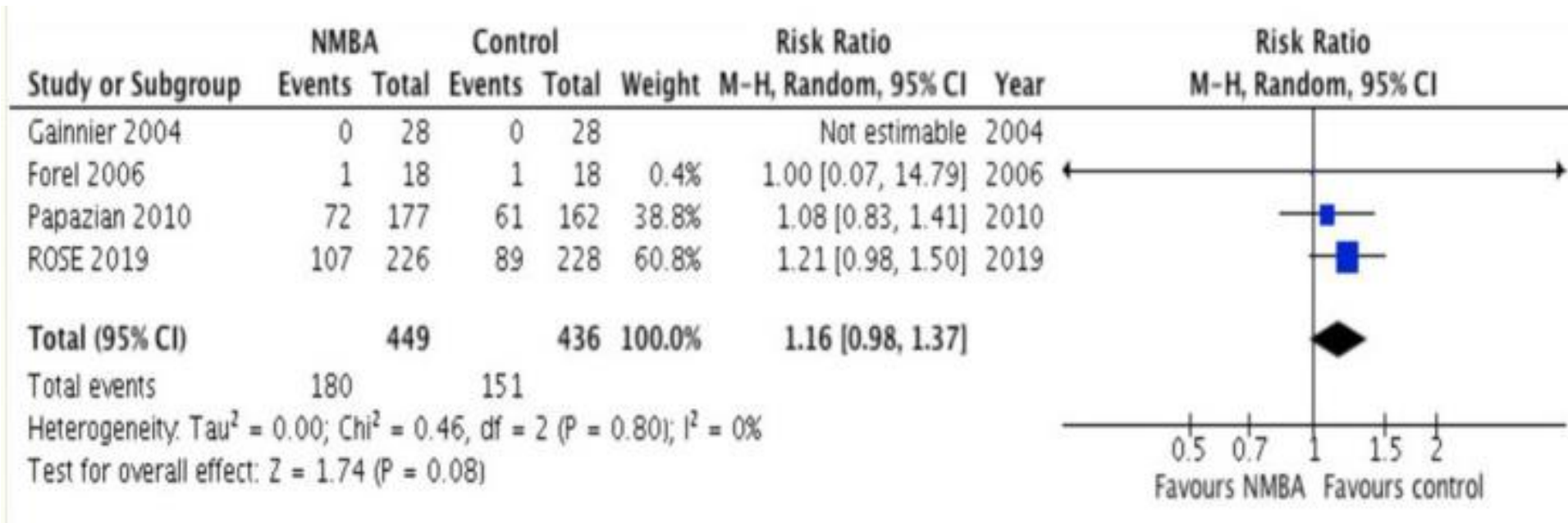


Association between neuromuscular blocking agents and neuromuscular dysfunction acquired in critical illness

Neuromuscular blocking agents in acute respiratory distress syndrome: updated systematic review and meta-analysis of randomized trials

Nehal Tarazan¹, Moayad Alshehri^{1,2}, Sameer Sharif³, Zainab Al Duhailib^{1,4}, Morten Hylander Møller⁵, Emilie Belley-Cote¹, Mohammed Alshahrani⁶, John Centofanti¹, Lauralyn McIntyre^{7,8}, Bandar Baw¹, Maureen Meade^{1,9}, Waleed Alhazzani^{1,9*} and for the GUIDE Group

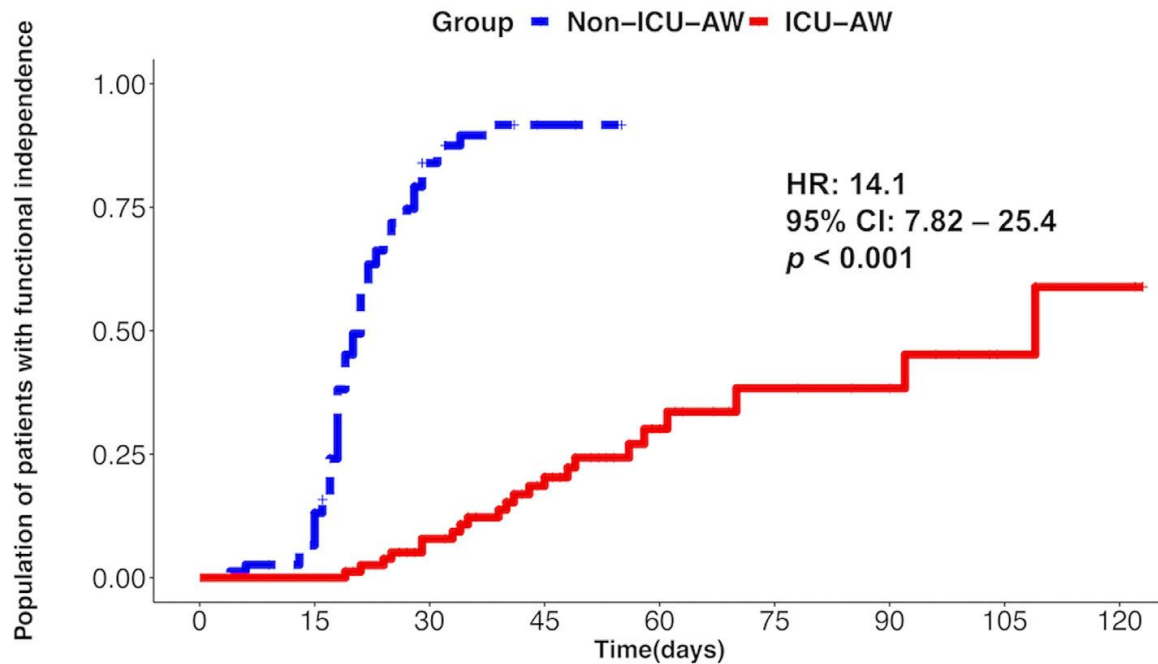
NM blocker 48시간 이내 사용한 4개의 RCT 상 차이 없음.



ICU-acquired weakness

Predictive factors and clinical impact of ICU-acquired weakness on functional disability in mechanically ventilated patients with COVID-19

Kanji Yamada, PT, PhD^{a,b}, Takeshi Kitai, MD, PhD^{a,c,*}, Kentaro Iwata, PT, PhD^{a,b}, Hiromasa Nishihara, PT^a, Tsubasa Ito, PT^a, Rina Yokoyama, PT^a, Yuta Inagaki, PT, MSc^a, Takayuki Shimogai, PT, MSc^a, Akihiro Honda, PT^a, Tetsuya Takahashi, PT, PhD^d, Ryo Tachikawa, MD, PhD^e, Chigusa Shirakawa, MD^e, Jiro Ito, MD^f, Ryutaro Seo, MD^g, Hirokazu Kuroda, MD^h, Asako Doi, MD, PhD^h, Keisuke Tomii, MD, PhD^e, Nobuo Kohara, MD, PhD^a



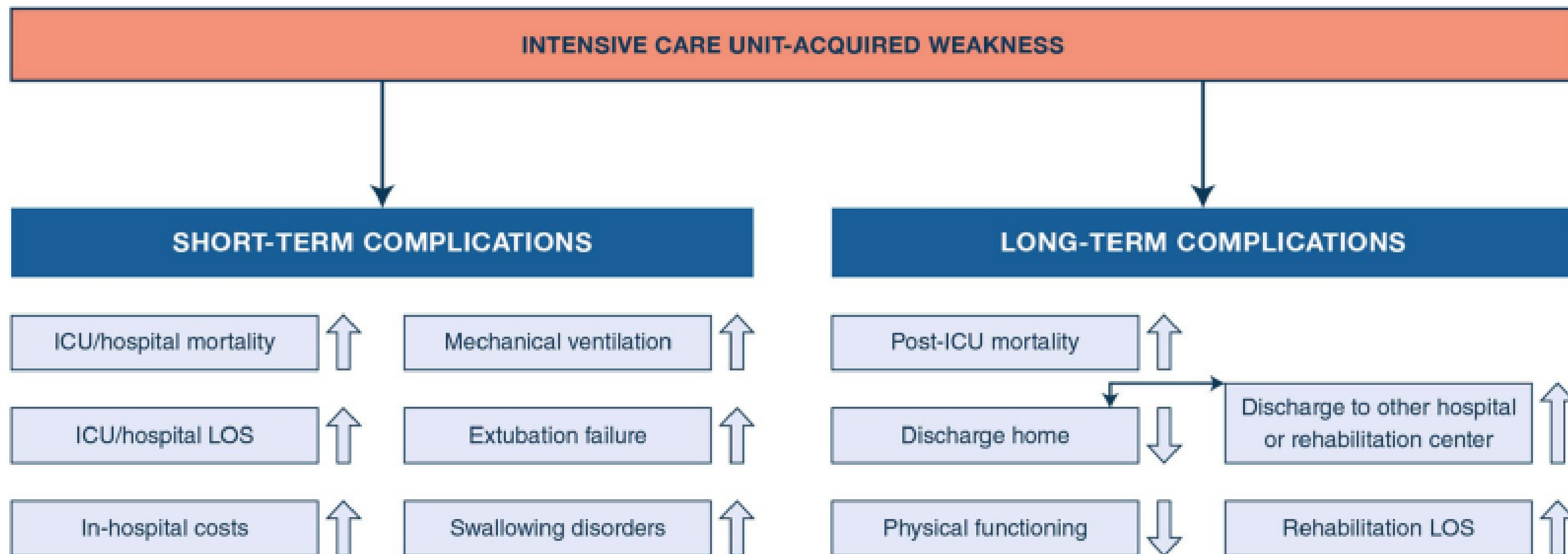
	0	15	30	45	60	75	90	105	120
■ Non-ICU-AW	77	71	9	2	0	0	0	0	0
■ ICU-AW	80	80	66	47	22	13	10	4	2

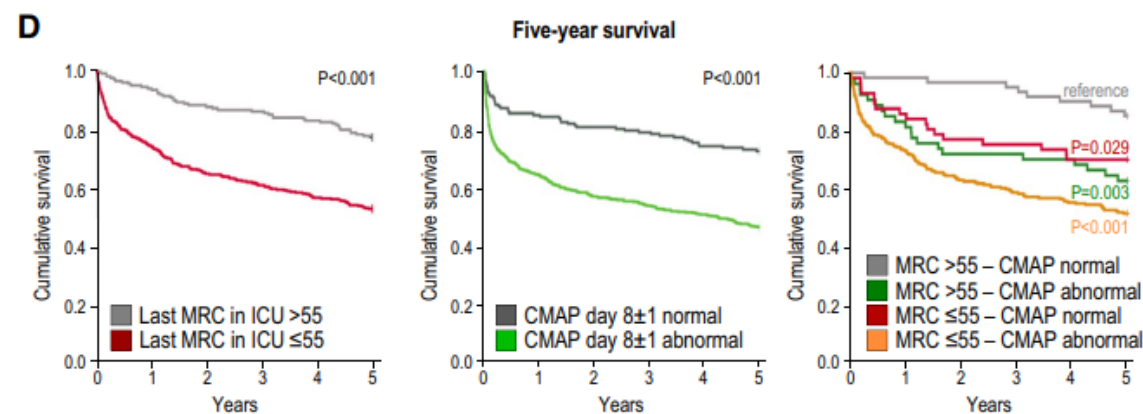
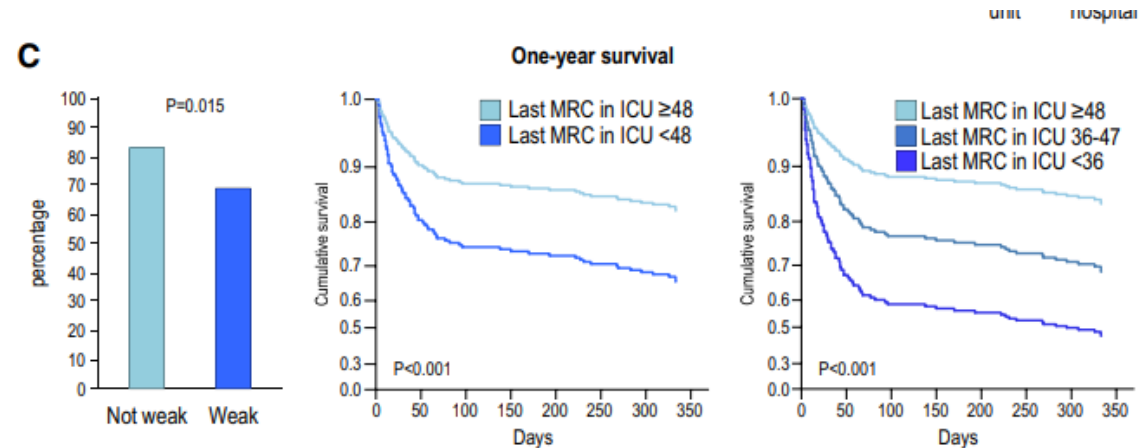
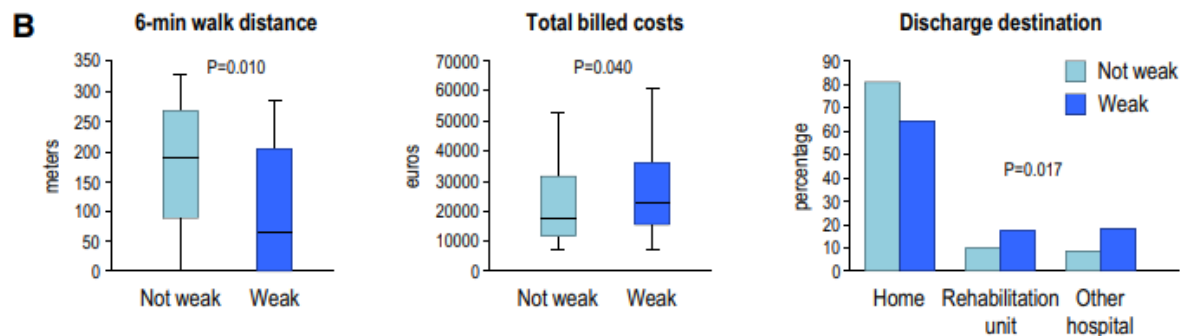
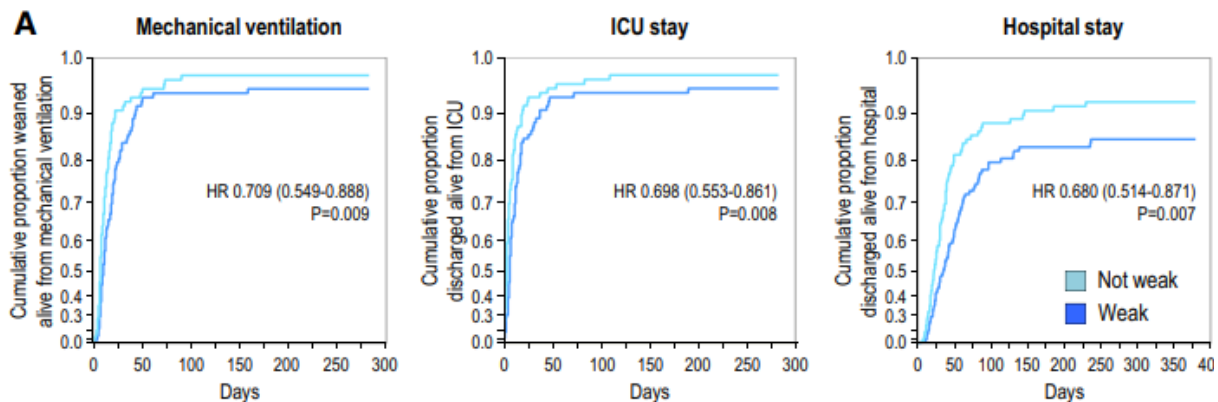
Single center, prospective observational study, Patients with COVID-19 in ICU

Primary outcome: development of ICU-AW
Non ICU AW n=77 vs. ICU AW n=80

	All (n = 157)	Non-ICU-AW (n = 77)	ICU-AW (n = 80)	P-Value
TREATMENTS RECEIVED				
ECMO (n,%)	0 (0)	0 (0)	0 (0)	0.999
CRRT (n,%)	9 (5.7)	1 (1.3)	8 (10.0)	0.045
Prone position (n,%)	60 (38.2)	11 (14.3)	49 (61.3)	<0.001
HFNC (n,%)	138 (87.9)	66 (85.7)	72 (90.0)	0.563
Mechanically ventilation				
Duration of ventilation (days)	8 (5–25)	5 (3–7)	25 (13–40)	<0.001
Extubation (n,%)	149 (94.9)	75 (97.4)	74 (92.5)	0.301
Re-intubation (n,%)	13 (8.3)	4 (5.2)	9 (11.2)	0.277
Tracheostomy (n,%)	39 (24.8)	0 (0)	39 (48.8)	<0.001
Neuromuscular blockade (n,%)	66 (42.0)	12 (15.6)	54 (67.5)	<0.001
Duration of blockade (days)	1 (1–2)	1 (1–2)	1.5 (1–2)	0.258
Sedation (n,%)	155 (98.7)	75 (97.4)	80 (100)	0.460
Duration of sedation (days)	8 (4–17)	4 (2–7)	16 (10–22)	<0.001

	OR	95% CI	<i>p</i>
VARIABLES			
Age, years	1.05	1.01–1.11	0.036
Men	1.61	0.58–4.71	0.370
APACHE II, points	1.08	0.98–1.20	0.141
CCI, points	0.85	0.58–1.24	0.5394
CFS, points	1.02	0.31–4.58	0.977
Neuromuscular blockade	7.79	2.87–23.3	<0.001
Pulse steroid therapy	3.78	1.49–10.1	0.006
Sepsis	6.94	2.33–24.0	<0.001
VAP	2.50	0.92–7.00	0.074





- **Neuromuscular blocker** 사용한다면 ?
- → **Deep sedation** 필요 !!!

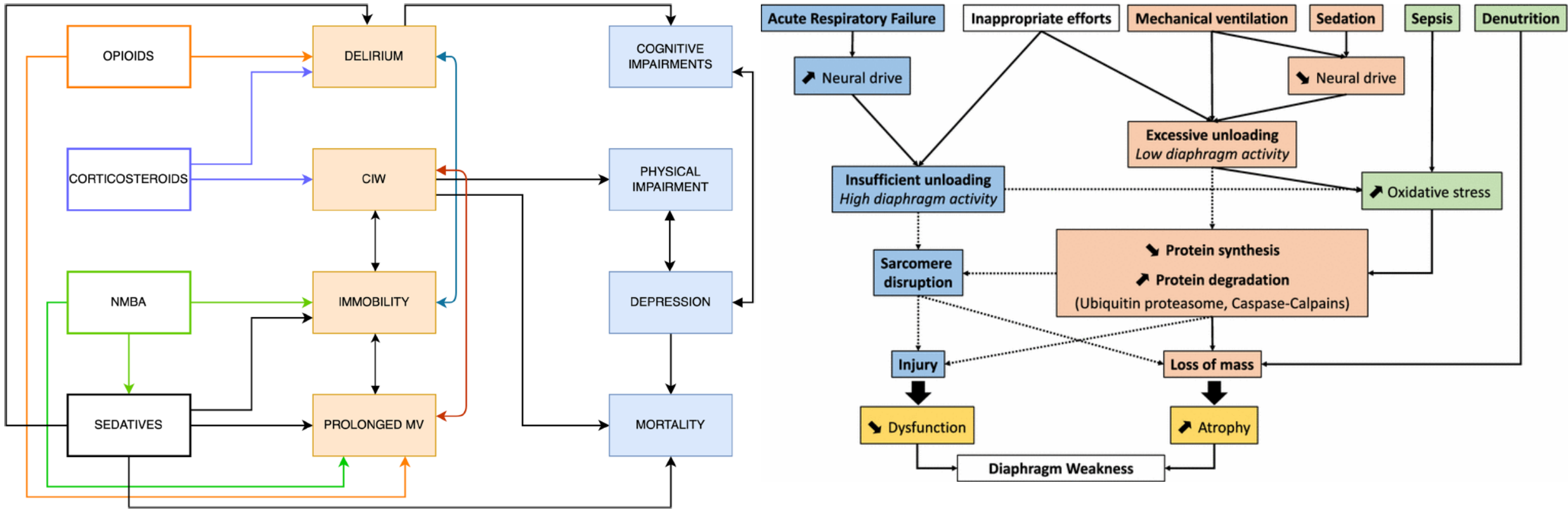
Assessing pain and anxiety in patients receiving NMBA's is difficult, if not impossible

- paralyzed without receiving adequate sedation reported feeling terrified and experiencing overwhelming panic

	Patients with Recall (n=4)	Patients without Recall (n=7)	p Value
Age (yrs)	64.5 ± 13.2	39.0 ± 21.3	0.071
Weight (kg)	84.2 ± 11.4	64.3 ± 10.1	0.023
GCS before paralysis	10.0 ± 3.3	6.3 ± 3.0	0.106
APACHE 2 score	16.5 ± 3.9	18.1 ± 4.5	0.394
Duration of TP (hrs)	103 ± 61	110 ± 61	0.706
Sedation (%) ^a	92.3	100	0.221
Time until evaluation (days) ^b	12.5 ± 10.2	14.6 ± 8.6	0.569
GCS at evaluation	13.8 ± 2.5	14.4 ± 1.5	0.575

	Never	Sometimes	Often	Almost Always
Ability to tell day of week and time of day	3		1	
Ability to sleep restfully	2	2		
Ability to breathe easily	2			2
Feelings of fear				4
Feelings of nervousness or worry				4
Feelings of reasonable comfort	3	1		
Feelings of pain	1	1	1	1
Feelings of hunger ^a	3			
Receipt of adequate pain relief	2	1		1
Receipt of explanation of events occurring	2	1		1
Receipt of reassurance from health care staff	1	1		2

Patients should receive an intravenous analgesic medication sufficient to provide acceptable pain relief, as well as a sedative with amnestic properties (e.g., propofol or benzodiazepine and NOT dexmedetomidine) to target a deep level of sedation.



SPECIAL ARTICLE

A Focused Update to the Clinical Practice Guidelines for the Prevention and Management of Pain, Anxiety, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

Agitation & Sedation	In mechanically ventilated adults admitted to the ICU, should dexmedetomidine, when compared with propofol, be used for sedation?	Adults admitted to the ICU who are mechanically ventilated and require sedation	Dexmedetomidine of any dose, route, duration, and frequency	Propofol of any dose, duration, frequency	<ol style="list-style-type: none"> 1) Occurrence of delirium 2) Duration of delirium 3) % of Richmond Agitation-Sedation Scale measurements inside target range 4) Duration of mechanical ventilation 5) ICU LOS 6) Use of additional rescue medications while in ICU 7) Mortality 8) Quality of life post-ICU/functional/cognitive abilities 9) Adverse events
Delirium	In adults admitted to the ICU, do antipsychotics administered for delirium compared with no antipsychotics, impact patient outcomes?	Adults with delirium who are admitted to the ICU	Any antipsychotic medication, of any dose, route, duration, or frequency	No antipsychotics	<ol style="list-style-type: none"> 1) Mortality 2) Duration of mechanical ventilation 3) Occurrence of delirium 4) Duration of delirium 5) ICU LOS 6) Hospital LOS 7) Quality of life post-ICU/functional/cognitive abilities 8) Occurrence of post-ICU anxiety/PTSD 9) Adverse events

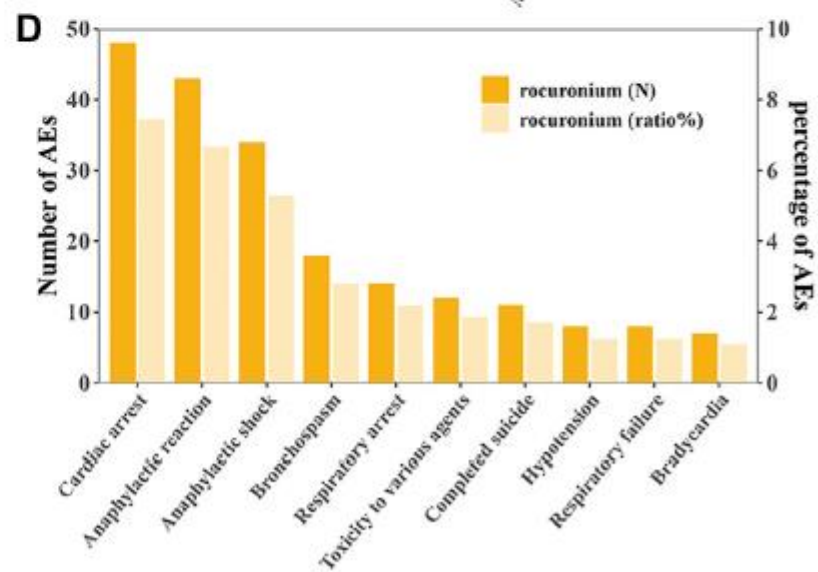
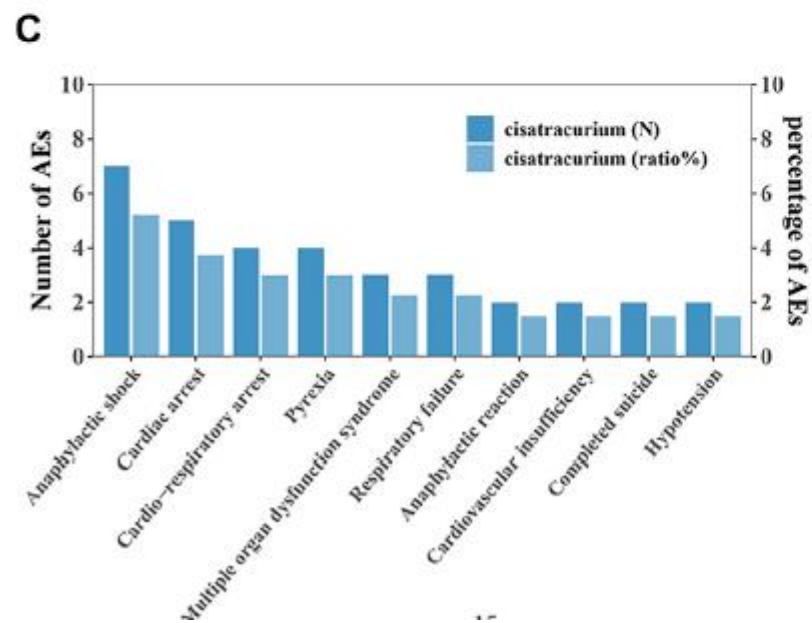
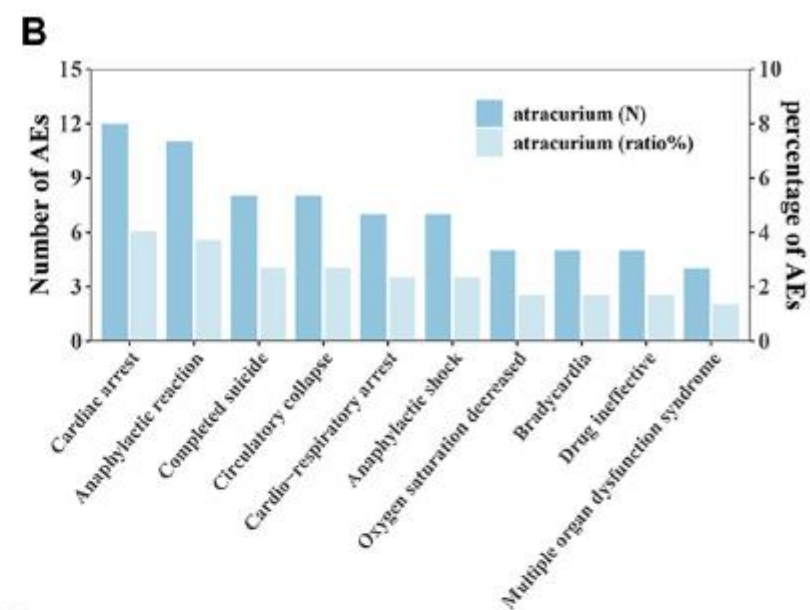
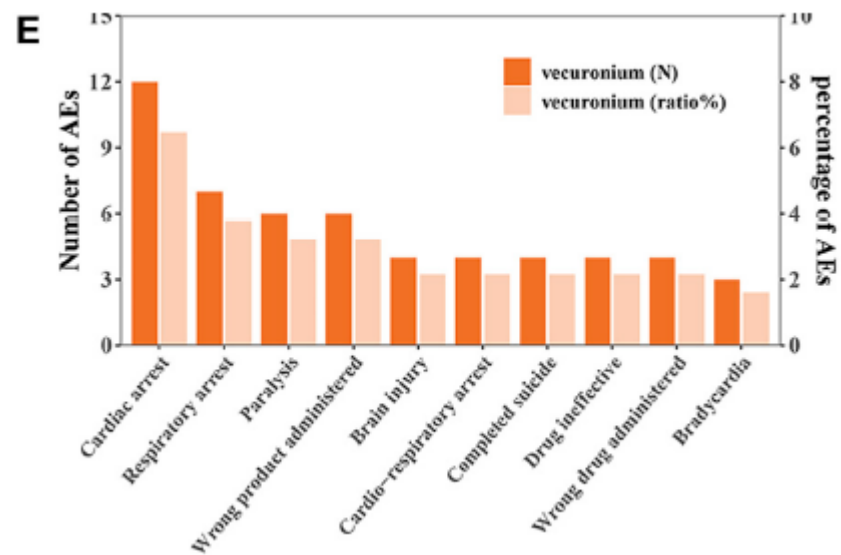
No.	Recommendations	Recommendation Strength, Direction, and Certainty of Evidence	Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption 2018 Recommendations
1	There is insufficient evidence to make a recommendation on the use of benzodiazepines to treat anxiety in adult patients admitted to the ICU	No recommendation; no evidence available	No recommendations previously existed
2	We suggest using dexmedetomidine over propofol for sedation in mechanically ventilated adult patients admitted to the ICU where light sedation and/or a reduction in delirium are of highest priorities	Conditional recommendation; for intervention; moderate certainty	We suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults (conditional recommendation, low quality of evidence)

Adverse events related to neuromuscular blocking agents: a disproportionality analysis of the FDA adverse event reporting system

Liangxia Li, Qianqian Xu, Yarui Liu, Liangfang Pang, Zhou Cui and Yuanyuan Lu*

Collected reports of atracurium, cisatracurium, rocuronium, and vecuronium as primary suspect drugs in the FDA adverse event reporting system, 1st quarter 2004-2023 11,518 NMBA-related AEs were reported in the FAERS database

	N ^a	ROR (95% CI)	IC (IC-2SD)
Atracurium			
Cardiac disorders	195	4.66 (4.01–5.41)	2.08 (1.84)
Immune system disorders	176	10.45 (8.94–12.22)	3.24 (2.95)
Pregnancy, puerperium and perinatal conditions	17	2.28 (1.41–3.67)	1.18 (0.40)
Respiratory, thoracic and mediastinal disorders	272	3.86 (3.39–4.39)	1.77 (1.56)
Vascular disorders	171	5.05 (4.31–5.91)	2.21 (1.95)
Cisatracurium			
Cardiac disorders	117	4.77 (3.93–5.79)	2.11 (1.79)
Hepatobiliary disorders	21	2.32 (1.51–3.58)	1.20 (0.49)
Immune system disorders	99	9.96 (8.09–12.25)	3.18 (2.76)
Investigations	82	1.35 (1.08–1.70)	0.41 (0.07)
Respiratory, thoracic and mediastinal disorders	104	2.35 (1.92–2.88)	1.15 (0.83)
Vascular disorders	76	3.72 (2.94–4.69)	1.81 (1.42)
Rocuronium			
Cardiac disorders	911	5.00 (4.66–5.36)	2.17 (2.07)
Immune system disorders	965	13.45 (12.57–14.39)	3.56 (3.45)
Injury, poisoning and procedural complications	869	1.18 (1.10–1.27)	0.22 (0.11)
Respiratory, thoracic and mediastinal disorders	871	2.68 (2.49–2.87)	1.31 (1.20)
Vascular disorders	532	3.46 (3.17–3.78)	1.72 (1.58)
Vecuronium			
Cardiac disorders	163	5.88 (4.23–5.88)	2.17 (1.90)
Immune system disorders	69	6.27 (3.86–6.27)	2.24 (1.81)
Injury, poisoning and procedural complications	240	2.26 (1.71–2.26)	0.84 (0.63)
Investigations	123	1.84 (1.27–1.84)	0.57 (0.29)
Respiratory, thoracic and mediastinal disorders	150	3.03 (2.16–3.03)	1.25 (0.99)
Vascular disorders	56	2.57 (1.51–2.57)	0.95 (0.53)



Characteristic	Depolarizing	Nondepolarizing					
	Succinylcholine	Aminosteroid			Benzylisoquinolinium		
		Pancuronium	Vecuronium	Rocuronium	Atracurium	Cisatracurium	Mivacurium
ED ₉₅ , mg/kg	0.5-0.6	0.07	0.05	0.3	0.2	0.05	0.08
Dose: intubating, mg/kg	0.5-1 (RSI: 1-1.2)	0.1	0.08-0.1	0.6-1 (RSI: 0.9-1.2)	0.4-0.5	0.1-0.2	0.25
Dose: bolus doses after intubation	1.0	0.02	0.02	0.1	0.1	0.15-0.2	0.05
Dose: continuous infusion, µg/kg/min	Not recommended	0.8-1.7	0.8-1.7	8-12	5-20	1-3	5-6
Onset (time to peak effect)	30-60 s	3-5 min	3-5 min	1-2 min	3-5 min	3-5 min	2-3 min
Duration	Ultrashort (5-10 min)	Long (60-90 min)	Intermediate (20-35 min)	Intermediate (20-35 min)	Intermediate (20-35 min)	Intermediate (20-35 min)	Short (12-20 min)
Metabolism/elimination	Plasma cholinesterase ^b	Renal > hepatic	Renal ≈ hepatic	Renal < hepatic	Plasma esterase and Hofmann elimination	Hofmann elimination	Plasma cholinesterase ^b
Active metabolites	None	3-desacetylpancuronium (50% potency)	3-desacetylvecuronium (50%-70% potency)	None	Laudanosine (possible CNS toxicity)	None	None
Effect on cardiac muscarinic receptors ^b	Stimulates	Blocks ++	None	Blocks +	None	None	None
Histamine release ^c	+	None	None	None	+	None	+
Evidence for critical illness polyneuromyopathy	n/a	+++	+++	+	+	+	n/a

Muscle Types and Their Responses to NMBAs

		ED 50	ED 90	Slope
		($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	($\mu\text{g}^{-1}\cdot\text{kg}^{-1}\cdot\text{min}$)
Pancuronium	Diaphragm	22 ± 2.8	38 ± 6.7	5.7 ± 1.2
	Tibialis anterior	9.4 ± 2.2*	16 ± 3.3*	7.4 ± 2.2*
Vecuronium	Diaphragm	71 ± 24 †	137 ± 51 †	5.1 ± 1.8
	Tibialis anterior	27 ± 5.9*†	36 ± 9.2*†	11 ± 4.3*
Rocuronium	Diaphragm	202 ± 70 †‡	362 ± 132 †‡	5.0 ± 0.6
	Tibialis anterior	88 ± 26*†‡	119 ± 35*†‡	11 ± 6.0*

- **Neuromuscular blocker** 사용을 안한다면?
- 대신 할 방법이 있을까?

Neuromuscular Blockade + Deep Sedation

Reduces self-inflicted lung injury in severe ARDS by eliminating vigorous inspiratory efforts and breath stacking

Improves oxygenation by preventing expiratory muscle activity ("anti-PEEP effect") and stabilizing alveolar recruitment

Lowers inflammatory cytokines (IL-1 β , IL-6, IL-8) compared to controls

Facilitates prone positioning, a key mortality-reducing intervention in severe ARDS⁴

Associated with survival benefit in **ACURASYS trial** (mortality HR 0.68 for PaO₂/FiO₂ <120)

Risks: Higher rates of cardiovascular events, ICU-acquired weakness

Spontaneous Breathing + Light Sedation

Preserves diaphragm function, reducing ventilator-induced diaphragmatic atrophy

Shortens ICU stay and increases ventilator-free days in mild-moderate ARDS

Reduces sedation-related complications (e.g., hypotension, delirium)

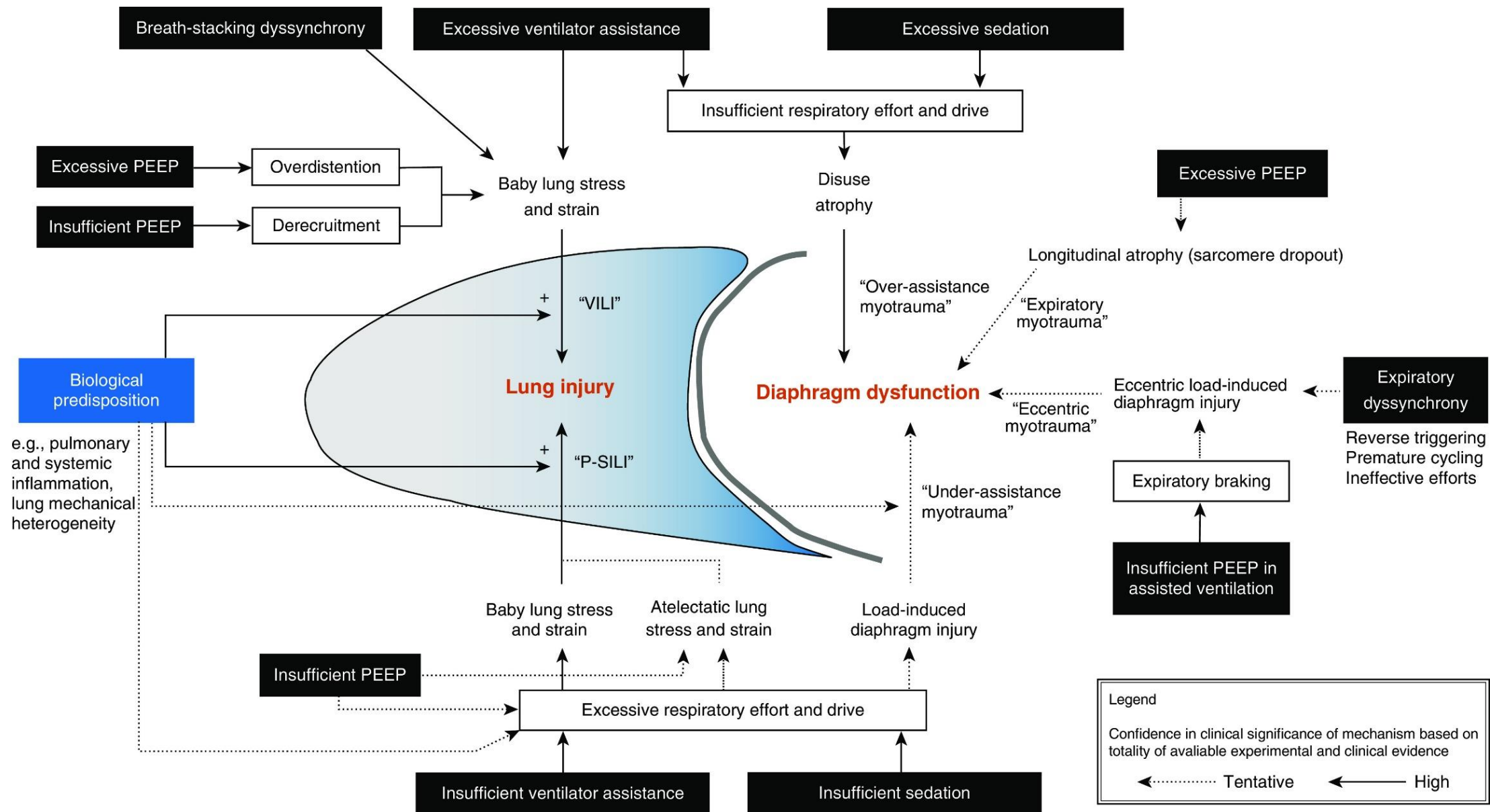
Improves hemodynamics by maintaining negative intrathoracic pressure

No mortality difference vs. NMBA in **ROSE trial** for moderate-severe ARDS

Risks: May worsen lung injury via pendelluft phenomena and excessive transpulmonary pressures in severe ARD

Spontaneous breathing in ARDS


Risk	Benefit
Worsens lung injury in severe ARDS through increased transpulmonary pressure swings	Prevents diaphragmatic atrophy by maintaining muscle activity, aiding weaning
Induces pulmonary edema via increased transmural vascular pressure	Improves ventilation-perfusion matching by recruiting dependent lung regions
Causes barotrauma (e.g., pneumomediastinum) from uncontrolled tidal volumes	Reduces sedation needs and preserves respiratory muscle function
Leads to rapid shallow breathing in early severe ARDS, increasing self-inflicted injury	Enhances oxygenation through better lung aeration, particularly in mild ARDS
Triggers patient-ventilator asynchronies (e.g., double triggering, reverse triggering)	Improves hemodynamics by increasing preload and reducing intrathoracic pressure
Elevates driving pressure due to pendelluft effects, worsening regional lung stress	Shortens ICU stay in mild-moderate ARDS when combined with pressure support



NARRATIVE REVIEW

Clinical strategies for implementing lung and diaphragm-protective ventilation: avoiding insufficient and excessive effort



Ewan C. Goligher^{1,2,3}, Annemijn H. Jonkman^{4,5}, Jose Dianti^{1,2}, Katerina Vaporidi⁶, Jeremy R. Beitler⁷, Bhakti K. Patel⁸, Takeshi Yoshida⁹, Samir Jaber¹⁰, Martin Dres^{11,12}, Tommaso Mauri^{13,14}, Giacomo Bellani¹⁵, Alexandre Demoule^{11,12}, Laurent Brochard^{1,5} and Leo Heunks^{4*} 

REVIEW



Advances in achieving lung and diaphragm-protective ventilation

Maarten J.W. van den Berg, Leo Heunks and Jonne Doorduyn

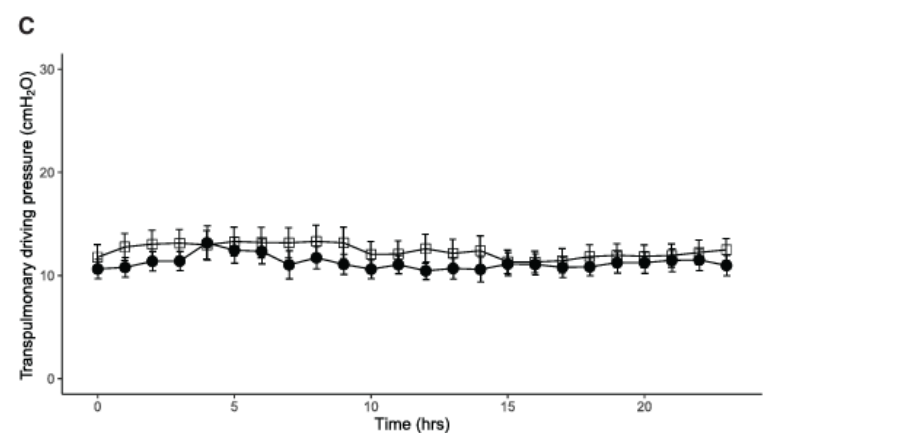
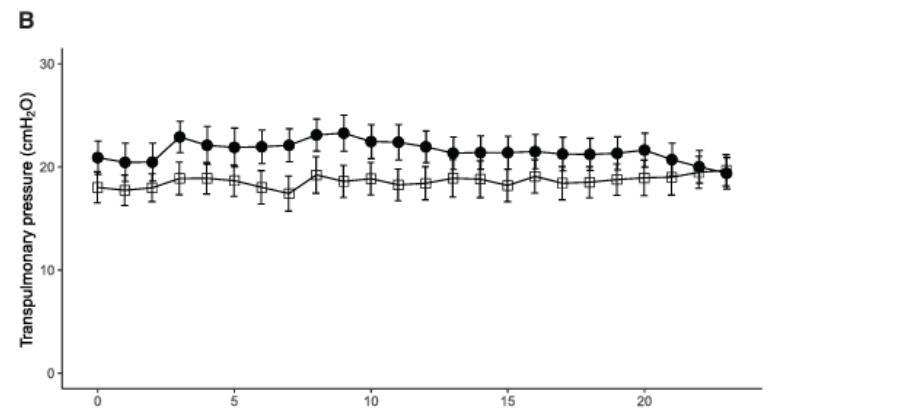
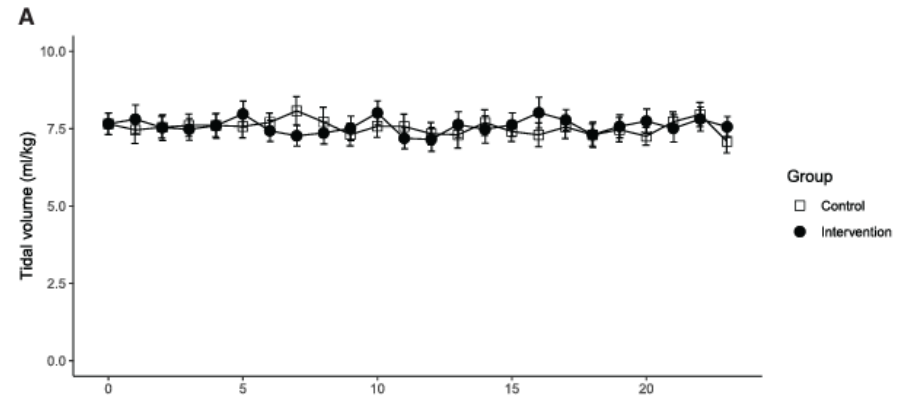
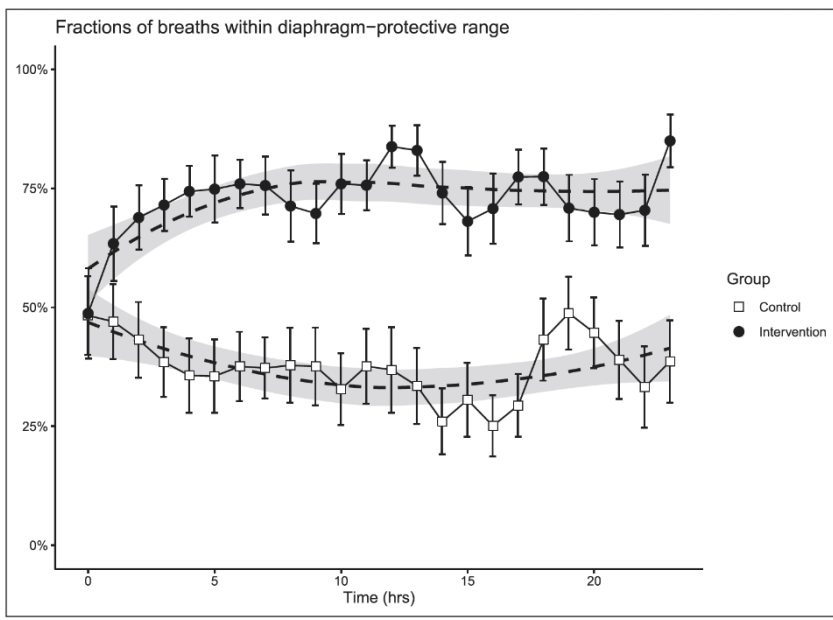
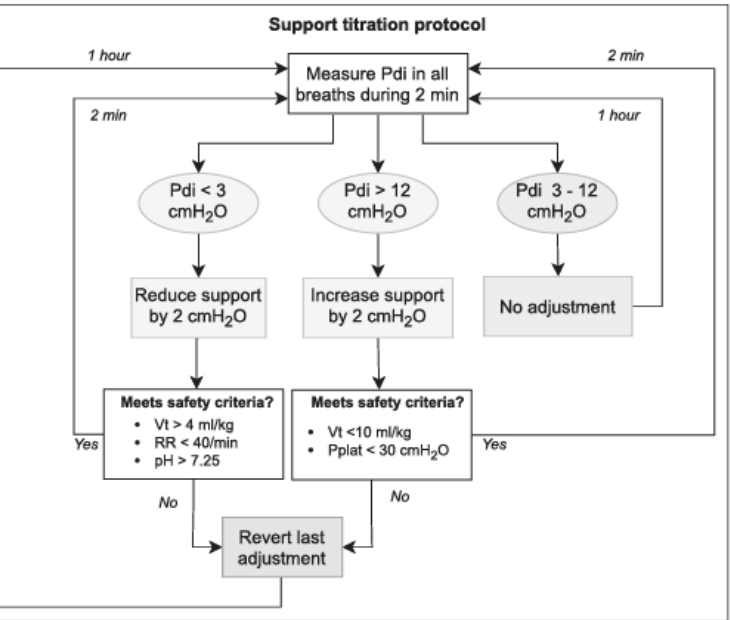
**CRITICAL CARE PERSPECTIVE**

Lung- and Diaphragm-Protective Ventilation

Ewan C. Goligher^{1,2,3}, Martin Dres^{4,5}, Bhakti K. Patel⁶, Sarina K. Sahetya⁷, Jeremy R. Beitler⁸, Irene Talias^{1,2,9}, Takeshi Yoshida¹⁰, Katerina Vaporidi¹¹, Domenico Luca Grieco^{12,13}, Tom Schepens¹⁴, Giacomo Grasselli^{15,16}, Savino Spadaro¹⁷, Jose Dianti^{1,2,18}, Marcelo Amato¹⁹, Giacomo Bellani²⁰, Alexandre Demoule^{4,5}, Eddy Fan^{1,2,3,21}, Niall D. Ferguson^{1,2,3,21,22}, Dimitrios Georgopoulos¹¹, Claude Guérin²³, Robinder G. Khemani^{24,25}, Franco Laghi^{26,27}, Alain Mercat²⁸, Francesco Mojoli²⁹, Coen A. C. Ottenheijm³⁰, Samir Jaber³¹, Leo Heunks^{32*}, Jordi Mancebo^{33*}, Tommaso Mauri^{13,14}, Antonio Pesenti^{13,14}, and Laurent Brochard^{1,9*}; for the Pleural Pressure Working Group, Acute Respiratory Failure Section of the European Society of Intensive Care Medicine

OPEN

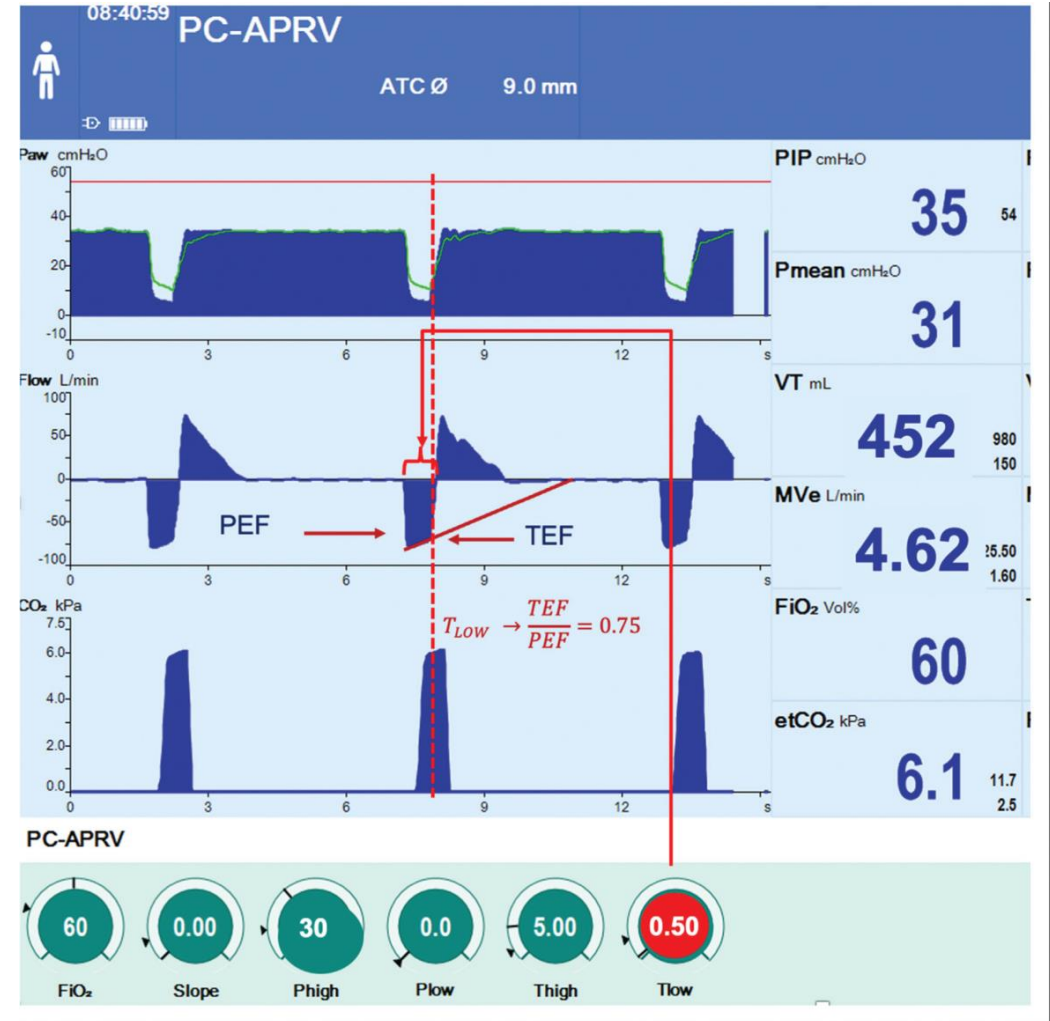
Lung- and Diaphragm-Protective Ventilation by Titrating Inspiratory Support to Diaphragm Effort: A Randomized Clinical Trial



Airway pressure release ventilation for lung protection in acute respiratory distress syndrome: an alternative way to recruit the lungs

Camporota, Luigi^{a,b}; Rose, Louise^{a,c}; Andrews, Penny L.^d; Nieman, Gary F.^e; Habashi, Nader M.^d

- Loss of surfactant function with acute lung injury causes regional alveolar instability (repetitive alveolar collapse and expansion – RACE) and overdistension-induced stress-multipliers, which are the mechanisms of VILI at the alveolar level.
- Surfactant dysfunction causes the lungs to become time-dependent and pressure-dependent.
- Airway pressure release ventilation using the TCAV method, based on this pathophysiologic knowledge, adjusts inspiratory and expiratory time to first stabilize and then gradually reopen collapsed lung units, counteracting the main drivers of VILI.
- The TCAV method is a paradigm shift in protective lung ventilation, that is, from the current low V_T to protect the ‘baby lung’ from overdistension approach, and the open lung approach, to a novel Stabilize the Lung Approach.

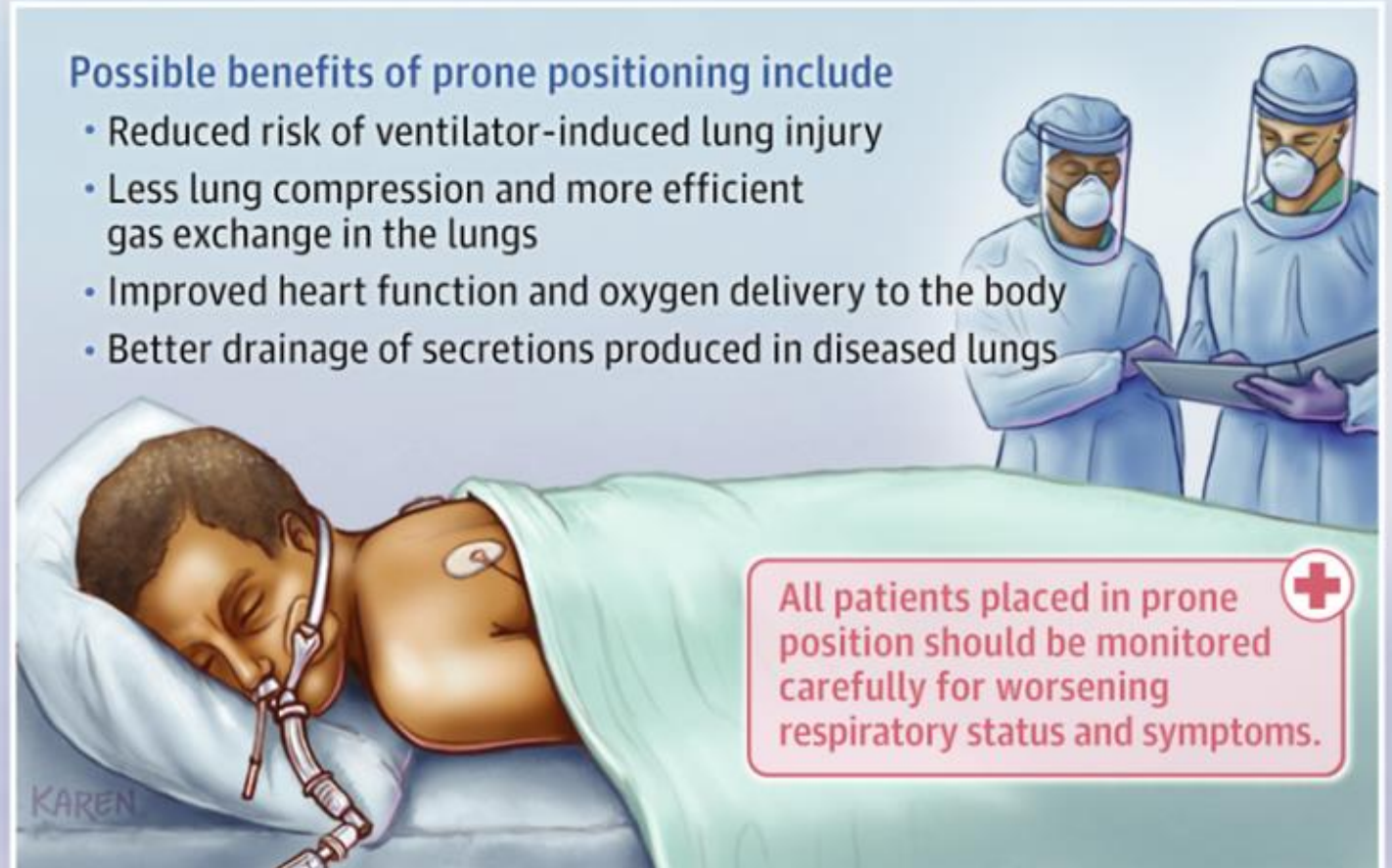


APRV is a pressure-controlled and time-cycled mode, in which spontaneous breathing can (although does not have to) occur throughout the breathing cycle

Prone positioning is the technique of placing patients with breathing difficulties on their stomach to help them breathe better. Prone positioning is generally reserved for sedated patients who require a breathing machine, known as a ventilator, but it may be beneficial for awake patients with COVID-19.

Possible benefits of prone positioning include

- Reduced risk of ventilator-induced lung injury
- Less lung compression and more efficient gas exchange in the lungs
- Improved heart function and oxygen delivery to the body
- Better drainage of secretions produced in diseased lungs

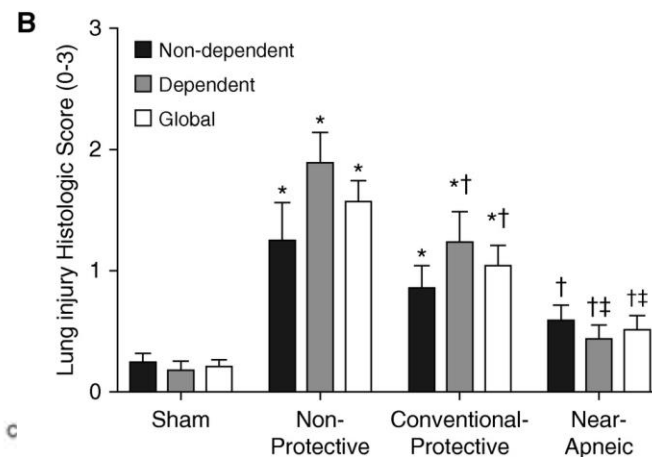
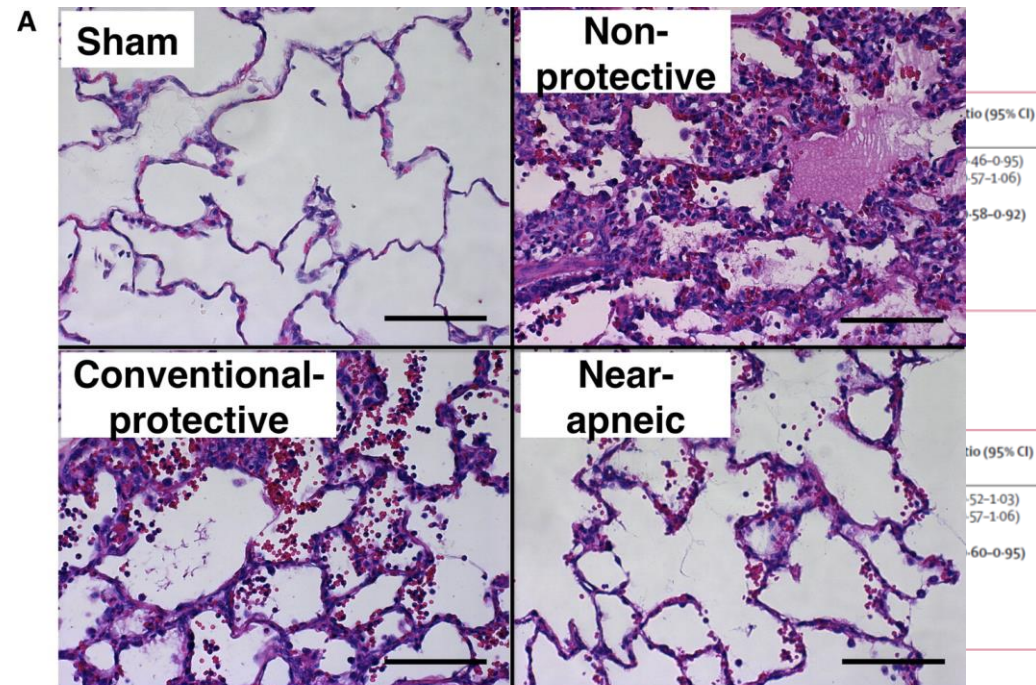


Prone Positioning in Severe Acute Respiratory Distress Syndrome (PROSEVA)

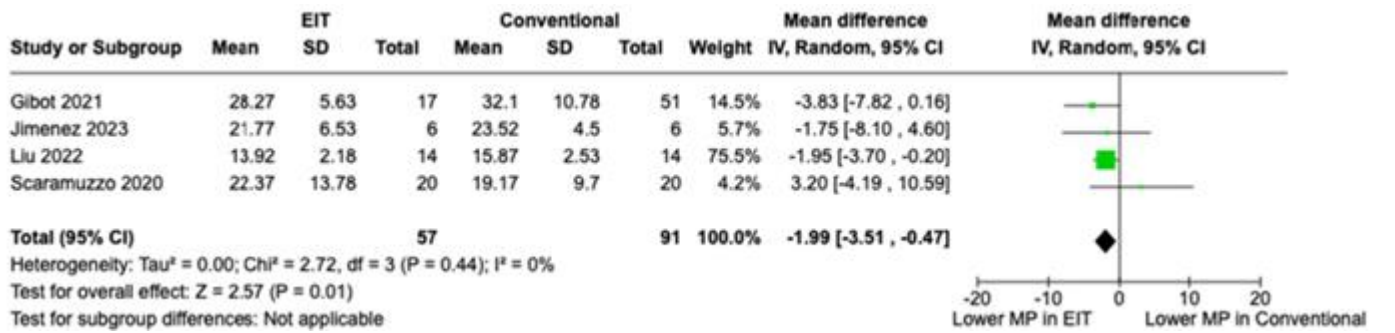
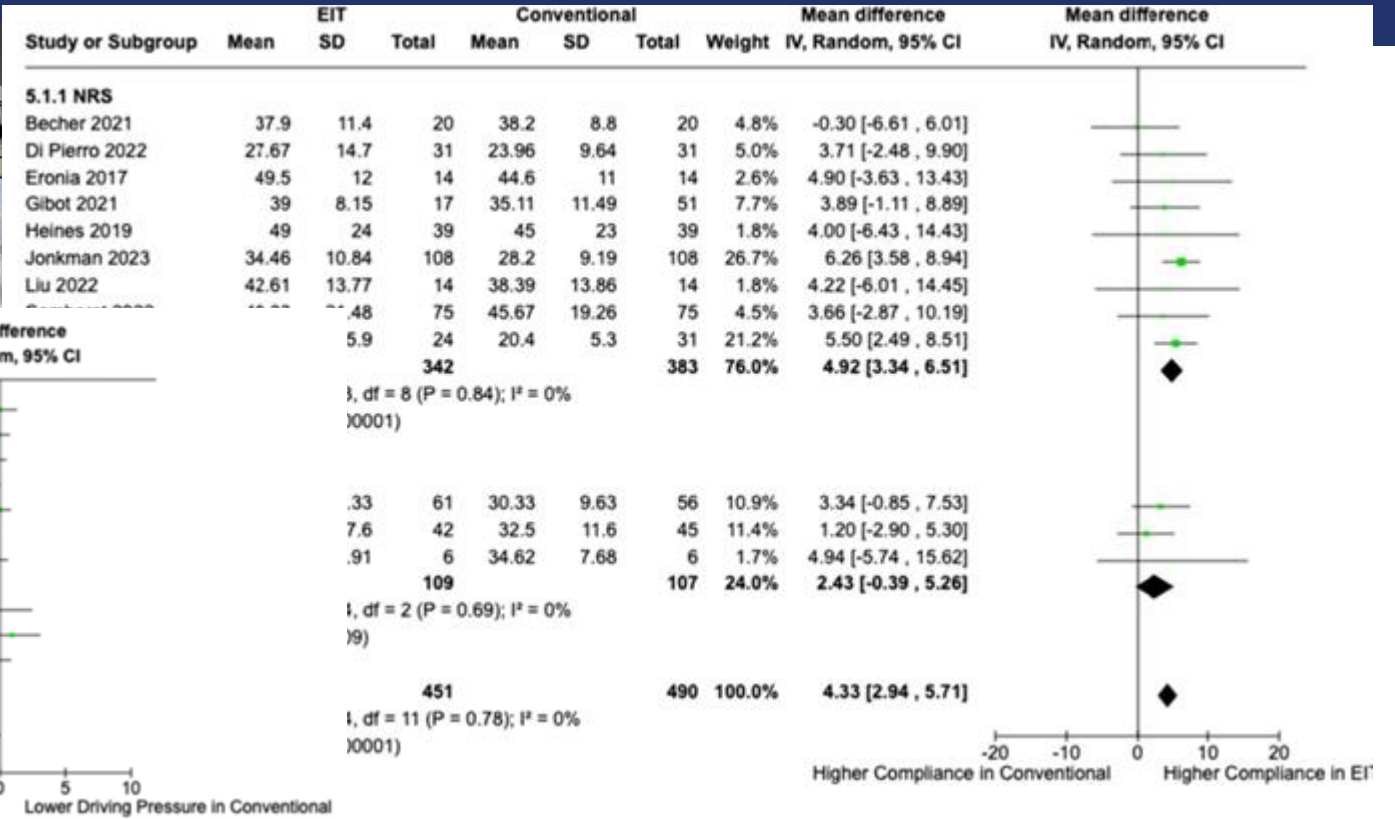
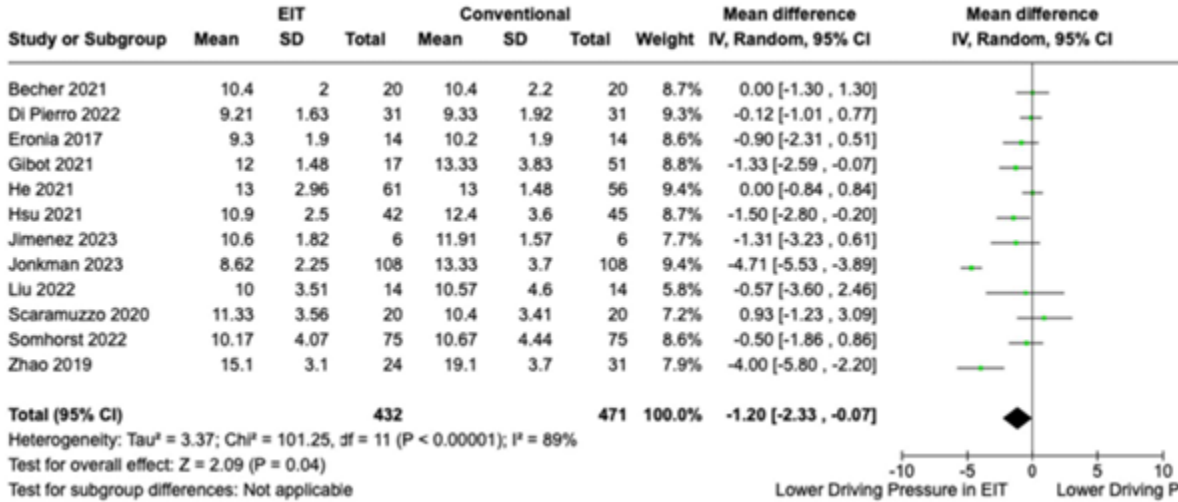
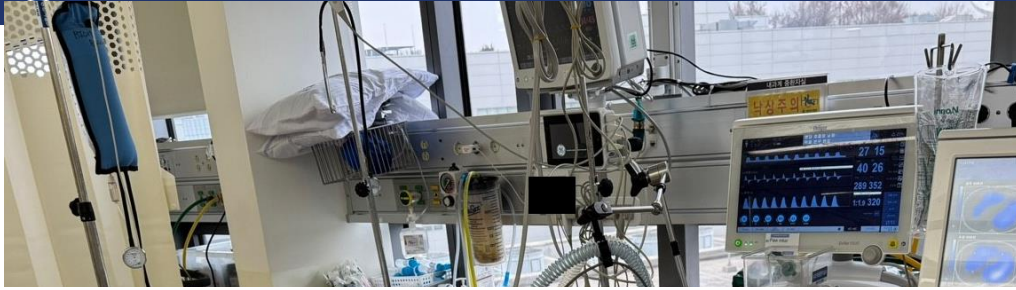
-16.8% lower 28 day mortality (primary outcome) and 17.4% lower 90 day mortality (secondary outcome) in intervention arm



Extracorp



c

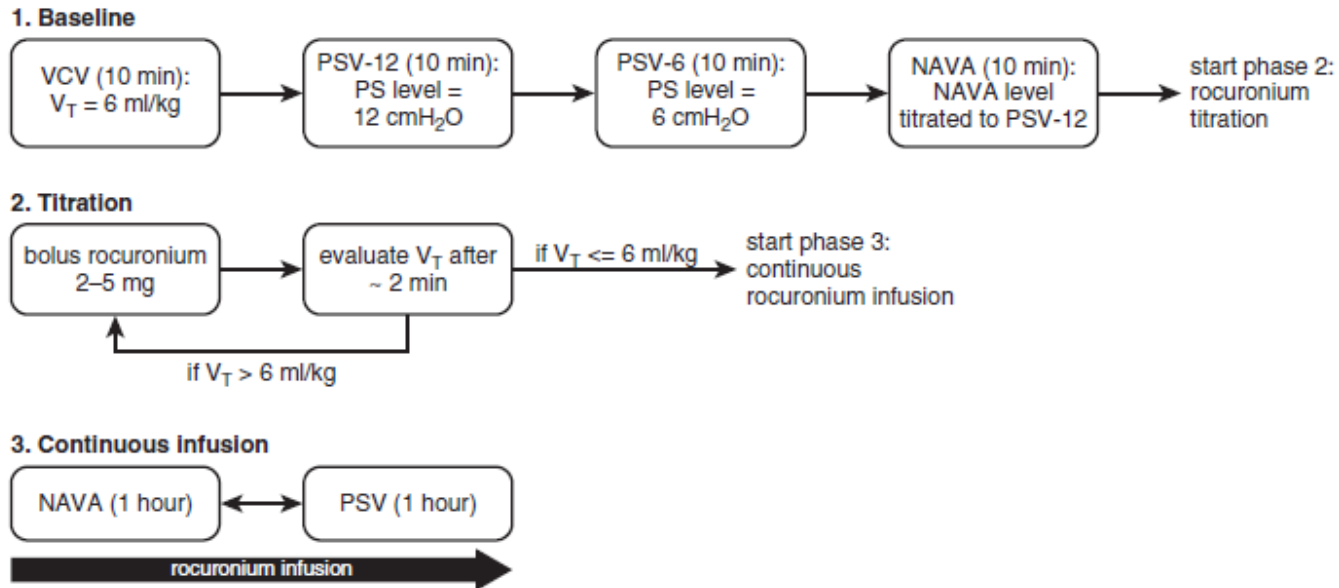


Optimal PEEP

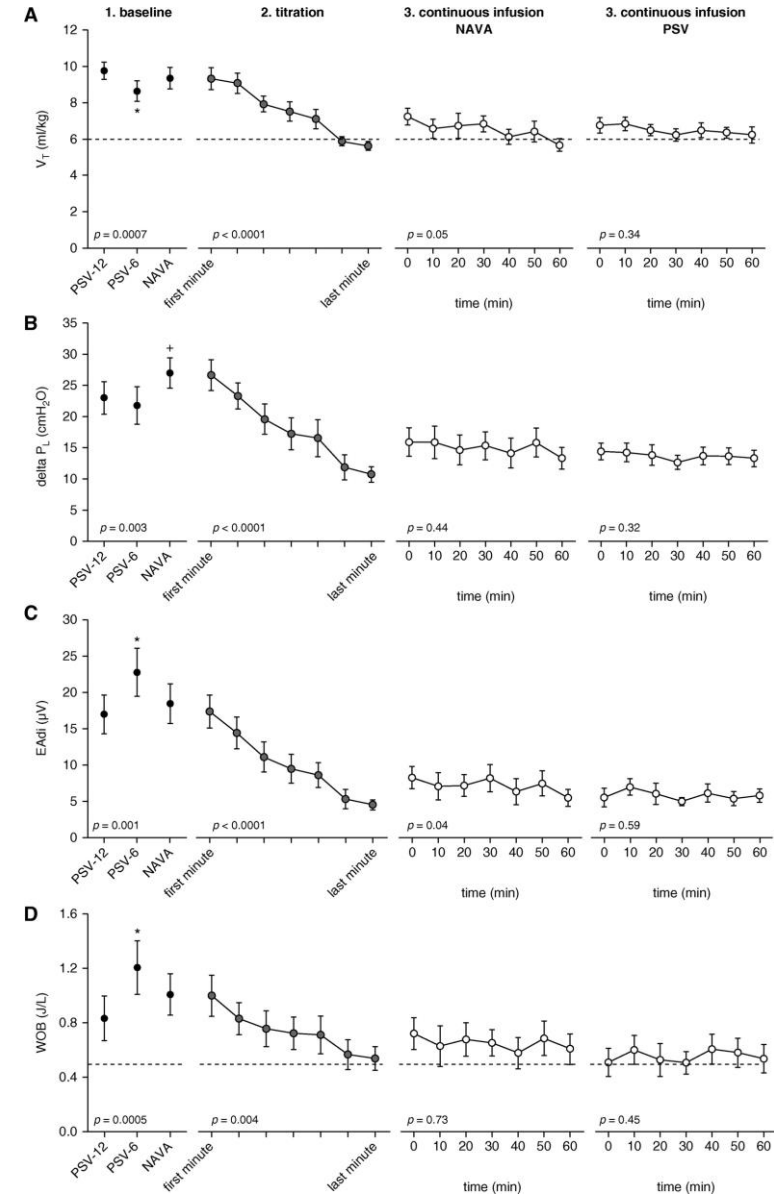
ORIGINAL ARTICLE

Partial Neuromuscular Blockade during Partial Ventilatory Support in Sedated Patients with High Tidal Volumes

Jonne Doorduyn¹, Joeke L. Nollet¹, Lisanne H. Roesthuis¹, Hieronymus W. H. van Hees², Laurent J. Brochard^{3,4}, Christer A. Sinderby^{3,4}, Johannes G. van der Hoeven¹, and Leo M. A. Heunks¹



partial neuromuscular blockade is an interesting compromise between total paralysis and strenuous breathing efforts, particularly when respiratory effort does inadequately respond to titration of ventilatory support or sedation.



Effects of extracorporeal CO₂ removal (ECCO₂R) on gas exchange and ventilator settings: A systematic review and meta-analysis

What is the impact of contemporary ECCO₂R systems on gas exchange and respiratory settings in critically ill adults with respiratory failure?

Primary outcomes: Changes in gas exchange and ventilator settings 24 hours after ECCO₂R initiation

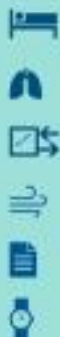
Outcome metrics: pH, PaCO₂, Tidal vol., Peak insp. pressure or PPlat, RR, PaO₂/FIO₂ ratio, PEEP

RCT's: Duration of ventilation, Length of stay (ICU, hospital), mortality (ICU, hospital, 60-day), health-related quality of life after 6m

Subgroups: Diagnoses, Lower- vs. Higher extraction ECCO₂R devices

Included

- Adults, in critical care or emergency setting
- ARDS, AECOPD, Bridge to LTX
- Undergoing ECCO₂R
- Invasive or non-invasive ventilation
- Observational studies (before/after comparison)
- RCT's
- January 2000 to March 2022



Data

49 studies included
 3 prospective open-label randomized studies
 28 retrospective observational studies
 18 prospective observational studies
 1672 ECCO₂R patients
 Median patients/study: 20 (7-186)



Used ECCO₂R extraction devices:



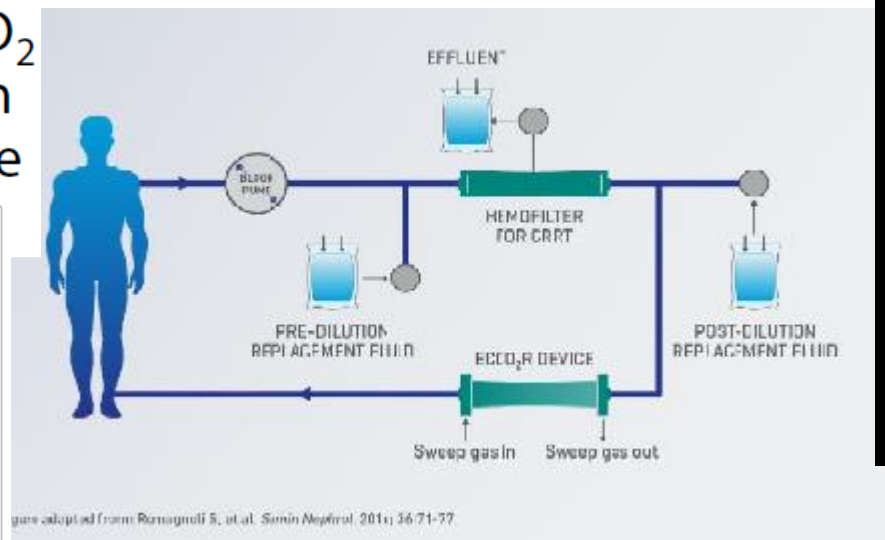
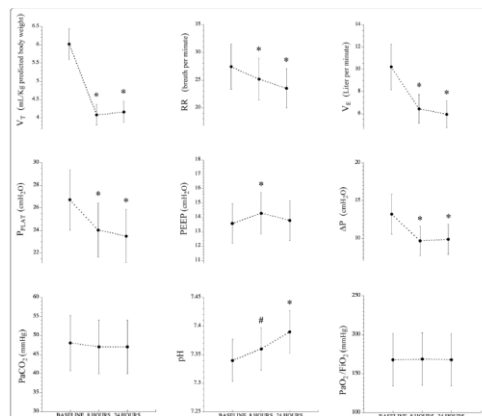
Results

- In all patient groups-ECCO₂R associated with significant decrease: acidosis, Tidal volume, PPlat, PaCO₂
- In ARDS and LTX patients increase: PaO₂/FIO₂ ratio
- Higher extraction devices reduced more efficiently: Resp. rate and PaCO₂
- 3 RCT's: ECCO₂R effect longer ICU and hospital stay no effect on mortality
- Robins-I: Only 4 studies: Low risk of bias Subgroup analysis: minimal bias impact on the parameters studied

-ECCO₂R effectively reduces PaCO₂ and acidosis allowing for less invasive ventilation. Higher-extraction devices may be more efficient.
 -RCT's have not shown any mortality benefit, ECCO₂R's effects on clinical outcome remain unclear.
 Future studies should target patient groups that may benefit from ECCO₂R.

SEVEN-DAY PROFILE PUBLICATION

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



Epithelial markers (principal source)

- Receptor for advanced glycation end products (alveolar epithelial type 1 cells)
- Surfactant protein D (alveolar epithelial type 2 cells)
- Club cell 16 (airway epithelial cells)

Endothelial markers (principal source)

- von Willebrand factor (endothelium and platelets)
- Angiopoietin 2 (endothelium and platelets)
- Intercellular adhesion molecule 1 (endothelium, epithelium and macrophages)
- Syndecan (endothelial glycocalyx)
- Endocan (endothelium)

Inflammatory markers (principal source)

- IL-6 (monocytes, macrophages, neutrophils and alveolar epithelium)
- IL-8 (monocytes, macrophages, endothelium and alveolar epithelium)
- Soluble tumour necrosis factor receptor 1 (alveolar epithelial type 1 and type 2 cells and macrophages)
- IL-1 β , IL-1 R antagonist (monocytes, macrophages and alveolar epithelium)
- Neutrophil extracellular traps (neutrophils)

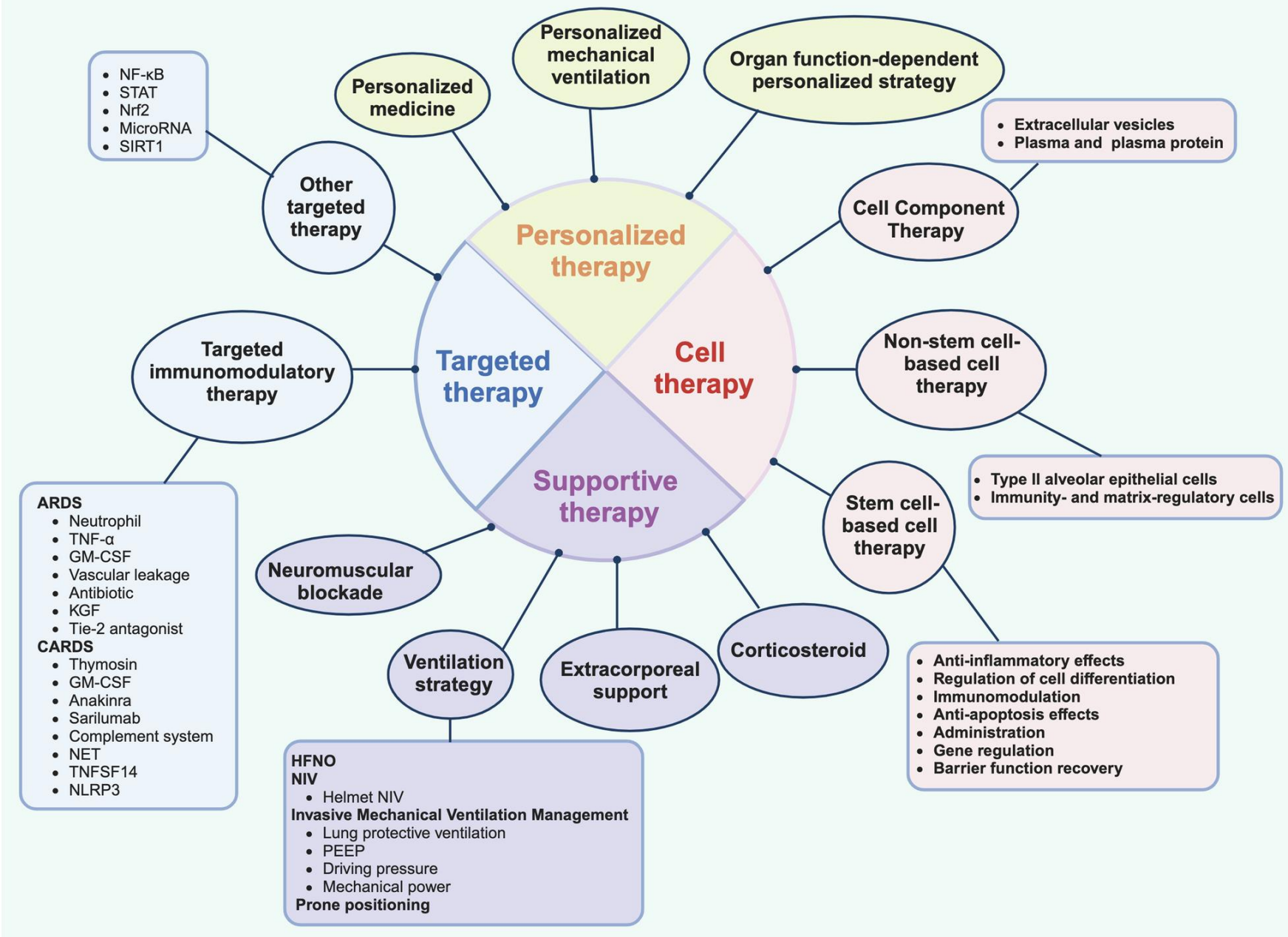
Coagulation and fibrinolysis markers (principal source)

- Protein C (plasma)
- Plasminogen activator inhibitor 1 (endothelium and macrophages)

Apoptosis markers (principal source)

- FAS and FasL (endothelium, alveolar epithelium and inflammatory cells)

- Corticosteroids.
- Cell therapy (MSC, alveolar type II cells, mononuclear cells, and immune and matrix regulatory cells)
- Target therapy



Con NMBA

Anaphylaxis

Risk of insufficient sedation and memorizing

➔ Lung atelectasis

➔ ICU-acquired weakness



Corticosteroids



Pro NMBA

➔ ARDS mortality

➔ Ventilator free days

➔ ICU free days

➔ Oxygenation

➔ Barotrauma

➔ Ventilator-induced lung injuries??

RDS

several strategies of ARDS

- Prone positioning
- Personalized mechanical ventilation
- ECMO
- Steroid and immunomodulatory therapy
- Etc.



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Thank you for attention !!!

