2025년도 제139차 춘계학술대회

Neuromuscular blocking agents in ARDS
Do they really work? – Pro

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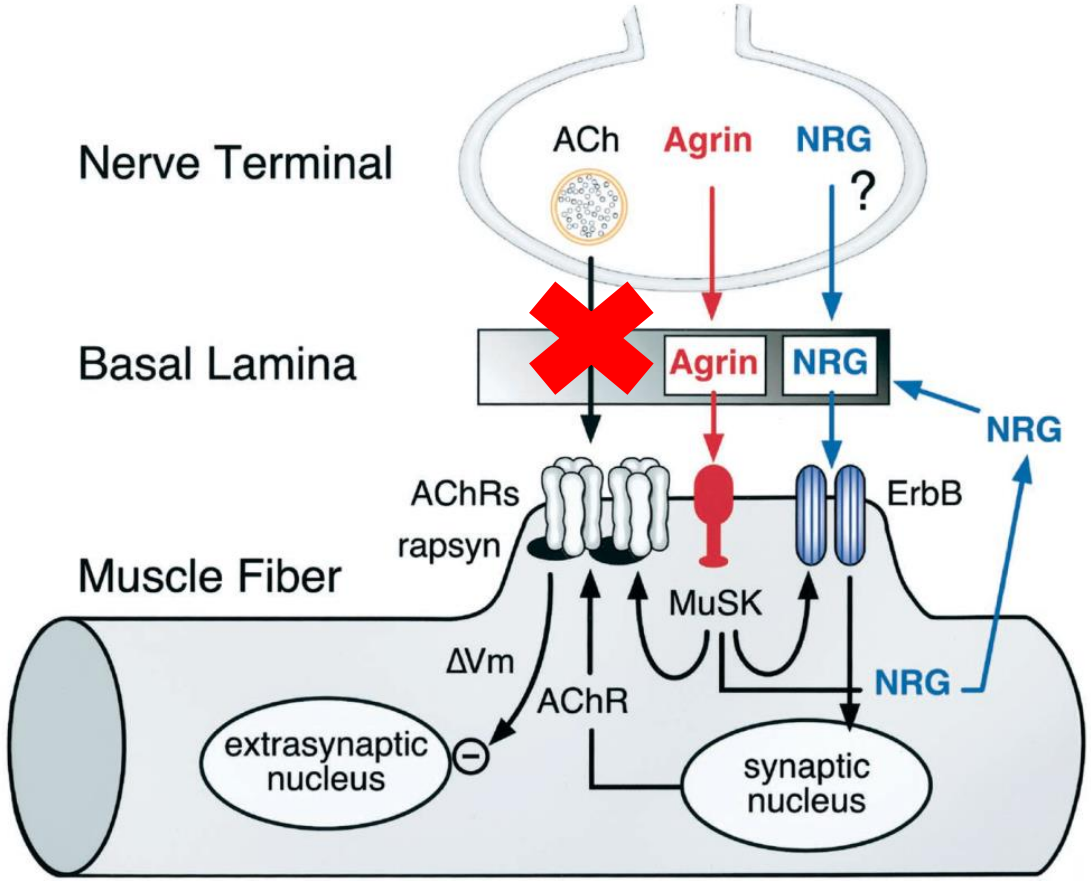
Disclosures

- The following presentation will NOT include discussion on any commercial products or service.
- I have no conflicts of interest with regard to the presentation.

Neuromuscular blocking agent (NMBA)



Anesthesiology 2002;96:202-31

Pharmacology of NMBA

- Depolarizing NMBA → bind and activate AChRs
  - Succinylcholine
  - Not used as continuous infusion

- Non-depolarizing NMBA → bind and competitively antagonize AChRs
  - Benzylisoquinolinium: atracurium, cisatracurium, mivacurium
    - Metabolized into inactive compounds by plasma esterases
    - Metabolism unrelated to renal of hepatic function
  - Amino steroidal compounds: rocuronium, vecuronium, pancuronium
    - Metabolized into active metabolites
    - Renal or liver failure → risk of accumulation

Pharmacology of NMBA

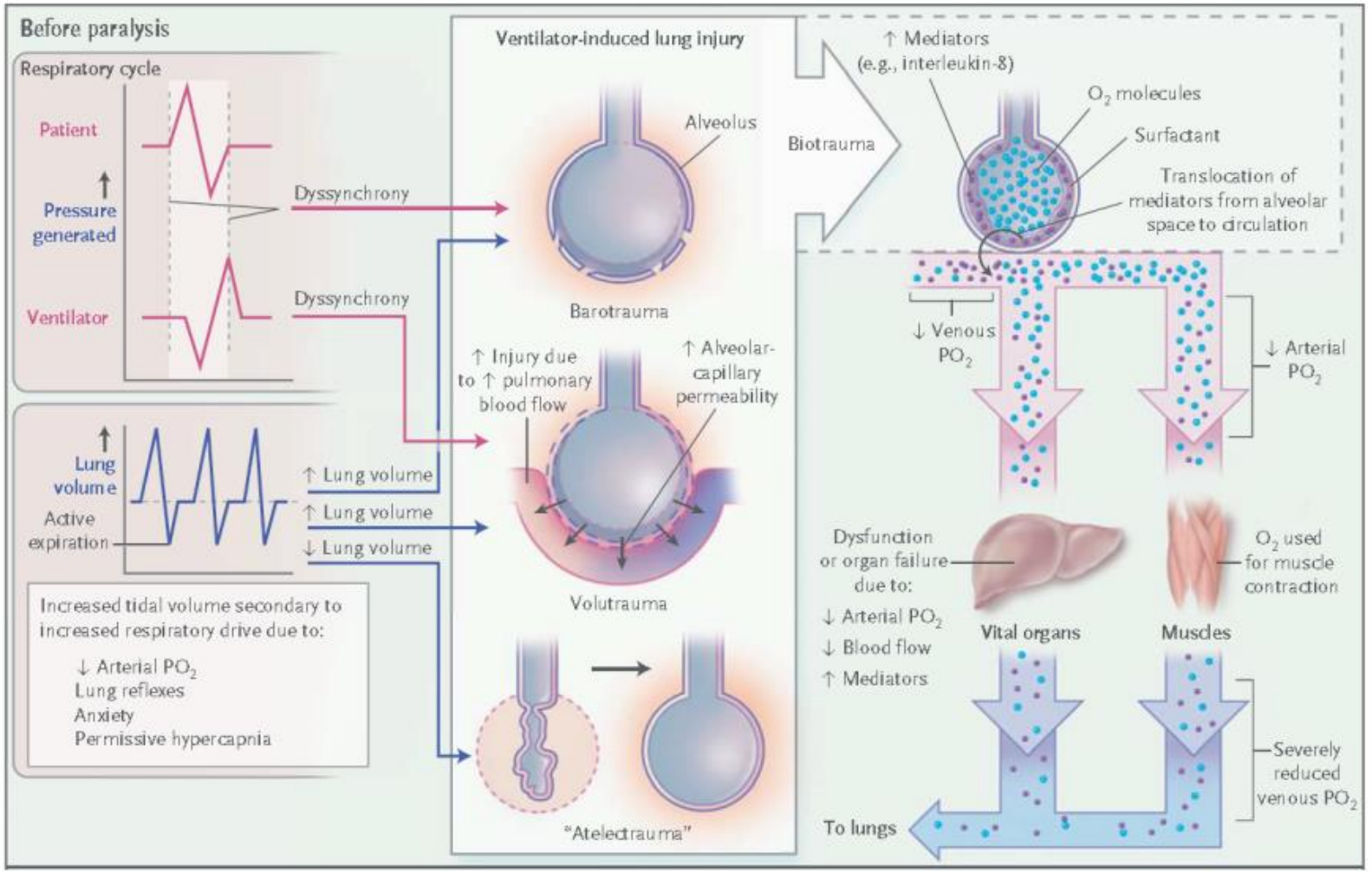
Agent	ED95/ Intubating dose (mg/kg)	Onset time (min)	Infusion dose (μg/kg/min)	Duration of action	Elimination
Succinylcholine	0.5–0.6/1–1.2	0.5–1 s	NF	10–12 min	Metabolized by plasma cholinesterase. No active metabolite
Rocuronium	0.3/0.6 (1.2 for rapid sequence induction)	1.5–3 (1 for rapide induction dose)	5–12	20–70 min	Eliminated by the liver (90%) and kidneys (10%). No active metabolite
Pancuronium	0.07/0.1	3–5	0.8–1.7	20–40 min	Eliminated by the liver (15%) and kidneys (85%). Active metabolite = 3-OH-pancuronium, accumulating in case of renal failure
Vecuronium	0.05/0.08–0.1	3–5	0.8–1.7	20–40 min	Eliminated by the liver (60%) and kidneys (40%). Active metabolite = 3-desacetyl-Vecuronium, accumulating in case of renal failure
Cisatracurium	0.05–0.07/0.15	4–7	1–3	35–50 min	Hofmann elimination. No active metabolite
Atracurium	0.25/0.5	3–5	10–20	30–45 min	Metabolized by plasma esterase and Hofmann elimination. Metabolite = laudanosine, possible neurologic toxicity at high continuous doses)
Mivacurium	0.08/0.25	2–3	5–6	12–20 min	Metabolized by plasma cholinesterase. No active metabolite

ED95 effective dose 95%: the amount of NMBA required to reduce twitch height by 95%. *NF* not feasible

Pathophysiology of NMBA in ARDS

- Reduction of patient-ventilator asynchrony
- Decrease in oxygen consumption
- Increased thoraco-pulmonary compliance and functional residual capacity
- Better regional distribution of tidal volume
- Anti-inflammatory effects

Reduction of patient-ventilator asynchrony



N Engl J Med 2010;363:1176-80

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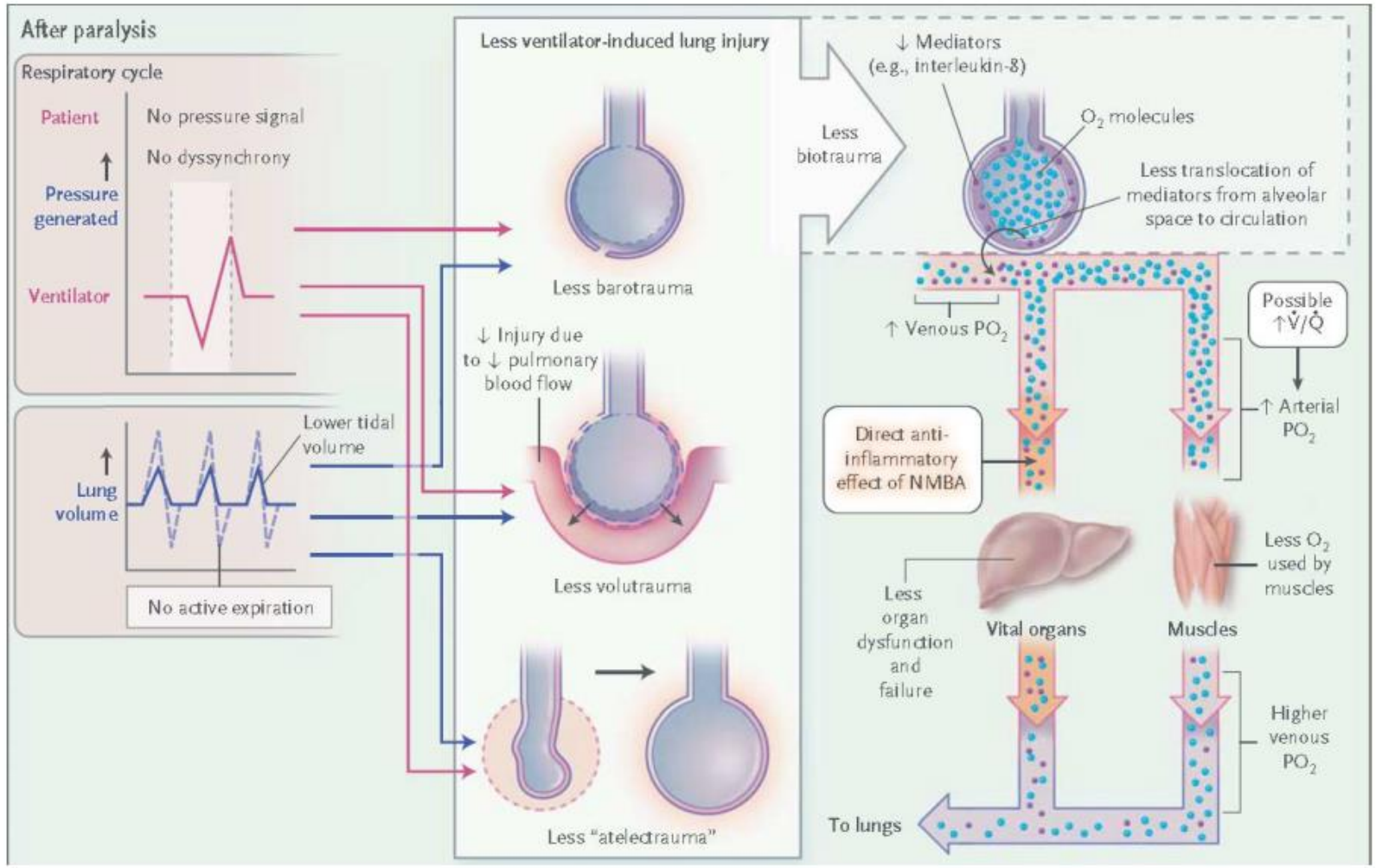
Reduction of patient-ventilator asynchrony



N Engl J Med 2010;363:1176-80

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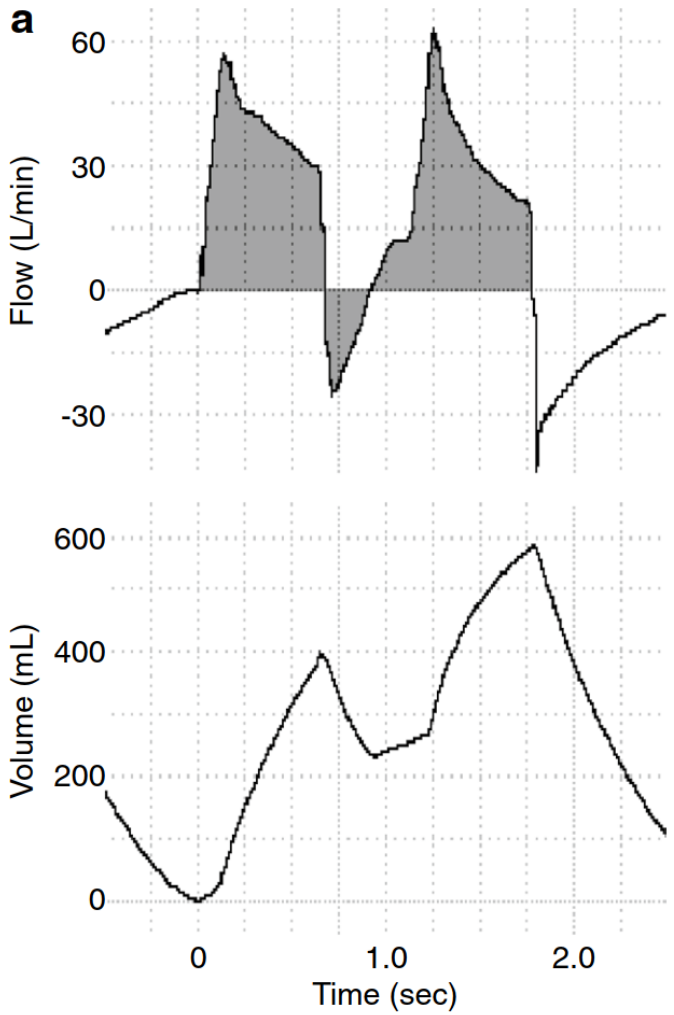
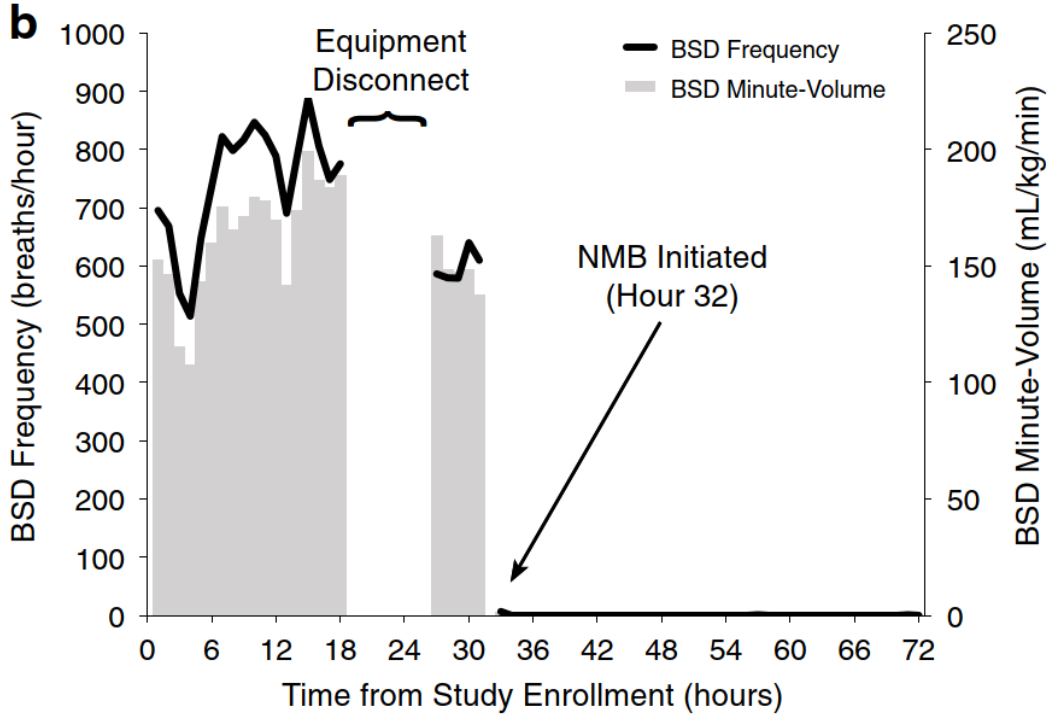
Reduction of patient-ventilator asynchrony



Breath stacking dyssynchrony



Intensive Care Med 2016;42:1427-36

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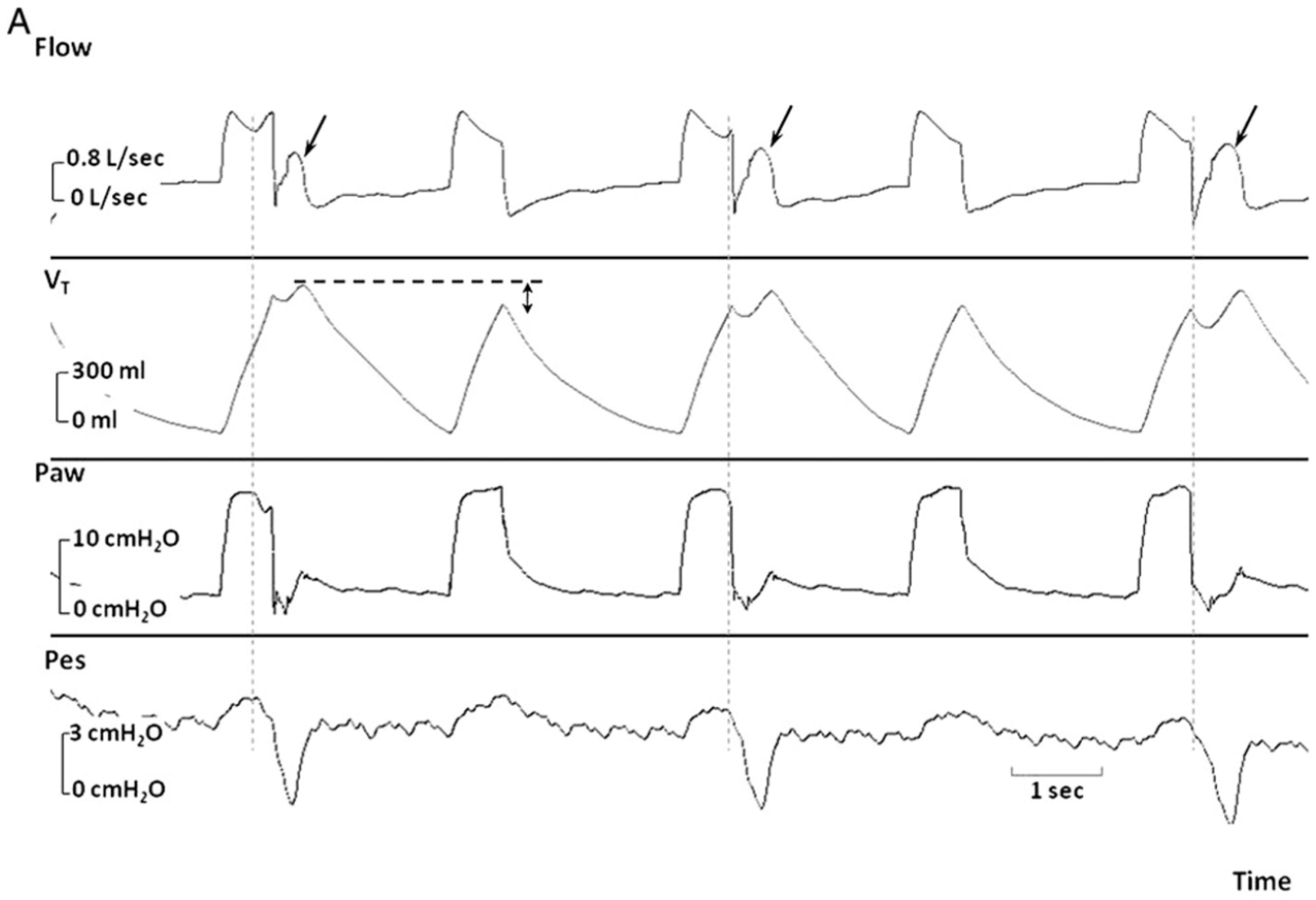
Reduction of patient-ventilator asynchrony

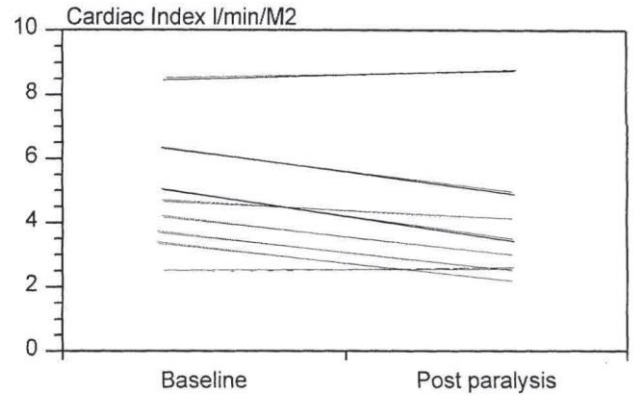
Reverse triggering

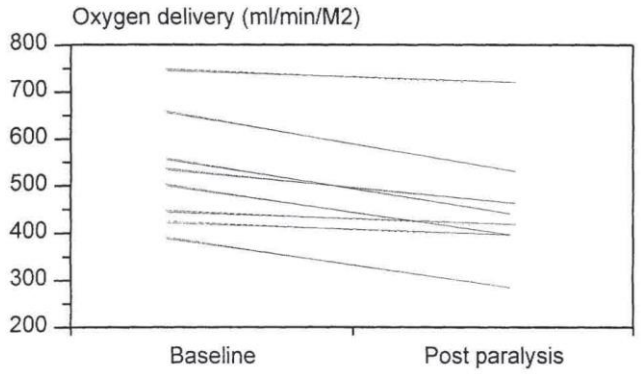


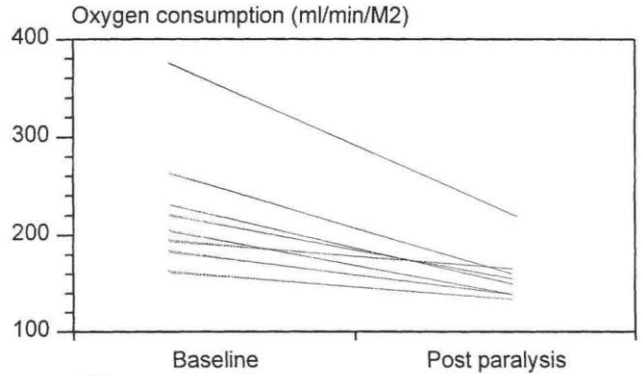
Chest 2013;143:927-38

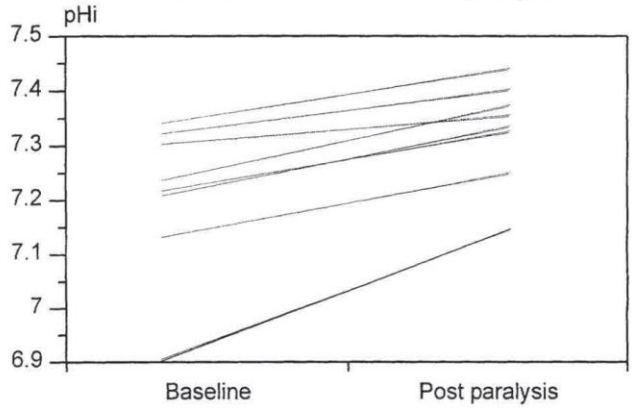
Decrease in oxygen consumption

- Mainly by eliminating muscular activity and improving systemic oxygenation
- Reduce respiratory demand and cardiac output → increase in SvO_2 and PaO_2









Chest 1996;109:1038-42

Increased thoraco-pulmonary compliance

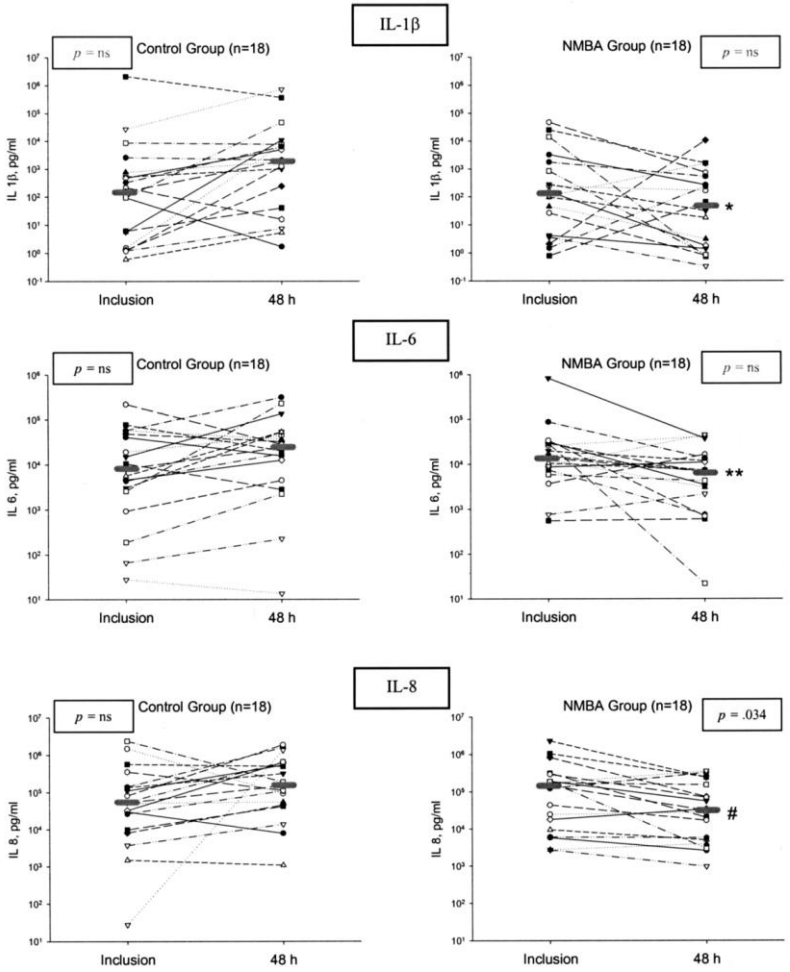
- PEEP maintenance + lower atelectasis in dependent regions of lungs
  → decrease in intra-pulmonary shunt

- Improve mechanical viscoelastic properties of chest wall

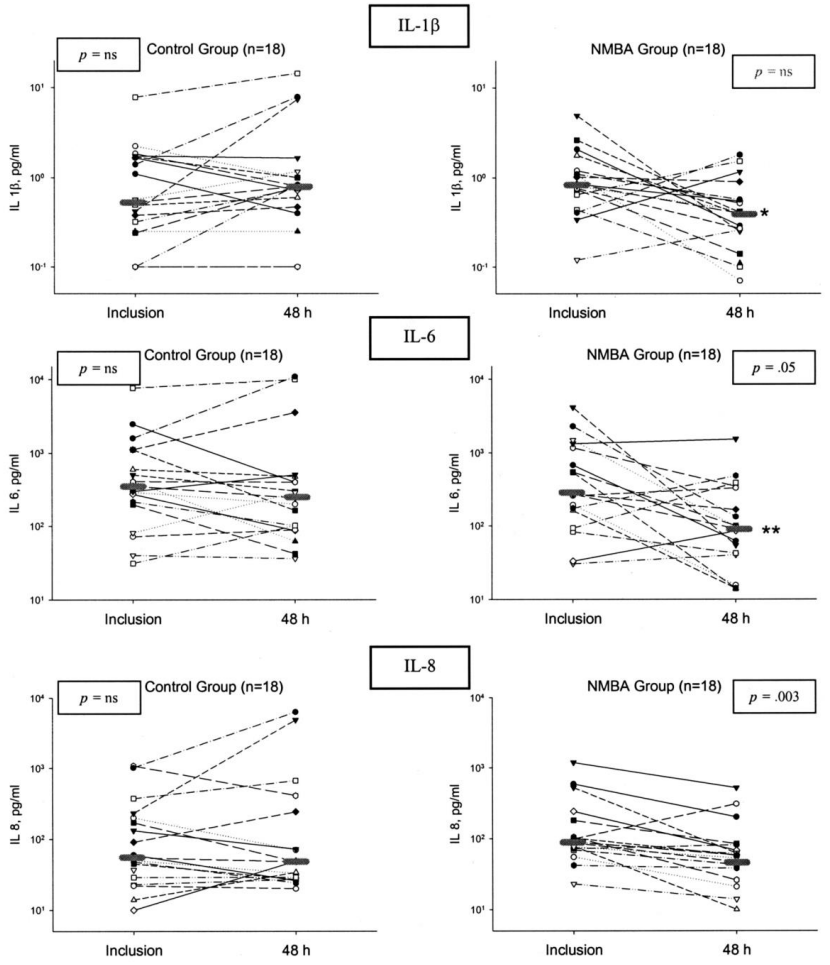
- Application of lower pulmonary pressure → more uniform distribution of lung perfusion → improved ventilation-perfusion ratio

Anti-inflammatory effects

Pulmonary epithelial lining fluid



Blood serum



Crit Care Med 2006;34:2749-57

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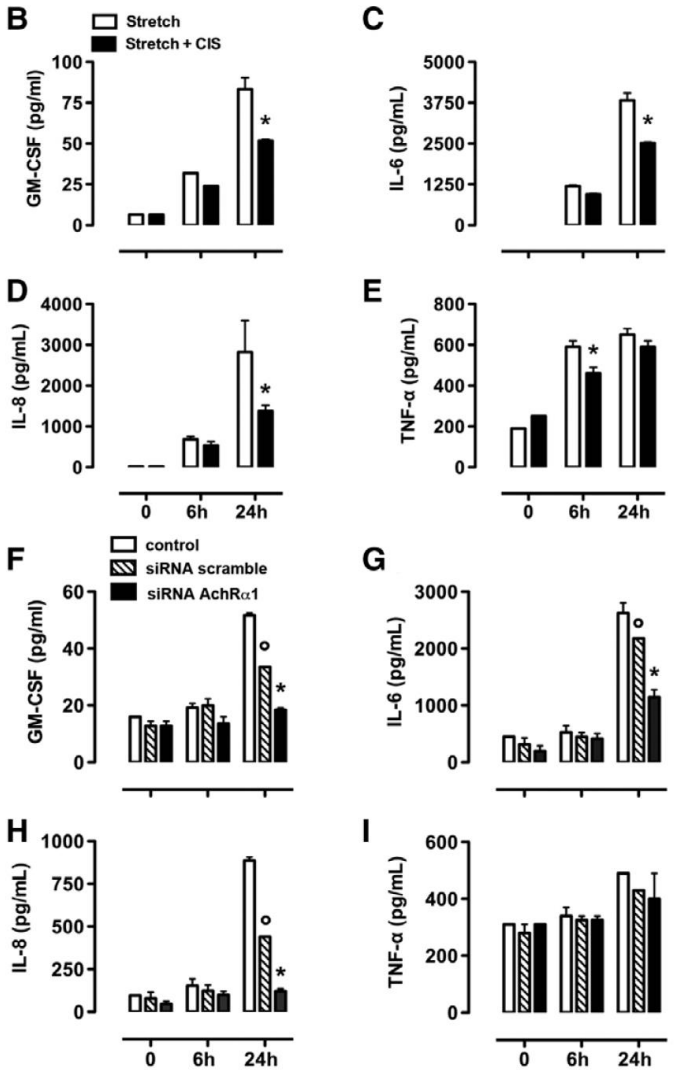
Anti-inflammatory effects



Anesthesiology 2016;124:132-40

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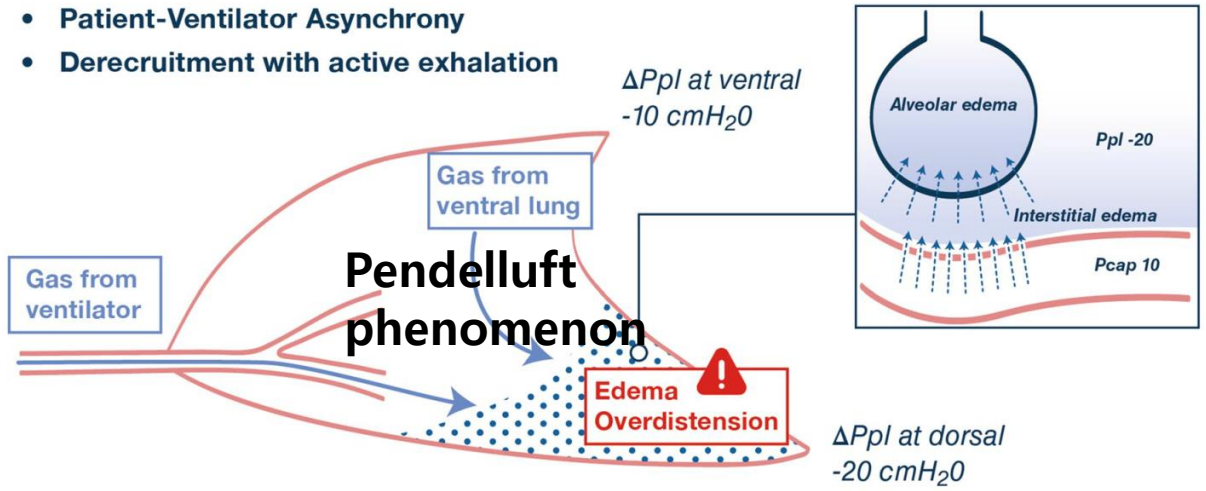
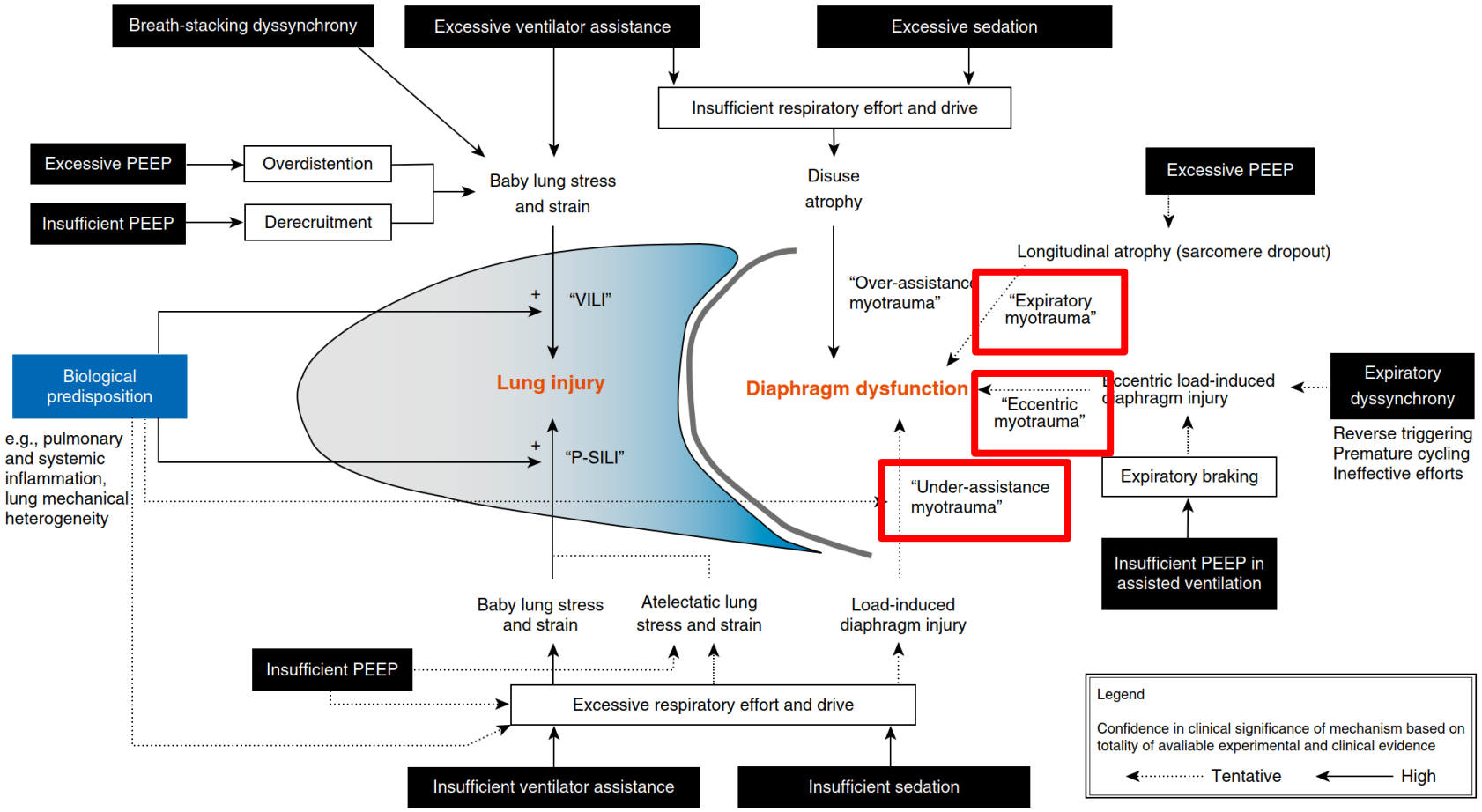
Patient self-inflicted lung injury (P-SILI)

Vigorous Spontaneous Effort Causes...

- Global Overdistension
- Maldistribution of Lung stress and Local Overdistension
- Increased Lung Perfusion and Lung Edema
- Patient-Ventilator Asynchrony
- Derecruitment with active exhalation



Load-induced diaphragm injury



Am J Respir Crit Care Med 2020;202:950-61

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NMBA and safety concerns

- ICU-acquired weakness
- Ventilator-associated pneumonia
- Pressure and corneal ulcers

ICU-acquired weakness

- Non-depolarizing NMBA may cause prolonged muscular weakness
- Risk is higher in pts with hepatic or renal dysfunction
- Long-term drug infusion and concomitant use of aminoglycosides or corticosteroids
  → decreased plasma clearance of NMBA
- Notable exception is **cisatracurium**: Hofmann elimination and different chemical structure
- More likely to occur with high dose of corticosteroids and prolonged administration of non-depolarizing, long-acting NMBA

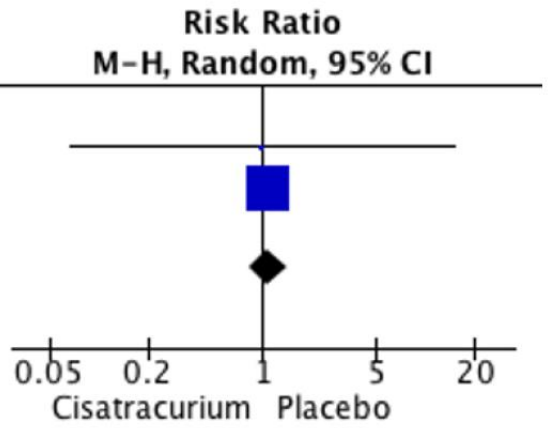
ICU-acquired weakness

Physicians are more likely to use short courses of short-acting NMBA and a low dose of corticosteroids → less likely to result in significant muscle weakness

	Cisatracurium		Placebo			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Gainnier 2004	0	28	0	28		Not estimable	2004
Forel 2006	1	18	1	18	1.0%	1.00 [0.07, 14.79]	2006
Papazian 2010	72	177	61	162	99.0%	1.08 [0.83, 1.41]	2010
Total (95% CI)		**223**		**208**	**100.0%**	**1.08 [0.83, 1.41]**	
Total events	73		62				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.96); $I^2 = 0\%$

Test for overall effect: Z = 0.57 (P = 0.57)



Crit Care 2013;17:R43

Ventilator-associated pneumonia

Ventilator-associated pneumonia and ICU mortality in severe ARDS patients ventilated according to a lung-protective strategy

Jean-Marie Forel[1], François Voillet[1], Daniel Pulina[1], Arnaud Gacouin[2], Gilles Perrin[3], Karine Barrau[4], Samir Jaber[5], Jean-Michel Arnal[6], Mohamed Fathallah[7], Pascal Auquier[4], Antoine Roch[1], Elie Azoulay[8] and Laurent Papazian[1*]

Table 6 Risk factors associated with the occurrence of bacterial VAP

	Hazard ratio	95% confidence interval for hazard ratio		*P*
		Lower	Upper	
Male sex	2.39	1.39	4.14	0.002
SAPS II on inclusion	0.99	0.97	1.00	0.14
Glasgow Coma Scale score on admission	0.93	0.88	0.98	0.01
PaO_2:FIO_2 on inclusion	0.99	0.99	1.00	0.54
Respiratory system compliance on inclusion	0.98	0.96	1.01	0.15
Received NMBA for 48 hours	1.03	0.69	1.54	0.88
Emergency reintubation	1.14	0.67	1.92	0.63
Tracheostomy	0.45	0.27	0.74	0.001
Transport out of the ICU	1.07	0.69	1.64	0.77
Enteral nutrition	0.56	0.33	0.97	0.04
Subglottic secretion drainage	0.52	0.27	0.99	0.05

Hazard ratios are for ventilator-associated pneumonia (VAP) versus no VAP by using the multistate model. NMBA, neuromuscular blocking agent.

Crit Care 2012;16:R65

Pressure and corneal ulcers

Prevalence, associated factors and outcomes of pressure injuries in adult intensive care unit patients: the DecubICUs study

Sonia O. Labeau[1,2], Elsa Afonso[2,3], Julie Benbenishty[4], Bronagh Blackwood[5], Carole Boulanger[6], Stephen J. Brett[7], Silvia Calvino-Gunther[8], Wendy Chaboyer[9], Fiona Coyer[11,12], Mieke Deschepper[13], Guy François[14], Patrick M. Honore[15], Radmilo Jankovic[16], Ashish K. Khanna[17,18], Mireia Llaurado-Serra[19], Frances Lin[9,10], Louise Rose[20,21,22,23], Francesca Rubulotta[7], Leif Saager[24,25], Ged Williams[26,27], Stijn I. Blot[1,2*], on behalf of the DecubICUs Study Team and the European Society of Intensive Care Medicine (ESICM) Trials Group Collaborators

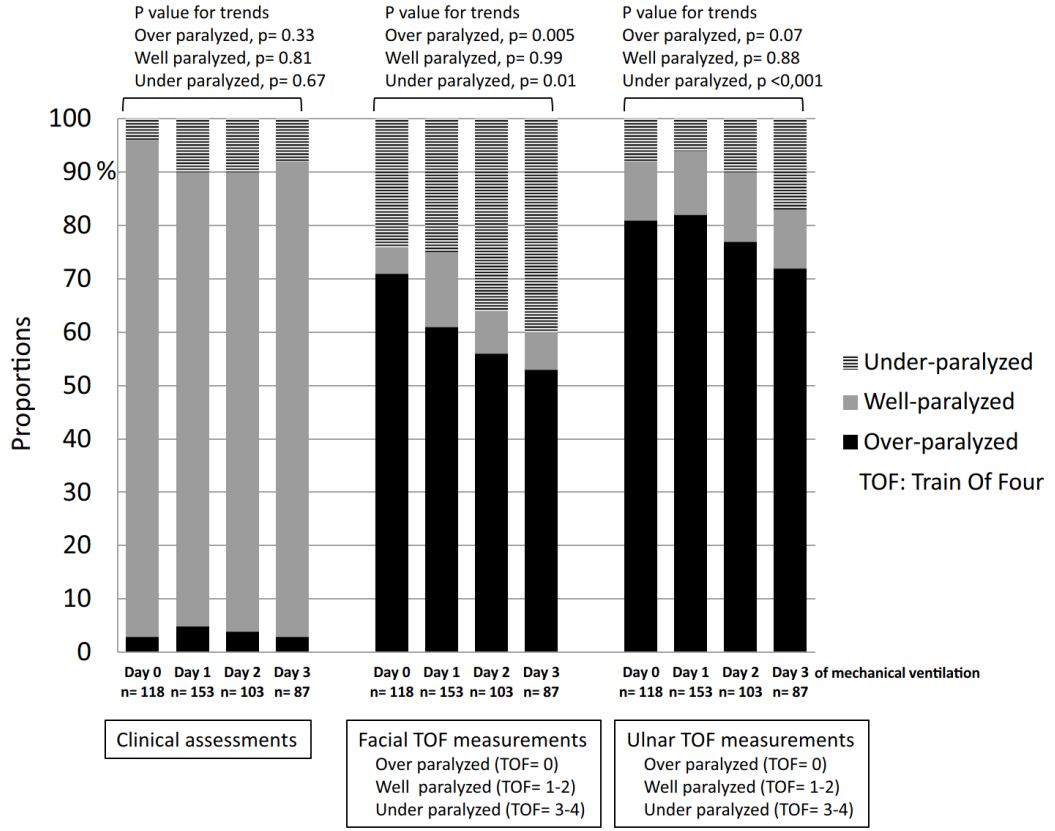
Table 3 Factors independently associated with ICU-acquired pressure injury

Variable	Odds ratio	95% confidence interval
Admission type: medical	1.15	0.94–1.4
Admission type: elective surgery	1.02	0.8–1.29
Admission type: emergency surgery	1.28	1.04–1.58
Age	1.005	1.0007–1.009
Male sex	1.21	1.08–1.36
Body Mass Index		
18.5–24.9: normal weight	Reference	
< 18–5: underweight	1.58	1.23–2.01
25–29.9: pre-obesity	1.03	0.9–1.17
≥ 30: obesity	0.98	0.84–1.14
Risk of pressure injury		
Braden score 19–23: no risk	Reference	
Braden score 15–18: mild risk	2.91	1.81–4.68
Braden score 13–14: moderate risk	5.23	3.25–8.42
Braden score 10–12: high risk	6.52	4.07–10.44
Braden score ≤ 9: very high risk	9.72	6.01–15.71
Acquired immune deficiency syndrome	1.52	0.74–3.11
Cirrhosis	0.89	0.65–1.22
Chronic obstructive pulmonary disease	1.24	1.03–1.49
Diabetes	1.05	0.92–1.2
Heart failure	1.07	0.92–1.25
Immunocompromised	1.27	1.04–1.55
Malignancy	0.95	0.8–1.14
Peripheral vascular disease	1.19	0.95–1.51
Days in ICU before study day		
0–3 days	Reference	
4–6 days in ICU before study day	2.28	1.90–2.74
7–9 days in ICU before study day	3.57	2.91–4.37
10–12 days in ICU before study day	4.12	3.29–5.17
> 12 days in ICU before study day	7.51	6.42–8.78
Mechanical ventilation on admission	1.26	1.11–1.43
Sedation	0.95	0.82–1.09
Muscle relaxant use	1.08	0.83–1.41
Vasopressor use	1.04	0.91–1.2
Renal replacement	1.34	1.14–1.58
Simplified Acute Physiology Score II score	1.006	1.002–1.01
Number of patients per nurse	0.91	0.83–0.99
Economy[a]		
High-income economy	Reference	
Upper-middle income economy	1.09	0.65–1.85
Low- + lower-middle income economy	1.82	1–3.29

Intensive Care Med 2021;47:160-9

Monitoring of NMBA

- Train of four (TOF): supramaximal electrical impulses at 2-Hz frequency applied every 0.5 s to ulnar nerve of non-paralyzed limb, or to facial nerve, produced four visualized muscle twitches



Ann Intensive Care 2017;7:10

Sedation monitoring in pts receiving NMBA

- Bispectral index (BIS) monitor: noninvasive processed EEG that can identify accidental awareness with recall (AWR) in pts undergoing general anesthesia
- BIS values of 40-60 minimize risk of AWR in operating rooms
- Concern for discordance in pts with critical illness-associated encephalopathy
- Electromagnetic fields from other devices in ICU might affect BIS readings
- Risk of under-sedating pts needs to be evaluated

NMBA use in ALVEOLI trial

Use of sedatives, opioids, and neuromuscular blocking agents in patients with acute lung injury and acute respiratory distress syndrome*

Alejandro C. Arroliga, MD; B. Taylor Thompson, MD; Marek Ancukiewicz, PhD; Jeffrey P. Gonzales, PharmD; Kalpalatha K. Guntupalli, MD; Pauline K. Park, MD; Herbert P. Wiedemann, MD; Antonio Anzueto, MD; for the Acute Respiratory Distress Syndrome Network

Continuous NMBAs were used at baseline in 30% and 25.4% of lower and higher PEEP groups, respectively, and in 45% and 33% of pts with lower and higher PEEP between day 0 and day 28

Table 4. Univariate and multivariate models for the intensity of NMBAs use

Variable	Univariate Model		Multivariate Model	
	Hazard Ratio with 95% CI	*P*-Value	Hazard Ratio with 95% CI	*P*-Value
Age	0.986 [0.981–0.992]	<0.0001	0.991 [0.984–0.997]	0.0044
Non-white Race	1.715 [1.382–2.112]	<0.0001	1.496 [1.198–1.868]	0.0004
Female Gender	0.977 [0.806–1.184]	0.8110	0.990 [0.802–1.221]	0.9235
Apache III (increase by 10 units)	1.141 [1.105–1.178]	<0.0001	1.092 [1.051–1.135]	<0.0001
Lung Injury Category				<0.0001
Trauma	1.513 [1.231–1.861]	<0.0001		
Sepsis	1.240 [1.103–1.394]	0.0003		
Multiple Transfusion	1.443 [1.218–1.710]	<0.0001		
Aspiration	1.017 [0.850–1.216]	0.8556		
Pneumonia	0.690 [0.589–0.807]	<0.0001		
P/F (increase by 10 mmHg)	0.922 [0.905–0.938]	<0.0001		
$A\text{-}aDO_2$ (increase by 10 mmHg)	1.035 [1.028–1.042	<0.0001	1.029 [1.022–1.037]	<0.0001
Plateau Pressure	1.072 [1.057–1.087]	<0.0001	1.058 [1.040–1.076]	<0.0001
# Organ Failures	1.190 [1.069–1.326]	0.0015	0.840 [0.840–1.069]	0.3823
Pre-enrollment Hospital Days	0.990 [0.970–1.009]	0.2992	0.987 [0.968–1.007]	0.1993
Higher PEEP Group	0.765 [0.658–0.962]	0.0182	0.791 [0.648–0.966]	0.0213
Tidal Volume [ml/kg]	0.948 [0.897–1.001]	0.0563	0.911 [0.857–0.969]	0.0029

Crit Care Med 2008;36:1083-8

LUNG-SAFE study

	Patients of No. (%) [95% CI]				
	All (n = 2377)	Mild[a] (n = 498)	Moderate[a] (n = 1150)	Severe[a] (n = 729)	*P* Value[b]
Neuromuscular blockade	516 (21.7) [20.1-23.4]	34 (6.8) [4.8-9.4]	208 (18.1) [15.9-20.4]	274 (37.8) [34.1-41.2]	<.001
Recruitment maneuvers	496 (20.9) [19.2-22.6]	58 (11.7) [9.0-14.8]	200 (17.4) [15.2-19.7]	238 (32.7) [29.3-36.2]	<.001
Prone positioning	187 (7.9) [6.8-9.0]	5 (1.0) [0.3-2.3]	63 (5.5) [4.2-7.0]	119 (16.3) [13.7-19.2]	<.001
ECMO	76 (3.2) [2.5-4.0]	1 (0.2) [0.05-1.2]	27 (2.4) [1.6-3.4]	48 (6.6) [4.9-8.6]	<.001
Inhaled vasodilators	182 (7.7) [6.6-8.8]	17 (3.4) [02.0-5.4]	70 (6.1) [4.8-7.6]	95 (13.0) [10.7-15.7]	<.001
HFOV	28 (1.2) [0.8-1.7]	3 (0.6) [0.1-1.7]	14 (1.2) [0.7-2.0]	11 (1.5) [0.8-2.7]	.347
None of the above	1431 (60.2) [58.2-62.2]	397 (79.7) [75.9-83.2]	750 (65.2) [62.4-68.0]	284 (39.0) [35.4-42.6]	<.001
Esophageal pressure catheter	19 (0.8) [0.04-1.4]	2 (0.4) [0.04-1.4]	8 (0.7) [0.3-1.3]	9 (1.2) [0.6-2.3]	.233
Tracheostomy	309 (13.0) [11.6-14.4]	48 (9.6) [7.1-12.6]	155 (13.5) [11.6-15.6]	106 (14.5) [12.1-17.3]	.034
High-dose corticosteroids[c]	425 (17.9) [16.4-19.5]	61 (12.3) [9.5-15.5]	194 (16.9) [14.7-19.2]	170 (23.3) [20.3-26.6]	<.001
Pulmonary artery catheter	107 (4.5) [3.7-5.4]	9 (1.8) [0.8-3.4]	53 (4.6) [3.4-6.0]	45 (6.2) [4.5-8.2]	.001

JAMA 2016;315:788-800

Randomized trials of NMBA in ARDS

Study	Experimental intervention	Study site/patient number	Enrollment criteria	Severity of ARDS	Ventilator strategies	Outcomes
Gainnier, 2004 [73]	Cisatracurium 50 mg bolus then 5 mcg/kg/min continuous infusion × 48 h Goal for paralysis train of four < 1	-France -4 medical, mixed medical/ surgical ICUs -56 adults	-ARDS (AECC) -PaO_2/FiO_2 < 150 -Enrolled < 36 h after ARDS onset	-SAPS II: 37.7 ± 0.7 vs. 37.6 ± 0.6; p = NS -PaO_2/FiO_2: 130 ± 34 vs. 119 ± 31; p = NS	-ARMA protocol -No weaning protocol -Volume assist-control -TV 6–8 mL/kg Deep Sedation	90-day day mortality ICU mortality cisatracurium 46.4% vs control 71.4%
Forel, 2006 [24]	Cisatracurium 0.2 mg/kg bolus then 5 mcg/kg/min continuous infusion × 48 h Goal for paralysis train of four < 1	-France -3 ICUs - adults -36 adults	-ARDS (AECC) -$PaO_2/FiO_2 \leq 200$ -Enrolled < 48 h after ARDS onset -Intubated < 48 h	-SAPS II: 49 ± 19 vs. 47 ± 15; p = NS	-ARMA protocol -No weaning protocol -Volume assist-control -TV 4–8 mL/kg Deep Sedation	ICU mortality cisatracurium 27.8% vs control 55.6% No difference in adverse events
Papazian, 2010 [37]	Cisatracurium 15 mg bolus then 37.5 mg/hr continuous infusion × 48 h No train of four monitoring	-France -20 ICUs -340 adults	-ARDS (AECC) -PaO_2/FiO_2 < 150 -Enrolled < 48 h after ARDS onset	-SAPS II: 50 ± 16 vs. 47 ± 14; p = 0.15 -PaO_2/FiO_2: 106 ± 36 vs. 115 ± 41; p = 0.03	-ARMA protocol -Weaning protocol -Volume assist-control -TV 6–8 mL/kg - Deep sedation	90-day mortality cisatracurium 31.6% vs control 40.7%; p = 0.08 28-day mortality cisatracurium 23.7% vs control 33.3%; p = 0.05 No difference in ICU-acquired paresis
Lyu, 2014 [74]	Vecuronium 0.1 mg/kg bolus then 0.05 mg/kg/hr infusion × 24–48 h	-1 ICU -China -48 adults	-ARDS (Berlin) -PaO_2/FiO_2 < 150 -Enrolled < 48 h after ARDS onset	-APACHE II: 18.20 ± 3.59 vs. 19.37 ± 4.14; p = NS -Baseline PaO_2/FiO_2: 140.95 ± 26.97 vs. 144.33 ± 24.09; p = NS	-No ventilation protocol -Volume assist-control -TV 4–8 mL/kg	21- day mortality vecuronium 20.8% vs 50% control; p = 0.4
Rao, 2016 [75]	Vecuronium 1μγ/ kg/ min continuous infusion	-China -1 ICU -41adults	ARDS (Berlin)	NA	-TV-6 ml/kg -Plateau Pressure ≤ 30	90-day mortality vecuronium 4.2% vs control 17.6%
Guervilly, 2017 [13]	Cisatracurium 15 mg bolus then 37.5 mg/hr continuous infusion × 48 h No train of four monitoring	-France -2 ICUs -24 adults	-ARDS (Berlin) -$PaO_2/FiO_2 \leq 200$ -Enrolled < 48 h after ARDS onset	-SAPS II: 47(37–54) vs. 48(42–62); p = 0.40 -PaO_2/FiO_2: 158(131–185) vs. 150(121–187); p = 0.40	-ARMA protocol -No weaning protocol -Volume assist-control -TV 6 mL/kg	ICU mortality cisatracurium 38.4% vs control 27.2%
Moss, 2019 [54]	Cisatracurium 15 mg bolus then 37.5 mg/hr continuous infusion × 48 h No train of four monitoring	-United States -48 ICUs -1006 adults	-ARDS (Berlin) -PaO_2/FiO_2 < 150 -Enrolled < 48 h after ARDS onset	-APACHE III: 103.9 ± 30.1 vs. 104.9 ± 30.1; p = NS - PaO_2/FiO_2: 98.7 ± 27.9 vs. 99.5 ± 27.9; p = NS	-ARMA protocol -High PEEP -Weaning protocol -Light sedation target for controls -Volume assist-control -TV 6 ml/kg	90-day mortality cisatracurium 42.5% vs 42.7% 28-day mortality cisatracurium 36.7% vs 37% No difference in ICU-acquired paresis

ACURASYS

Significantly more 28 d VFDs and less barotrauma in cisatracurium group

ROSE

VFDs at d 90 were not different, NMBA did not decrease pneumothorax, more serious CV events in cisatracurium group

Comparison of ACURASYS and ROSE trials

	ACURASYS [37]	ROSE [54]
Time from ARDS to inclusion (hours, median, IQR)	16 (6–29)	7.6 (3.7–15.6)
Time from MV initiation to inclusion (hours, median, IQR)	NMBAs 22 (9–41) Placebo 21 (10–42)	NA
Excluded before enrollment because already receiving NMBAs (*n*)	42	655
NMBAs stop before the 48th hour	No	If $FiO_2 \leq 0.4$ and PEEP ≤ 8 cmH_2O after 12 h
NMBAs use after the 48th hour	Weaning attempt at day 3 if $FiO_2 \leq 0.6$	Left to the discretion of the treating clinician
Patients from the control group requiring NMBAs for injurious MV (%)	56	17–36
PEEP strategy (cmH_2O)	Moderate PEEP (ARMA (6)) NMBAs 9.2 ± 3.2 Placebo 9.2 ± 3.5	High PEEP (ALVEOLI (5)) NMBAs 12. 6 ± 3.6 Control 12.5 ± 3.6
Prone positioning use (%)	NMBAs 28 Placebo 29	NMBAs 16.8 Control 14.9
MV weaning protocolized	Yes	NA
90-day mortality (%)	NMBAs 31.6 Placebo 41.4	NMBAs 42.5 Control 42.8

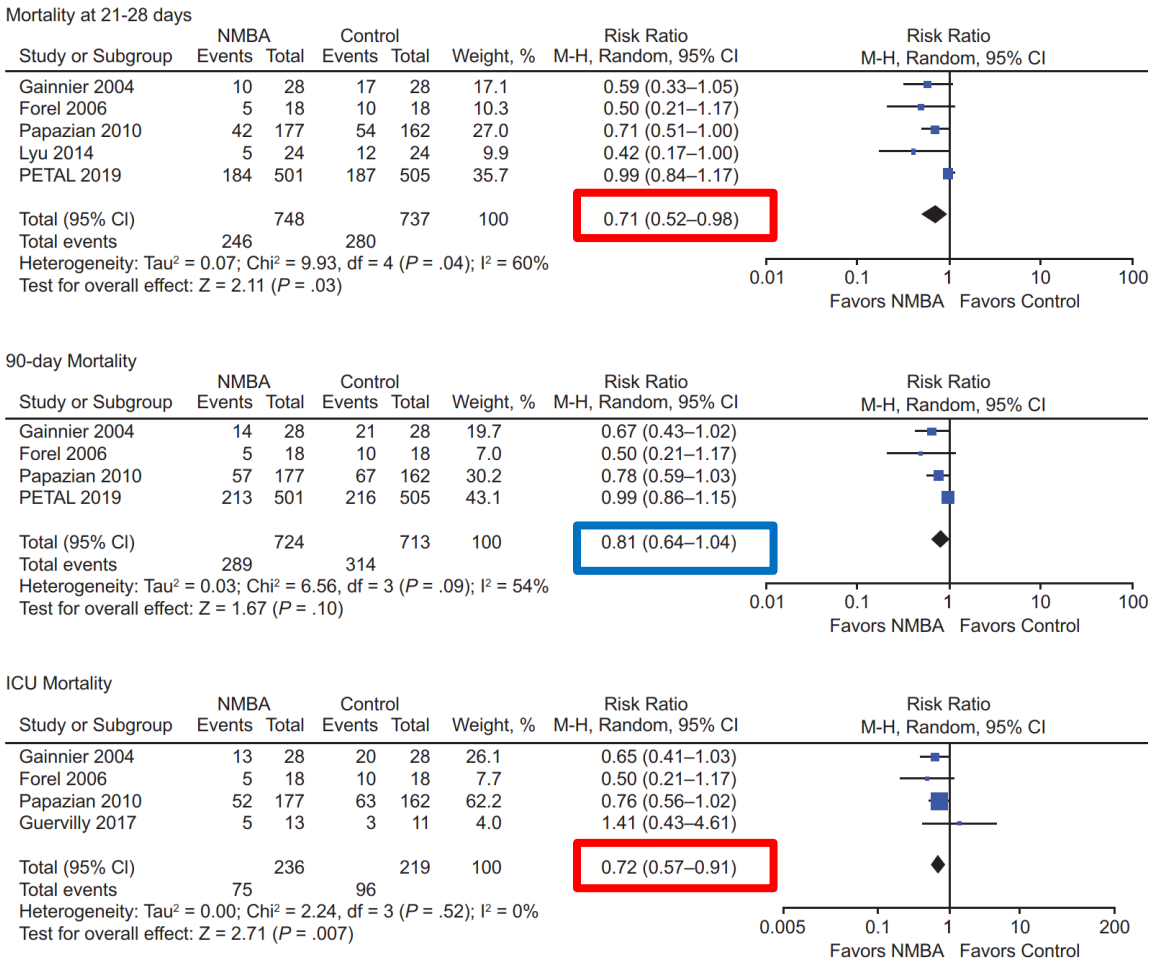
Implications from these two trials

- Differences in PEEP and sedation strategies may alter level of VILI in both intervention and control arms in both trials
  → complex interplay among pt effort, sedation, NMBA, and ventilator Mx in ARDS

- Very early use of NMBA, before optimizing MV and sedation, using high PEEP strategy may not modify outcomes

- NMBA integrated into overall strategy including optimal PEEP, prone positioning, and rapid implementation of spontaneous breathing may improve prognosis

Meta-analysis



Respir Care 2021;66:120-8

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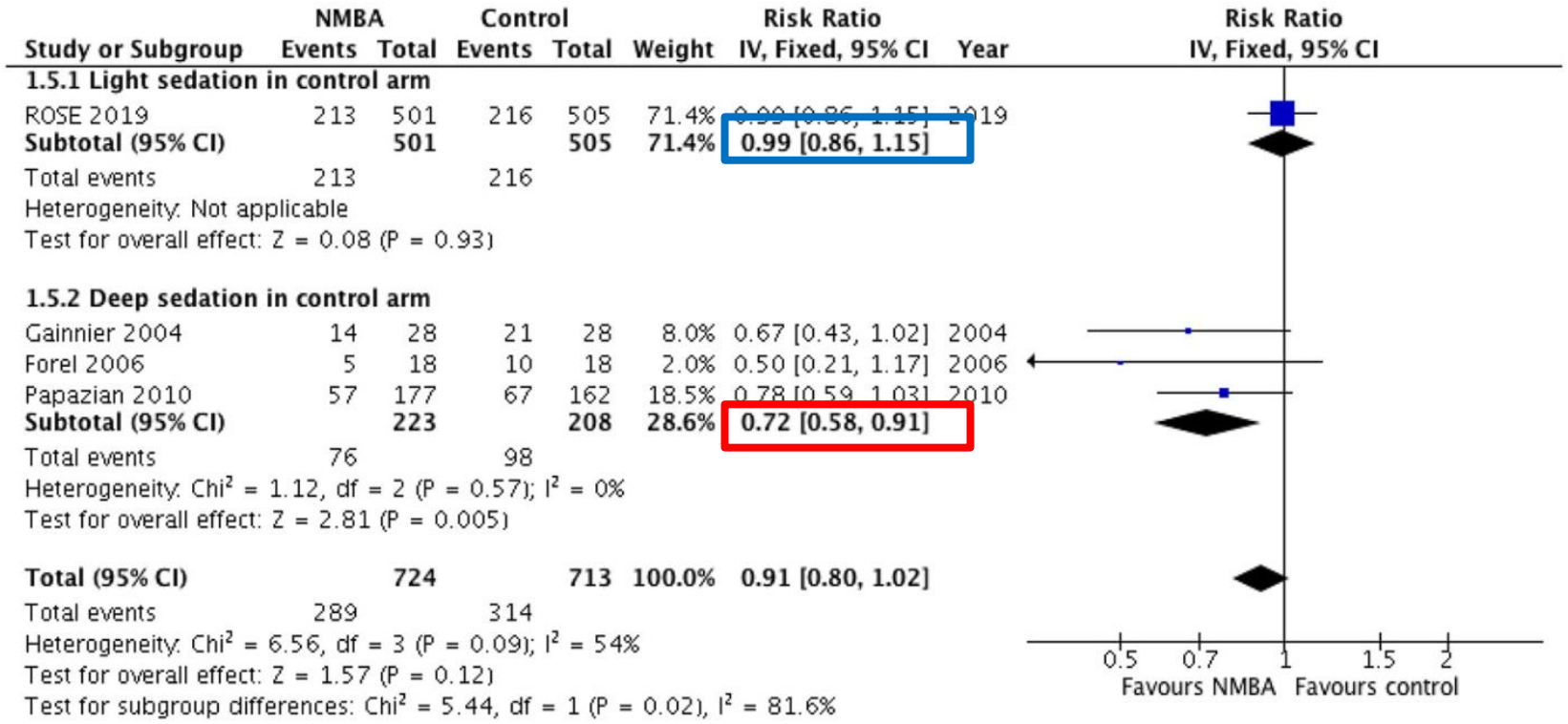
Meta-analysis



NMBA in COVID-19 ARDS

Early short course of neuromuscular blocking agents in patients with COVID-19 ARDS: a propensity score analysis

Gianluigi Li Bassi[1,2,3,4,5,6*†], Kristen Gibbons[7†], Jacky Y. Suen[1,2], Heidi J. Dalton[8], Nicole White[4], Amanda Corley[1,2], Sally Shrapnel[2,9], Samuel Hinton[2], Simon Forsyth[2], John G. Laffey[10], Eddy Fan[11], Jonathon P. Fanning[1,2,5,6], Mauro Panigada[12], Robert Bartlett[13], Daniel Brodie[14], Aidan Burrell[15], Davide Chiumello[16,17], Alyaa Elhazmi[18], Mariano Esperatti[19], Giacomo Grasselli[11,17], Carol Hodgson[15], Shingo Ichiba[20], Carlos Luna[21], Eva Marwali[22], Laura Merson[23], Srinivas Murthy[24,25], Alistair Nichol[15,26,27], Mark Ogino[28], Paolo Pelosi[29,30], Antoni Torres[3,31], Pauline Yeung Ng[32] and John F. Fraser[1,2,3,4,5,6] on behalf of The COVID-19 Critical Care Consortium

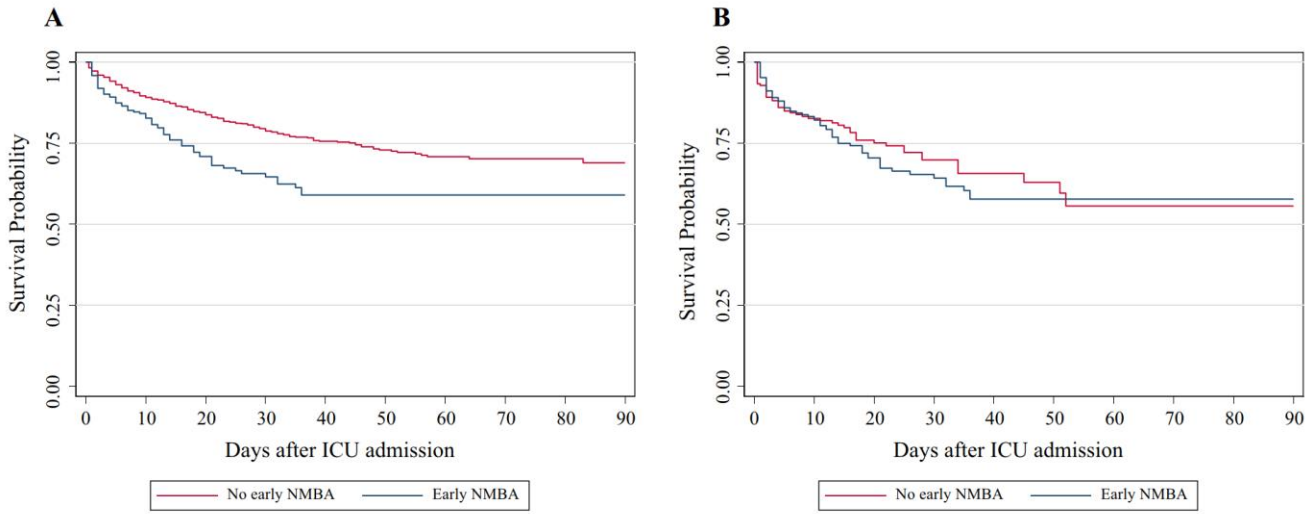


Fig. 3 Unadjusted Kaplan–Meier event curves for in-hospital mortality from commencment of invasive mechanical ventilation to 90 days. **A** Before propensity score matching, 90-day ICU Kaplan-Meier curves differed between patients undergoing up to three-day NMBA therapy, within 48 hours from commencement of IMV, in comparison with those who did not ($N = 1953$, $p < 0.001$). **B** After propensity score matching, no difference in survival between patients undergoing NMBA therapy in comparison with those who did not was found ($N = 420$, due to equally sized cohorts post propensity score matching, $P = 0.537$). *NMBA* neuromuscular blocking agent, *ICU* intensive care unit

Crit Care 2022;26:141

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NMBA in COVID-19 ARDS

Lower Driving Pressure and Neuromuscular Blocker Use Are Associated With Decreased Mortality in Patients With COVID-19 ARDS

Bo Young Lee, Song-I Lee, Moon Seong Baek, Ae-Rin Baek, Yong Sub Na, Jin Hyoung Kim, Gil Myeong Seong, and Won-Young Kim

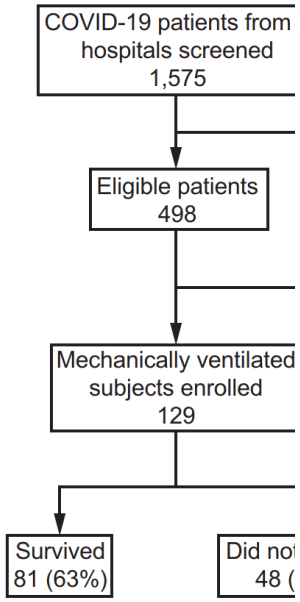
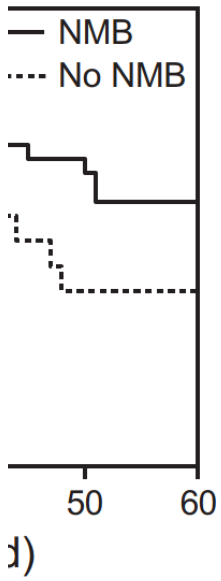


Table S5. Clinical outcomes of subjects according to neuromuscular blocker duration

	NMB ≥6 d (n = 48)	NMB <6 d (n = 50)	*P*
Mortality			
ICU	20 (42)	10 (20)	.02
Hospital	21 (44)	14 (28)	.10
28-d	14 (29)	9 (18)	.19
60-d	19 (40)	12 (24)	.10
Ventilator weaning	24 (51)	40 (80)	.003
Ventilator-free days at day 28	4.7 ± 7.5	13.1 ± 10.1	< .001
Length of hospital stay, d	26 (17–43)	27 (21–41)	.76
Tracheostomy	18 (38)	9 (18)	.031
RRT during ICU stay	12 (25)	9 (18)	.40
Superinfection	30 (63)	24 (48)	.15

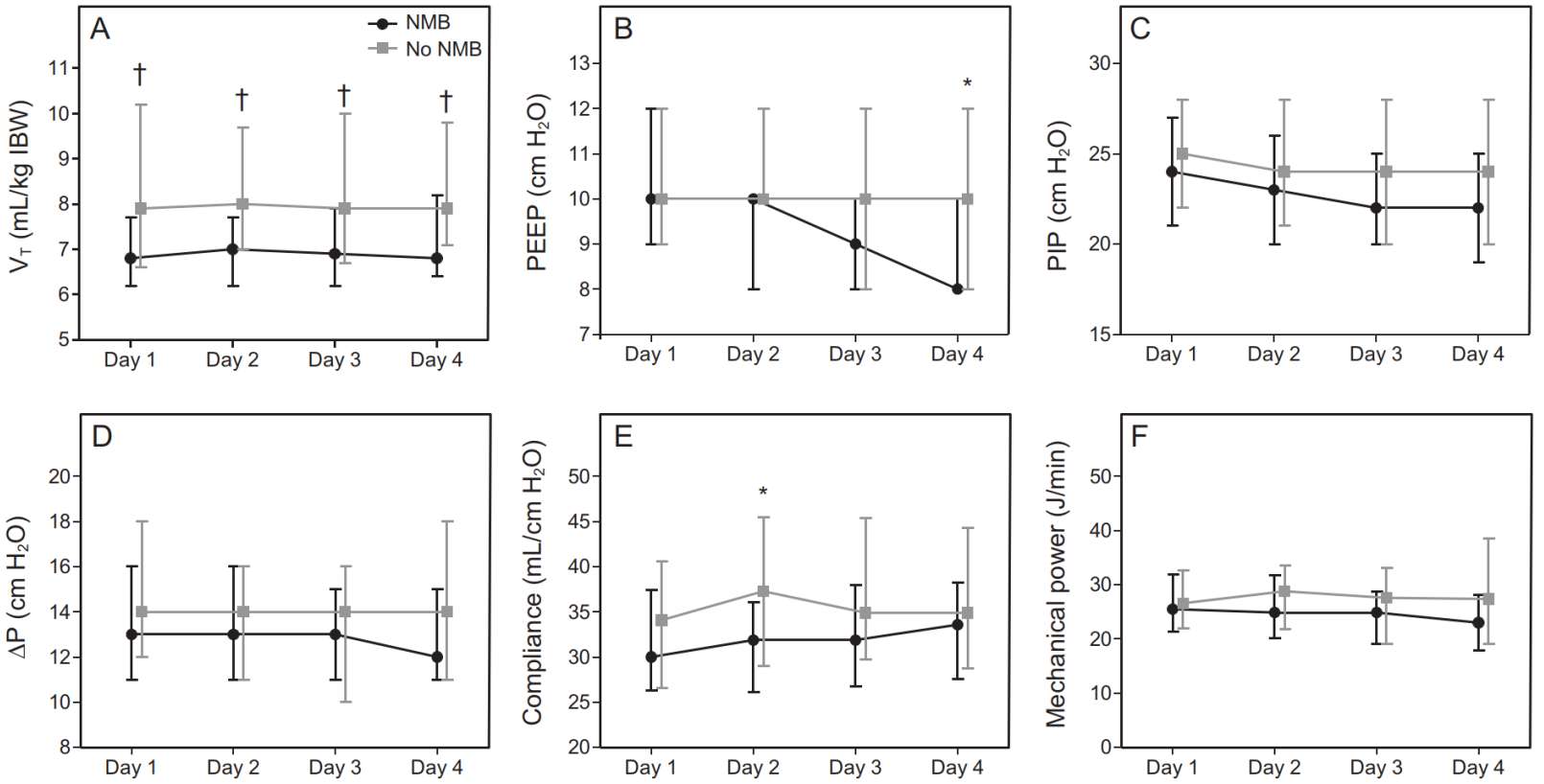
Data are presented as the number (%), mean ± standard deviation, or median (interquartile range). The *P*-values are calculated using the Mann-Whitney *U* test for continuous variables and chi-square test or Fisher's exact test for categorical variables.

NMB = neuromuscular blocker; RRT = renal replacement therapy.



Respir Care 2022;67:216-26

NMBA in COVID-19 ARDS



Respir Care 2022;67:216-26

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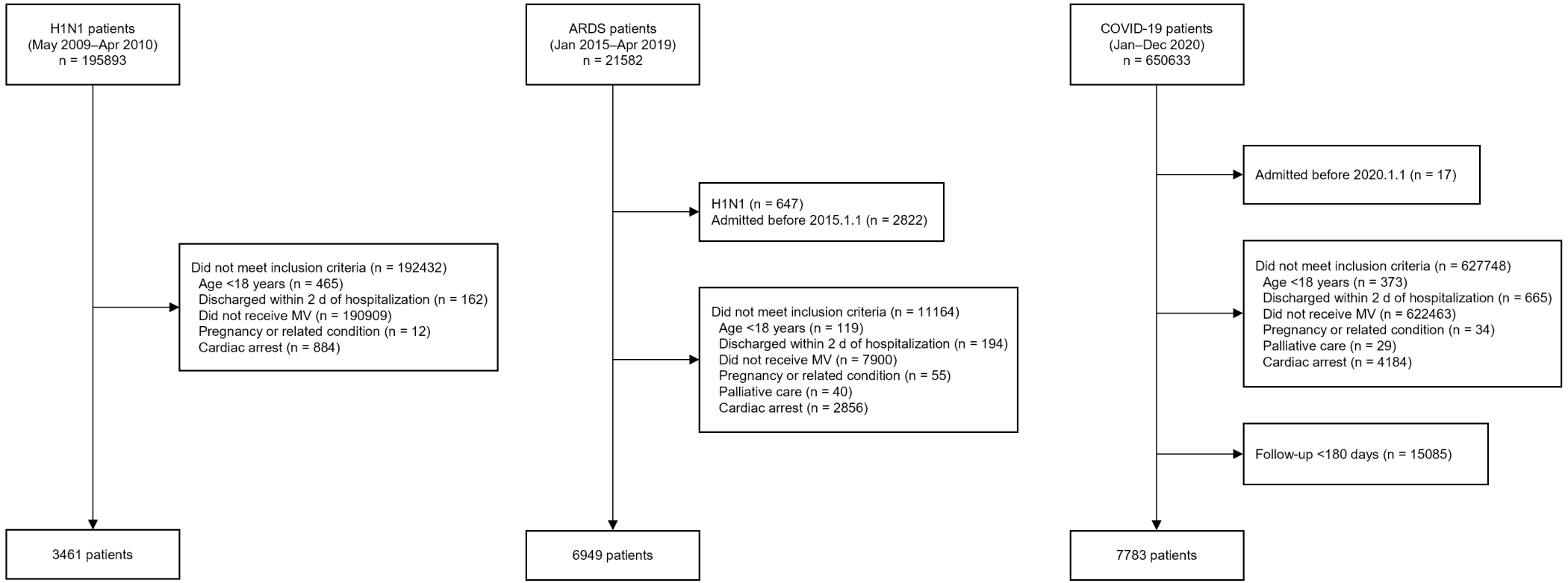
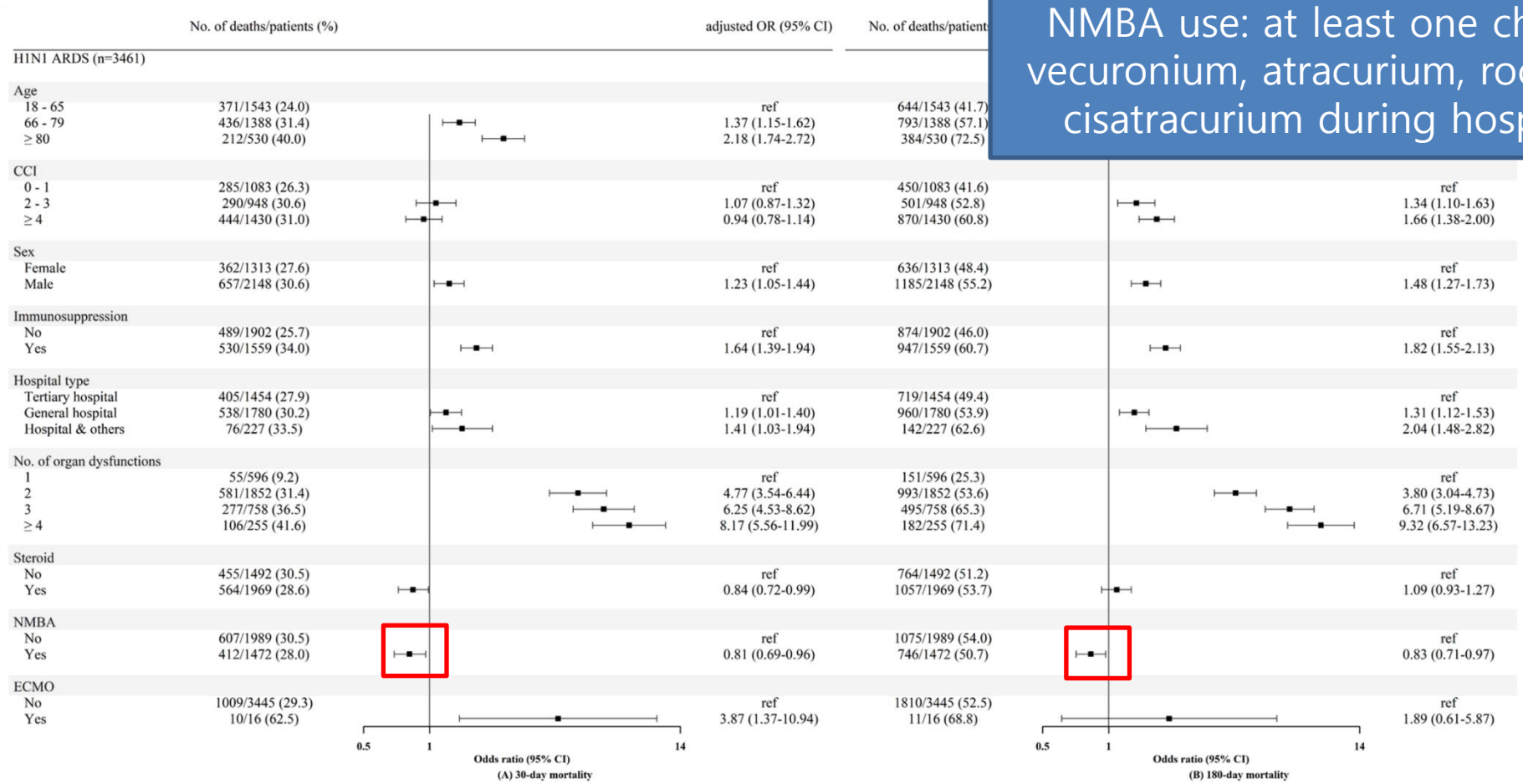
ARDS 공단연구



Unpublished data

ARDS 공단연구

NMBA use: at least one charge for IV vecuronium, atracurium, rocuronium, or cisatracurium during hospitalization

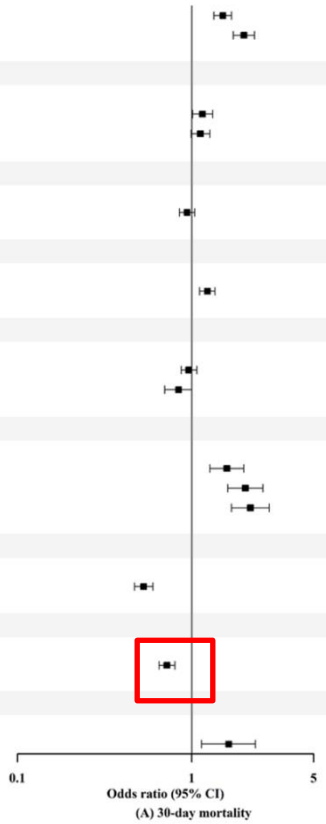


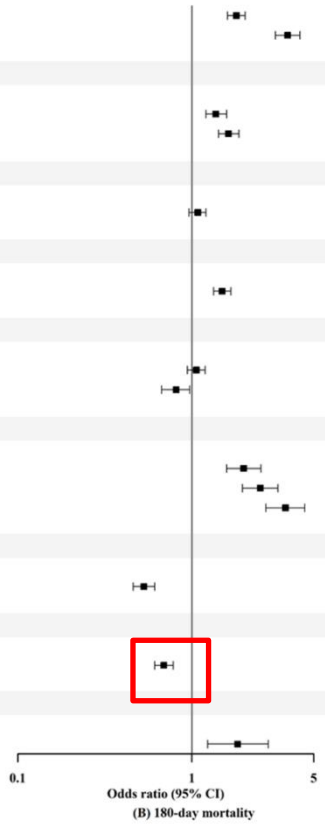
	No. of deaths/patients (%)	adjusted OR (95% CI)	No. of deaths/patients	
H1N1 ARDS (n=3461)				
Age				
18 - 65	371/1543 (24.0)	ref	644/1543 (41.7)	
66 - 79	436/1388 (31.4)	1.37 (1.15-1.62)	793/1388 (57.1)	
≥ 80	212/530 (40.0)	2.18 (1.74-2.72)	384/530 (72.5)	
CCI				
0 - 1	285/1083 (26.3)	ref	450/1083 (41.6)	ref
2 - 3	290/948 (30.6)	1.07 (0.87-1.32)	501/948 (52.8)	1.34 (1.10-1.63)
≥ 4	444/1430 (31.0)	0.94 (0.78-1.14)	870/1430 (60.8)	1.66 (1.38-2.00)
Sex				
Female	362/1313 (27.6)	ref	636/1313 (48.4)	ref
Male	657/2148 (30.6)	1.23 (1.05-1.44)	1185/2148 (55.2)	1.48 (1.27-1.73)
Immunosuppression				
No	489/1902 (25.7)	ref	874/1902 (46.0)	ref
Yes	530/1559 (34.0)	1.64 (1.39-1.94)	947/1559 (60.7)	1.82 (1.55-2.13)
Hospital type				
Tertiary hospital	405/1454 (27.9)	ref	719/1454 (49.4)	ref
General hospital	538/1780 (30.2)	1.19 (1.01-1.40)	960/1780 (53.9)	1.31 (1.12-1.53)
Hospital & others	76/227 (33.5)	1.41 (1.03-1.94)	142/227 (62.6)	2.04 (1.48-2.82)
No. of organ dysfunctions				
1	55/596 (9.2)	ref	151/596 (25.3)	ref
2	581/1852 (31.4)	4.77 (3.54-6.44)	993/1852 (53.6)	3.80 (3.04-4.73)
3	277/758 (36.5)	6.25 (4.53-8.62)	495/758 (65.3)	6.71 (5.19-8.67)
≥ 4	106/255 (41.6)	8.17 (5.56-11.99)	182/255 (71.4)	9.32 (6.57-13.23)
Steroid				
No	455/1492 (30.5)	ref	764/1492 (51.2)	ref
Yes	564/1969 (28.6)	0.84 (0.72-0.99)	1057/1969 (53.7)	1.09 (0.93-1.27)
NMBA				
No	607/1989 (30.5)	ref	1075/1989 (54.0)	ref
Yes	412/1472 (28.0)	0.81 (0.69-0.96)	746/1472 (50.7)	0.83 (0.71-0.97)
ECMO				
No	1009/3445 (29.3)	ref	1810/3445 (52.5)	ref
Yes	10/16 (62.5)	3.87 (1.37-10.94)	11/16 (68.8)	1.89 (0.61-5.87)

Unpublished data

ARDS 공단연구

	No. of deaths/patients (%)	adjusted OR (95% CI)	No. of deaths/patients (%)	adjusted OR (95% CI)
non-H1N1-COVID-19 ARDS (n=6949)				
Age				
18 - 65	922/2592 (35.6)	ref	1421/2592 (54.8)	ref
66 - 79	1352/2908 (46.5)	1.51 (1.34-1.69)	2048/2908 (70.4)	1.80 (1.60-2.02)
≥ 80	786/1449 (54.2)	1.99 (1.73-2.29)	1181/1449 (81.5)	3.54 (3.01-4.17)
CCI				
0 - 1	764/1970 (38.8)	ref	1105/1970 (56.1)	ref
2 - 3	941/2058 (45.7)	1.15 (1.01-1.32)	1408/2058 (68.4)	1.37 (1.20-1.58)
≥ 4	1355/2921 (46.4)	1.12 (0.99-1.27)	2137/2921 (73.2)	1.62 (1.42-1.86)
Sex				
Female	1139/2475 (46.0)	ref	1672/2475 (67.6)	ref
Male	1921/4474 (42.9)	0.94 (0.85-1.04)	2978/4474 (66.6)	1.08 (0.96-1.20)
Immunosuppression				
No	1432/3364 (42.6)	ref	2114/3364 (62.8)	ref
Yes	1628/3585 (45.4)	1.23 (1.11-1.36)	2536/3585 (70.7)	1.49 (1.33-1.67)
Hospital type				
Tertiary hospital	1357/3167 (42.8)	ref	2062/3167 (65.1)	ref
General hospital	1413/3096 (45.6)	0.96 (0.87-1.07)	2153/3096 (69.5)	1.06 (0.94-1.19)
Hospital & others	290/686 (42.3)	0.84 (0.70-1.00)	435/686 (63.4)	0.81 (0.67-0.97)
No. of organ dysfunctions				
1	140/400 (35.0)	ref	214/400 (53.5)	ref
2	1410/3299 (42.7)	1.59 (1.27-1.99)	2174/3299 (65.9)	1.98 (1.58-2.49)
3	1007/2148 (46.9)	2.03 (1.61-2.56)	1473/2148 (68.6)	2.47 (1.95-3.12)
≥ 4	503/1102 (45.6)	2.17 (1.69-2.78)	789/1102 (71.6)	3.44 (2.66-4.45)
Steroid				
No	957/1701 (56.3)	ref	1311/1701 (77.1)	ref
Yes	2103/5248 (40.1)	0.53 (0.47-0.60)	3339/5248 (63.6)	0.53 (0.46-0.61)
NMBA				
No	1315/2616 (50.3)	ref	1916/2616 (73.2)	ref
Yes	1745/4333 (40.3)	0.72 (0.65-0.80)	2734/4333 (63.1)	0.69 (0.61-0.78)
ECMO				
No	2995/6818 (43.9)	ref	4556/6818 (66.8)	ref
Yes	65/131 (49.6)	1.63 (1.14-2.32)	94/131 (71.8)	1.83 (1.23-2.74)





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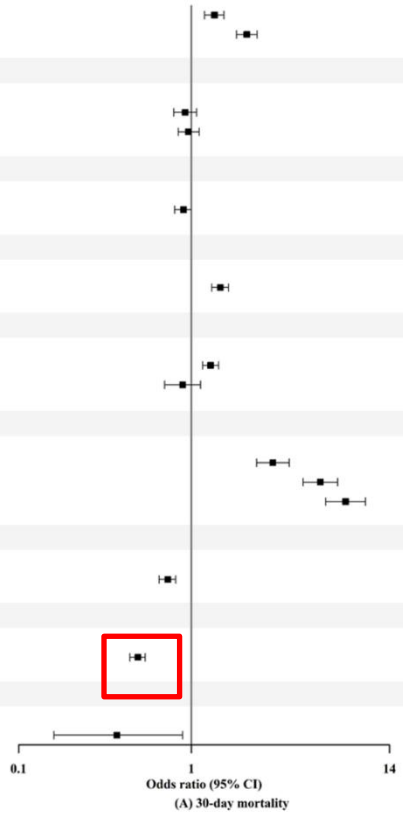
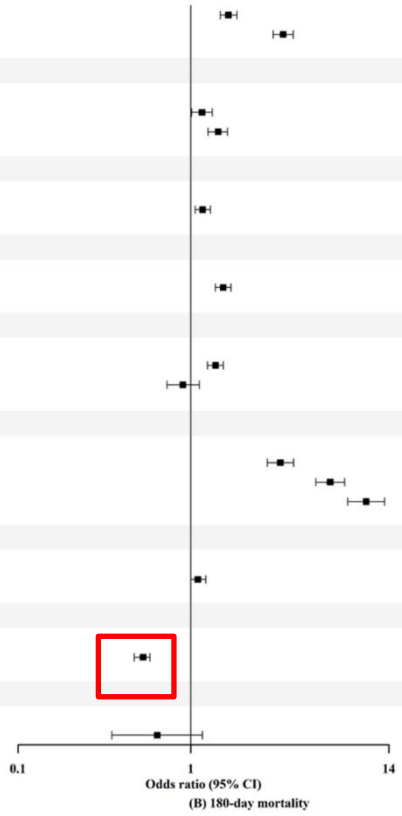
ARDS 공단연구

	No. of deaths/patients (%)	adjusted OR (95% CI)	No. of deaths/patients (%)	adjusted OR (95% CI)
COVID-19 ARDS (n=7783)				
Age				
18 - 65	613/2887 (21.2)	ref	1043/2887 (36.1)	ref
66 - 79	850/2993 (28.4)	1.36 (1.19-1.54)	1531/2993 (51.2)	1.65 (1.48-1.85)
≥ 80	2248/3433 (65.5)	2.09 (1.82-2.40)	1254/1903 (65.9)	3.42 (2.99-3.91)
CCI				
0 - 1	483/1998 (24.2)	ref	753/1998 (37.7)	ref
2 - 3	591/2190 (27.0)	0.92 (0.79-1.07)	1047/2190 (47.8)	1.16 (1.01-1.33)
≥ 4	1107/3595 (30.8)	0.96 (0.84-1.11)	2028/3595 (56.4)	1.44 (1.26-1.63)
Sex				
Female	873/2913 (30.0)	ref	2413/4870 (49.5)	ref
Male	1308/4870 (26.9)	0.90 (0.80-1.00)	1415/2913 (48.6)	1.17 (1.06-1.30)
Immunosuppression				
No	1027/4036 (25.4)	ref	1775/4036 (44.0)	ref
Yes	1154/3747 (30.8)	1.47 (1.31-1.64)	2053/3747 (54.8)	1.54 (1.39-1.71)
Hospital type				
Tertiary hospital	1151/4404 (26.1)	ref	2052/4404 (46.6)	ref
General hospital	919/2922 (31.5)	1.29 (1.16-1.44)	1576/2922 (53.9)	1.39 (1.25-1.54)
Hospital & others	111/457 (24.3)	0.89 (0.70-1.13)	200/457 (43.8)	0.90 (0.73-1.12)
No. of organ dysfunctions				
1	109/904 (12.1)	ref	214/904 (23.7)	ref
2	1097/4318 (25.4)	2.96 (2.38-3.68)	2008/4318 (46.5)	3.30 (2.77-3.93)
3	695/1925 (36.1)	5.57 (4.43-7.01)	1155/1925 (60.0)	6.41 (5.29-7.77)
≥ 4	280/636 (44.0)	7.80 (5.98-10.16)	451/636 (70.9)	10.34 (8.10-13.21)
Steroid				
No	885/2917 (30.3)	ref	1333/2917 (45.7)	ref
Yes	1296/4866 (26.6)	0.73 (0.65-0.81)	2495/4866 (51.3)	1.10 (1.00-1.22)
NMBA				
No	1211/3373 (35.9)	ref	1942/3373 (57.6)	ref
Yes	970/4410 (22.0)	0.49 (0.44-0.54)	1886/4410 (42.8)	0.53 (0.47-0.58)
ECMO				
No	2175/7733 (28.1)	ref	3809/7733 (49.3)	ref
Yes	6/50 (12.0)	0.37 (0.16-0.89)	19/50 (38.0)	0.64 (0.35-1.17)





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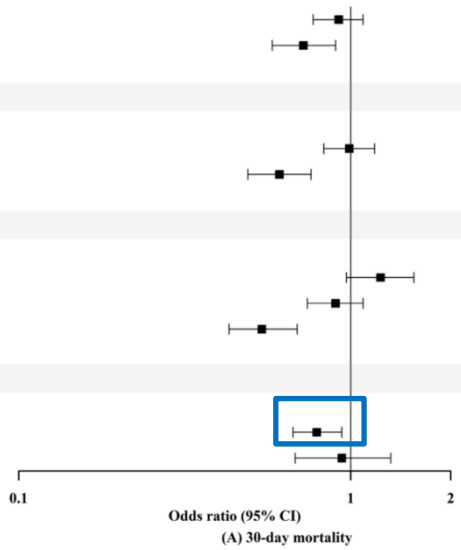
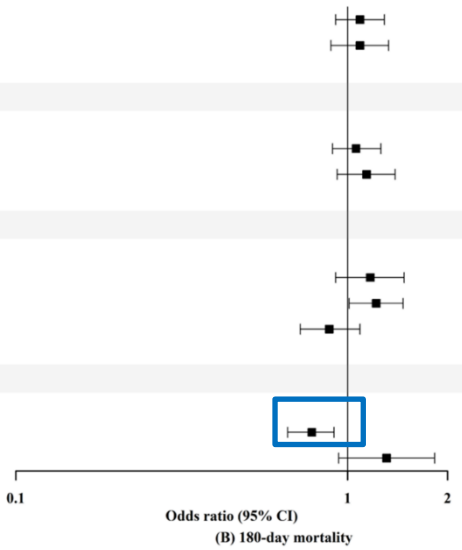
ARDS 공단연구

	No. of deaths/patients (%)	adjusted OR (95% CI)	No. of deaths/patients (%)	adjusted OR (95% CI)
H1N1 ARDS (n=3461)				
Cumulative dose of Steroid				
No use	455/1492 (30.5)	ref	764/1492 (51.2)	ref
<250 mg	381/1252 (30.4)	0.92 (0.77-1.09)	678/1252 (54.2)	1.09 (0.92-1.29)
≥250 mg	183/717 (25.5)	0.72 (0.58-0.90)	379/717 (52.9)	1.09 (0.89-1.33)
Total days of Steroid use				
No use	455/1492 (30.5)	ref	764/1492 (51.2)	ref
<3 days	397/1266 (31.4)	0.99 (0.83-1.18)	663/1266 (52.4)	1.06 (0.90-1.26)
≥3 days	167/703 (23.8)	0.61 (0.49-0.76)	394/703 (56.0)	1.14 (0.93-1.39)
Steroid use				
No use	455/1492 (30.5)	ref	764/1492 (51.2)	ref
Hydrocortisone	171/445 (38.4)	1.23 (0.97-1.55)	265/445 (59.6)	1.17 (0.92-1.48)
Methylprednisolone	269/901 (29.9)	0.90 (0.74-1.09)	502/901 (55.7)	1.22 (1.01-1.47)
Dexamethasone	124/623 (19.9)	0.54 (0.43-0.69)	290/623 (46.5)	0.88 (0.72-1.09)
Total days of NMBA use				
No use	607/1989 (30.5)	ref	1075/1989 (54.0)	ref
<3 days	349/1280 (27.3)	0.79 (0.67-0.94)	625/1280 (48.8)	0.78 (0.66-0.91)
≥3 days	63/192 (32.8)	0.94 (0.68-1.32)	121/192 (63.0)	1.31 (0.94-1.83)





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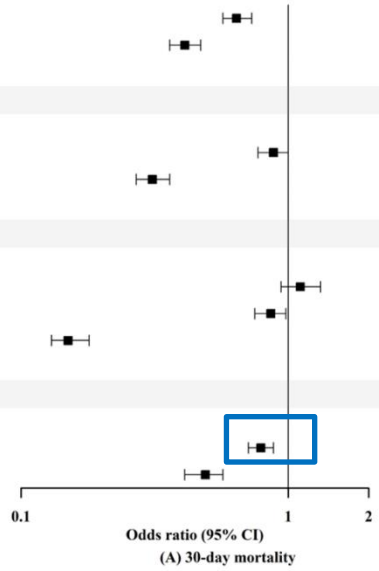
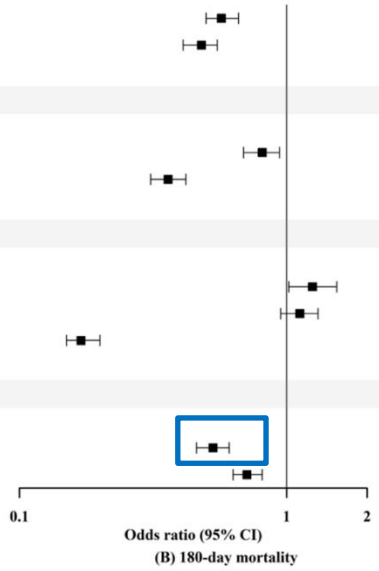
ARDS 공단연구

	No. of deaths/patients (%)	adjusted OR (95% CI)	No. of deaths/patients (%)	adjusted OR (95% CI)
non-H1N1-COVID-19 ARDS (n=6949)				
Cumulative dose of Steroid				
No use	957/1701 (56.3)	ref	1311/1701 (77.1)	ref
<250 mg	1291/2886 (44.7)	0.64 (0.57-0.73)	1885/2886 (65.3)	0.57 (0.50-0.66)
≥250 mg	812/2362 (34.4)	0.41 (0.36-0.47)	1454/2362 (61.6)	0.48 (0.41-0.55)
Total days of Steroid use				
No use	957/1701 (56.3)	ref	1311/1701 (77.1)	ref
<3 days	1269/2410 (52.7)	0.88 (0.77-1.00)	1744/2410 (72.4)	0.81 (0.69-0.94)
≥3 days	834/2838 (29.4)	0.31 (0.27-0.36)	1595/2838 (56.2)	0.36 (0.31-0.42)
Steroid use				
No use	957/1701 (56.3)	ref	1311/1701 (77.1)	ref
Hydrocortisone	537/914 (58.8)	1.11 (0.94-1.32)	738/914 (80.7)	1.25 (1.02-1.54)
Methylprednisolone	1265/2421 (52.3)	0.86 (0.75-0.98)	1906/2421 (78.7)	1.12 (0.95-1.31)
Dexamethasone	301/1913 (15.7)	0.15 (0.13-0.18)	695/1913 (36.3)	0.17 (0.15-0.20)
Total days of NMBA use				
No use	1315/2616 (50.3)	ref	1916/2616 (73.2)	ref
<3 days	1446/3380 (42.8)	0.79 (0.71-0.88)	2162/3380 (64.0)	0.53 (0.46-0.61)
≥3 days	299/953 (31.4)	0.49 (0.41-0.57)	572/953 (60.0)	0.71 (0.63-0.81)





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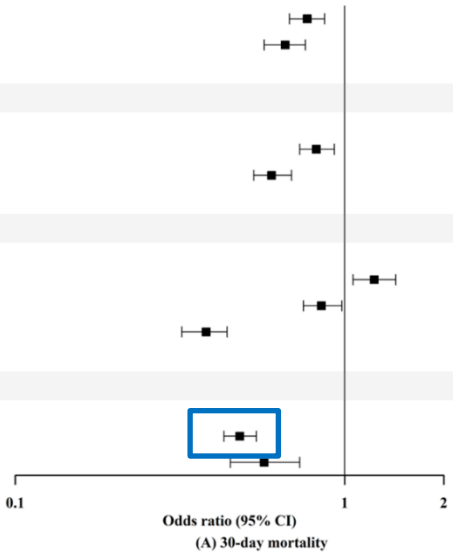
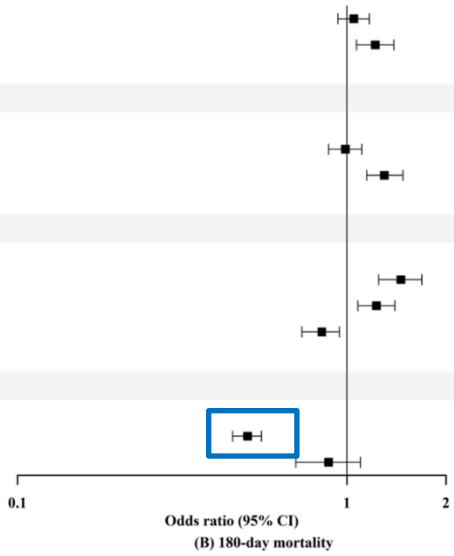
ARDS 공단연구

	No. of deaths/patients (%)	adjusted OR (95% CI)	No. of deaths/patients (%)	adjusted OR (95% CI)
COVID-19 ARDS (n=7783)				
Cumulative dose of Steroid				
No use	885/2917 (30.3)	ref	1333/2917 (45.7)	ref
<250 mg	878/3134 (28.0)	0.77 (0.68-0.87)	1584/3134 (50.5)	1.05 (0.94-1.17)
≥250 mg	418/1732 (24.1)	0.66 (0.57-0.76)	911/1732 (52.6)	1.22 (1.07-1.39)
Total days of Steroid use				
No use	885/2917 (30.3)	ref	1333/2917 (45.7)	ref
<3 days	819/2860 (28.6)	0.82 (0.73-0.93)	1381/3860 (35.8)	0.99 (0.88-1.11)
≥3 days	477/2006 (23.8)	0.60 (0.53-0.69)	1114/2006 (55.5)	1.30 (1.15-1.48)
Steroid use				
No use	885/2917 (30.3)	ref	1333/2917 (45.7)	ref
Hydrocortisone	470/1153 (40.8)	1.23 (1.06-1.43)	716/1153 (62.1)	1.46 (1.25-1.69)
Methylprednisolone	555/1896 (29.3)	0.85 (0.75-0.98)	1024/1896 (54.0)	1.23 (1.08-1.40)
Dexamethasone	271/1817 (14.9)	0.38 (0.32-0.44)	755/1817 (41.6)	0.84 (0.73-0.95)
Total days of NMBA use				
No use	1211/3373 (35.9)	ref	1942/3373 (57.6)	ref
<3 days	867/3991 (21.7)	0.48 (0.43-0.54)	1654/3991 (41.4)	0.50 (0.45-0.55)
≥3 days	103/419 (24.6)	0.57 (0.45-0.73)	232/419 (55.4)	0.88 (0.70-1.10)





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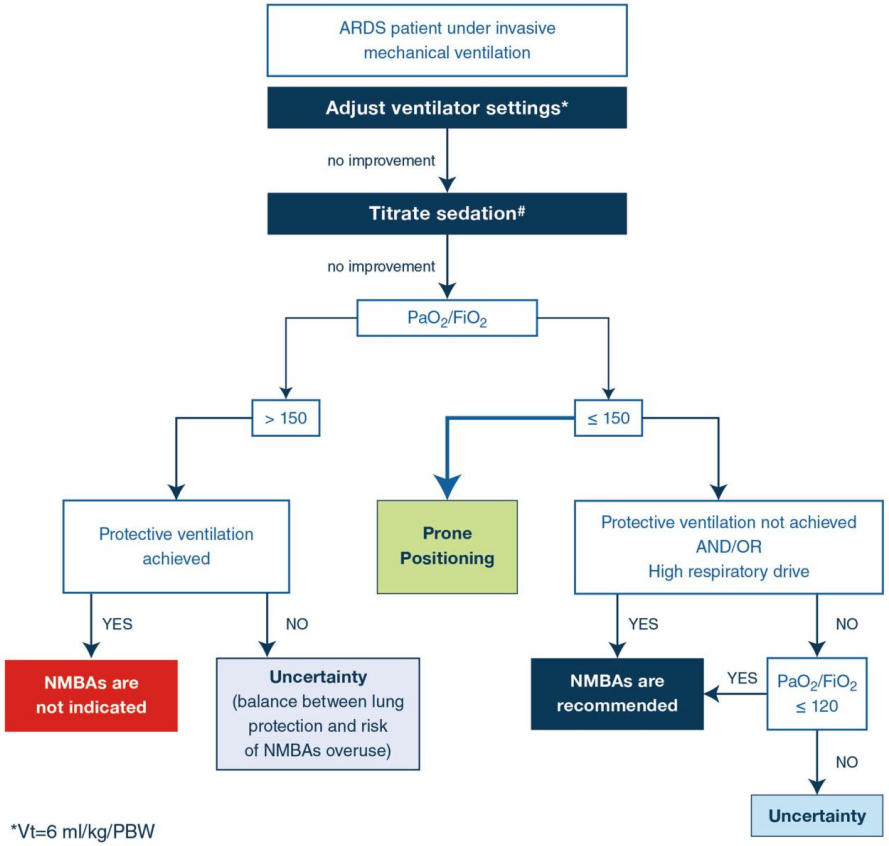
Conclusions



*Vt=6 ml/kg/PBW
Titrated PEEP
Plateau pressure ≤ 30 cmH_2O

RASS from -4 to -5

More research is needed

- Benefits observed may not apply to all NMBAs, considering that cisatracurium has been used in all RCTs

- Optimal duration of infusion needs to be evaluated according to pts' profiles and/or responses to Tx

- Use of NMBA in pts without moderate to severe hypoxemia but with large swings in transpulmonary pr deserves to be further explored