Neuromuscular Blocking Agents Use in ARDS

Subjects: Critical Care Medicine

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Acute respiratory distress syndrome (ARDS) accounts for a quarter of mechanically ventilated patients, while during the pandemic, it overwhelmed the capacity of intensive care units (ICUs). Lung protective ventilation (low tidal volume, positive-end expiratory pressure titrated to lung mechanics and oxygenation, permissive hypercapnia) is a non-pharmacological approach that is the gold standard of management. Among the pharmacological treatments, the use of neuromuscular blocking agents (NMBAs), although extensively studied, has not yet been well clarified.

neuromuscular blocking agents | muscular relaxants | ARDS | survival | lung injury

1. Introduction

The acute respiratory distress syndrome (ARDS) was first described in 1967 as a condition of respiratory failure that resembles the respiratory distress syndrome in infants [1]. The syndrome may originate from pulmonary (pneumonia, aspiration and chemical inhalational insults) or extra-pulmonary (trauma, burns, sepsis and pancreatitis) causes and it is acute in onset (within five days of the illness onset/insult). The inflammatory process results in increased vascular permeability (thus, a non-cardiac origin), leading to alveolar infiltration, increased lung weight and the loss of aerated lung tissue. Bilateral pulmonary infiltrates result in hypoxemia and decreased lung compliance [2].

Annually, ARDS accounts for 10% of intensive care unit (ICU) admissions and 24% of patients receiving mechanical ventilation [3]. Attributable mortality remains high, ranging from 35% to 46% and is associated with a degree of lung impairment [2][3]. Survivors may have significant impairments in their quality of life both regarding physical and neurocognitive functions, derangements that may persist for as long as 5 years after recovery from ARDS [4]. During the last three years, the novel coronavirus disease (COVID-19) has severely burdened healthcare system capacities in many parts of the world. A high proportion of patients require hospitalization, and a small subset will develop severe respiratory failure. Due to its pandemic nature (a substantial number of patients suffering at the same period), COVID-19 ARDS patients have overwhelmed ICUs [5][6][7]. Moreover, a high mortality has been reported in those patients receiving invasive mechanical ventilation (IMV), in the range of 47.9–84.4% [5][6][8].

Irrespective of the cause, a definite ARDS treatment is lacking. Its management mainly relies on supportive care, while lung-protective mechanical ventilation strategy is one of the major prerequisites. This includes the application

of a low tidal volume on the mechanical ventilation and monitoring of inspiratory pressures, so that the plateau pressure does not exceed the value of 30 cm H_2O and/or the driving pressure is kept below 14 cm H_2O [9][10]. The application of higher positive-end expiratory pressure (PEEP), a strategy that has been adopted to minimize atelectrauma in recent decades [11], has been highly debated in ARDS management in the COVID-19 era [12][13][14], while proning became a routine clinical practice, and more than 60% of the patients are proned early after intubation [15]. Concerning pharmacological treatments, apart from the recently endorsed corticosteroids and IL-6 receptor antagonist, conferring a variable, clinically significant, survival benefit to COVID-19 patients [16][17][18], neuromuscular blocking agents (NMBAs) are also being used in the management of ARDS [3]. The rational for their use is to harmonize the patient–ventilator interaction, thus reducing the risk of progression to ventilator-induced lung injury (VILI), and a more homogenous distribution of pressurization during tidal ventilation [19]. The use of paralytics varies widely in everyday clinical practice [3]. Two large randomized clinical trials have conferred a bidirectional change in the clinical use of NMBAs in ARDS, as they report conflicting results mainly concerning mortality [20][21]. COVID-19 provided a “bolus” of ARDS patients.

2. Rationale for NMBA Use in ARDS

In ARDS, the adoption of a lung protective ventilator strategy may diminish the risk of ventilator-induced lung injury and is associated with improved survival [9][10]. The use of NMBAs may facilitate lung protective ventilation, preventing spontaneous respiratory activity, thus limiting the risk of generation of large transpulmonary pressure swings, when strong inspiratory efforts occur. Moreover, expiratory efforts may lead to loss of aeration in dependent lung regions (de-recruitment), if pleural pressure is higher than the applied PEEP [22]. As a consequence, NMBAs may control tidal volumes and PEEP throughout the airways, minimizing the risk of barotrauma, volutrauma and atelectrauma. Finally, abolishing spontaneous efforts, NMBAs harmonize the patient–ventilator interaction. Vigorous spontaneous respiratory efforts may increase global transpulmonary pressures and tidal volumes and cause lung overdistension [23]. The deleterious effects of increased lung stress may also be present at a local level, involving certain lung regions, especially in dependent lung zones when the Pendelluft phenomenon occurs—the redistribution of air in lung regions from adjacent alveoli, causing local overdistension [24]. Moreover, some forms of asynchrony, such as the double triggering–delivery of a second tidal volume before complete exhalation, may result in the delivery of higher than set tidal volumes, increasing the local lung stress in the already-injured lung units [25]. As a result, increased respiratory drive, due to the underlying disease or triggered by increased $PaCO_2$ (permissive hypercapnia), which may aggravate lung injury, is blunted with the use of NMBAs. It should also be mentioned that negative intrathoracic pressures may increase the intrathoracic blood volume, increasing lung perfusion; in the already-injured lung parenchyma, the capillary endothelium is already affected (increased permeability). Thus, additional lung damage occurs from the so-called negative pressure pulmonary edema [26].

Studies with daily interruption of sedation showed that patients had a shorter duration of mechanical ventilation, ICU stay and at least no negative effect on mortality [27][28]. These trials did not exclusively include ARDS patients. On the other hand, in ARDS patients, the decreasing work of breathing decreases the oxygen consumption by the

respiratory muscles. It has been found that muscular paralysis results in the decrease in cardiac output and whole-body oxygen consumption, thus it has been speculated that blood flow is redistributed from the respiratory muscles to other vascular beds [29]. Finally, an anti-inflammatory role of NMBAs has been proposed. In patients with moderate and severe ARDS, the early use of muscular relaxants was associated with decreased concentrations of pulmonary and systemic proinflammatory markers, namely IL-1β, IL-6 and IL-8 [30]. Sottile et al., in a secondary analysis of the ARMA study, demonstrated that, in patients with PaO_2/FiO_2 < 120 mmHg receiving low tidal volume ventilation, a reduction in markers representing endothelial and epithelial lung injury was noted for each day of NMBA use [31]. The effects could be attributed to the decrease in lung inflammation, translated in a reduction in biotrauma, resulting from the optimization of patient–ventilator synchrony, or to a direct anti-inflammatory effect of myorelaxants, as shown in animal studies [32].

3. Data on NMBA Use in ARDS

Seven RCTs have been conducted evaluating the benefits, if any, of NMBA use in ARDS patients [20][21][22][30][33][34][35]. The earliest four studies were performed in France [21][22][30][34], two subsequent studies in China [33][35] and the latest, also including the larger number of patients, was performed in USA [20]. The studies have provided conflicting results, so that they have changed the clinical practice in a bidirectional way. Especially when considering the most influential ones (ACURASYS and ROSE study) with the highest recruitment, certain differences have been addressed, although the design of the ROSE study was carefully selected to allow direct comparisons to ACURASYS [20][21].

In the first study in the field, Gainnier et al. randomized 56 patients with moderate and severe ARDS within 36 h of the patients meeting the eligibility criteria. The patients assigned to the NMBAs group received cisatracurium at a dose of 5 µg/kg/min (cumulative dose of 1324 ± 197 mg) after a bolus infusion of 50 mg. The study found that the early use of NMBAs resulted in sustained improvements in oxygenation after 48 h of infusion, persisting during the 120 h of the study period. Hospital mortality on day 28th, 60th and ICU mortality did not differ (**Table 1**).

Table 1. Patient characteristics and outcomes in the seven randomized controlled trials and the COVID-19 ARDS studies concerning NMBA use in ARDS.

	Patients	Primary End Point	Time of Inclusion	NMBA	Dose	Monitoring	Duration	Sedation	PEEPtot	VT	Pplat	PaO_2/FiO_2	Proning	Steroids	Barotrauma	VAP	ICUAW	VFD 28/60	Mortality
Gainnier [24]	56	Effect on oxygenation after 120 h	Within 36 h meeting inclusion criteria	cis	50 mg bolus	TOF every 8 h	48	midazolam sufentanil	12.3 ± 3	7.1 ± 1.1	27.1	130 ± 34	14.3%	7.1%	0	46%	0	D28: 3.7 ± 37.2	D28: 35.7%
2004	PaO_2/FiO_2 < 150 mmHg				5 µg/kg/min	Ramsey 6												D60: 19 ± 320.3	D60: 46.4%
																			ICU:

	Patients	Primary End Point	Time of Inclusion	NMBA	Dose	Monitoring	Duration	Sedation	PEEPtot	VT	Pplat	PaO_2/FiO_2	Proning	Steroids	Barotrauma	VAP	ICUAW	VFD 28/60	Mortality
																			46.4%
					actual: 1324 ± 197				11.4 ± 2.5	7.4 ± 31.9	26.1 ± 4	119 ± 31	14.3%	14.3%	1	57%	0	D28: 1.7 ± 35.3 (NS)	D28: 60.7 (p = 0.061)
																		D60: 9.8 ± 16.9 (0.071)	D60: 64.3% (p = 0.18)
																			ICU: 71.4% (p = 0.057)
Forel [30]														5.5%					
2006	36	Effect on pulmonary and systemic proinflammatory cytokines	48 h of ARDS onset	cis	bolus 0.2 mg/kg	TOF every 8 h	48 h		13.2 ± 2.7	6.5 ± 0.7	27.5 ± 4.4		0		0		1	D28: 6 ± 8.6	ICU: 27.8%
	PaO_2/FiO_2 < 200 mmHg				5 µg/kg/min				11 ± 2.7 (p < 0.05)	7 ± 30.7	24.8 ± 35.7			0	0		1	D28: 5.4 ± 6.4 (ns)	ICU: 55.6% (NS)
Guervilli [22]	30	Effect on respiratory mechanics	48 h of ARDS onset	cis	bolus 15 mg	TOF	48 h	midazolam/sufentanil	11 (10–11.5)	6.2 (5.9–6.8	23 (19–26)	158 (131–185)						D28: 7 (0–20)	ICU: 38%
2017	PaO_2/FiO_2 100–150 mmHg				37.5 mg/h	Ramsey 6						150 (121–187)						D28: 8(0–18)	ICU: 27% (p = 0.6)
Rao [35]	41			vecuronium	actual: 1595 mg (1221–1830)				7.84 ± 2.94							4.2%		D28: 17.9 ± 2.77.4	D28: 4.2%
2016	ARDS pts																		90: 4.2%
																0		D28: 17.1 ± 8.2	D28: 11.8%
									5.88 ± 1.96										90: 17.6%

	Patients	Primary End Point	Time of Inclusion	NMBA	Dose	Monitoring	Duration	Sedation	PEEPtot	VT	Pplat	PaO_2/FiO_2	Proning	Steroids	Barotrauma	VAP	ICUAW	VFD 28/60	Mortality
Lyu [33] 2014	96			vecuronium	0.05 mg/kg/h		24–48 h					140.95 ± 26.97							D21: 16.7%
	PaO_2/FiO_2 < 200 mmHg (24)																		D21: 25% (p = 0.035)
	PaO_2/FiO_2 < 100 mmHg (24)											144.33 ± 24.09							D21: 20.8%
																			D21: 50% (0.477)
Papazian [21]	340		48 h of ARDS onset	cis	bolus 15 mg	Ramsay 6		midazolame	9.2 ± 3.2	6.55 ± 1.12	25 ± 5.1	106 ± 36	28%	16%	4%		28D: 70.8%	28D: 10.6 ± 9.7	28D: 23.7%
2010	PaO_2/FiO_2 < 150 mmHg	90-day mortality	actual inclusion time: 16 h		37.5 mg/h			sufentanil									icu discharge: 64.3%	90D: 53.1 ± 35.8	ICU: 29.4%
								ketamin											In hospital: 32.2%
								propofole											
									9.2 ± 3.5	6.48 ± 0.92	24.4 ± 4.7	115 ± 41	29% [30]	23%(p = 0.1)	11.7% (p = 0.01)		28D:67.5% (p = 0.64)	28D: 8.5 ± 9.4 (p = 0.04)	28D: 33.3% (p = 0.05)
																	icu discharge: 68.5% (p = 0.51)	90D: 44.6 ± 37.5 (p = 0.03)	ICU: 38.9% (p = 0.06)
																			In hospital: 32.2% (p = 0.08)
ROSE [20]	1006	90-day mortality	48 h of ARDS onset	cis	bolus: 15 mg	Ramsey 5–6	48 h		12.6 ± 3.6	6.3 ± 0.9	25.5 ± 6.0	98.7 ± 27.9	16.8%	17%	4%		D7: 41%	D28: 9.6 ± 10.4	D90: 42.5%

signs of sociated nmHg to tion was ree days ay have reported atory and nation of on in the NMBA group. The authors point that, by abolishing expiratory efforts, a significant amount of derecruitment during expiration can be achieved [22]. There are two Chinese RCTs using vecuronium as the NMBA: Lyu et al. randomized 96 patients with moderate (48 patients) and severe ARDS (48 patients). The patients with PaO_2/FiO_2 < 100 mmHg receiving 24–48 h vecuronium presented significant improvements in oxygenation, perfusion and multiple severity scores, while they had also lower 21-day mortality rates (20.8 vs. 50%, p = 0.04) [33]. Both studies did not report significant adverse effects with the use of aminosteroidal NMBAs.

The most robust evidence concerning the use of NMBAs in ARDS patients comes from the two largest RCTs (ACURASYS and ROSE studies), although reporting conflicting results [20][21]. The ACURASYS study was a multicenter RCT, conducted in France, which randomized 340 patients to receive a 48 h of cisatracurium infusion or placebo, within 48 h of ARDS diagnosis [21]. The primary outcome was 90-day mortality. The study team followed the same NMBA administration protocol as the previous studies [22][30][34]. Using a continuous infusion of 37.5 mg (after a bolus of 15 mg) of cisatracurium, as it had been found adequate to sustain paralysis in the previous studies, no peripheral nerve simulation was performed. The authors found that the hazard ratio for death at 90 days in the cisatracurium group compared to the placebo group was 0.68 (95% confidence interval (CI), 0.48 to 0.98; p = 0.04) after adjustment for the baseline PaO_2/FiO_2, SAPS II and plateau pressures. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (p = 0.08). Patients in the intervention group had also more VFD in the first 28 days (10.6 ± 9.7 vs. 8.5 ± 9.4, p = 0.04) and an increased hazard ratio for weaning from mechanical ventilation by day 90 (HR 1.41 95% CI 1.08 to 1.83; p = 0.01). Barotrauma was significantly more frequent in the placebo group (4 vs. 11.7%, p = 0.01).

In 2014, the National Heart, Lung and Blood Institute (NHLBI) launched the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network to conduct phase III trials to test treatments with the potential to improve

	Patients	Primary End Point	Time of Inclusion	NMBA	Dose	Monitoring	Duration	Sedation	PEEPtot	VT	Pplat	PaO_2/FiO_2	Proning	Steroids	Barotrauma	VAP	ICUAW	VFD 28/60	Mortality
2019	PaO_2/FiO_2 < 150 mmHg		actual randomization time: 8 h		37.5 mg continuous infusion	RASS −5											D28:46.8%		D28: 36.7%
						Ramsey 2–3			12.5 ± 3.5	6.3 ± 0.9	25.7 ± 6.1	99.5 ± 27.9	14.9%	16.4%	6.3%		D7: 31.3%	D28:9.9 ± 10.9	D90: 42.8%
						RASS 0 to −1											D28:27.5%		D28: 37%
Courcelle [36]	407	NMBA use					5 days (IQR 2–10)		<48 h: 12 (10–14)	6.1 (5.8–6.6)	23 (20–26)	126 (88–162)	65%					D28: 0 (0–16)	ICU: 38%
2020	PaO_2/FiO_2 < 150 mmHg	28-day outcomes											Propensity cohort 78%						
	COVID-19 ARDS						[21]												
[28]									>48 h: 11 (10–13)	6.1 (5.8–6.6)	24 (21–26)	120 (87–157)	90% ($p < 0.001$)					D28: 0 (0–10)	ICU: 41% ($p = 0.54$)
													propensity cohort: 80% ($p = 0.86$)						
Lee [37]	129	ICU mortality					5 days (4–9)		survivors: 10 (9–12)	7 (6.2–7.9)		123 (87–197)	16%	92%			53% (superinfection rate)	8.2 ± 9.7	ICU 37%
2022	COVID-19 ARDS												survivors: 20%	91%					mild ARDS: 20%
												[40]	non-survivors: 10%	94%					moderate ARDS: 40%
									non-survivors: 10 (10–12)	6.8 (6.2–8.3)		109 (85–134)							severe ARDS: 43%
Li Bassi [38]																			
2022	1953	90-day mortality							No NMBA: 12 ± 3	7.1 ± 1.4	25.4 ± 5.7	98.1 ± 31.1	8.6%	21.3%	12.4%				

not differ across the patients in both study arms, while patients receiving muscular relaxants presented serious cardiovascular adverse effects (one death from complete heart block and refractory shock) [20]. There are certain differences that may explain the contradictory results in these two RCTs. Firstly, the approach concerning the ARDS treatment was quite different. The amount of PEEP used in ROSE trial was much higher than the one used in the ACURASYS study (12.6 ± 3.6 vs. 9.2 ± 3.2 cm H_2O), prone positioning was less frequently used (16% vs. 29%), while the patient enrollment in the ROSE study was too quick (actual time of enrollment was 8 h from meeting eligibility criteria). Some patients might have improved in the next few hours only with the application of the ventilator (i.e., PEEP application) and not be eligible for the study.

References

1. Ashbaugh, D.G.; Bigelow, D.B.; Petty, T.L.; Levine, B.E. Acute Respiratory distress in adults. Lancet 1967, 2, 319–323.
2. Fan, E.; Brodie, D.; Slutsky, A.S. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. JAMA 2018, 319, 698–710.
3. Bellani, G.; Laffey, J.G.; Pham, T.; Fan, E.; Brochard, L.; Esteban, A.; Gattinoni, L.; van Haren, F.; Larsson, A.; McAuley, D.F.; et al. LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, Patterns of Care, and Mortality for Patients with Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016, 315, 788–800.
4. Herridge, M.S.; Tansey, C.M.; Matté, A.; Tomlinson, G.; Diaz-Granados, N.; Cooper, A.; Guest, C.B.; Mazer, C.D.; Mehta, S.; Stewart, T.E.; et al. Canadian Critical Care Trials Group. Functional

	Patients	Primary End Point	Time of Inclusion	NMBA	Dose	MonitoringDuration	Sedation	PEEPtot	VT	Pplat	PaO_2/FiO_2	Proning	SteroidsBarotrauma	VAP	ICUAW	VFD 28/60	Mortality
	COVID-19 ARDS (moderate and severe)							No NMBA(PS): 11.9 ± 2.73.1	7.4 ± 1.6	25 ± 2.75.9	86 ± 30.7	10.5%	22.9%	9.6%			
	242 with early NMBA						48 h: 74.4%	NMBA: 12.8 ± 3.3	6.9 ± 1.4	26.1 ± 2.75.1	88.5 ± 29.3	21.5%	19.8%	9.6%			
							72 h: 25.6%	NMBA (PS): 12.8 (3.3)	6.8 ± 1.4	26.2 ± 2.75	88.6 ± 29.7	21.9%	19%	10.4%			
Nunez-Seisderos [39]	70 survivors with COVID-19 ARDS	ICUAW		cis	cumulative dose: 739 mg (283–1425)		5 days (2–8)				81 (64–97.75)	91.4%	100%		65.7%	IMV DUR: 13 (7–22.5)	

6. Richardson, S.; Hirsch, J.S.; Narasimhan, M.; Crawford, J.M.; McGinn, T.; Davidson, K.W.; The Northwell COVID-19 Research Consortium; Barnaby, D.P.; Becker, L.B.; Chelico, J.D.; et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020, 323, 2052–2059.
7. Grasselli, G.; Zangrillo, A.; Zanella, A.; Antonelli, M.; Cabrini, L.; Castelli, A.; Cereda, D.; Coluccello, A.; Foti, G.; Fumagalli, R.; et al. COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020, 323, 1574–1581.
8. Lim, Z.J.; Subramaniam, A.; Ponnapa Reddy, M.; Blecher, G.; Kadam, U.; Afroz, A.; Billah, B.; Ashwin, S.; Kubicki, M.; Bilotta, F.; et al. Case Fatality Rates for Patients with COVID-19 Requiring Invasive Mechanical Ventilation. A Meta-analysis. Am. J. Respir. Crit. Care Med. 2021, 203, 54–66.
9. Acute Respiratory Distress Syndrome Network; Brower, R.G.; Matthay, M.A.; Morris, A.; Schoenfeld, D.; Thompson, B.T.; Wheeler, A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N. Engl. J. Med. 2000, 342, 1301–1308.
10. Amato, M.B.; Meade, M.O.; Slutsky, A.S.; Brochard, L.; Costa, E.L.; Schoenfeld, D.A.; Stewart, T.E.; Briel, M.; Talmor, D.; Mercat, A.; et al. Driving pressure and survival in the acute respiratory distress syndrome. N. Engl. J. Med. 2015, 372, 747–755.
11. Brower, R.G.; Lanken, P.N.; MacIntyre, N.; Matthay, M.A.; Morris, A.; Ancukiewicz, M.; Schoenfeld, D.; Thompson, B.T.; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N. Engl. J. Med. 2004, 351, 327–336.
12. Gattinoni, L.; Chiumello, D.; Caironi, P.; Busana, M.; Romitti, F.; Brazzi, L.; Camporota, L. COVID-19 pneumonia: Different respiratory treatments for different phenotypes? Intensive Care Med. 2020, 46, 1099–1102.
13. Tsolaki, V.; Siempos, I.; Magira, E.; Kokkoris, S.; Zakynthinos, G.E.; Zakynthinos, S. PEEP levels in COVID-19 pneumonia. Crit. Care 2020, 24, 303.

14. Grasselli, G.; Tonetti, T.; Protti, A.; Langer, T.; Girardis, M.; Bellani, G.; Laffey, J.; Carrafiello, G.; Carsana, L.; Rizzuto, C.; et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: A multicentre prospective observational study. Lancet Respir. Med. 2020, 8, 1201–1208.
15. Langer, T.; Brioni, M.; Guzzardella, A.; Carlesso, E.; Cabrini, L.; Castelli, G.; Dalla Corte, F.; De Robertis, E.; Favarato, M.; Forastieri, A.; et al. PRONA-COVID Group. Prone position in intubated, mechanically ventilated patients with COVID-19: A multi-centric study of more than 1000 patients. Crit. Care 2021, 25, 128.
16. Angus, D.C.; Derde, L.; Al-Beidh, F.; Annane, D.; Arabi, Y.; Beane, A.; van Bentum-Puijk, W.; Berry, L.; Bhimani, Z.; Bonten, M.; et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients with Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA 2020, 324, 1317–1329.
17. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. Lancet 2021, 397, 1637–1645.
18. REMAP-CAP Investigators; Gordon, A.C.; Mouncey, P.R.; Al-Beidh, F.; Rowan, K.M.; Nichol, A.D.; Arabi, Y.M.; Annane, D.; Beane, A.; van Bentum-Puijk, W.; et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with COVID-19. N. Engl. J. Med. 2021, 384, 1491–1502.
19. Slutsky, A.S. Neuromuscular blocking agents in ARDS. N. Engl. J. Med. 2010, 363, 1176–1180.
20. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network; Moss, M.; Huang, D.T.; Brower, R.G.; Ferguson, N.D.; Ginde, A.A.; Gong, M.N.; Grissom, C.K.; Gundel, S.; Hayden, D.; et al. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. N. Engl. J. Med. 2019, 380, 1997–2008.
21. Papazian, L.; Forel, J.M.; Gacouin, A.; Penot-Ragon, C.; Perrin, G.; Loundou, A.; Jaber, S.; Arnal, J.M.; Perez, D.; Seghboyan, J.M.; et al. ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. N. Engl. J. Med. 2010, 363, 1107–1116.
22. Guervilly, C.; Bisbal, M.; Forel, J.M.; Mechati, M.; Lehingue, S.; Bourenne, J.; Perrin, G.; Rambaud, R.; Adda, M.; Hraiech, S.; et al. Effects of neuromuscular blockers on transpulmonary pressures in moderate to severe acute respiratory distress syndrome. Intensive Care Med. 2017, 43, 408–418.
23. Yoshida, T.; Nakahashi, S.; Nakamura, M.A.M.; Koyama, Y.; Roldan, R.; Torsani, V.; De Santis, R.R.; Gomes, S.; Uchiyama, A.; Amato, M.B.P.; et al. Volume-controlled Ventilation Does Not Prevent Injurious Inflation during Spontaneous Effort. Am. J. Respir. Crit. Care Med. 2017, 196, 590–601.
24. Yoshida, T.; Torsani, V.; Gomes, S.; De Santis, R.R.; Beraldo, M.A.; Costa, E.L.; Tucci, M.R.; Zin, W.A.; Kavanagh, B.P.; Amato, M.B. Spontaneous effort causes occult pendelluft during

mechanical ventilation. Am. J. Respir. Crit. Care Med. 2013, 188, 1420–1427.

25. Beitler, J.R.; Sands, S.A.; Loring, S.H.; Owens, R.L.; Malhotra, A.; Spragg, R.G.; Matthay, M.A.; Thompson, B.T.; Talmor, D. Quantifying unintended exposure to high tidal volumes from breath stacking dyssynchrony in ARDS: The BREATHE criteria. Intensive Care Med. 2016, 42, 1427–1436.
26. Kallet, R.H.; Alonso, J.A.; Luce, J.M.; Matthay, M.A. Exacerbation of acute pulmonary edema during assisted mechanical ventilation using a low-tidal volume, lung-protective ventilator strategy. Chest 1999, 116, 1826–1832.
27. Kress, J.P.; Pohlman, A.S.; O'Connor, M.F.; Hall, J.B. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N. Engl. J. Med. 2000, 342, 1471–1477.
28. Olsen, H.T.; Nedergaard, H.K.; Strøm, T.; Oxlund, J.; Wian, K.A.; Ytrebø, L.M.; Kroken, B.A.; Chew, M.; Korkmaz, S.; Lauridsen, J.T.; et al. Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients. N. Engl. J. Med. 2020, 382, 1103–1111.
29. Marik, P.E.; Kaufman, D. The effects of neuromuscular paralysis on systemic and splanchnic oxygen utilization in mechanically ventilated patients. Chest 1996, 109, 1038–1042.
30. Forel, J.M.; Roch, A.; Marin, V.; Michelet, P.; Demory, D.; Blache, J.L.; Perrin, G.; Gainnier, M.; Bongrand, P.; Papazian, L. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit. Care Med. 2006, 34, 2749–2757.
31. Sottile, P.D.; Albers, D.; Moss, M.M. Neuromuscular blockade is associated with the attenuation of biomarkers of epithelial and endothelial injury in patients with moderate-to-severe acute respiratory distress syndrome. Crit. Care 2018, 22, 63.
32. Fanelli, V.; Morita, Y.; Cappello, P.; Ghazarian, M.; Sugumar, B.; Delsedime, L.; Batt, J.; Ranieri, V.M.; Zhang, H.; Slutsky, A.S. Neuromuscular Blocking Agent Cisatracurium Attenuates Lung Injury by Inhibition of Nicotinic Acetylcholine Receptor-α1. Anesthesiology 2016, 124, 132–140.
33. Lyu, G.; Wang, X.; Jiang, W.; Cai, T.; Zhang, Y. Clinical study of early use of neuromuscular blocking agents in patients with severe sepsis and acute respiratory distress syndrome. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2014, 26, 325–329. (In Chinese)
34. Gainnier, M.; Roch, A.; Forel, J.M.; Thirion, X.; Arnal, J.M.; Donati, S.; Papazian, L. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit. Care Med. 2004, 32, 113–119.
35. Rao, Z.L.J.; Ma, Y.; Li, X.; Xue, J.; Tian, L.; Zhou, W.; Kuang, Y. To retain spontaneous breathing or eliminate spontaneous breathing with neuromuscular blockers in acute respiratory distress syndrome patients? Chin. Crit. Care Med. 2016, 28, 973–977.

36. Courcelle, R.; Gaudry, S.; Serck, N.; Blonz, G.; Lascarrou, J.B.; Grimaldi, D.; On Behalf the COVADIS Study Group. Neuromuscular blocking agents (NMBA) for COVID-19 acute respiratory distress syndrome: A multicenter observational study. Crit. Care 2020, 24, 446.
37. Lee, B.Y.; Lee, S.I.; Baek, M.S.; Baek, A.R.; Na, Y.S.; Kim, J.H.; Seong, G.M.; Kim, W.Y. Lower Driving Pressure and Neuromuscular Blocker Use Are Associated with Decreased Mortality in Patients With COVID-19 ARDS. Respir. Care 2022, 67, 216–226.
38. Alhazzani, W.; Møller, M.H.; Arabi, Y.M.; Loeb, M.; Gong, M.N.; Fan, E.; Oczkowski, S.; Levy, M.M.; Derde, L.; Dzierba, A.; et al. Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020, 46, 854–887.
39. Núñez-Seisdedos, M.N.; Lázaro-Navas, I.; López-González, L.; López-Aguilera, L. Intensive Care Unit-Acquired Weakness and Hospital Functional Mobility Outcomes Following Invasive Mechanical Ventilation in Patients with COVID-19: A Single-Centre Prospective Cohort Study. J. Intensive Care Med. 2022, 37, 1005–1014.
40. Huang, D.T.; Angus, D.C.; Moss, M.; Thompson, B.T.; Ferguson, N.D.; Ginde, A.; Gong, M.N.; Gundel, S.; Hayden, D.L.; Hite, R.D.; et al. Reevaluation of Systemic Early Neuromuscular Blockade Protocol Committee and the National Institutes of Health National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Network Investigators. Design and Rationale of the Reevaluation of Systemic Early Neuromuscular Blockade Trial for Acute Respiratory Distress Syndrome. Ann. Am. Thorac. Soc. 2017, 14, 124–133.