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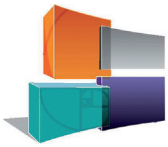

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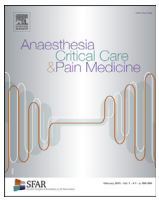

Editorial

Neuromuscular blocking agents as part of lung-protective strategy in severe ARDS patients

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Neuromuscular blocking agents (NMBAs) improve thoraco-pulmonary compliance with better adaptation to the ventilator and inhibition of expiratory muscle activity, resulting in an increased trans-pulmonary pressure at expiration [1]. Changes in ventilation-perfusion relationship might be related to a more uniform distribution of pulmonary perfusion due to the application of lower pulmonary pressures with an associated decrease in lung overdistension. Another hypothesis could be a better regional distribution of tidal volume, avoiding or limiting the overdistension of high compliance territories and improving the recruitment of areas with smaller compliance. NMBAs avoid asynchronies and limit the occurrence of high transpulmonary pressure swings during inspiratory efforts [2]. The use of NMBAs may also limits ventilator-induced lung injuries (VILI) progression with an associated decrease in the incidence of barotrauma and pneumothoraces [3] and a decreased production of proinflammatory cytokines in both lung and blood compartments [4]. Ten years ago, the ACURASYS study [3] showed that NMBAs integrated in a global lung-protective strategy were associated with an improved outcome in moderate-to-severe ARDS patients. It is worth noting that the strategy used in the ACURASYS study associated a 48-hour period of NMBAs use with a protective mechanical ventilation according to the one used in the ARMA study [5], and as soon as possible, a quick transition towards pressure support (PS) ventilatory mode allowing spontaneous breathing mostly from the 3rd day.

The recent ROSE (Reevaluation Of Systemic Early Neuromuscular Blockade) study [6] is a randomised, multi-centre, open-label study involving emergency departments and ICUs (48 hospitals across the USA) comparing the use of cisatracurium with management by light sedation very early in the course of moderate-to-severe ARDS. Patients admitted to the emergency department or in ICU for ARDS of less than 48 hours and having a PaO2/FiO2 ratio $<$ 150 mmHg were eligible. Arterial gas was not mandatory and patients could be included using an algorithm based on SpO2. Among the many exclusion criteria was prior continuous or at least two-fold administration of NMBAs for the management of ARDS, and a PaO2/FiO2 ratio exceeding 200 mmHg between the time patients presented inclusion criteria and randomisation (i.e., a patient could have more than 150 mmHg PaO2/FiO2 ratio at randomisation). There was a strong incentive to include patients as early as possible, sometimes before admission to intensive care. The primary endpoint was hospital mortality from any cause at day 90. There were many secondary goals including neuro-cognitive and physical assessment at 1 year. The study was conceived as a study of superiority from one strategy to the other.

1. Main differences with the ACURASYS strategy

Some important methodological differences have to be highlighted (Table 1). There was no optimisation and standardisation of mechanical ventilation (adjustment of tidal volume, PEEP) before inclusion. Also there was no optimisation of sedation (dose increase) before inclusion in order to improve patient-ventilator harmony. Treatment was optimised by increasing sedation after inclusion in the interventional arm, by increasing PEEP levels after administration of NMBAs. This strategy was associated with hypotensive episodes, which was absolutely not the case in ACURASYS [3]. Indeed, in this latter study, sedation and mechanical ventilation settings were optimised prior randomisation and no haemodynamic consequences were observed after inclusion. Moreover, a high PEEP strategy (according to the ALVEOLI study [7]) was applied in both arms of the ROSE study [6], while a moderate PEEP strategy, according to the ARMA study [5], was used in the ACURASYS study [3]. This is a crucial point, as it has recently been shown that a high PEEP strategy without any personalisation worsens the outcome [7]. It probably explains transient haemodynamic impairment reported in the ROSE trial [6]. Another major point is that there was no incentive to use prone positioning in ROSE [6]. In case of recourse to prone position, it was recommended not to use it during the first 12 hours after inclusion. Finally, there was a strong and protocolised exhortation to change the ventilatory mode at the end of the first 48 hours in ACURASYS [3] with the use of PS and daily mechanical ventilation withdrawal tests (decrease of PEEP, lower level of pressure support) while no such protocolised encouragement in ROSE [6] was reported.

Patients were therefore included in ROSE [6] earlier than in ACURASYS [3] (median time were respectively 8 h and 16 h). The

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Table 1
Comparison of ACURASYS and ROSE [3,6].

	ACURASYS [3]	ROSE [6]
Prior randomisation	Sedation/MV adjustments	Tidal volume adjustment
After randomisation	Placebo/NMBA	Sedation/NMBA/PEEP adjustment
PaO2/FiO2 at randomisation 150-200 mmHg	None	*N* patients not provided
Inclusion site	ICU	ICU or emergency department
Patients from the control group requiring NMBA for injurious MV	56%	Between 17 and 36%
MV settings	Assist-control mode Moderate PEEP strategy	Volume or pressure-controlled mode High PEEP strategy
Prone position use	29%	16%
Day-90 mortality in the NMBA group	31.6%	42.5%

MV: mechanical ventilation; NMBA: neuromuscular blocking agent.

lack of optimisation of the mechanical ventilation settings prior inclusion is testified by the high rate of eligible patients ($N = 658$ patients) who were excluded because their oxygenation status improved from inclusion to randomisation with a PaO2/FiO2 ratio > 200 mmHg [6]. As 1006 patients were included [6], it means therefore that 40% of eligible patients improved in a short period of time. Moreover, it was also specified that patients with a PaO2/FiO2 ratio between 150 and 200 mmHg were randomised [6]. In addition, 655 eligible patients were not included because they received at least two NMBAs injections prior to randomisation [6]. That is, 40% of the patients who presented inclusion criteria were treated with NMBAs and not considered for randomisation. It might be because clinicians thought it better to paralyse these patients than to run the risk of including them in the control group, which constitutes a serious bias. In the ACURASYS study [3], only 42 patients were not included because they received continuous infusion of NMBAs prior inclusion.

Another mean to evaluate the ARDS severity is to identify how many patients from the control group received NMBAs because of an excessive plateau pressure. Despite the fact that a lower PEEP strategy was used in the ACURASYS trial [3] and a higher plateau pressure tolerated, more patients in this study received NMBAs as rescue (56%) than in the ROSE study [6]. However, the exact number in this latter study is not provided. It is only specified that 17% of patients in the control group received a NMBA during the first 48 hours, 8% from 48 to 96 hours and 11% patients after 4 days. The total number of patients in the control group who received a NMBA at any time for the management of ARDS is not given, but is comprised between 17% and 36%.

Regarding the main objective of ROSE [6], hospital mortality at day 90 was 42.5% in the interventional group and 42.8% in the control group. Finally, there was no difference in mortality at day 90 between the control groups of ROSE and ACURASYS, even if 10 years separate the two studies [3,6]. But the major point is that day 90 mortality was significantly lower in the interventional group of ACURASYS (31.6%) as compared with the interventional group of ROSE (42.5%), which is a very crucial point. Apart from the PEEP strategy, which could at least partly explain the early deaths observed in ROSE [6], other factors could explain these results. The first one is the use of prone positioning. Only 16% of patients included in the ROSE study were prone as compared with 29% in the ACURASYS study [3,6]. Finally, we shall bear in mind that 91% of patients included in the prone group of the PROSEVA study received NMBAs [8].

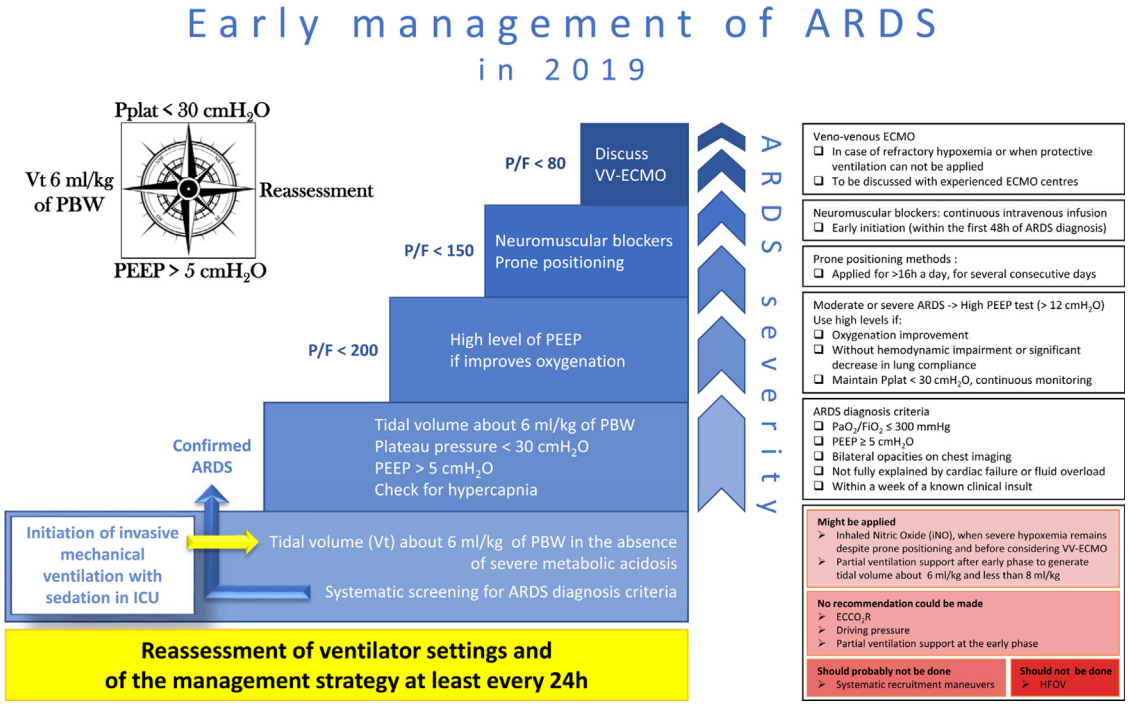

Fig. 1. Therapeutic algorithm for the early ARDS management [9].

2. Implications

The ROSE study [6] is an essential contribution showing that we cannot dissociate the use of NMBAs from other cares dedicated to ARDS patients regarding lung protection (Fig. 1). NMBAs should be considered as an adjuvant to integrate in a global strategy. The ROSE trial shows that a very early use of NMBAs, before any optimisation of mechanical ventilation settings and sedation adjustments (allowing the adaptation patient-ventilator with correction of gas exchange, thus making possible to avoid NMBAs) does not change the outcome. The ACURASYS strategy [3] included pre-inclusion optimisation, ARMA moderated PEEP strategy [5], short period of muscle relaxation, prone positioning and mechanical ventilation weaning using pressure support. In the ROSE study [6] there were no prior optimisation of mechanical ventilation, a high PEEP strategy, no incentive for rapid weaning from mechanical ventilation using a ventilatory mode allowing spontaneous ventilation, and a parsimonious recourse to the prone positioning.

From our point of view, ROSE [6] explored a more extensive and privileged use of NMBAs. To redo ACURASYS, it would have been necessary, at least, to include patients after optimisation of sedation and mechanical ventilation. In ROSE [6], the authors do not provide the total amount of sedatives and analgesics used. We have to stress that in ACURASYS [3] there was no difference between the two groups regarding the amount of sedatives received (no "oversedation" in the control group).

The use of NMBAs should be integrated into an overall strategy including the reduction of tidal volume, a reasoned use of PEEP according to its impact on gas exchange and haemodynamic status, the use of prone positioning and a ventilatory mode, allowing spontaneous ventilation as soon as possible... in a word, what has been put forward by the recent formal guidelines proposed by French experts in the field (Fig. 1) [9].

Disclosure of interest

The authors declare that they have no competing interest.

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Laurent Papazian[a,b,*], Sami Hraiech[a,b], Laure Cazenave[c,d], Jean-Marie Forel[a,b]

[a] *Marseille Public University Hospital System, North Hospital, Service de Médecine Intensive et Réanimation, 13015 Marseille, France*
[b] *University of Aix-Marseille, Faculty of Medicine, Centre d'Études et de Recherches sur les Services de Santé et qualité de vie EA 3279, 13005 Marseille, France*
[c] *Hospices Civiles de Lyon, France*
[d] *Groupe Jeune - French Society of Anaesthesia and Critical Care Medicine*

[*] Corresponding author at: Service de Médecine Intensive et Réanimation, North Hospital, Chemin des Bourrely, 13015 Marseille, France
E-mail address: laurent.papazian@ap-hm.fr (L. Papazian).