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Rescue therapy for refractory ARDS should be offered early: no

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Clinical vignette A previously healthy 51-year-old woman was admitted to the ICU with severe community acquired pneumonia. She required intubation and mechanical ventilation 6 h after admission. Her respiratory status declined continuously over the next few hours and her $\text{PaO}_2/\text{FIO}_2$ ratio was 65 with a PEEP of 8 cmH_2O at 12 h after admission (plateau pressure was 28 cmH_2O). She was hemodynamically stable and had normal renal function.

Despite the remarkable hypoxemia in this case of severe ARDS, there is no rush to ECMO for several reasons; each related to the fact that aspects of the patient's current ventilator and non-ventilator management should be optimized prior to consideration of ECMO.

First of all, a low-volume, low-pressure ventilation strategy should be undertaken according to the protocols of the ExPress [1] or ARDSNet ARMA [2] trials. We are not

given information about the selected tidal volume (VT). However, it should be based on predicted body weight (PBW). As the patient in this case is a woman, it should be mentioned that clinicians tend to use actual body weight instead of PBW for assigning VT and therefore over-ventilate women and people who are of shorter stature [3]. PEEP should be set initially according to the protocol used (standard or high PEEP strategy) [4, 5] and is almost certainly too low in this case. Titration of PEEP may benefit the patient. Bear in mind that after raising PEEP, plateau pressure (Pplat) may increase well above 30 cmH_2O . However, should the lung be recruited by the increase in PEEP, Pplat would then decrease. Furthermore, the assessment of oxygenation response to PEEP also requires only a few minutes [6]. Is there room for Pplat greater than 30 cmH_2O due to impairment of elastic properties of the chest wall? Grasso et al. [7] were able to avoid ECMO in seven severe influenza A(H1N1)-associated ARDS patients with high chest wall elastance that allowed the PEEP to be raised in order to reach a transpulmonary pressure of 25 cmH_2O . Such measurements require the insertion of an esophageal balloon. A more common way of setting PEEP is to use a PEEP/ FIO_2 table. Suppose FIO_2 is 0.80 in this case, PaO_2 would be 52 mmHg and hence PEEP should range from 14 to 22 cmH_2O depending on the PEEP/ FIO_2 table [4, 5]. Even though the current concept for setting PEEP is the prevention of the cyclical opening and closing of alveoli during tidal breaths, in a patient like this, the oxygenation response to PEEP is relevant. The post hoc analysis of the trials on PEEP observed that the oxygenation response to PEEP was associated with better outcomes in ARDS patients [8]. Chiumello et al. [9] found that the PEEP/ FIO_2 table was the only way to set lower PEEP in patients with low potential of recruitment and higher PEEP in patients with high potential of recruitment. In line with the above considerations, a recruitment maneuver should be considered in this patient [10] followed by a higher level of PEEP than prior to the procedure.

Fig. 1 Management algorithm for patients with ARDS

The second aspect of her care to optimize is sedation and neuromuscular blockade. Deep sedation should be provided to reduce oxygen consumption and improve ventilator synchrony and, once a level of deep sedation is reached, a

neuromuscular blocking agent should be promptly started, ideally using cisatracurium for 48 h. With this medication, the oxygenation improves, the rate of pneumothorax is reduced, and the survival is improved [11].

The third item to consider is the fluid balance. With her normal renal function and stable hemodynamics, this patient is a good candidate for receiving early diuretics. Although a large randomized controlled trial failed to show a beneficial effect on mortality [12], a conservative fluid strategy was associated with improvement in the oxygenation index and improvements in ventilator- and ICU-free days. A separate randomized placebo-controlled trial showed that furosemide plus albumin significantly improved oxygenation in hypoproteinemic (plasma protein less than 6 g/dl) ARDS patients [13]. Should this patient be hypoproteinemic, this strategy is quite simple to improve oxygenation, and could be considered.

The fourth opportunity for optimization is in the use of prone positioning. The completion of previous steps should only require a couple of hours and, if the patient is still sufficiently hypoxemic, prone position should be instituted given that there are no known contraindications. Caution should be applied in centers that do not have extensive experience with prone positioning. In patients with ARDS and severity criteria ($\text{PaO}_2/\text{FIO}_2$ less than 150 mmHg with PEEP of at least 5 cmH₂O and FIO_2 of at least 0.6) a significant improvement in survival was demonstrated as compared to the supine position in the PROSEVA trial [14]. This benefit was also observed in the lowest quartile of $\text{PaO}_2/\text{FIO}_2$ at the time of randomization, which ranged from 45 to 87 mmHg. The current case in question is in this range. Prone positioning should be performed in a complete prone position and for a prolonged session (16 consecutive hours or more as scheduled in PROSEVA).

The fifth item to consider would be inhaled pulmonary vasodilators: inhaled epoprostenol or inhaled nitric oxide.

These medications can be used in severe hypoxemia to improve oxygenation by dilating pulmonary vascular beds in those areas of the lungs where ventilation is preserved, thereby decreasing the proportion of blood shunted through areas of poor ventilation. It can be started while the patient is still in the supine position but several studies found an additive effect of prone position and nitric oxide on oxygenation. That said, these medications do not change overall outcomes and, given that the degree of hypoxemia in this case is not immediately life-threatening, delaying the decision for ECMO in order to institute these medications may not be necessary.

Where in the course of treating this patient should we consider ECMO (Fig. 1)? In a patient without life-threatening hypoxemia, we would allow at least 6 h to decide whether or not ECMO should be undertaken. The following criteria for initiating ECMO in ARDS patients have been recently proposed [15]: $\text{PaO}_2/\text{FIO}_2$ ratio less than 80 despite high PEEP (15–20 cmH₂O) for at least 6 h in patients with potentially reversible respiratory failure, or hypercapnia with acidemia (pH less than 7.15) or Pplat greater than 35–45 cmH₂O, depending on the patient's body habitus. A similar strategy is being tested in a multicenter randomized controlled trial and final results are expected in the near future.

Conflicts of interest Dr. Brodie previously received research support and provided research consulting for Maquet Cardiovascular. He is on the medical advisory board of ALung Technologies and Kadence (Johnson & Johnson). All compensation for his consulting goes to Columbia University.

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