Intensive Care Med (2015) 41:923–925
DOI 10.1007/s00134-015-3721-5

EDITORIAL

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Rescue therapy for refractory ARDS should be offered early: yes

Received: 13 February 2015
Accepted: 25 February 2015
Published online: 20 March 2015

For contrasting viewpoints, please go to
doi:10.1007/s00134-015-3704-6 and doi:10.1007/s00134-015-3708-2.

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Clinical vignette A previously healthy 51-year-old woman (height 165 cm, weight 60 kg) 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. Twelve hours after admission, blood gases were as follows: pH = 7.36, $PaCO_2$ = 47 mmHg, PaO_2 = 65 mmHg, HCO_3^- = 26 mmol/L on FiO_2 = 100 %, Vt set at 340 ml, PEEP at 8 cmH_2O, respiratory rate at 28/min, and plateau pressure measured at 28 cmH_2O. She was hemodynamically stable and had a normal renal function.

This patient has severe ARDS according to the Berlin definition [1]. This patient has very low respiratory system compliance (18 ml/cmH_2O) and is ventilated with a high driving pressure (20 cmH_2O). Hypoxemia is extremely severe with a high oxygenation index (43 cmH_2O/mmHg). Recent clinical studies showed that hospital mortality in patients experiencing such severe forms of ARDS ranges from 45 to 60 % [1–6].

What are the first-line options in this situation?

This patient receives only 8 cmH_2O of PEEP. While higher PEEP confers a survival advantage in severe ARDS patients [7], higher levels of PEEP in this patient very likely will further increase the plateau pressure to levels that are certainly associated with an increased risk of ventilator-induced lung injury. Inhaled nitric oxide might have improved arterial oxygenation although this intervention was not shown to improve long-term survival. On the other hand, prone positioning should be rapidly initiated for more than 16 h since a significant increase in survival [8] has been observed in patients with severe ARDS with this maneuver. This patient should also receive continuous infusion of neuromuscular blockade agents [9].

What is the rationale for applying "ultraprotective" MV in this situation?

Lung hyperinflation occurs in approximately 30 % of ARDS patients ventilated using the protective ARDSNet strategy [10]. Moreover, Hager and co-workers retrospectively analyzing data of the "ARDSNet" trial group show a linear relationship between mortality and P_{plat}—a linear relationship in the sense that the lower P_{plat}, the lower the mortality, even for P_{plat} less than 30 cmH_2O [11]. In a proof of concept study, Terragni et al. [12] demonstrated that very low tidal volume ventilation

(3.5–5 ml/kg) and lower P_{plat} (less than 25 cmH_2O) enhance lung protection as indicated by the significant attenuation of the pro-inflammatory signal observed a the pulmonary level.

Because Vt reduction to below 6 ml/kg to achieve P_{plat} less than 25 cmH_2O may induce severe hypercapnia, this "ultraprotective" MV strategy may not be possible without the recourse to extracorporeal carbon dioxide removal ($ECCO_2$-R) which only provides CO_2 removal or venovenous extracorporeal membrane oxygenation (ECMO) which achieves complete extracorporeal blood oxygenation and CO_2 removal.

Why should ECMO be initiated rapidly in this patient?

The patient's lung mechanics and blood gases should be carefully monitored during the prone positioning trial and after turning the patient back to the supine position. In the situation of major improvement of lung compliance and blood oxygenation following this trial, conventional MV should be continued until the patient can be safely extubated. Alternatively, if low respiratory system compliance and severe hypoxemia persist, venovenous ECMO should be instituted as soon as possible for the following reasons.

First, to achieve "ultraprotective" low volume and low pressure MV in this severely hypoxemic patient, ECMO should be preferred over $ECCO_2$-R. Under ECMO, Vt should be dramatically reduced to achieve P_{plat} less than 25 cmH_2O, with PEEP greater than 12 cmH_2O, since these settings were shown to be independently associated with better outcomes [4, 13].

Second, modern ECMO devices are simpler, safer, require less anticoagulation, and are associated with fewer bleeding complications and it is now possible to support patients for weeks [14].

Third, recent series and a randomized trial demonstrated better survival for patients receiving ECMO for severe ARDS [2–4, 15]. The CESAR trial [3] evaluated a strategy of transfer to a single center which had ECMO capability while the patients randomized to the control group received conventional MV. Mortality or severe disability 6 months after randomization was lower for the 90 patients randomized to the ECMO group (37 vs 53 %, $p = 0.03$). Interestingly, more than 60 % of the randomized patients suffered pneumonia and their mean PaO_2/FiO_2 (76 mmHg) was higher than that of the patient described herein. A British collaborative cohort series of pandemic influenza A (H1N1)-induced ARDS patients also showed significantly lower mortality (24 vs 51 %) after propensity matching for 80 patients transferred to ECMO referral centers [2].

Fourth, factors strongly associated with poorer outcomes in series of severe ARDS patients receiving ECMO were older age, a greater number of days of MV before ECMO, a higher number of organ failures, low pre-ECMO respiratory system compliance, absence of paralysis or prone positioning before ECMO, and immunosuppression [15, 16]. Based on these factors, predictive survival models have been developed to help clinicians select appropriate candidates for ECMO. Interestingly, according to the recently developed RESP [15] and PRESERVE [16] scoring systems, hospital mortality after ECMO initiation would be less than 20 % for the patient described above, should ECMO support be initiated within 48 h of tracheal intubation.

Lastly, a high incidence of cognitive impairment and psychiatric symptoms was demonstrated in long-term survivors of acute lung injury in the Fluid and Catheter Treatment Trial [17]. In that study, lower PaO_2 [86 (70–98) vs 71 (67–80) mmHg, $p = 0.02$] was associated with cognitive and psychiatric impairment 12 months following randomization. It can therefore be hypothesized that ECMO might improve long-term quality-of-life and cognitive function by improving blood oxygenation in severely hypoxemic ARDS patients. Indeed, patients randomized to the ECMO arm of the CESAR trial [3] or the 67 long-term survivors of the French multicenter ECMO-treated ARDS cohort [16] exhibited comparable or better of health-related quality-of-life scores than those reported by patients with less severe ARDS treated with conventional management [18].

In conclusion, a strong pathophysiological rationale and data from recent studies of ECMO for severe ARDS argue for the early initiation of ECMO in the patient described above. This strategy might decrease mortality from 45–50 % to less than 20 %, with potentially less cognitive and psychiatric impairment and improved health-related quality-of-life in long-term survivors. The currently ongoing ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial (NCT01470703) [19], an international multicenter randomized controlled trial comparing conventional MV with prone positioning to ECMO in very severe ARDS patients (PaO_2/FiO_2 less than 80 mmHg), might confirm this hypothesis.

Conflicts of interest Dr. Combes is the primary investigator of the EOLIA trial, NCT01470703, a randomized trial of VV-ECMO supported in part by MAQUET. Dr. Combes has received honoraria for lectures from MAQUET. Prof. Ranieri consulted for Hemodec, ALung, Maquet. He also lectured for Novalung. He was the PI of a Maquet supported trial on ECCO2R in patients with COPD.

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