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FOCUS EDITORIAL

Focus on ECMO and $ECCO_2R$ in ARDS patients

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The technical aspects of veno-venous extracorporeal membrane oxygenation (vv-ECMO) are still improving, permitting the treatment of ARDS patients with very severe hypoxaemia. A recent German survey showed that the incidence of vv-ECMO in the population increased from 1.0:100,000 inhabitants/year in 2007 to a maximum of 3.0:100,000 in 2012, and then stabilised at 2.4:100,000 in 2014 [1]. The in-hospital mortality slightly decreased over time but remained high, at 58.1% in 2014. This real-life mortality rates in an unselected population of patients undergoing ECMO for ARDS is even higher than previously reported. The extracorporeal CO_2-removal ($ECCO_2$-R) is a modification of ECMO characterised by a reduction in extracorporeal blood and sweep gas flow. The aims of $ECCO_2$-R are: (1) the management of acute 'isolated' hypercapnic respiratory failure, (2) the reduction of tidal volume (3–4 ml/kg) and the control of hypercapnia, and (3) the avoidance of intubation in exacerbated chronic obstructive lung disease. While in the latter situation a number of small observational studies or case reports exerted promising results, the scientific evidence for the use and benefit of $ECCO_2$-R in ARDS patients is limited [2].

The prospective observational study by Hermann et al. [3], investigating the efficacy and safety of a novel pump-driven ECCO2-R-system demonstrated a significant, but 'intensity'-dependent, amount of CO_2 removal between 40 and 70 ml/min. The CO_2 transfer was dependent on the amount of blood flow (0.5–2.0 l/min) and sweep gas flow. A rapid normalisation of hypercapnia secondary to higher blood flows (>1.0 l/min) and a moderate increase in oxygenation were found. However, very high sweep gas flows (higher than 10 l/min) were associated with a deterioration in O_2 and CO_2 transfer. Based on these study results, it is recommended to use $ECCO_2$-R settings that combine moderate blood flow (1–1.5 l/min) and sweep gas flow (2–8 l/min) to achieve the best clinical effect and to avoid adverse effects. The combination of $ECCO_2$-R and renal replacement therapy was investigated in 11 patients with ARDS and acute renal failure [4]. A membrane oxygenator was inserted in a continuous RRT system, resulting in an average CO_2 removal rate of 80 ml/min (corresponds to a reduction of ≈20% of the arterial $PaCO_2$ level). Consequently, the tidal volume was lowered from 6 to 4 ml/kg and the plateau pressure could be reduced from 25 to 21 cm H_2O ($p < 0.01$); no adverse events were reported. It is concluded that the combination of $ECCO_2$-R with renal replacement therapy allows a safe and adequate blood 'purification' of renal- and pulmonary-associated substances together while enhancing lung protective ventilation in critically ill patients. The trend towards a 'personalised medicine' has reached intensive care medicine and the management of ARDS patients should be revisited accordingly [5]. $ECCO_2$-R could become an important part of such a project in a 'balanced' portfolio of extracorporeal lung support. Although vv-ECMO remains the first choice in patients with refractory hypoxaemia, $ECCO_2$-R might be a helpful tool when a tidal volume reduction results in insufficient CO_2 excretion or uncontrolled hypercapnia. To fulfil such a project, additional prospective randomised studies investigating the efficacy and potentially adverse effects of $ECCO_2$-R in ARDS are warranted.

Although improvement in the management of patients presenting severe ARDS has been achieved, haemorrhage remains the most frequent complication in patients undergoing ECMO, with an incidence that varies from 20

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to 56% [6]. Intracranial haemorrhage occurs in around 5% of patients undergoing vv-ECMO [7]. Haemorrhage appears to also be a common issue in patients undergoing $ECCO_2$-R, with around one-third of them developing bleeding [8]. Importantly, haemorrhage is independently associated with the risk of death, making it a priority to optimise haemostasis balance in these patients.

Many factors related to patients, circuit and treatment may lead to an increased risk of haemorrhage. Haemostasis anomalies due to the underlying disease include disseminated intravascular coagulation and thrombocytopenia. In a cohort of 100 patients undergoing ECMO for ARDS, Abrams et al. have identified patient severity and severe thrombocytopenia at the time of ECMO cannulation to be independently associated with the occurrence of severe thrombocytopenia within ECMO course [9]. Platelet dysfunction, acquired von Willebrand disease and consumption of coagulation factors are the results of blood flow through the circuit and may contribute to haemorrhage [9]. Finally, anticoagulation with heparin, administered to offset the increased risk of thrombotic events secondary to the contact between blood and non-endothelial surface, has been found to be significantly associated with haemorrhage [6]. Improvement in technologies with the utilisation of coated circuits has reduced thrombotic risk. As a result, a lower level of anticoagulation administration may be used; however, the optimal anticoagulation regimen remains unknown. Recommendations on anticoagulation and transfusion in patients undergoing vv-ECMO and $ECCO_2$-R are mainly based on experts' opinion. A low haemoglobin (Hb) threshold (7 g/dl) that reduces red blood cells (RBC) exposure and adverse events related to RBC transfusion, appears to be safe [10]. Nonetheless, in cases of persistent severe hypoxia, a higher Hb threshold (10 g/dl) may prevent against severe tissue hypoxia [11]. Although some observational studies suggest that low-dose heparin is safe, thrombotic events are likely to be underdiagnosed and underreported, and the extracorporeal life support organisation recommends therapeutic anticoagulation in these patients. Studies aiming to identify what transfusion strategies benefit these patients and to determine the anticoagulation regimen that will decrease bleeding without increasing thrombosis are warranted. During both vv-ECMO and $ECCO_2$-R, a key prognostic factor might be mechanical ventilation settings. Recent reports [12, 13] suggest that there is no consensus regarding the optimal ventilator settings even if a decrease in tidal volume and plateau pressure are usually applied. There is a need for studies aiming to evaluate if a dramatic reduction in tidal volume, respiratory rate and plateau pressure would reduce ventilator-induced lung injury. This would be a key point when interpreting the results of randomised controlled trials on vv-ECMO in ARDS patients.

From an organisational point of view, patients requiring these supports should be treated in referral centres, as there is a correlation between the number of treated vv-ECMO patients/year and patient outcome. It is also urgent that international and national intensive care societies support and recommend the applying of a universal nurse-to-patient ratio of at least 1:1 in patients undergoing ECMO [14]. Finally, many aspects of the treatment by these sophisticated tools remain unresolved and need additional research [15].

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Compliance with ethical standards

Conflicts of interest
Cécile Aubron and Laurent Papazian do not have any conflict of interest to declare regarding this manuscript.

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