Combined use of extracorporeal membrane oxygenation and activated protein C for severe acute respiratory distress syndrome and septic shock

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Several anticoagulation strategies are used in patients who receive extracorporeal membrane oxygenation (ECMO). We report 2 cases in which activated protein C (APC; Xigris; Eli-Lilly, Indianapolis, Ind) and ECMO were used concomitantly for severe refractory acute respiratory distress syndrome (ARDS) and septic shock. Both patients had a good outcome. Heparin-coated ECMO circuits and intravenous APC without other intravenous anticoagulants might represent a possible anticoagulation regimen in this patient population.

CLINICAL SUMMARY

Patient 1

The patient was a 60-year-old man hospitalized because of community-acquired pneumonia. On admission, he had severe hypoxemia (partial pressure of oxygen in arterial blood divided by inspired fraction of oxygen [$\text{PaO}_2/\text{FiO}_2$] = 95) and rapidly required endotracheal intubation, mechanical ventilation, broad-spectrum antibiotics, corticosteroids, and APC. Twenty-four hours later, he was transferred to a tertiary care facility to receive continuous renal replacement therapy for acute renal failure and management of septic shock. His oxygenation deteriorated ($\text{PaO}_2/\text{FiO}_2$ = 85) despite administration of 100% oxygen and high-frequency oscillation ventilation. The patient was started on venovenous ECMO. The right femoral vein and right internal jugular vein were cannulated percutaneously (28Fr and 19Fr canulae; Biomedicus; Medtronic, Minneapolis, Minn). The oxygenator (Quadrox D; Maquet, Hirrlingen, Germany) and the circuit were heparin coated. APC was used from the day before initiation of ECMO for 96 hours. After the end of the APC infusion, intravenous heparin was administered on day 3 to achieve a target partial thromboplastin time of 60 to 100 seconds. No thrombotic or hemorrhagic complications were observed. ECMO was finally weaned after 2 unsuccessful attempts, and antibiotics were tailored to treat the *Stenotrophomonas maltophilia* and *Staphylococcus*

aureus that were cultured from the patient's bronchial secretions. The total ECMO support lasted 5 days. The patient was weaned from the ventilator 13 days after initiation of mechanical ventilation and discharged to a peripheral hospital after 14 days.

Patient 2

In a previously healthy 16-year-old girl who presented with sore throat and fatigue, a rapid test confirmed the diagnosis of mononucleosis. Over the next 48 hours, she experienced severe hypoxic respiratory failure, acute renal failure, and septic shock. She was treated with endotracheal intubation, continuous renal replacement therapy, broad-spectrum antibiotics, corticosteroids, and APC. Despite attempts at high-frequency oscillation ventilation and inhaled nitric oxide, the $\text{PaO}_2/\text{FiO}_2$ ratio decreased to 42. Emergency venovenous ECMO was instituted with a right internal jugular inflow and a left femoral vein outflow (25Fr and 19Fr canulae, heparin-bonded circuit, and oxygenator). The ECMO support lasted 5 days. APC was used during the 4 first days on ECMO, and no anticoagulation was used thereafter. No thrombotic or hemorrhagic complications were observed. The patient was successfully weaned after 5 days on ECMO, she was extubated after 11 days, and she returned home after 20 days. The only positive culture was EBV in bronchial secretions.

The leukocyte counts, platelet counts, and coagulation profiles of both patients are displayed in Figure 1. The pressure gradient across the oxygenator and the preoxygenator pressures are displayed in Figure 2.

DISCUSSION

Severe sepsis complicated by ARDS is associated with high mortality. Patients with these conditions are treated aggressively with early, goal-directed therapy¹ and might benefit from the administration of APC² through its anti-inflammatory and antithrombotic properties. The use of APC has been associated with a significant bleeding risk and has not been reported in patients who are also receiving ECMO.

ECMO is a last-resort option for life support in patients who have refractory ARDS. Despite disappointing initial results,³ ECMO remains a lifesaving option in carefully selected patients. Recent data suggest improved survival in ECMO-treated patients compared with those receiving conventional treatment.⁴

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FIGURE 1. A, Leukocyte count (WBC) from day 0 to day 5 on extracorporeal membrane oxygenation (ECMO). Both patients experienced a decrease in their leukocyte counts while receiving treatment for sepsis. B, Platelet count (Plt) from day 0 to day 5 on ECMO. Patient 1 had a normal platelet count throughout the ECMO run. Patient 2 had moderate thrombocytopenia for 2 days during the ECMO run. C, Partial thromboplastin time (PTT) during the ECMO run. After 72 hours on ECMO, heparin infusion was initiated in patient 1. The initial high PTT at initiation of heparin on day 3 in patient 1 might have been caused by an interaction between APC and heparin. D, International normalized ratio (INR) during the ECMO run. The initial abnormal INR in patient 1 was rapidly corrected during ECMO. Squares, patient 1; diamonds, patient 2.

Anticoagulation for ECMO is controversial and is relatively contraindicated in patients at high risk for bleeding. Anticoagulants that have been used with ECMO include unfractionated and low-molecular-weight heparin, argatroban, and hirudin.⁵ We report 2 patients with septic shock and ARDS in which tip-to-tip heparin-coated circuits and APC

were used as principal modalities of anticoagulation. There were no complications in either case. The other inflammatory and coagulation parameters corrected progressively while the patients received ECMO and APC, no anemia was observed, and renal and neurologic function recovered completely in both cases. No evidence of clotting in the ECMO circuit was observed. Formal anticoagulation with intravenous heparin might not be required for ECMO with heparin-bonded circuits in patients who are already receiving APC.

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FIGURE 2. Preoxygenator pressure and pressure decrease across oxygenator. There were no abnormalities in these pressures for either patient. ECMO, Extracorporeal membrane oxygenation. Squares, Patient 1; diamonds, patient 2.