# β-Blockers to Optimize Peripheral Oxygenation During Extracorporeal Membrane Oxygenation: A Case Series

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***Objectives:*** **Veno-venous extracorporeal membrane oxygenation (ECMO) is a well-established therapy in patients affected by respiratory failure and unresponsive to conventional therapy. Despite technical innovations, some limitations still exist, the most important one being refractory hypoxemia. This problem is linked partially to the mixture between patients' blood and ECMO fully oxygenated blood. In the present work, the reduction of cardiac output was proposed for the treatment of refractory hypoxemia in patients with high-flow ECMO and high endogenous cardiac output.**

***Design:*** **An observational study.**

***Setting:*** **A university hospital.**

***Participants:*** **Three consecutive patients suffering from persisting severe hypoxemia despite high-flow ECMO and with concomitant high cardiac output (>7 L/min).**

***Intervention:*** **A bolus dose of 500 μg/kg and a continuous infusion of esmolol was used and titrated to an $SpO_2$ >92%.**

***Measurements and Main Results:*** **Esmolol administration was safe and highly beneficial in terms of peripheral oxygenation. $PaO_2$ increased from 54 to 90 mmHg, from 50 to 94 mmHg, and from 49 to 66 mmHg during the first 12 hours of esmolol treatment in the 3 patients.**

***Conclusions:*** **In selected septic, tachycardic patients with a high cardiac output, veno-venous ECMO, led to improvement of peripheral oxygenation with the addition of a short-acting β-blocker infusion.**



***KEY WORDS: extracorporeal membrane oxygenation (ECMO), acute respiratory distress syndrome (ARDS), β-blockers, esmolol, refractory hypoxemia, intensive care, anesthesia***

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) can support or substitute for respiratory function in patients affected by severe respiratory failure, most commonly caused by acute respiratory distress syndrome (ARDS). Veno-venous (V-V) ECMO is indicated to support lung function and oxygenation, whereas veno-arterial (V-A) ECMO is a heart-lung machine that offers the possibility to sustain both oxygenation and perfusion.[1,2]

Since its early application in humans in 1972, innovation in technical materials has led to benefits in terms of applicability, ease of cannulation, performance, durability of the circuit, limited thrombus formation, hemolysis, low inflammatory response, and gas exchange.[1,2] Nevertheless, despite technical improvements, it often happens that peripheral oxygenation obtained by V-V ECMO is not satisfactory. Low arterial $PaO_2$ during V-V ECMO currently is managed either by increasing ECMO flow (and thus the percentage of oxygenated blood that will mix with the patient's own venous blood) or by applying V-A ECMO to bypass the lung-heart system. Both solutions may not improve the oxygenation adequately and/or can be associated with complications.[1-3]

The authors hereby describe, for the first time, a third method to deal with the insufficient peripheral oxygenation in V-V ECMO–treated septic patients with a high cardiac output. With the hypothesis that the ratio between V-V ECMO–oxygenated blood and the patients' venous blood can be raised by decreasing the patients' cardiac output, the authors decreased heart rate and contractility with a continuous titrated infusion of a short-acting β-blocker.

## MATERIAL AND METHODS

After Ethical Committee approval and patients or next-of-kin written consent, three consecutive patients with ARDS and hypoxia refractory to medical therapy undergoing lung-protective ventilation strategy[4] and high-flow V-V ECMO were included in the study. On admittance to the intensive care unit, all the patients were septic according to standard definitions. Two patients suffered from a bacterial pneumonia; 1 suffered from $H_1N_1$ influenza A lung infection. All patients were receiving norepinephrine.

Patients were treated according to the Surviving Sepsis Campaign guidelines except for the blood product administration (hemoglobin target considered: 10 mg/dL) and the coagulation management (including antiplatelet therapy, unfractionated heparin, and antithrombin administration), which were titrated according to ECMO requirements.[3,5] Patients were treated according to standard protective ventilation strategies, providing a tidal volume of 4 to 8 mL/kg ideal body weight, a peak pressure ≤26 $cmH_2O$, and a positive end-expiratory pressure level not exceeding 15 $cmH_2O$ in a pressure-controlled modality.[4] In case of refractory hypoxemia despite ventilatory and medical therapy (oxygenation index >30, ratio $PaO_2/F_IO_2$ ≤100 mmHg, plateau pressure ≥30 $cmH_2O$ with a 4-mL/kg tidal volume ventilation),[6] patients were evaluated for V-V ECMO use. ECMO was not started in patients with severe comorbidities (eg, cancer), contraindications to anticoagulation therapy, or ventilatory support provided for more than 7 days.[3] Cannulation of the femoral vein and the jugular vein were conducted percutaneously with 22F to 24F Quickdraw femoral venous cannulae (Edward Lifesciences LLC, Irvine, CA). The authors used a centrifugal Maquet PLS 2050 ECMO circuit (MAQUET GmbH & Co KG, Rastatt, Germany) and a Maquet Quadrox PLS Jostra oxygenator (MAQUET GmbH & Co KG). A temperature-controlled device was provided by Maquet (MAQUET GmbH & Co KG). Anticoagulation was achieved by a continuous intravenous infusion of unfractioned heparin titrated to maintain an activated coagulation time >160 seconds and <200 seconds. In case of persisting severe hypoxemia (peripheral $O_2$ saturation <91% or $PaO_2/F_IO_2$ <100 mmHg despite ECMO treatment) and

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concomitant high cardiac output (>7 L/min), esmolol administration was initiated. A bolus dose of 500 μg/kg and a continuous infusion of esmolol were used and titrated to an $SpO_2$ >92%.

Baseline monitoring consisted of invasive pressure monitoring, pulse oximetry, continuous electrocardiography, urine output, and central venous pressure. A baseline chest radiogram was performed and repeated as needed. Daily transesophageal echocardiographic evaluation was performed to assess left and right ventricular function, pulmonary hypertension, intravascular volume status, and correct positioning of the jugular cannula. Thermodilution cardiac output measurements were performed. Arterial blood gas analysis was performed every hour. The evaluation of hematocrit, the coagulation profile (ie, activated coagulation time, prothrombin time, partial thromboplastin time, antithrombin III, free hemoglobin, fibrinogen, and D-dimer), and electrolytes was performed every 6 hours or when deemed necessary. Continuous clinical monitoring for bleeding was done, and laboratory measurement was requested more frequently if necessary. Daily evaluations of cardiac enzymes, hepatic enzymes, and creatinine were performed. Blood gas analysis from radial artery and from preoxygenator/postoxygenator venous blood was performed daily. The continuous evaluation of the ECMO circuit, clotting formation, and the pressure difference were performed.

## RESULTS

Three consecutive patients with ARDS and refractory hypoxemia (patient A: $PaO_2$ = 54 mmHg, patient B: $PaO_2$ = 50 mmHg, and patient C: $PaO_2$ = 49 mmHg) despite protective mechanical ventilation (positive end-expiratory pressure ≥10, 100% $F_IO_2$) and high-flow V-V ECMO positioned in the last 24 hours were analyzed. In all the patients, the chest x-rays showed diffuse injury with bilateral alveolar infiltrates. The hemodynamic evaluation showed an endogenous cardiac output ≥7 L/min in all patients, whereas blood gas analysis showed a large decrease in oxygenation from postoxygenator to radial artery sample site. Patients' details are presented in Table 1 and Figure 1.

Patients started esmolol treatment on their first day on ECMO, and the dosage ranged between 50 and 80 μg/kg/min thereafter without adverse effects (bradycardia, hypotension, or hemodynamic instability). During the first 12 hours of treatment with esmolol, decreased values of heart rate (from 125 to 80 beats/min in patient A, from 125 to 90 beats/min in patient B, and from 125 to 80 beats/min in patient C) and endogenous cardiac output (from 8 to 5.5 mL/min in patient A, from 7 to 5 mL/min in patient B, and from 8 to 6.5 mL/min in patient C) were reported. A concomitant quick improvement of peripheral oxygenation was documented ($PaO_2$ patient A: from 54 to 90 in the first 12 hours and then up to 105 within 24 hours, $PaO_2$ patient B: from 50 to 94 in the first 12 hours and then up to 135 within 24 hours, and $PaO_2$ patient C: from 49 to 66 in the first 12 hours and then up to 100 within 24 hours). Patients A and C also were treated with renal replacement therapy. Blood gases documented good performance of the ECMO oxygenator during the days of treatment.

## DISCUSSION

The authors suggest, for the first time, that the reduction of native cardiac output through short-acting β-blocker administration in selected patients with ARDS and refractory hypoxia despite ECMO support immediately increases peripheral oxygenation. ECMO is a well-established therapy in neonatal, pediatric, and adult patients affected by respiratory and/or cardiac failure unresponsive to conventional therapy. The Extracorporeal Life Support Organization provides the most important source of information on ECMO, and according to its guidelines, in hypoxic respiratory failure from any cause (primary or secondary), V-V ECMO support is considered adequate when the $O_2$ arterial saturation is greater than 80% and venous saturation is greater than 70%. However, such an oxygenation profile might be questionable because 80% oxygen arterial saturation might be too low with regard to tissue oxygenation and may lead to a negative prognosis. In the present authors' opinion, ECMO management should be aimed to obtain better oxygenation levels while avoiding excessive respiratory stress to the lungs.

Hypoxemia during ECMO is linked mostly to (1) the mixture between the blood fully oxygenated by ECMO and the patient's own venous blood; (2) the rate of recirculation in between the cannulae, which decreases the outlet-inlet $O_2$ difference per unit of blood; and (3) the inability of the diseased lung to provide further oxygenation together with the shunt because of the bronchial circulation that can further worsen the arterial $PaO_2$. Of course, high $F_IO_2$ should be set in ventilatory flow as well as in the ECMO oxygenator to increase peripheral oxygen saturation, but the strategy could be inadequate.[3] Moreover, intensivists often attempt to increase ECMO performance by increasing flow.[3] However, this can result in severe hemolysis and might be ineffective. V-A ECMO usually provides good arterial oxygenation, but it is more invasive and often associated with vascular injury, embolic events, and the potential hypoxic Harlequin syndrome.[2] Nevertheless, the question about the way to improve ECMO performance to a significant extent, without exposing patients to major risks, is still unsolved. Paralyzing the patients, cooling them, and using a second oxygenator are among the options that might be considered. In the authors' experience, paralyzing a deeply sedated patient may only slightly improve oxygenation, whereas cooling and using a second oxygenator can be effective but can open the way to other potential complications and further costs. The authors think that a trial with ultra–short-acting β-blockade for a few hours is worth trying before setting up new more invasive and expensive strategies. In the authors' view, a shunt between the blood fully oxygenated by ECMO and the patient's own venous blood should be modified in selected patients. In fact, patients affected by severe pneumonia often present a hyperdynamic circulation with high cardiac output. Additionally, many patients also suffer from intrinsic myocardial dysfunction and receive inotropic drugs.[7]

The possible beneficial effect of reducing cardiac output on intrapulmonary shunt and overall arterial oxygen saturation previously has been reported[8-11] in acute hypoxemic states. A decrease in intrapulmonary shunting has been accomplished by reducing cardiac output either with drugs or taking advantage of the hemodynamic effects of positive-pressure ventilation on venous return and right ventricular function. However, the well-known beneficial effects of protective ventilation[12] in the setting of ARDS and hypoxemic acute lung diseases contributed to diverting attention away from hemodynamics to ventilation in the acute respiratory treatment. Moreover, the intro-