Combined extracorporeal CO2 removal and renal replacement therapy in a pregnant patient with COVID-19: a case report

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ABSTRACT

Background. Pregnant women are at high risk of Coronavirus disease 2019 (COVID-19) complications, including acute respiratory distress syndrome. Currently, one of the cornerstones in the treatment of this condition is lung-protective ventilation (LPV) with low tidal volumes. However, the occurrence of hypercapnia may limit this ventilatory strategy. So, different extracorporeal CO_2 removal ($ECCO_2R$) procedures have been developed. $ECCO_2R$ comprises a variety of techniques, including low-flow and high-flow systems, that may be performed with dedicated devices or combined with continuous renal replacement therapy (CRRT).

Case description. Here, we report a unique case of a pregnant patient affected by COVID-19 who required extracorporeal support for multiorgan failure. While on LPV, because of the concomitant hypercapnia and acute kidney injury, the patient was treated with an $ECCO_2R$ membrane inserted in series after a hemofilter in a CRRT platform. This combined treatment reducing hypercapnia allowed LPV maintenance at the same time while providing kidney replacement and ensuring maternal and fetal hemodynamic stability. Adverse effects consisted of minor bleeding episodes due to the anticoagulation required to maintain the extracorporeal circuit patency. The patient's pulmonary and kidney function progressively recovered, permitting the withdrawal of any extracorporeal treatment. At the 25th gestational week, the patient underwent spontaneous premature vaginal delivery because of placental abruption. She gave birth to an 800-gram female baby, who three days later died because of multiorgan failure related to extreme prematurity.

Conclusions. This case supports using $ECCO_2R$-CRRT combined treatment as a suitable approach in the management of complex conditions, such as pregnancy, even in the case of severe COVID-19.

KEYWORDS: pregnancy, COVID-19, lung-protective ventilation, hypercapnia, CO_2 removal, acute kidney injury, continuous renal replacement therapy

Introduction

Pulmonary involvement in Coronavirus disease 2019 (COVID-19) is highly heterogeneous, with clinical presentation ranging from asymptomatic forms to acute respiratory distress syndrome (ARDS) [1]. This heterogenicity may be explained by demographic factors, history of comorbidities, distinctive genetic background, and pharmacological treatments [2].

Among the different populations of COVID-19 patients, pregnant women deserve specific attention. Indeed, these patients, due to immunological and cardiorespiratory changes occurring in pregnancy, are at risk of the more severe complications of the disease, including ARDS [3, 4].

Most patients with ARDS require mechanical ventilation (MV), and in some cases also extracorporeal respiratory support (ECLS) [5].

These therapies encompass extracorporeal membrane oxygenation (ECMO) and the extracorporeal carbon dioxide removal system ($ECCO_2R$). Briefly, ECMO takes over the gas exchange function of the lungs ensuring full oxygenation and CO_2 removal, while $ECCO_2R$ is a CO_2 removal system that does not affect oxygenation, and whose principal aim is consenting to lung protection (Table 1).

Extracorporeal life support (ECLS)			
		Indications	**Main Effects**
Extracorporeal Membrane Oxigenation (ECMO)	**VA-ECMO** **VV-ECMO** **VVA-ECMO***	Cardiac failure Respiratory failure with severe hypoxemia Cardio-respiratory failure	Hemodynamic support Oxygenation and decarboxylation Hemodynamic and respiratory support
Extracorporeal Carbon dioxide Removal ($ECCO_2R$)	**VV-$ECCO_2R$ (low-flow)** **AV-$ECCO_2R$ (high-flow)**	Respiratory failure with severe hypercapnia	Decarboxylation (lung protection)

Table 1: Nomenclature and clinical indications of the extracorporeal life support systems. Abbreviations: A, arterial; V, venous. *Other techniques of triple cannulation ECMO have also been described (for a full description, see Ref [32]).

Growing evidence suggests that similarly to other forms of ARDS, also in COVID-19 pneumonia lung-protective ventilation (LPV) – defined by low tidal volume (TV) of 4-6 ml/kg of predicted body weight (PBW) and plateau pressure (Pplat) less than 30 cmH2O – could constitute the most appropriate approach to limit ventilator-induced lung injury (VILI) [6, 7]. However, one of the main concerns regarding the use of LPV is the risk of developing hypercapnia, which may limit the clinical application of this strategy [8]. This is why $ECCO_2R$ techniques have been developed [9]. They include low-flow or high-flow systems that may be performed with dedicated platforms or, alternatively, combined with continuous renal replacement therapy (CRRT). The suitability of $ECCO_2R$ and CRRT ($ECCO_2R$-CRRT) combination, providing simultaneous CO_2 removal and kidney support, has been reported in recent studies in patients with sepsis, chronic obstructive pulmonary disease, and ARDS, both in small retrospective and prospective studies [10]. As expected, the clinical experience of $ECCO_2R$-CRRT in patients with COVID-19 is very limited [11], while it is completely absent in pregnant women. So, here we report our experience with a unique case of a pregnant woman with multiorgan failure (MOF), occurring as a sequela of COVID-19 and treated with a combined $ECCO_2R$-CRRT strategy.

Case description

In November 2020, a 34-year-old pregnant woman in the 19th week of gestational age, without past medical history, was admitted to the Emergency Department of a peripheral hospital because of dyspnea. The molecular nasal swab resulted positive for SARS-CoV-2 infection, so a diagnosis of COVID-19 was made. At admission, the patient presented dyspnea, with a respiratory rate (RR) of 24 breaths/minute, mean arterial pressure (MAP) was 72 mmHg, heart rate (HR) of 120 beats/minute, and peripheral oxygen saturation (SpO2) 90%. Laboratory examinations showed a white blood cell count (WBC) of 16.9 x 103/µL, anemia (Hb 9.1 g/dl), elevated lactate dehydrogenase (LDH 462 U/L), C-reactive protein (CRP) 203 mg/dl, serum creatinine (sCr) of 0.8 mg/dl and normal electrolytes levels.

She was initially treated with an oxygen mask at FiO2 60%, but after the worsening of the PaO2/FiO2 ratio to 120 mmHg, respiratory support with helmet continuous positive airway pressure (CPAP) at FiO2 100% was started. Three days after, because of further deterioration of respiratory function, the patient was transferred to the ICU, where invasive mechanical pressure-controlled ventilation (PCV) was started. The patient underwent cycles of prolonged prone positioning lasting 16 hours/day. Seven days after ICU admission, a percutaneous tracheostomy was performed.

During the hospitalization, the patient presented septic shock associated with evidence of colonization of the lower respiratory tract with Burkholderia cepacia.

Therefore, after infectious disease consultation, large-spectrum antimicrobial therapy with meropenem, ceftazidime/avibactam, and *amphotericin B was initiated.* On day 22, due to the clinical complexity of the case, the patient was centralized to our third-level University Hospital. At that time, beyond antimicrobial treatments, the patient was on therapy with corticosteroids, low molecular weight heparin, and norepinephrine (0.25 mcg/kg/min).

The molecular nasal swab for SARS-CoV-2 was negative, while laboratory examinations showed: sCr 1.6 mg/dl, LDH 492 U/L, and CRP 131 mg/dl. MAP was 88 mmHg and PaO_2/FiO_2 ratio 188 mmHg, in PCV with FiO_2 0.6, according to an LPV strategy (TV 4.5 ml/PBW).

A CT scan showed extensive *bilateral* ground glass opacities *associated* with *thickened interlobular* and *intralobular septa, without signs of pulmonary embolism.*

The gynecological evaluation showed regular placental circulation and a vital fetus compatible with gestational age. Two days after the admission to our ICU, the patient presented a deterioration of gas exchanges, with the progressive onset of hypercapnia ($PaCO_2$ 80) with pH 7.43, mmHg, base excess (BE) 25.7 mmol/l, HCO_3^- 53 mmol/L, lactate 0.6 mmol/l.

The day after, due to the persistence of hypercapnia ($PaCO_2$ 75.5 mmHg) and the ongoing AKI (as evidenced by increased sCr levels to 2.5 mg/dl and reduced urinary output to 0.5 ml/kg/h), $ECCO_2R$ treatment in association with renal support was started.

$ECCO_2R$ was provided using a polymethylpentene, hollow fiber, gas-exchanger membrane (1.35 m^2 multi$ECCO_2R$, Eurosets, Medolla, Italy). The $ECCO_2R$ membrane was inserted in series after a hemofilter (Ultraflux AV 1000S 1.8 m^2, Fresenius Medical Care, Bad Homburg, Germany) in the Multifiltrate CRRT platform (Fresenius Medical Care, Bad Homburg, Germany) (Figure 1).

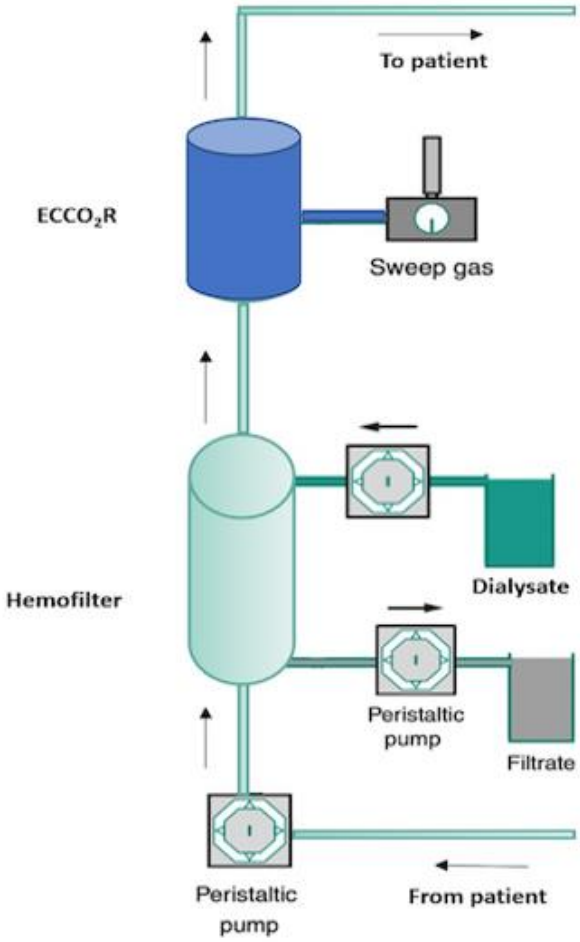

Figure 1: Schematic representation of the circuit used to treat the patient reported in this case. ECCO2R membrane was set after the hemofilter to obtain combined ECCO2R and RRT. Anticoagulation was provided by systemic heparinization. ECCO2R: extracorporeal CO2 removal; RRT: renal replacement therapy.

$ECCO_2R$-CRRT was set in continuous venovenous hemodialysis (CVVHD) mode and was commenced, through a 13.5 Fr central venous catheter, at a blood flow of 300 ml/min, with a sweep gas flow of 5 l/min. CVVHD was delivered with an effluent dose of 25 ml/kg/h and net ultrafiltration of 1 ml/kg/h. Systemic anticoagulation was obtained by continuous administration of unfractionated heparin (UFH), with a target-activated partial thromboplastin time (aPTT) of 70-80 seconds. Table 2 reassumes the ventilatory and hemodynamic parameters collected during $ECCO_2R$-CRRT treatment.

At the end of the $ECCO_2R$-CRRT treatment cycle, $PaCO_2$ was 54 mmHg and pH 7.41. During the treatment, TV, PEEP, and Pplat were maintained according to LPV, while RR was reduced. The PaO_2/FiO_2 ratio increased from 202 to 338 mmHg and the hemodynamics remained stable.

Overall, $ECCO_2R$-CRRT lasted four days (with the change of hemofilter on the third day) and was discontinued due to a sustained improvement in hypercapnia and concern about mild hemorrhagic complications (hematuria and bleeding from tracheostomy). After $ECCO_2R$ treatment termination, CRRT was continued because of persistent AKI and oliguria, using regional citrate as an anticoagulation strategy. Then, no further bleeding episodes occurred. During the $ECCO_2R$-CRRT cycle, the fetal status was constantly monitored, revealing a vital fetus with normal HR (mean values of about 130 beats/minute) and movements. However, two weeks after $ECCO_2R$ discontinuation, corresponding to the 25th gestational week, the patient underwent spontaneous premature vaginal delivery because of placental abruption. She gave birth to an 800-gram female baby admitted to the

Neonatal Intensive Care Unit, where she died three days later because of multiorgan failure related to extreme prematurity.

	Pre	6 h	12 h	Day 1*	Day 2 *	Day 3	Day 4 End	Day 5 Post
Blood flow, ml/min	–	300	300	300	300	300	300	150
Sweep gas flow, l/min	–	5	5	5	5	3	4.5	–
aPTT, sec	39.8	84.1	79.7	77	72.4	53	56.2	46.6
Heparin dose (UI/h)	1000	1300	1250	1400	1400	1100	1200	750
Diuresis, ml/kg/h	0.5	0.5	0.5	0.3	0.2	0.3	0.3	0.3
CRRT effluent rate, ml/kg/h	–	25	25	25	25	30	25	25
CRRT ultrafiltration rate, ml/kg/h	–	1	1	2	2	3	3	2
Arterial blood gas								
pH	7.39	7.4	7.32	7.29	7.32	7.33	7.38	7.41
$PaCO_2$, mmHg	75.5	63	66	67.2	58	73	57	54
PaO_2, mmHg	111	138	158	132	178	119	202	135
HCO_3^-, mmol/l	46.6	39	34	31.5	30.3	35	33.5	27.1
BE, mmol/l	19.3	11.8	7.1	4.6	3.1	11.2	7	0.3
Ventilator parameters								
TV, ml/PBW	4.3	3.6	2.5	3.5	4	3.6	4.5	4.5
RR, breaths/min	35	28	26	26	26	26	26	26
Pplat, cmH_20	28	28	27	27	27	27	27	27
PEEP, cmH_2O	12	12	12	14	12	12	12	12
PaO2/FiO2 ratio, mmHg	220	276	395	330	356	238	404	338
Hemodynamic parameters								
Mean arterial pressure, mmHg	95	98	94	77	84	97	87	95
Heart rate, beats/min	118	100	89	100	125	120	130	128
Norepinephrine dose, mcg/kg/min	0.3	0.25	0.1	0.15	0.15	0.3	0.3	0.25

Table 2: Time course of operation characteristics, ventilatory and hemodynamic parameters during $ECCO_2R$-CRRT treatment.

aPTT: activated partial thromboplastin time; COVID-19: coronavirus disease 2019; CRRT: continuous renal replacement therapy; $ECCO_2R$: extracorporeal carbon dioxide removal; FiO_2: fraction of inspired oxygen; HCO_3^-: bicarbonate; BE: base excess; PaCO2: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; PBW: predicted body weight; PEEP: positive end-expiratory pressure; Pplat: plateau pressure; RR: respiratory rate; TV: tidal volume.

*** Bleeding complications**

During the following days, the patient's conditions stabilized, while kidney function and diuresis increased, with the possibility of withdrawing CRRT (for a total treatment duration of 21 days). At that time, ventilatory parameters were TV 4.6 ml/PBW, Pplat 28 cmH_2O, RR 30 breaths/min, and FiO_2 0.45, while ABG showed pH 7.45, $PaCO_2$ 59 mmHg and PaO_2 111 mmHg.

One week later, it was possible to shift to pressure support ventilation, and then the patient was completely weaned from mechanical ventilation (Figure 2). Finally, she was transferred to the Rehabilitation Clinics, from which she was discharged one month later, with complete renal recovery.

Figure 2: Time course and main clinical events occurring during the hospitalization. ICU: intensive care unit; MV: mechanical ventilation; ECCO2R: extracorporeal CO2 removal; CRRT: continuous renal replacement therapy.

Discussion

To our knowledge, here we present the first case of a pregnant woman affected by COVID-19 treated with a combined $ECCO_2R$-CRRT approach.

The management of this patient offers the possibility to discuss some points of crucial relevance in clinical practice. First, as already reported, we found that COVID-19-related MOF may also occur in young people without significant medical history. This observation was especially valid in patients who, such as in our case, resulted affected by COVID-19 during the first pandemic waves, when vaccination and antiviral drugs were still unavailable [12]. COVID-19-related organ damage may be a direct consequence of infection or a sequela of the complications developing during the disease course. In our case, while acute lung injury was directly attributable to COVID-19, the pathogenesis of severe kidney injury was less clear and not specifically studied, being probably the consequence of multiple factors, including hemodynamic instability, nephrotoxic drugs, and ARDS-related AKI [13]. Moreover, in line with available Literature, it is possible that pregnancy constituted an additional risk factor for a severe form of COVID-19 [14].

Then, we observed that using a low-flow $ECCO_2R$-CRRT in a single circuit effectively controlled hypercapnia, allowing the maintenance of the LPV strategy.

Briefly, $ECCO_2R$ is a technique that, taking advantage of its high diffusivity, removes CO_2 without providing significant oxygenation [15].

It consists of a circuit where blood is drained through a cannula from a central vein or artery and returned to the venous system after CO_2 removal by a membrane lung (acting as an artificial gas exchanger). Inside the membrane lung, a “sweep gas” (medical air or oxygen) running along the other side of the membrane generates a diffusion gradient driving CO_2 removal.

Many different devices and membrane lungs are available, but essentially $ECCO_2R$ devices can be grouped into two main categories: arteriovenous pumpless systems (AV-$ECCO_2R$) and venovenous pump-driven devices (VV-$ECCO_2R$) [16]. In turn, VV-$ECCO_2R$ may be performed with low-flow or high-flow systems. Low-flow $ECCO_2R$ systems operate with a low blood flow rate (between 200 and 400 ml/min) and offer the possibility of using CRRT platforms and dual-lumen dialysis catheters.

Conversely, high-flow systems (i.e., blood flow rate higher than 500 ml/min) require dedicated devices and larger cannulas. Apart from technical issues, the main difference between these two strategies is the effectiveness of CO_2 removal. So, while a blood flow rate of 200-300 ml/min may remove 40-60 ml CO_2/min, representing 20%-25% of total CO_2 production, an increase in the blood flow rate may remove until 150 ml CO_2/min, representing approximately 50%-60% of total CO_2 [17, 18].

However, experimental evidence suggests that, due to limitations of blood flow and membrane efficiency, the actual removal capacity is inferior and, in particular, low-flow systems may remove up to 25% of carbon dioxide production [19].

In our case, since the patient did not present respiratory acidosis and the goals of the treatment were maintaining LPV and supporting kidney function, a low-flow $ECCO_2R$-CRRT approach was chosen. This combined treatment allowed for controlling fluid balance and kidney function replacement, leading to the stability of both ventilatory and maternal and fetal hemodynamic parameters. The effectiveness and suitability of combined $ECCO_2R$-CRRT treatment are in line with what is described in previous case reports and clinical studies on ARDS patients in different clinical contexts [20–22].

So, for example, Nentwich et al. evaluated twenty hypercapnic critically ill patients with renal failure who were treated with a combined system incorporating a membrane lung in series with a hemofilter on a conventional CRRT circuit. They found that this system was effective in decreasing $PaCO_2$ and reducing ventilation requirements with a decrease in TV [23].

Regarding the specific setting of pregnant women, experience with ECLS is scarce.

Recently, a systematic review evaluated 358 patients undergoing ECLS in the peripartum period, including 81 pregnant women [24]. The most common indications for ECLS were ARDS and cardiac failure. Despite some episodes of major bleeding and the need for preterm delivery in about 50% of the cases, overall maternal survival at 30 days was 75% and fetal survival was 64.7%. Therefore, these data support the use of ECLS in peripartum women. However, looking at specific ECLS techniques, only a few patients underwent $ECCO_2R$ and none of them were in combination with CRRT [25, 26]. If the information on the general population is poor, data on pregnant patients with COVID-19 are completely lacking. In general, the experience of $ECCO_2R$ in COVID-19 is limited. Ding et al. reported the data of twelve COVID-19 patients with refractory hypercapnia treated with a low-flow $ECCO_2R$ system based on the CRRT platform [27]. They observed the application of the $ECCO_2R$ system enabled CO_2 removal associated with a significant decrease in TV and Pplat. However, none of these patients had AKI at the initiation of $ECCO_2R$-CRRT treatment.

Similarly, Husain-Syed F. et al. in a small prospective study that enrolled four patients, including one with AKI, reported that treatment with an $ECCO_2R$ circuit inserted in a CRRT platform was safe and feasible, both when used alone and in combination with renal support treatment [28]. However, although effective, this approach is not risk-free. The review of the pertinent Literature has shown that the $ECCO_2R$-related adverse effects include hemorrhages, heparin-induced thrombocytopenia, circuit clot, and limb ischemia [29].

In our patient, the main adverse events consisted of bleedings related to the anticoagulation required to maintain the patency of a low-flow extracorporeal circuit. This aspect should be considered when prescribing $ECCO_2R$-CRRT. Indeed, while in clinical trials and daily practice the most diffuse strategy is systemic anticoagulation with heparin, the possibility to use citrate-based regional anticoagulation could promote the investigation of alternative anticoagulation protocols (for example, combining low-dose systemic UFH with regional citrate anticoagulation in the CRRT circuit) [5]. Finally, it should be noticed that, despite numerous studies reporting the benefits of $ECCO_2R$

[30], the recent REST trial has questioned the usefulness of $ECCO_2R$, showing non-additional advantages of this treatment in patients with acute hypoxemic respiratory failure treated with low tidal volume mechanical ventilation [31]. However, these results are inconclusive since this study may be underpowered to detect significant findings.

Conclusions

Since the limitations of available studies, mainly due to the small number of patients enrolled and short observation time, further evidence from specific-designed randomized clinical trials and high-quality prospective studies is needed to determine the actual clinical impact of $ECCO_2R$ on specific patient populations and guide decision-making.

In the meantime, we believe that the available evidence is strong enough to support the use of $ECCO_2R$, also integrated into a CRRT circuit, in selected patients in the context of multi-organ supportive therapy. In this view, continuous active reporting of clinical experience and cohort studies remain essential to define and confirm the suitability and safety of this approach.

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