Case report

Spontaneous breathing during extracorporeal membrane oxygenation treatment of sickle cell disease acute chest syndrome

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ABSTRACT

Sickle cell disease (SCD) is a hereditary hemoglobinopathy resulting in sickling hemoglobin. Acute chest syndrome (ACS) is a serious complication of SCD and an important cause of morbidity and mortality. Management of ACS is complex and may necessitate mechanical ventilation and veno-venous extracorporeal membrane oxygenation (VV-ECMO) therapy in the more severe cases.

We present herein the case of a young female adult (19 y.o.) with SCD who developed severe respiratory failure due to ACS occurring twice within 15 months and treated by VV-ECMO. We describe the management of ACS with VV-ECMO using two different approaches, namely with and without mechanical ventilation.

1. Introduction

Acute chest syndrome (ACS) is the most frequent cause of death in patients with Sickle Cell Disease (SCD). ACS is a pulmonary syndrome characterized by fever, cough, chest pain and dyspnea, accompanied by a new pulmonary infiltrate on chest X-ray [1].

In instances of severe acute respiratory failure in which conventional therapy (i.e. protective lung ventilation, prone positioning or use of curare) was unsuccessful, veno-venous extracorporeal membrane oxygenation (VV-ECMO) therapy has proven to be beneficial [2].

There are very little data regarding VV-ECMO in ACS including a few case reports [3–8]. Current guidelines relative to ACS management do not recommend its use as conventional therapy [9].

We present herein the case of a young female adult (19 y.o.) with SCD who developed severe respiratory failure due to ACS. This patient was successfully treated in part with VV-ECMO, twice over a period of 15 months, with and without mechanical ventilation.

Her medical history consisted in SS homozygous sickle cell disease with chronic pulmonary hypertension (with no right heart dysfunction) and mitral annuloplasty for the treatment of rheumatic valvulopathy. She had already had several complications of SCD, including transfusional iron overload as well as several vaso-occlusive crises mostly caused by urinary tract infections.

2. Case report

2.1. First ACS

The patient was hospitalized in the emergency unit for a vaso-occlusive crisis related to a urinary tract infection with an Escherichia coli bacteremia.

Initial treatment consisted in 2 red blood cell transfusions (hemoglobin at 6.9 g dl-1), antibiotic treatment (CEFOTAXIME and AMIKAGINE) and analgesic treatment.

The patient developed a secondary ACS necessitating an increase in oxygen flow rate and was subsequently admitted in our ICU (Fig. 1).

Despite the administration of high flow nasal oxygenation, hematosis remained severely impaired and respiratory conditions worsened. Mechanical ventilation was initiated with lung-protective ventilation and administration of neuromuscular blockade.

Lung compliance was altered, including a Plateau pressure (Pplat) of 30 cmH2O with a Positive End-Expiratory Pressure (PEEP) of 5 cmH2O. Hematosis remained extremely impaired with severe respiratory acidosis (Pco2 at 133 mmHg, pH at 6.9) and severe hypoxemia (Pco2 at 60 mmHg with FiO2 100%).

Hemodynamic conditions worsened after intubation due to an increase in pulmonary hypertension (PH) (SPAP > 70 mmHg) with acute cor pulmonale and right ventricular failure assessed by transthoracic
echocardiography (TTE). Left ventricular function was intact and cardiac output was preserved. Optimal perfusion of the right ventricle (RV) was maintained by administration of vasopressor treatment (norepinephrine). RV post-charge was decreased by inhalation of nitric oxide (NO) (20 ppm) and reduction in PEEP.

Given the disastrous hemodynamic and respiratory conditions, use of prone position was excluded.

VV-ECMO was considered in this case as a rescue therapy. RESP score was 1 [7]. ECMO was implanted less than one hour after endotracheal intubation. Initial ECMO flow was 5–5.5 L/min with a sweep gas of 6 L/min.

Both respiratory and hemodynamic conditions were quickly improved. Oxygenation and decarboxylation were obtained within a few hours. Ultra-protective ventilation was performed with 2 ml kg⁻¹ tidal volume and Pplat <25 cmH2O. Vasopressor treatment was weaned after 6 hours of ECMO. TTE showed a regression of the acute cor pulmonale at day 1 (D1). Inhaled NO (INO) therapy was discontinued at D1 after cannulation and curare drug infusion at D2. VV-ECMO ran for 7 days without any specific complications.

Definitive extubation occurred 16 days after admission (9 days after VV-ECMO withdrawal), following one extubation failure.

Treatment with CEFOTAXIME and SPIRAMYCINE was continued for 7 days without documented infection. Blood exchange transfusion with 7 units of packed red blood cells was performed in a second phase ahead of clinical condition degradation. The transfusion decreased Hemoglobin S (HbS) level from 17% to 5% (HbS value was not known prior to erythrocytapheresis).

2.2. Second ACS

One year after the first ACS episode, the patient presented a second respiratory failure episode following a vaso-occlusive crisis.

Prior to admission in our unit, initial management of the crisis consisted in massive hydration, blood transfusion (4 units of PRBC), lung antibiotic therapy with CEFTRIAXONE and SPIRAMYCINE as well as analgesic therapy. The patient’s clinical condition (pain, dyspnea) and biological disorder (inflammatory syndrome) initially improved.

The patient was subsequently transferred to our center after a worsening of her condition consisting in hypercapnic acute respiratory failure despite adequate vaso-occlusive crisis therapy.

At admission, the patient presented fever and dyspnea with no other specific sign of organ failure. X-ray and CT-scan showed major and bilateral alveolar condensation, cardiomegaly and moderate pleural effusion (Fig. 2), with no sign of profound infection. TTE showed a pattern of acute cor pulmonale (increased SPAP > 60 mmHg, paradoxic septum, mild right ventricular dysfunction (TAPSE at 10mm)), while cardiac output was increased (cardiac index 5 L.min.m⁻²) along with moderate mitral regurgitation. Blood gas revealed a hypercapnic acidosis (pH at 7.28, PaCO2 at 55 mmHg) with mild hypoxemia (PaO2/FiO2 ratio at 140). The patient also presented acute biological renal failure (urea at 0.97 g l⁻¹, creatinine at 18.3 mg l⁻¹), while diuresis was maintained with no evidence of an obstructive cause.

ACS in this instance was secondary to probable infection and pulmonary vasculopathy decompensation sustained by massive supply of fluid (crystalloid and blood transfusion). Initial therapies included empiric antibiotic therapy (PIPERACILLINE-TAZOBACTAM, SPIRAMYCINE), non-invasive ventilation mask alternated with high flow nasal oxygen therapy, diuretic therapy with systemic vasodilator for right ventricular failure, and blood exchange transfusion (HbS at 31% at admission).

Despite the above treatments, hypercapnic acidosis worsened with severe hypoxemia and respiratory failure.

Given the unfavorable evolution and in order to avoid the undesirable effect of mechanical ventilation on right heart condition, VV-ECMO cannulation was performed under spontaneous breathing two days after admission.

Target-controlled infusion of low-dose PROPOFOL combined with local LIDOCAINE application was used for anesthesia during cannulation.

Initial settings were: patient FiO2 0.5, ECMO FiO2 1, ECMO sweeping at 1 L.min⁻¹, ECMO output at 1.7 L.min⁻¹. Normalthermia was maintained.

A therapeutic dosage of unfractionated heparin was immediately initiated to avoid thrombosis. Hemorrhagic shock occurred within a few hours due to a large femoral hematoma caused by the femoral cannulation which was corrected with favorable evolution after blood transfusion (2 packed blood cells, 2 frozen plasma, 1 platelet concentrate), fluid therapy and transitory use of small-dose norepinephrine. Unfractionated heparin was temporarily halted.

There was an initial improvement under VV-ECMO and sodium depletion therapy. The patient no longer showed signs of respiratory distress, while renal function and blood gas were normalized.

Secondary gasometric and clinical deterioration occurred after 3 days of VV-ECMO introduction with hypercapnia and acute respiratory distress with few arguments for cardiac causes. TTE showed an elevation of cardiac strain with a moderate mitral dysfunction; cardiac biomarkers such as B-type natriuretic peptide (BNP) were very high (>2000 pg/ml). Diuretic therapy was intensified.

No other major undesirable events occurred until VV-ECMO removal after weaned trial at day 19.

In this instance, right heart management was essentially achieved with depletion therapy and decarbonization with VV-ECMO. No specific pulmonary hypertension drugs such as NO or prostacyclin-analog or mechanical ventilation were used.

Patient was fully discharged from hospital 11 days later.

3. Discussion

We describe above the first case of spontaneous breathing during VV-ECMO therapy in the setting of sickle-cell disease acute chest syndrome. There are only sparse data regarding treatment of ACS with ECMO, with only a few case reports, a retrospective observational trial and no comparative study [3–5,7–10]. In these latter case reports, VV-ECMO was used successfully as a solution after failure of standard conventional therapy including mechanical ventilation.

The first portion of our report described the above method of
which is common in severe ACS from 13 to 86% of cases according to found that 60% of patients with severe ACS had pulmonary hyperten-

sion [11]. Inhaled NO was used in 64% of case [10]. There is a lack of evidence to assess Boissier et al. reported 22 adults patients with ACS treated with ECMO, treatment failure in adult SCD patients with mild to moderate ACS [13].

These conditions can lead to the development of acute cor pulmonale increases IHM [17].

In the case of the second ACS episode in our patient, a different strategy was chosen. VV-ECMO was first introduced due to the possibility of right heart decompensation provoked by mechanical ventilation.

This latter approach highlights a new means of managing ACS in light of a good clinical tolerance. The main impediment was due to an improper gas exchange with a major hypercapnia. Severe ACS crises are very often associated with pulmonary hypertension and can exacerbate a preexisting pulmonary hypertension. These conditions can lead to the development of acute cor pulmonale which is common in severe ACS from 13 to 86% of cases according to previous studies [10,11]. The development of acute right ventricular failure is a combination of an established pulmonary vascular disease complicated by acute disorders: excessive preload, excessive afterload, impaired myocardial contraction [16]. In our case, the initial strategy was to counter excessive preload and afterload with diuretic therapy and systemic vasodilator respectively. The other main therapeutic axis was to correct metabolic anomalies such as sepsis (antibiotic therapy). In the absence of cardiogenic shock nor hypotension, other specific treatment such as vasopressor or inotrope therapy were not indicated. Veno-arterial ECMO instead of VV-ECMO should have been discussed if a shock occurred.

Pulmonary hypertension and acute cor pulmonale are associated with a higher risk of death [11]. While inhospital mortality (HM) due to ACS is low (near 2%), the use of mechanical ventilation greatly increases IHM [17].

Spontaneous breathing during VV-ECMO is well described during the bridge to lung transplantation for patients with end stage pulmonary
disease due to pulmonary fibrosis or pulmonary hypertension with good results on post-transplant recovery versus mechanical ventilation [18]. These medical conditions represent situations where elevated pulmonary pressure and moderate to severe right ventricular insufficiency are common, such as in ACS.

From this perspective, VV-ECMO as second line treatment prior to mechanical ventilation thus appeared as a good compromise for maintaining homeostasis without deterioration of the right heart condition. However, the impact of ECMO in ACS and SCD remains uncertain. Patients with SCD have increased risks of hemolysis, cerebral thrombosis and vasocclusion which are also specific complications of ECMO.

Particularly, hemolysis which is a common complication of ECMO affecting 18% of patients and can potentiate vaso-occlusive phenomenon in SCD patients should be repeatedly monitored [19]. In the present instance, biological markers of HbS and hemolysis were repeatedly monitored in order to avoid the vicious pathophysiological circle of ACS [9].

| Year | Author | Patient | Type of ECMO | Duration of ECMO | Outcome |
|------|--------|---------|--------------|------------------|---------|
| 2011 | Hoffman et al. [6] | 28 yo male | VV | 12 days | Discharge from hospital |
| 2012 | Grein et al. [4] | 21 yo male | VV | 11 days | Discharge from hospital, normal pulmonary and cardiac function at 1-month follow-up |
| 2016 | Parhar et al. [8] | 18 yo female | VV | 12 days | Discharge from hospital, respiratory insufficiency at 6-month follow-up |
| 2017 | Seweralthabab et al. [5] | 25 yo female | VV | 20 days | Discharge from hospital, normal pulmonary function at 3-month follow-up |
| 2017 | Mashhour et al. [3] | 14 yo male | VV | 5 days | Discharge from ICU after day 30 |
| 2019 | Al-Sawaf et al. [7] | 21 yo male | VV | 7 days | Discharge from hospital after 4 weeks |
| 2019 | Boissier et al. [10] | 22 adults from 2009 to 2017 | VV (45%) & VA (55%) | 6 days [2-8 days] | 73% in-ICU mortality |

Summary of reports about management of ACS with ECMO. Case reports about pediatric patients under 14 yo were excluded. Abbreviations: yo: years-old; VV: veno-venous; VA: veno-arterial. For Boissier et al. report, duration of ECMO is expressed as median [interquartile range].
Current improvements in ECMO oxygenator and pump technologies also help in preventing such events [20]. ECMO cannulation may also lead to hemorrhagic problems such as those encountered herein, multiple transfusions increased the risk for alloimmunization and hyperhemolysis reactions for these patients. At least, use of ECMO in ACS should be used cautiously in the presence of a history of cerebral events.

Table 1 summarized case reports and one retrospective trial about use of ECMO in ACS in adult patients.

Boisnier et al. related a high in-ICU mortality rate of 73% in the unique cohort of severe ACS adult patients (n = 22) treated with ECMO [10].

Further prospective investigations are needed to conclude on the effective contribution of ECMO for management of refractory ACS.

4. Conclusion

In conclusion, VV-ECMO represents a valid alternative to conventional ACS therapy including mechanical ventilation in selected clinical situations where mechanical ventilation can prove harmful. Such procedure must however be used cautiously and performed by an experienced ECMO team.

Declaration of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcrr.2019.100924.

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