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Case Report
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Thrombotic Events Related to Extracorporeal Membrane Oxygenation in COVID-19-Associated Severe Acute Respiratory Distress Syndrome

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Abstract

Hypercoagulopathy associated with the novel coronavirus disease (COVID-19) is the leading cause of acute respiratory distress syndrome (ARDS), multiple organ failure, and mortality. Extracorporeal membrane oxygenation (ECMO) has been used to manage patients with COVID 19-associated severe respiratory or cardiac failure. In this report, we aim to summarise our experience with deadly thrombotic complications during venovenous ECMO (vvECMO) treatment in 6 patients with COVID-19-associated ARDS between March 19, 2020 and April 20, 2020. Based on our experience with 6 COVID-19-associated ARDS patients on ECMO, we intend to raise awareness regarding thrombotic complications leading to mortality.

Keywords: Acute respiratory distress syndrome, extracorporeal membrane oxygenation, hypercoagulability, severe acute respiratory syndrome-related coronavirus, thrombosis

Introduction

Hypercoagulopathy associated with COVID-19 is the leading cause of acute respiratory distress syndrome (ARDS), multiple organ failure, and mortality.[1] Several patients develop thrombotic complications due to this uncontrolled immune thrombotic response which might be a major risk factor related to the development of ARDS and progression from ARDS to death.[1] Extracorporeal membrane oxygenation (ECMO) has been used to manage patients with COVID-19-associated severe respiratory or cardiac failure.[2-4] We aim to summarise our experience with deadly thrombotic complications during venovenous ECMO (vvECMO) treatment in 6 patients with COVID-19 associated ARDS between March and April, 2020.

Case Presentation

All patients were male with a mean age of 48.8 (36–68) years and a body mass index (BMI) of 35 (31.1–38.9). The time between symptom initiation to intensive care unit (ICU) admission was 9.5 days, and the mean Acute Physiology and Chronic Health Evaluation (APACHEII) and median Sepsis-Related Organ Failure Assessment (SOFA) scores on admission to the ICU were 19.16 (24–16) and 7.3 (5–10), respectively. The comorbidities were: 1 patient with hypertension, 2 with diabetes, and 1 with coronary artery disease. ECMO was started relatively early after ICU admission (5.8 days), due to the severe hypoxemia [PaO_2/FiO_2 52.73(42–62)] not responding to prone positioning. The mean SOFA score before ECMO was 12.5 (7–16), and all patients were on vasopressor support. Each patient received 100 IU kg^{-1} unfractionated heparin before percutaneous cannulation to achieve an activation coagulation time target of 180–220 seconds. All patients were on prone positions with a median positive

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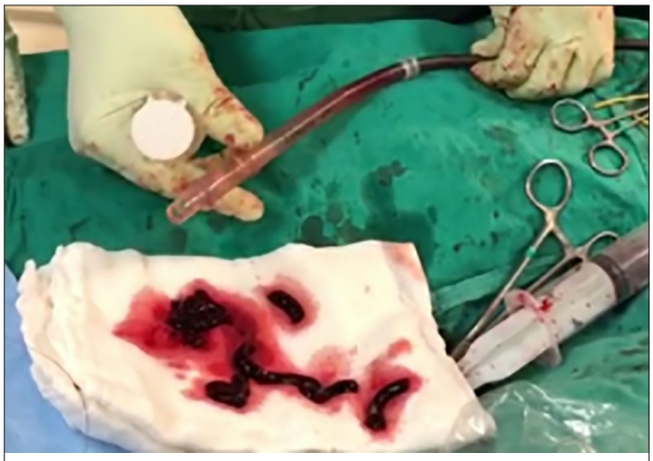

Figure 1. Cannula thrombosis during percutaneous cannula insertion

end-expiratory pressure (PEEP) of 13.7 (12–14), peak pressure of 32.6 (30–40), and P/F ratio (52.73) below 70. The laboratory data indicated hyperinflammatory and hypercoagulable state with high C- reactive protein (CRP) levels 206.6 (15.8–438) mg L^{-1}, interleukin-6 (IL-6) levels 3275.2 (32.63-6799) pg mL^{-1}, ferritin levels 1588 (354.9–2705) ng mL^{-1}, d-dimer levels 13942 (3460–>20000) µg L^{-1}, and fibrinogen levels 556.7 (432–824) ng mL^{-1} with normal platelet counts 296.533 (439.000–212.000) $10^3/\mu L$. There were 2 patients (2/6) with cannula thrombosis during percutaneous cannula insertion (Figure 1). The first patient needed an urgent cannula change, however, a surgical cannula insertion also resulted in thrombosis which led to the patient's death. In the second patient, an additional dose of heparin after cannula thrombosis led to a massive haemorrhage leading to death. Both patients were on a prophylactic dose of anticoagulation therapy with low-molecular-weight heparin (LMWH) and the d-dimer levels were above 20000. After these dreadful experiences, we changed our anticoagulation strategy to a more aggressive approach including a therapeutic dose of LMWH (Enoxaparin 6000 anti- XaIU/0.6 mL 2x1) together with acetylsalicylic acid (ASA) (100 mg 1x1) and dipyridamole (75 mg 2x1). Although we did not encounter any cannula thrombosis during the percutaneous cannula insertion, 3 (3/6) of our patients developed thrombotic events during the ECMO treatment. We had 1 major oxygenator thrombosis one day after starting the vvECMO treatment (Figure 2), and 1 circuit plugging in the renal replacement system. One patient had an intracardiac thrombosis diagnosed by echocardiography; the patient passed away due to circulatory failure on the same day (Figure 3).

Main Points:

- Many patients with COVID-19 develop venous and arterial thrombotic complications due to this uncontrolled immune thrombotic response which might be a major risk factor related to the development of ARDS and progression from ARDS to death.
- Extracorporeal membrane oxygenation (ECMO) has been used to manage patients with COVID-19-associated severe respiratory or cardiac failure. ECMO cannula thrombosis and oxygenator thrombosis have been reported in patients with COVID-19.
- We aim to summarise our experience with deadly thrombotic complications during venovenous ECMO.
- During ECMO in COVID-19 patients, special attention should be given to thrombosis prevention.

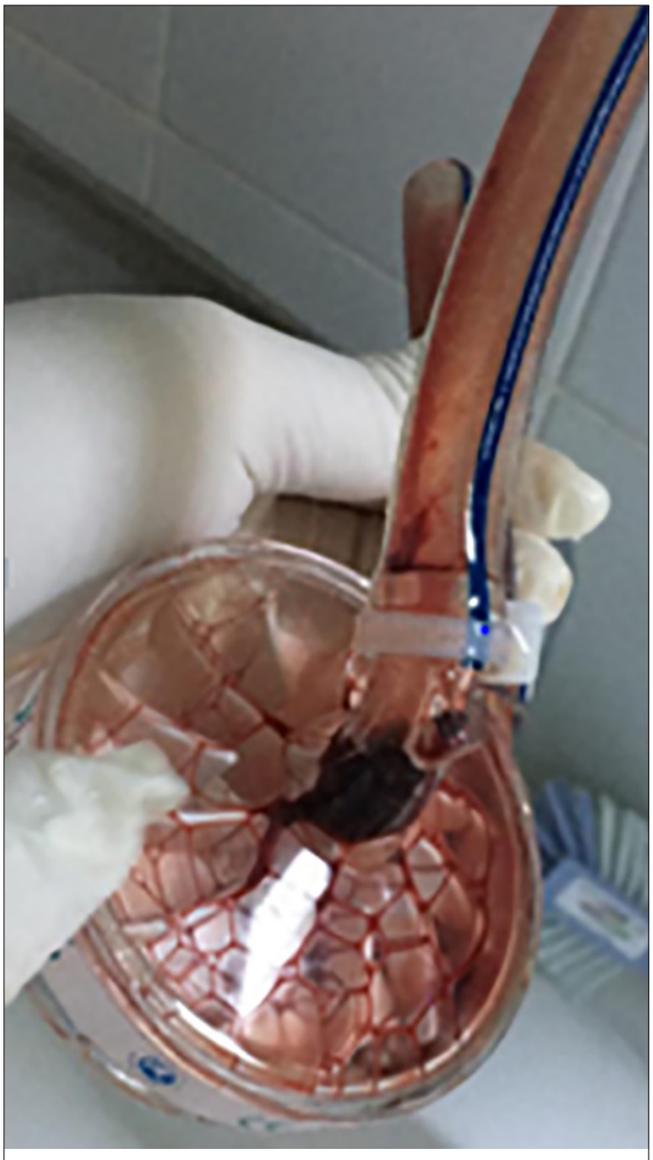

Figure 2. Major oxygenator thrombosis one day after starting the vvECMO treatment
vvECMO: venovenous extracorporeal membrane oxygenation

Discussion

COVID-19 related acute respiratory failure and ARDS are the leading causes of mortality during the pandemic, and

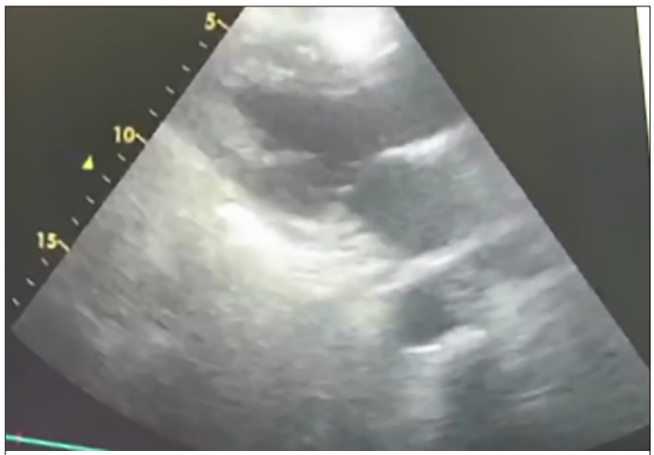

Figure 3. Intracardiac thrombosis diagnosed by echocardiography

they affect male over the age of 45 more severely.[5,6] Obesity and associated conditions such as hypertension, cardiovascular disease, and diabetes were among the most common comorbidities in a sample of 2269 deceased COVID-19 patients.[7] Emerging global data indicate that obese COVID-19 patients have a more severe course, and the severity has been directly correlated with increasing Body mass index (BMI).[8] The patients included in this study were male, had comorbid illnesses, and high BMIs.

The results of the studies published during the COVID-19 outbreak show that the mortality rate of adult patients with ARDS due to COVID-19 undergoing ECMO is approximately 82.3%.[9] The hypercoagulable state associated with increased d-dimer, fibrinogen concentration, and normal platelet levels is the key feature of thrombotic events in COVID-19 patients.[10,11] Recent reports have observed frequent venous thromboembolic complications in COVID-19 patients requiring ICU admission.[5,12] Clotting of indwelling catheters, dialysis filters, ECMO oxygenators, and arterial thrombotic events including acute limb ischemia or stroke were reported.[4,5] In COVID-19 patients, in spite of VTE prophylaxis, the risk is doubled by prothrombotic activity leading to a higher rate of VTE in ICU patients.[12]

In general, obese individuals are at higher risk of devoloping VTE.[8] According to a report, despite a high target and close monitoring of anticoagulation,[13] 100% of COVID-19 patients supported by vvECMO experienced VTE.

Despite the aggressive anticoagulation treatment that ECMO our patients, except the first 2 patients due to having prophylaxis before ECMO initiation, were receiving, they experienced thrombotic. Increasing the heparin dose after a circuit thrombosis resulted in haemorrhage in one patient. We have not been able to monitor anti-factorXa in our cohort to confirm the therapeutic use of heparin; however, therapeutic anticoagulation monitored using anti-factorXa showed no reduction in thromboembolism events.[13] The defective interplay between coagulation and inflammations is the leading cause of intravascular coagulation and organ dysfunction in COVID-19 patients.[14] Abnormal coagulation profiles were reported to be associated with poor outcome.[12] We observed hyperinflammatory and hypercoagulable state for all patients. Very low levels of antithrombinIII(ATIII) 48 (25–67) were measured in 4 patients; for such patients, we tried to achieve normal levels with fresh frozen plasma (FFP) administration in order to treat heparin resistance. Despite being on prophylactic dose LMWH,[15] reduced ATIII levels were reported in a cohort of 8 out of 10 COVID-19 patients on ECMO with confirmed thrombosis.

Conclusion

It is apparent that the coagulopathy associated with ECMO in patients with COVID-19-associated ARDS is complex and deserves special attention. Anticoagulation is principally achieved by dosing an unfractionated heparin infusion for ECMO although other intravenous agents such as bivalirudin and argatroban are becoming increasingly popular. However, there is no consensus on the administration and monitoring of anticoagulation during ECMO and the management of ECMO-related haemorrhage and thrombosis. Based on our experience with 6 patients with COVID-19-associated ARDS on ECMO, we intend to raise awareness regarding thrombotic complications leading to mortality. While considering the risk-to-benefit ratio of performing ECMO in COVID-19 patients, special attention should be given to thrombosis prevention.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul Faculty of Medicine Ethics Committee (08.05.2020 / 9 numbered meeting-file number: 2020/523).

Informed Consent: Written informed consent could not be obtained from patients due to a retrospective case series.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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