


Cryotherapy: A Safe Approach to Pulmonary Hemorrhage During VV-ECMO

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Abstract

The number of hospitals with veno-venous extracorporeal membrane oxygenation (VV-ECMO) capabilities is expanding. To support an ECMO program, centers must be equipped to handle associated complications such as pulmonary hemorrhage. We describe a case series of 4 patients with life-threatening pulmonary bleeding and central airway obstruction. A therapeutic approach of anticoagulation cessation coupled with cryoextraction via flexible bronchoscopy led to successful restoration of airway patency without any adverse events. A low threshold to stop anticoagulation with a strong consideration of bronchoscopy with cryotherapy for pulmonary toilet should be done in patients with pulmonary hemorrhage during VV-ECMO.

Keywords

acute respiratory distress syndrome, ARDS, extracorporeal life support, extracorporeal membrane oxygenation, hemoptysis, pulmonary hemorrhage, cryotherapy, bronchoscopy

Introduction

The use of veno-venous extracorporeal membrane oxygenation (VV-ECMO) to support patients with severe pulmonary dysfunction is growing. The number of ECMO centers has increased from 83 to 492 in the past 30 years, along with a significant increase in the number of annual ECMO runs from 1644 to 16 605.¹ The spread of the coronavirus disease 2019 (COVID-19) and propensity for those with COVID-19 to develop acute respiratory distress syndrome (ARDS) has led to further expansion.² To have a successful ECMO program, centers must have more than just clinical expertise. A system in place to deal with commonly encountered complications is important to consider. One of the more devastating complications includes pulmonary hemorrhage, which can lead to life-threatening, acute obstruction of the tracheobronchial tree and interference with gas exchange.³ The 2016 Extracorporeal Life Support Organization registry described pulmonary hemorrhage in 6.1% of patients on ECMO.⁴ Bleeding and thrombosis in patients receiving ECMO is a major cause of morbidity and mortality.⁴ Thoracic hemorrhage when compared with other sources of bleeding such as gastrointestinal, diffuse, cerebral, and cannulation site has been identified as the most common source.⁵

Presented here are 4 cases of pulmonary hemorrhage in patients with severe ARDS requiring VV-ECMO. The cessation of anticoagulation and addressing reversible factors aided in preventing further bleeding and allowed for a bedside bronchoscopic intervention to clear the central airways. Cryo-probe bronchoscopy was used in all cases to clear large blood clots and debris promoting restoration of airway patency and gas exchange.

Both anticoagulant-free ECMO and cryoextraction for pulmonary hemorrhage are novel to the care of ECMO patients with limited supporting data available in the literature.^{6–9} These cases support the feasibility and safety of such an approach to VV-ECMO complicated by severe pulmonary hemorrhage.

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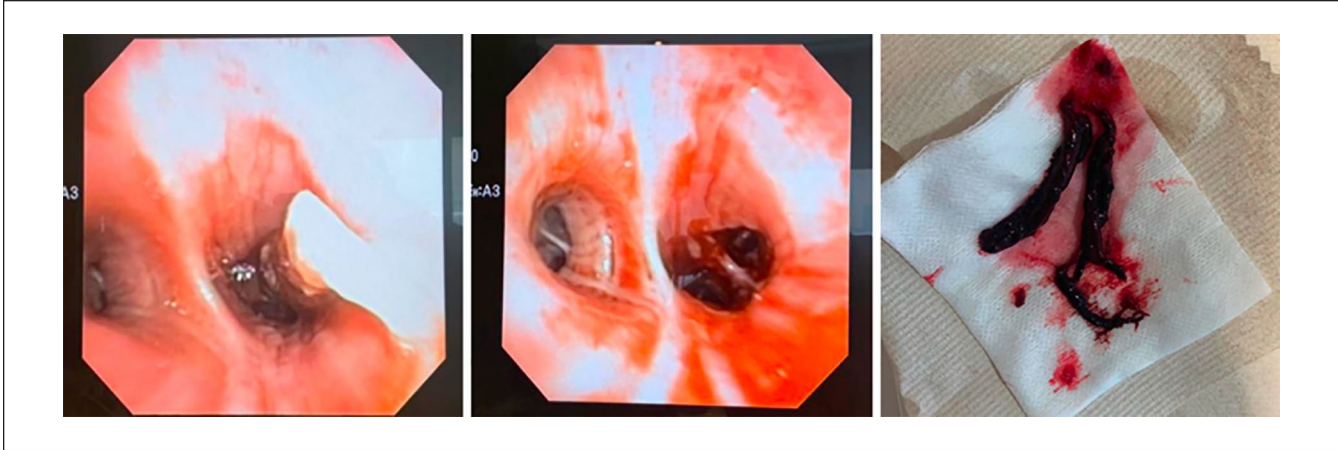


Figure 1. Bronchoscopic view of main carina and coagulated blood extracted using cryotherapy.

Results

Patient 1

A 39-year-old Hispanic man with COVID-19-induced ARDS requiring VV-ECMO (cannulation on hospital day 1) was admitted to our institution. The ECMO cannulation was indicated due to refractory hypoxemia with $\text{PaO}_2 / \text{FiO}_2 < 70$ despite prone ventilation, lung protective ventilator strategy, and paralysis. Systemic anticoagulation was maintained with heparin infusion with anti-Xa goals of 0.3 to 0.5. He developed pulmonary hemorrhage on hospital day 14. The initial approach to stop the hemorrhage included transfusion of platelets and fresh frozen plasma as well as systemic tranexamic acid. Bleeding continued despite these measures and progressed to severe pulmonary hemorrhage on hospital day 16. Flexible bronchoscopy with topical tranexamic acid, cold saline, and 1% epinephrine were used to stop the bleeding. Unfortunately, hemorrhage continued despite these measures ultimately requiring multiple sessions of cryoprobe bronchoscopy (hospital days 16, 17, and 18). These procedures were tolerated well without complications. Heparin was held for 4 hours after each of the first 2 bronchoscopies but was restarted given the concern for potential COVID hypercoagulability and circuit thrombosis. After the third major bleeding episode and need for bronchoscopy, heparin was stopped permanently. Transfusion goals throughout his stay were to keep hemoglobin greater than 7 g/dL, platelets greater than 100 000, and INR less than 1.5. Transfusion was used to reduce risk of hemorrhage and not for resuscitation. The patient remained hemodynamically stable throughout each bleeding episode. Ventilator management focused on an ultra-lung protective strategy (goal tidal volume < 4 cc/kg) with the use of pressure control ventilation with the settings of an inspiratory pressure (IP) of 20 cm H_2O over a post end-expiratory pressure (PEEP) of 10 cm H_2O . These settings provided tidal volumes in the range of 100 to 200 cc per breath. There was little change in the tidal

volumes before or after each bronchoscopy. The patient expired on hospital day 20 due to superimposed bacterial infection and multi-organ failure.

Patient 2

A 59-year-old Caucasian man was admitted for COVID-19 ARDS and staphylococcus pneumonia requiring VV-ECMO cannulation on hospital day 12. ECMO was indicated due to an inability to ventilate with a $\text{pH} < 7.2$ and PCO_2 greater than 80 despite a respiratory rate greater than 30 while maintaining safe airway pressures. Pulmonary hemorrhage started on hospital day 22. Attempts were made to stop the bleeding with flexible bronchoscopy using saline lavage on hospital days 22 and 24. On hospital day 26, he developed worsening bleeding which required emergent bronchoscopy after failed nebulized tranexamic acid administration. The bronchoscopy demonstrated near complete thrombosis of the respiratory tree (Figure 1). A successful cryo-probe bronchoscopy was performed to open the airway, and a bronchial blocker was placed in the left lower lobe due to ongoing bleeding. Initial treatment plan included the cessation of systemic anticoagulation due to this hemorrhage. However, a large, mobile clot was identified on the ECMO drainage cannula by ultrasonography. Therefore, a heparin drip was re-initiated the following day. Five days later, he developed massive hemoptysis resulting in an inability to oxygenate despite increasing ECMO blood flow and the support provided. Emergent cryoprobe bronchoscopy revealed a large fibrinous clot occluding the left lower basilar segments. This was removed, and he was maintained off heparin for the remainder of his ECMO course. The patient was ventilated using pressure control ventilation for the majority of his time on ECMO with initial settings of IP of 15 cm H_2O over a PEEP of 10 cm H_2O . As his compliance improved, this was changed to volume control ventilation targeting a tidal volume of 6 cc/kg and maintenance of a plateau pressure of less than 30 cm

H₂O. He was successfully decannulated on hospital day 36 and subsequently discharged to rehab. He has returned home and is fully functional.

Patient 3

A 53-year-old Hispanic man with COVID-19 ARDS requiring VV-ECMO for refractory hypoxemia despite optimization of medical therapy was admitted to our intensive care unit. Systemic heparin was used for anticoagulation. He developed oropharyngeal bleeding on hospital day 13 not amenable to topical or systemic tranexamic acid. This was further complicated by pulmonary hemorrhage on hospital day 22. Cause of the bleeding was suspected to be multifactorial due to uremia, disseminated intravascular coagulation (DIC), and use of systemic anticoagulation. Successful therapeutic approach included cessation of anticoagulation, continuous renal replacement therapy (CRRT), desmopressin administration, cryoprecipitate transfusion to maintain fibrinogen level over 150 mg/dL, and a brief stoppage of systemic anticoagulation. On hospital day 33, bleeding recurred and was controlled only after the use of cryo-probe bronchoscopy. Heparin was continued until the next day when another major bleeding event occurred requiring an additional session of cryo-probe bronchoscopy. For the remainder of the hospitalization, anticoagulation was discontinued. Two more sessions of cryo-probe bronchoscopy were required on hospital days 35 and 47 to remove coagulated blood. Given the patient's obesity and concern for development of atelectasis, assisted pressure release ventilation (APRV) was used by implementing the time-controlled adaptative ventilation protocol (TCAV). His pressure high (Phigh) was kept at 28 cm H₂O and pressure low (Plow) at 0 cm H₂O. Time low (Tlow) was adjusted based on the patient's lung compliance, targeting a dump volume of 4 to 6 cc/kg and flow termination of 50% to 75% of peak expiratory flow. These settings did not differ during the bronchoscopy procedures. He was successfully decannulated and discharged to a subacute rehab.

Patient 4

A 59-year-old Caucasian man with recently diagnosed hairy cell leukemia presented with severe ARDS due to legionella pneumonia requiring VV-ECMO support. ECMO was indicated due to refractory hypoxemia with worsening acidosis and inability to ventilate. His hospitalization was complicated by septic shock and acute kidney injury requiring renal replacement therapy. Due to thrombocytopenia, uremia, and systemic anticoagulation, he developed massive hemoptysis on hospital day 6. Transfusion of platelets, continuation of CRRT, cessation of anticoagulation, and an initial session of cryotherapy was suspected to be successful in stopping the bleeding. He had recurrent bleeding due to ongoing thrombocytopenia and his underlying malignancy requiring repeat

cryo-probe bronchoscopy on hospital days 17, 21, 23, and 27. A variety of ventilator strategies were used for the care of this patient. Initially, this was pressure control (IP of 15 cm H₂O with a PEEP of 10 cm H₂O) followed by a brief period of APRV and then ultimately volume control. The tidal volumes were based on maintenance of plateau pressure of less than 28 cm H₂O and liberalized as his compliance improved. He was ultimately decannulated and discharged from the hospital. His malignancy is in remission after chemotherapy, and he has experienced full renal recovery. He is living at home independently.

Discussion

We identified a total of 14 cryotherapy sessions performed on 4 different patients. Pertinent laboratory data at the time of each cryo-probe session are represented in Table 1. The patients were all male sex with a median age of 56 years (range, 39-59 years old). Cryotherapy with flexible bronchoscopy was performed by the interventional pulmonary team at bedside in the ICU. No procedure-related complications, including increased hemorrhage, pneumothorax, or bronchial wall injury, were identified. There was minimal change in oxygen requirements (mean change in FiO₂ 1.07%) or arterial oxygenation (mean change in PaO₂ -1.64 mmHg) (Table 2). No changes were made on the ventilator or ECMO flows both before and after the procedure. Prior to the use of cryo-probe bronchoscopy, other therapeutic options were exhausted based on the clinical scenario (Table 3).

All patients were on heparin infusion at the time of initial bleeding. The post-hemorrhage treatment and anticoagulation approach varied for each patient with details described in the case descriptions as well as in Figure 2. The approach was determined by the perceived risk versus benefit of holding anticoagulation. In total, ECMO was delivered without systemic anticoagulation for 49% of the days on ECMO (15%, 20%, 56%, and 81% for each patient, respectively). There were no detected embolic events or episodes requiring emergent circuit change due to thrombosis while off systemic anticoagulation. Subjectively, there was not a greater accumulation of membrane clot than would be expected in the patients off systemic anticoagulation.

The default approach to maintaining a VV-ECMO circuit should include full-dose anticoagulation with an understanding that bleeding complications may occur.¹⁰ Factors in addition to an anticoagulated state that may make the patient more prone to bleeding include uremia, DIC, and the use of antiplatelet drugs. Bleeding may be more prominent in patients with COVID-19.¹¹ ECMO centers must have an approach to when such bleeding occurs. It has been our experience that traditional therapies to control pulmonary bleeding may be inadequate.

Several published case reports describe the application of cryo-probe bronchoscopy for pulmonary hemorrhage. The

Table 1. Summary of Pertinent Laboratory Data at Time of Cyro-Probe Bronchoscopy.

	Hemoglobin (g/dL)	Platelets (10^3)	BUN (mg/dL)	Anti-Xa (U/mL)	Fibrinogen (mg/dL)	PT (seconds)	PTT (seconds)
Case 1							
Bronchoscopy 1	7.8	172	12	0.32			
Bronchoscopy 2	7	122	14	0.43	401		
Bronchoscopy 3	6.6	111	18			12.8	
Case 2							
Bronchoscopy 1	7.9	199	12	0.5	425	14.2	91.7
Bronchoscopy 2	8.1	140	41			13.7	49.7
Case 3							
Bronchoscopy 1	8.2	110	145	0.34	219		
Bronchoscopy 2	8.2	106	148	0.4		12.3	33.2
Bronchoscopy 3	8.1	110	112	<0.1	175	12.4	32.3
Bronchoscopy 4	8.1	78	51				
Case 4							
Bronchoscopy 1	7.5	35	102	0.54	492		99.5
Bronchoscopy 2	7.6	98	68				
Bronchoscopy 3	8.4	71	52				
Bronchoscopy 4	7.9	65	42			12.3	32.9
Bronchoscopy 5	8.8	91	28				

Table 2. Summary of Oxygenation Changes Before and After Each Cryo-Bronchoscopy.

	SpO ₂ pre / post (change)	PaO ₂ pre / post (change) ^a	FiO ₂ pre / post (change)
Case 1			
Bronchoscopy 1	93% / 94% (1%)	70 / 89 (19)	40% / 40% (0%)
Bronchoscopy 2	96% / 96% (0%)	59 / 61 (2)	100% / 100% (0%)
Bronchoscopy 3	94% / 96% (2%)	82 / 65 (-17)	40% / 60% (20%)
Case 2			
Bronchoscopy 1	99% / 98% (-1%)	122 / 117 (-5)	90% / 80% (-10%)
Bronchoscopy 2	95% / 90% (-5%)	126 / 70 (-56)	60% / 55% (-5%)
Case 3			
Bronchoscopy 1	97% / 93% (-4%)	69 / 66 (-3)	80% / 80% (0%)
Bronchoscopy 2	95% / 94% (-1%)	76 / 76 (0)	70% / 70% (0%)
Bronchoscopy 3	93% / 97% (4%)	66 / 72 (6)	100% / 100% (0%)
Bronchoscopy 4	93% / 99% (6%)	71 / 75 (4)	70% / 70% (0%)
Case 4			
Bronchoscopy 1	92% / 90% (-2%)	91 / 93 (2)	100% / 100% (0%)
Bronchoscopy 2	94% / 96% (2%)	74 / 92 (18)	60% / 60% (0%)
Bronchoscopy 3	97% / 97% (0%)	89 / 72 (-17)	40% / 40% (0%)
Bronchoscopy 4	94% / 95% (1%)	66 / 78 (12)	50% / 60% (10%)
Bronchoscopy 5	91% / 98% (7%)	67 / 81 (14)	40% / 40% (0%)
Average	0.71%	-1.5 mmHg	1.07%

^aUnit in mmHg.

largest series consists of 30 patients for a total of 38 cryo-therapy sessions highlighting the safety of the procedure.¹² Its use has also been described in patients requiring VV-ECMO,^{13,14} the largest of which consists of a 16-patient cohort, 11 of which were on ECMO support.⁹ Reference to anticoagulation approach is not mentioned in these articles. Nor is the application to the COVID-19 population described.

The cases described here demonstrate that the cessation of anticoagulation should be done and can be done without

concern for significant risk. Furthermore, cryo-probe bronchoscopy should be the standard approach to extraction of large blood clots from the tracheobronchial tree that is not amenable to traditional therapeutic interventions. We believe VV-ECMO programs need to have cryotherapy with a team able and willing to perform the procedure at the patient's bedside as it can be done safely and effectively in this population.

Limitations of this article arise from the small number of included patients. There is no control group to which

Table 3. Summary of Pulmonary Hemorrhage Day, Number of Cryo-Bronchoscopy, and ECMO Days Off Anticoagulation.

Case no.	Initial pulmonary hemorrhage	Treatment approach prior to cryo-probe bronchoscopy	No. of cryo-probe bronchoscopy	No. of days ECMO run off anticoagulation (%)
1	Hospital day 14	Platelets, FFP, systemic TXA, bronchoscopy with saline, 1% epinephrine, topical TXA	3 sessions: hospital days 16, 17, 18	3 out of 20 (15%)
2	Hospital day 22	Fob with saline, nebulized TXA, bronchoscopy with saline	2 sessions: hospital days 26, 32	5 out of 25 (20%)
3	Hospital day 22	CRRT, desmopressin, cryoprecipitate, bronchoscopy with saline	4 sessions: hospital days 33, 34, 35, 47	44 out of 78 (56%)
4	Hospital day 6	Platelets, CRRT, bronchoscopy with saline	5 sessions: hospital days 6, 17, 21, 23, 27	22 out of 27 (81%)

Abbreviations: CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; TXA, tranexamic acid.

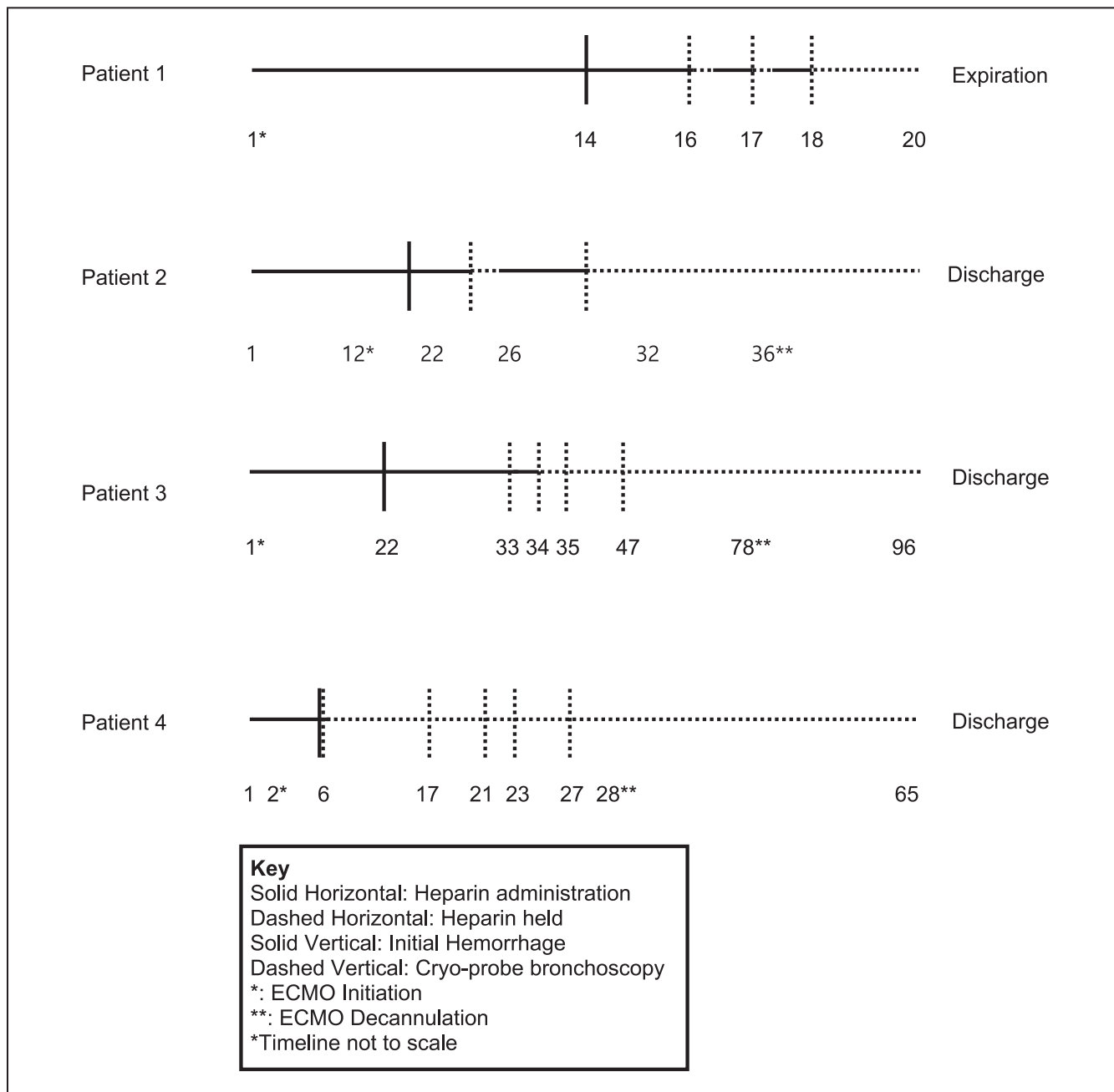


Figure 2. Timeline of anticoagulation and cryo-probe bronchoscopy.

to compare treatment of pulmonary hemorrhage without cryotherapy. Although all patients tolerated this procedure, objective measures as to the benefit aside from airway clearance is not known.

Conclusions

Pulmonary bleeding is a known complication of VV-ECMO. Although systemic anticoagulation should remain the norm for patients requiring mechanical circulatory support, physicians should have a multitude of tools to manage bleeding complications which might arise. Cryo-probe bronchoscopy is a viable, safe, and often successful option for extraction of large blood clots from the trachea-bronchial tree. The VV-ECMO programs would benefit from having cryotherapy available for bedside intervention in the setting of severe pulmonary hemorrhage.

Declaration of Conflicting Interests

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Ethics Approval

Ethical approval to report this case series was obtained from Cooper Health IRB. ID No 20-591.

Informed Consent

Informed consent for patient information to be published in this article was not obtained because it was waived by IRB. No identifiable features present in submission.

References

1. ECLS Registry Report International Summary – April 2021. Ann Arbor, MI: ELSO Edition (2021) <https://www.else.org/Registry/Statistics/InternationalSummary.aspx> April 2021.
2. Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet*. 2020;396:1071-1078.
3. Vaquer S, Haro C, Peruga P, et al. Systemic review and meta-analysis of complications and mortality of veno-venous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome. *Ann Intensive Care*. 2017;7:51.
4. Thiagarajan R, Barbaro R, Rycus PT. Extracorporeal life support organization registry international report 2016. *ASAIO*. 2017;63:60-67.
5. Ried M, Sommerauer L, Lubnow M, et al. Thoracic bleeding complications in patients with venovenous extracorporeal membrane oxygenation. *Ann Thorac Surg*. 2018;106(6):1668-1674.
6. Krueger K, Schmutz A, Zieger B, Kalbhenn J. Venovenous extracorporeal membrane oxygenation with prophylactic subcutaneous anticoagulation only: an observational study in more than 60 patients. *Artif Organs*. 2017;41(2):186-192.
7. Radchenko C, Alraiyes AH, Shojaee S. A systemic approach to the management of massive hemoptysis. *J Thoracic Dis*. 2017;9:S1069-S1086.
8. DiBardino DM, Lanfranco AR, Haas AR. Bronchoscopic cryotherapy: clinical applications of the cryoprobe, cryospray, and cryoadhesion. *Ann Am Thorac Soc*. 2016;13(8):1405-1415.
9. Schmidt LH, Schulze AB, Goerlich D, et al. Blood clot removal by cryoextraction in critically ill patients with pulmonary hemorrhage. *J Thorac Dis*. 2019;11(10):4319-4327.
10. ELSO Anticoagulation Guideline – 2014. Ann Arbor, MI: ELSO <https://www.else.org/portals/0/files/elseoanticoagulationguideline8-2014-table-contents.pdf> 2014.
11. Ripoll B, Rubino A, Besser M, et al. Observational study of thrombosis and bleeding in COVID-19 VV ECMO patients. *Int J Artif Organs*. 2021;45:239-242. doi:10.1177/0391398821989065.
12. Sriratanaviriyakul N, Lam F, Morrissey BM, Stollenwerk N, Schivo M, Yoneda KY. Safety and clinical utility of flexible bronchoscopic cryoextraction in patients with non-neoplasm tracheobronchial obstruction: a retrospective chart review. *J Bronchology Interv Pulmonol*. 2015;22(4):288-293.
13. Chen T, Yao L, Zhu C. Venovenous extracorporeal membrane oxygenation combined with fiberoptic bronchoscopy-associated CO2 cryotherapy in the treatment of massive hemoptysis in pregnancy: a case report. *Int J Gen Med*. 2020;13:1291-1296.
14. Cook MI, Papadimos TJ. The use of cryotherapy via bronchoscopy for removal of obstructing tracheobronchial thrombi. *Int J Crit Illn Inj Sci*. 2015;5(3):215-216.