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Management of massive airway hemorrhage associated with extracorporeal membrane oxygenation: A retrospective case series study

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Abstract

Background and Aims: Extracorporeal membrane oxygenation (ECMO) is an important means of treating patients with respiratory failure. Massive airway hemorrhage is a rare complication of ECMO, with high mortality. The aim of this study was to provide a reference for improving the success rate of treatment of this complication by analyzing and summarizing patient clinical data.

Methods: We searched PubMed, Medline, and EMBASE databases for case reports of massive airway bleeding associated with ECMO from January 2000 to January 2022 and included one case treated at our facility. All patients were disconnected from the ventilator, and the endotracheal tube was clamped during treatment, resulting in complete airway packing for hemostasis. The clinical data of these patients were analyzed.

Results: Through searching and further screening, two works of literature reported four cases that met our inclusion criteria. Including our patient's case, five patients were included in this study (four adults and one neonate). The longest ECMO treatment time before bleeding was 14 days, and the shortest was 20 min. In all patients, conservative treatment was ineffective after a major airway hemorrhage. They were disconnected from the ventilator and the tracheal tube was clamped for 13–72 h. The four adult patients underwent bronchial artery embolization in the interventional radiology suite. All patients' bleeding stopped after treatment; they were successfully weaned off ECMO and discharged.

Conclusions: Treatment measures to disconnect the ventilator and clamp the endotracheal tube with full support from ECMO are feasible for massive airway bleeding associated with ECMO. Early bronchial arteriography and embolization can prevent rebleeding.

KEYWORDS

bleeding, cryotherapy, ECMO, extracorporeal membrane oxygenation, hemoptysis

1 | INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) draws venous blood from the patient through dedicated vascular access and pumps it into an artificial lung known as an oxygenator. This process removes carbon dioxide, oxygenates the blood, and returns the oxygen-rich blood to the patient. It can therefore support a failing heart and/or lung.[1] Veno-venous (VV) ECMO supports only the lungs, while veno-arterial (VA) ECMO supports both the lungs and the heart.[2] ECMO has become an important supportive measure for severe cardiopulmonary failure and is widely used in adults and children. ECMO also plays an important role in supporting patients with severe coronavirus disease (COVID-19),[3,4] and can be said to give these patients a second life.

However, patients supported with ECMO face complications and associated risks. Bleeding and thrombosis are major complications of ECMO.[5] In particular, patients with severe COVID-19 are more likely to experience complications.[6] Bleeding is often associated with anticoagulation and may include gastrointestinal bleeding, intracerebral hemorrhage, and massive airway bleeding. One study showed that the incidence of massive hemorrhage associated with ECMO was 30.9%, and airway bleeding accounted for 26% of hemorrhages associated with ECMO.[5] Although massive airway hemorrhage (>300 mL/day) associated with ECMO is rare, it can be a fatal complication associated with increased mortality.[7]

Conservative treatment of massive airway hemorrhage associated with ECMO has poor efficacy and a high in-hospital mortality rate.[7] In the case of ineffective conservative treatment, disconnecting the ventilator and clamping the tracheal tube is a feasible method, resulting in complete airway blockage and achieving hemostasis. Once the tracheal tube is clamped, the patient's respiratory function is completely lost, and treatment is completed with the support of ECMO.

We searched for relevant cases in the literature and combined them with our case of massive airway hemorrhage associated with ECMO. The clinical data related to all these cases were analyzed and summarized, aiming to provide a reference for improving the success rate of treatment of this complication.

2 | METHODS

2.1 | Literature screening

2.1.1 | Search strategy

A literature search was performed using three databases: PubMed, Medline, and EMBASE. A comprehensive search was performed for case reports of massive airway bleeding associated with ECMO from January 2000 to January 2022, and the searched keywords included: extracorporeal circulation, ECMO, bleeding, hemoptysis, airway bleeding, and pulmonary hemorrhage. The relevant articles were screened and selected for inclusion by two authors, and disagreements were resolved through consensus and voting. The retrieved cases were analyzed together with our case. The literature screening process is shown in Figure 1.

Our case included in this study was approved by the First Affiliated Hospital of Xi'an Jiaotong University Ethics Committee. The patient was informed, and written consent was documented in the patient's medical records. All procedures performed in the current study were in accordance with the Declaration of Helsinki.

2.2 | Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Case report of massive airway hemorrhage associated with ECMO. (2) The case met the definition of massive airway hemorrhage and management: bleeding from the tracheal tube (>300 mL/day) that could not be controlled by conventional measures, such as correction of coagulopathy, bronchoscopy with cold saline or diluted epinephrine lavage, and lung isolation with a bronchial blocker.[7] Treatment consisted of disconnecting the patient from the ventilator and clamping the endotracheal tube to provide complete airway packing. (3) Either the text description or imaging data showed that the patient's lungs were filled with blood. (4) The patient's onset and treatment processes were clearly described in the case report, and relevant data could be extracted.

The exclusion criteria were as follows: (1) The medical records were insufficient and data extraction could not be carried out. (2) A single lung or part of a lung lobe/segment was not filled with blood, or the amount of bleeding did not meet the definition criteria for massive airway hemorrhage. (3) ECMO support was initiated after massive airway hemorrhage, or massive airway bleeding occurred without ECMO. (4) The tracheal tube was not clamped during the treatment. (5) The literature had been duplicated. (6) Patients or guardians voluntarily terminated treatment.

2.3 | Study selection

After searching the relevant databases and conducting rigorous screening, two works of literature met the requirements and were included.[7,8] The data of four patients were reported in the two works, and we diagnosed and treated one patient.[9] Therefore, five patients were included in this study.

2.4 | Data collection

We collected data on the relevant cases reported in the included literature and that of the case we diagnosed and treated. The

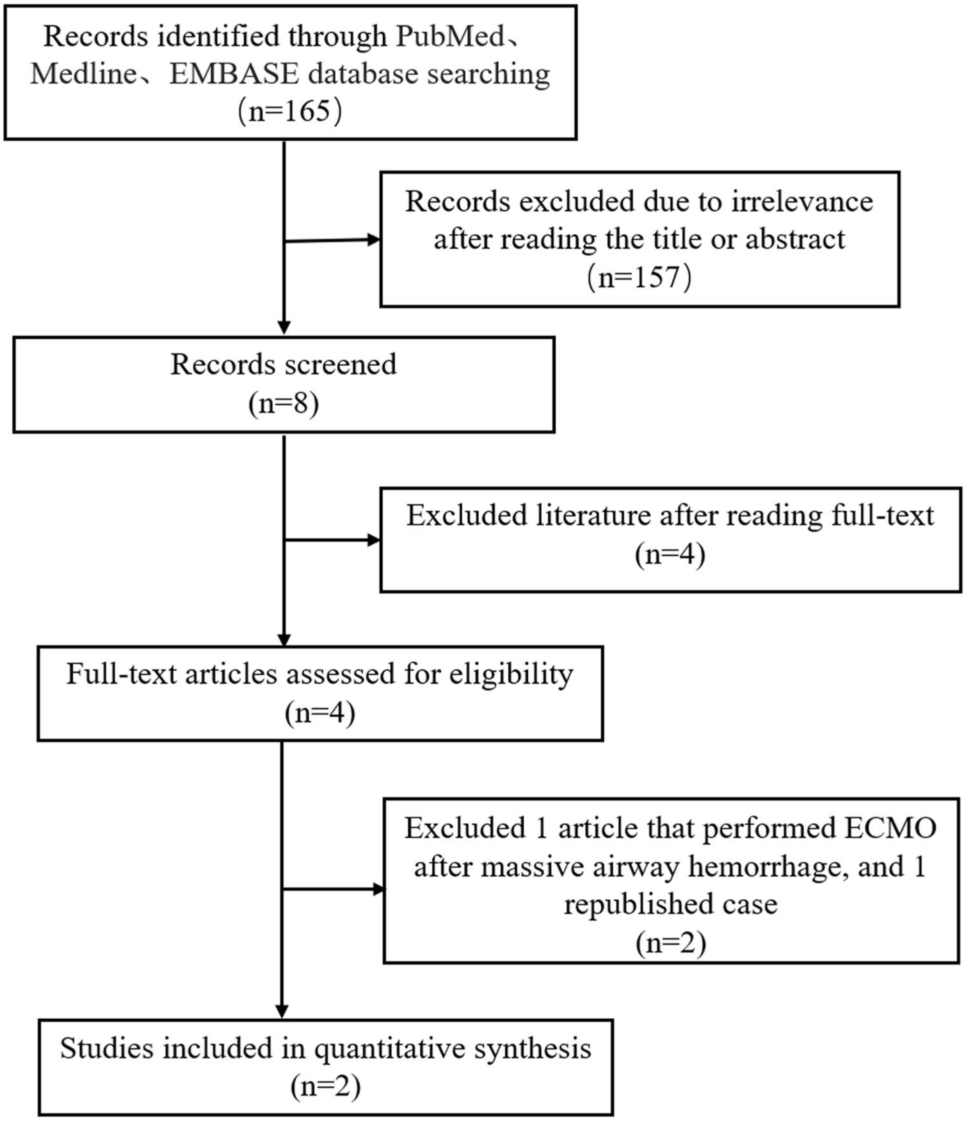

FIGURE 1 Flowchart of literature screening.

following data were collected, collated, and analyzed: demographic data, ECMO indications, adjuvant therapy used, type and duration of ECMO support, duration of ECMO support before massive airway hemorrhage, oxygenator replacement, blood product transfusion, type of anticoagulant and duration of use, artificial airway clamping time, angiography and embolization data, measures of blood clot removal, and patient outcomes.

2.5 | Statistical analyses

All collected data were collated and analyzed using Microsoft Excel. Days on ECMO and days on ECMO before hemorrhage are expressed in days, endotracheal tube clamp duration is expressed in hours, and related items were collated in summary tables.

3 | RESULTS

3.1 | Patient characteristics

The patients included were one male and four females. They comprised one neonate and four adults, and the adults were aged 49–59 years. Two patients had underlying diseases, including one patient with breast cancer and another with Sjögren's syndrome and Hashimoto's thyroiditis. Four patients were treated with VA-ECMO due to cardiogenic shock and circulatory instability, and one was treated with VV-ECMO due to severe acute respiratory distress syndrome (ARDS) caused by COVID-19. Massive airway hemorrhage occurred as quickly as 20 min after starting ECMO support, with the longest taking 14 days. The neonate was not administered anticoagulant medication before hemorrhaging; however, the adult

TABLE 1 Patient characteristics.

	Patient 1[7]	Patient 2[7]	Patient 3[7]	Patient 4[8]	Patient 5[9]
Age, years	49	57	56	Neonate	59
Sex	Female	Male	Female	Female	Female
Underlying disease	Breast cancer	Undescribed	Undescribed	None	Sjögren's syndrome and Hashimoto's thyroiditis
Reasons for ECMO	Cardiomyopathy after adriamycin chemotherapy for breast cancer, acute decompensated heart failure	Cardiogenic shock due to myocardial infarction	Left coronary artery occlusion, development of malignant ventricular tachycardia, circulatory instability	Neonatal sepsis and progressive heart failure	Severe ARDS caused by COVID-19
ECMO	VA-ECMO	VA-ECMO	VA-ECMO	VA-ECMO	VV-ECMO
Days on ECMO, days	14	20	17	5	88
Days on ECMO before hemorrhage, days	2	1	3	20 min	14
Anticoagulation therapy before hemorrhage	Heparin	Integrin for stent protection[a]	Integrin for stent protection[a]	None	Heparin and Nafamostat mesylate
Bleeding time point	After manipulation of the Swan–Ganz catheter	After coronary stent placement	After coronary stent placement	20 min after ECMO treatment	No special operation
Bleeding site	Right lung	Lower lobe of left lung	Left main bronchus	Left and right lung	Left and right lung
Outcome	Survived	Survived	Survived	Survived	Survived

[a]Drug-eluting stent that required the use of Integrellin®.

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease; ECMO, extracorporeal membrane oxygenation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VV-ECMO, veno-venous extracorporeal membrane oxygenation.

patients were administered anticoagulants, with heparin being the most common drug used. Massive airway hemorrhage occurred in the patients who underwent VA-ECMO after invasive operations (manipulation of Swan–Ganz catheter, coronary stent placement, etc.). The bleeding sites were different in all five patients. The minimum duration of ECMO support was 3 days, and the maximum was 88 days. All five patients were successfully weaned from ECMO and were sufficiently stable to be discharged from the hospital (Table 1).

3.2 | Treatment measures after hemorrhage

Anticoagulants were discontinued immediately after the discovery of massive airway hemorrhage in all patients for a maximum of 168 h. Conservative treatments, including fiberoptic bronchoscopy, epinephrine (1/10,000), thrombin, tranexamic acid, and ice saline airway lavage and/or lung isolation with a bronchial blocker, were unsuccessful. Endotracheal tube clamping was performed to provide complete airway tamponade after conservative treatment had failed. The tracheal tube clamping time was between 13 and 72 h. All adult patients underwent bronchial artery embolization in the interventional radiology suite. No obvious bleeding site was found in three patients, and the bleeding stopped after empirical bilateral bronchial artery embolization. Three patients experienced two hemorrhages and two vascular interventions. Three adult patients underwent oxygenator changes during ECMO treatment, and the VV-ECMO-treated patient underwent four changes using five oxygenators (Table 2).

4 | DISCUSSION

In recent years, ECMO has progressed in technology and management; however, the mortality rate of patients treated with ECMO remains high.[10] On one hand, this is related to the critical condition of these patients, and on the other hand, this is related to the high complication rate of ECMO.[10–12] Massive airway hemorrhage is one of the potentially fatal complications of ECMO, and the use of anticoagulants further increases the risk thereof. Once a massive airway hemorrhage occurs in patients, it is often difficult to control with conventional treatment methods. Some studies have reported a method for treating massive airway hemorrhage during ECMO.[7,13] In our facility, a patient with severe ARDS caused by COVID-19 had a massive airway hemorrhage during ECMO treatment. We optimized this method (Figure 2) for treatment, and the patient recovered and was discharged from the hospital.[9] This approach can also be used in patients with massive airway hemorrhage unassociated with ECMO but still requiring full support from ECMO.[14]

Massive airway hemorrhage associated with ECMO is more common in anticoagulation overdose or bronchial artery rupture.[15] The longer the ECMO treatment, the greater the risk of complications. Massive airway hemorrhage can occur at any time during ECMO therapy. In the four patients reported in the literature,[7,8] the shortest elapsed time before a massive airway hemorrhage occurred was 20 min after commencing ECMO treatment, and the longest was 3 days. Our patient[9] had a respiratory indication, was on VV-ECMO for 88 days, and developed a spontaneous massive airway hemorrhage after 14 days on ECMO. Vascular endothelial injury and changes in coagulation mechanisms in patients with COVID-19 exacerbate the risk of airway bleeding,[5] which may be one of the reasons for the spontaneous bleeding in our patient.

Among the patients included in this study, one developed a massive airway hemorrhage after placement of the Swan–Ganz catheter during ECMO.[7] An indwelling Swan–Ganz catheter has also been associated with the occurrence of pulmonary artery rupture (incidence: 0.03%–0.2%),[13] with the risk of mortality approaching 70%.[16] Furthermore, two patients developed massive airway hemorrhage after coronary stent placement and were not excluded because we considered this an invasive procedure.

When a patient has a massive airway hemorrhage, due to the extensive bleeding, both lungs rapidly fill with blood and it is difficult to distinguish from which part of the lungs the hemorrhage originates. Therefore, selective lung isolation is often not feasible. Prompt prevention of continued bleeding is critical, and conservative treatments are ineffective and rarely stop the bleeding.[7,13] Tracheal tube clamping significantly reduces the need for blood transfusions; therefore, the risk of transfusion-related lung injury may be reduced. In this method, airway tamponade therapy with endotracheal tube clamping does not cause significant respiratory complications or infection.[14]

Although the discontinuation of anticoagulant administration is beneficial for bleeding control, aortography and selective bronchial arteriography should be performed earlier when the tracheal tube is clamped to identify possible bleeding sites and perform vascular embolization. Bronchial artery embolization can be used as a lifesaving intervention in patients with massive airway hemorrhage, with success rates ranging from 82% to 100% to control the bleeding immediately after embolization.[17] Bronchial artery rupture is most common in cases of massive airway hemorrhage. If angiography fails to find bleeding vessels, early empirical bilateral bronchial artery embolization is beneficial to control bleeding and reduce mortality rates.[7,18] A retrospective study showed that patients who underwent early (<3 days) arterial embolization had lower 7-day mortality rates (1.3% vs. 4.0%) and a shorter duration of mechanical ventilation compared with those who underwent late (>3 days) arterial embolization.[19] Therefore, all patients with massive airway hemorrhage should undergo bronchial artery embolization as soon as possible. Among the five patients we included, three had no bleeding site detected by angiography, all underwent early empirical bilateral bronchial artery embolization, and the bleeding stopped after embolization. One patient still had active bleeding after left bronchial artery embolization, and the bleeding stopped after empirical right bronchial artery embolization. Repeated bronchoscopy risks worsening bleeding, and clamping the endotracheal tube can cause airway tamponade to achieve hemostasis. Further, early arteriography and

TABLE 2 Treatment measures after hemorrhage.

	Patient 1[7]	Patient 2[7]	Patient 3[7]	Patient 4[8]	Patient 5[9]
Time without anticoagulation therapy (h)	60	72	72	>48	168
Total number of packed red cell transfusions (U)	7	21	9	Undescribed	30
Conservative treatment	Epinephrine (1/10,000) and iced saline airway lavage, bronchoscopy	Epinephrine (1/10,000) and iced saline airway lavage, bronchoscopy	Epinephrine (1/10,000) and iced saline airway lavage, bronchoscopy	Endotracheal application of epinephrine or surfactant, bronchoscopy	Epinephrine (1/10,000), thrombin, tranexamic acid and ice saline airway lavage, bronchoscopy
Lung isolation with bronchial blocker	Yes, failed	Undescribed	Yes, failed	No	No
Endotracheal tube clamp duration (h)	36	13	48	63	72
Rebleeding after loosening the tracheal tube	No	Yes, 2 total bleeds	Yes, 2 total bleeds	Yes, 2 total bleeds	Yes, 2 total bleeds
Bronchial arteriogram	Yes, no extravasation of contrast medium	Yes, no extravasation of contrast medium	Yes, active bleeding from the left bronchial artery	Not performed	Yes, no extravasation of contrast medium
Intravascular embolization	Yes, embolization of bilateral bronchial arteries was empirically carried out	Yes, embolization of bilateral bronchial arteries was empirically carried out	Left main bronchial artery and empirical right main bronchial artery embolization	Not performed	Yes, embolization of bilateral bronchial arteries was empirically carried out
Successful embolization	No	Yes, with 2 procedures	Yes, with 2 procedures	Not performed	Yes, with 2 procedures
Clearance of blood clots after loosening the endotracheal tube	Bronchoscopy	Undescribed	Undescribed	Bronchoscopy	Bronchoscopy, urokinase, bronchoalveolar lavage
Change of oxygenator	No	Yes	Yes	No	Yes, 4 changes using 5 oxygenators

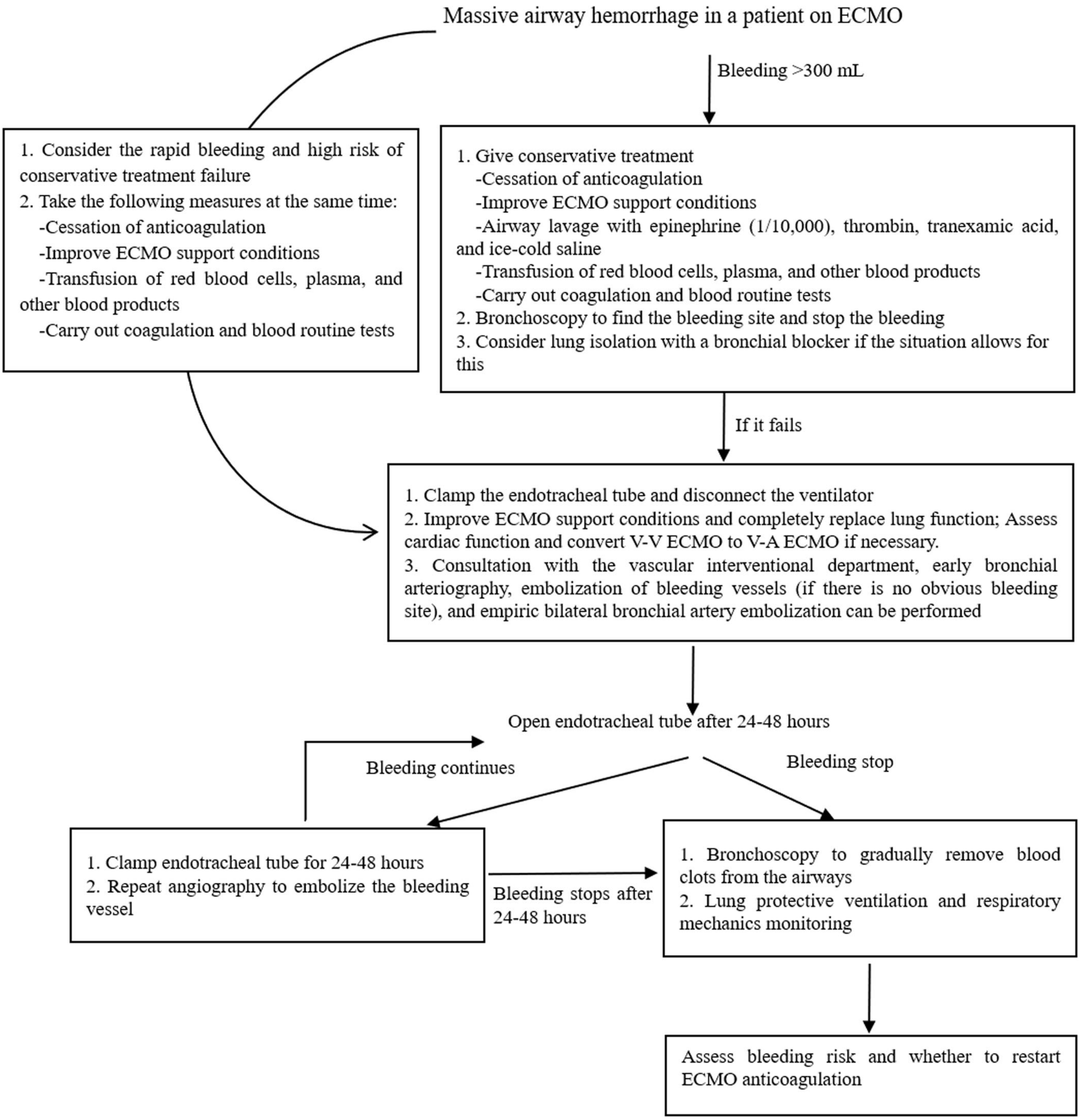

FIGURE 2 Management of massive airway hemorrhage in patients on ECMO. ECMO, extracorporeal membrane oxygenation; VA-ECMO, veno-arterial ECMO; VV-ECMO, veno-venous ECMO.

vascular embolization will prevent continued bleeding and hemodynamic deterioration.[7,18]

The endotracheal tube can be loosened after clamping for 24–48 h. If there is still active bleeding after releasing the clamp, the endotracheal tube can be re-clamped for a further 24–48 h. Once the patient no longer has active bleeding, restarting anticoagulation therapy should be considered. Prolonged discontinuation of anticoagulant administration may increase the risk of oxygenator dysfunction and thromboembolism. Anticoagulation therapy should be restarted as early as possible under close monitoring if permitted. In all five patients in this study, anticoagulation therapy was discontinued for between 48 and 168 h. Oxygenators were changed in three patients during ECMO treatment. Our patient underwent ECMO for the longest period, with four changes using five oxygenators during 88 days of ECMO.

Repeated bronchoscopy should be performed after the airway is opened, and the airway should be cleared of blood clots. After clamping, the endobronchial lining becomes fragile, and blood clot removal should be undertaken with caution as it may cause rebleeding if performed incorrectly. Cryoprobe bronchoscopy is a viable, safe, and often successful option for extracting large blood clots from the tracheobronchial tree.[19] Bronchoscopy and cryotherapy can be used for the removal of large airway clots. Repeated bronchoscopic saline lavage can be performed to remove blood clots from the small airways and alveoli, and small doses of urokinase can be used locally to dissolve them.[20,21]

After the blood clot in the large airway is cleared, mechanical ventilation should be restarted, positive end-expiratory pressure (PEEP) and tidal volume should be titrated, and respiratory mechanics should be monitored, which is beneficial for the recovery of lung function and helps to prevent mechanical ventilation-related lung injury. The patient we treated received super lung-protective ventilation (tidal volume 1 mL/kg) after we cleared blood clots from the large airways using cryotherapy. Fiberoptic bronchoscopy and bronchoalveolar lavage were performed one to two times a day to remove blood clots from the small airways and alveoli; however, it was difficult to remove these clots. In the process of clearing, we used 1000 U urokinase/site to dissolve the blood clots and received good results. No bleeding reoccurred.

Although a limitation of this study is the small number of reported cases, we have developed a protocol for massive airway hemorrhage on ECMO, which was effective in our patient based on four cases in the literature.

5 | CONCLUSIONS

Although the specific cause of massive airway hemorrhage associated with ECMO is unknown, it is feasible to disconnect the ventilator and clamp the endotracheal tube after bleeding with full support from ECMO. Utilizing early bronchial arteriography to detect possible bleeding sites and vascular embolization can prevent rebleeding and stabilize hemodynamics. Additionally, fiberoptic bronchoscopy and cryotherapy are effective methods of removing blood clots. In the future, we look forward to studies including more cases to further demonstrate the effectiveness of this treatment modality.

AUTHOR CONTRIBUTIONS

Hong Zhou: Conceptualization; data curation; writing—original draft. **Qindong Shi**: Conceptualization; data curation; formal analysis. **Litao Guo**: Conceptualization; data curation; formal analysis; funding acquisition; writing—original draft; writing—review and editing.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article. All authors have read and approved the final version of the manuscript. Prof. Litao Guo had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

This study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from the patient in the present study. The patient consented to the publication of her images and data in this case report.

TRANSPARENCY STATEMENT

The lead author Litao Guo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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