Evaluation of the Nautilus Smart Extracorporeal Membrane Oxygenation in Patients With Hemostatic Alteration: A Case Series

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The intricate management of hemostatic disorders in extracorporeal membrane oxygenation (ECMO) assisted patients poses challenges, particularly when procoagulant administration is necessary. We hereby report the performance of the Nautilus* Smart ECMO Module in three patients with hemostatic disorders. We collected data from ECMO procedures with Nautilus* Smart ECMO Module and analyzed the performance: the operating pressures and resistance of the device in addition to the coagulation status of the patients. During the three procedures, partial pressure oxygen post-oxygenator (paO_2) stayed above 100 mm Hg and partial pressure carbon dioxide post-oxygenator ($paCO_2$) did not exceed 45 mm Hg. Membrane FiO_2 (fractional inspired O_2) did not exceed 75% and air flow remained within a 1:1 ratio with blood flow in veno-arterial ECMO (V-A) and within 1:2 in veno-venous ECMO (V-V). There was no evidence of excessive operating pressure for the device, with a pressure drop consistently below 28 mm Hg and a maximum peak resistance of 7 Δmm Hg/L/min. The Nautilus* Smart ECMO Module showed good performance in patients with hemostatic disorders despite the implications associated with procoagulant administration. *ASAIO Journal* 2024; XX:XX–XX

Key Words: Nautilus Smart ECMO, ECMO, coagulation disorders, hemostatic alteration, mechanical circulatory support, veno-venous ECMO, veno-arterial ECMO, postcardiotomy ECMO, oxygenator performance, case series

Introduction

Over the past 50 years, there has been a remarkable evolution in the use of extracorporeal membrane oxygenation (ECMO) for the treatment of patients with cardiac or respiratory pathologies. The management of diseases associated with ECMO assistance is becoming progressively intricate, especially in patients with hemostatic alteration.[1]

In such cases, the necessity of administering procoagulants[2] may arise, posing potential adverse effects such as thrombus formation, reduction in gas exchange, and decrease of oxygenator performance, especially in patients with contraindication to coagulation, significant bleeding, or inability to support high flows.

Ensuring optimal coagulation management in ECMO patients is a focus point for the effective implementation of assistance, particularly in relation to the specific type of oxygenator employed.

The current literature doesn't provide evidence addressing the use of specific ECMO devices in patients with hemostatic alteration. Most of the available literature focused on general coagulation effects in ECMO rather than specific device consideration for this patient population. Therefore, we herein report a series of cases where we investigated the performance[3] of the Nautilus* Smart ECMO Module (Medtronic, Minneapolis, MN), in patients with hemostatic disorders.

Materials and Methods

Laboratory Blood Test and Device Data Collection

During the entire time of ECMO-support, the following variables associated with the oxygenator performance were collected:

- Blood flow (BF), airflow (AF), and membrane FiO_2.
- pO_2 and pCO_2 in the device, before and after the membrane, and in the patients' blood.
- Pressure pre-oxygenator (P_{IN}), pressure post-oxygenator (P_{OUT}), differential pressure ($\Delta P = P_{IN} - P_{OUT}$), and resistance ($R = \Delta P/BF$).

All the data collected from the device are associated with coagulation status of the patients in relation to our coagulation protocol:

- Activated partial thromboplastin time (aPTT), aPTT ratio, international normalized ratio (INR), antithrombin III (ATIII), D-dimers (DDs), fibrinogen (FIB), platelet (PLT), and hemoglobin (Hb)
- PLTs, fresh frozen plasma (FFP), and red blood cells (RBC) units administered during the ECMO support.

Routine Anticoagulation Management

We described our local practice for anticoagulation management in patients undergoing ECMO:

- A standard dose of 5,000 IU of heparin is administrated during cannulation. Subsequently, a comprehensive coagulation status analysis, including aPTT, aPTT ratio, INR, ATIII, DDs, FIB, and PLT is analyzed. Continuous

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heparin at a rate of 500 UI/hour is started after 24 hours from the beginning of ECMO without any bleeding status (laboratory tests, clinical conditions).
- During the treatment, we performed thromboelastography (TEG) assessments twice a day employing kaolin and heparinase tests.
- The regulation of heparin infusion is based on TEG exam in correlation with aPTT results, with minimal variation to prevent fluctuations in the coagulation state.
- In the case of hemostatic disorders, consideration may be given to administering a dose of procoagulant factors, guided by the result of the TEG.
- PLTs are transfused, when the count drops below 50,000, in the post-oxygenator line to mitigate PLT sequestration.
- RBCs are transfused with Hb below 10 g/dl.

Extracorporeal Membrane Oxygenation Setting and Device Data Collection

The following setting was used in all the patients:

- 3/8″ with Custom Perfusion Tubing System Phisyo Coated (Livanova, Mirandola, Italy).
- Rotaflow Centrifugal Pump (Maquet, Getinge, Sweden).
- Nautilus* Smart ECMO Module (Medtronic): Balance Biosurface non heparin coating with a reduced membrane area, low priming volume, and integrated pressure system (Figure 1).
- The type of cannulation depended on the ECMO configuration (V-A or V-V). In cases 1 and 3, the cannulas used had a heparin coating, whereas in case 2 had a biocompatible and biostable co-polymer (Elast-Eon). The details of cannulation setup are reported in description of the case series.

Figure 1. Nautilus Smart Extracorporeal Membrane Oxygenation Module (Medtronic) reproduced with permission of Medtronic.

Patients Selection

In this report, we focused on patients with hemostatic disorders. In the specific:

- Significant postoperative bleeding requiring high-dose procoagulants to stabilize their hemostatic status.
- Contraindications to anticoagulation.
- Inability to maintain optimal ECMO flow without anticoagulation therapy.
- Both short and long-term support scenarios were taken into consideration for comprehensive evaluation of varying durations of ECMO assistance.

In 2023, we performed 63 ECMO. In our institution, we use various types of oxygenators based on factors such as diagnosis, predicted length of stay, and considerations regarding current availability of device.

Among these cases, only three patients involved in hemostatic alteration, and all of them had been treated with Nautilus Smart.

Case 1

A 58 year old man underwent Surgical Aortic Valve Replacement in July 2023 due to severe Aortic Stenosis. Three months later, the patient presented symptoms of dyspnea and fever. Echocardiography showed a detachment of the prosthesis requiring admission to the cardiac surgery intensive care unit in stable condition. Due to a progressive worsening of clinical conditions and the onset of Pulmonary Edema, the patient was intubated and an urgent Aortic Valve Replacement and coronary artery bypass graft were performed.

Complex weaning from cardiopulmonary bypass required maximum inotropic support and Intra-Aortic Baloon Pump (IABP) (Maquet). Despite this, a circulatory support using V-A ECMO became necessary with trans-apical venting. We used a 15 Fr/15 cm Arterial Cannula (Maquet) in left Femoral Artery with a 7 Fr catheter for limb distal reperfusion (Arrow, Teleflex, Morrisville, NC) and a 25 Fr/55 cm Multihole Venous Cannula (Maquet) in the right Femoral Vein.

Transapical left venting is performed with a 19 Fr/23 cm Arterial Cannula (Maquet) connected to the ECMO venous line through a 1/4″ tube, using a dedicated flowmeter for venting monitoring.

Within the first 12 hours, due to the severity of bleeding (1,500 ml) and hemodynamic instability, the patient was transfused with 8 units RBC and 2 units FFP. Laboratory tests and TEG exams indicated profound coagulopathy characterized by low levels of clotting factors and PLTs. Specific procoagulant agents, including 2,000 IU Human Prothrombin Complex (Kedcom, Kedrion Biopharma) and 1 unit PLT, were administered to promote hemostasis and restore clotting function.

Despite aggressive management, over the subsequent 24 hours, persistent bleeding (800 ml) required 5 units RBC and additional procoagulant therapy including 1,500 IU Human Prothrombin Complex, 3 grams Fibrinogen (HFC; FIBRYGA,

Octapharma AG) and 5 mg Recombinant Factor VIIa (Eptacog Alpha Activated) (Novoseven, Novo Nordisk, Denmark).

During treatment, the medical team executed four cycles of Leucodepletion with Cytosorb (Cytosorbents, Princeton, NJ).

At 72 hours the patient achieved hemodynamic stability and started the continuous heparin infusion at a rate of 500 IU/hour adjusted based on aPTT and TEG results. However, a decrease of PLTs count to 20,000 was observed, prompted suspicion of heparin-induced thrombocytopenia (HIT) that necessitated suspension of heparin and the administration of 2 units PLT.

Following the thrombocytopenia, heparin infusion was discontinued for the rest of the ECMO-support. Despite this, subsequent days on ECMO remained stable. However, lab tests and TEG showed hemostatic changes, requiring transfusions of 5 RBC units, 2 FFP units, and 1 PLT unit.

Extracorporeal membrane oxygenation support was maintained for 17 days until the patient's demise.

Case 2

A 66 year old female underwent a right lower lobectomy with atypical resection of the upper right lobe due to adenocarcinoma in May 2023. Postoperative complications led to subsequent hospitalization for fever and dyspnea. computed tomography (CT) imaging revealed bronchopleural fistula at the resection site necessitating an urgent pneumonectomy. One month later, a further intervention was scheduled to close the bronchopleural fistula using an omental patch. However, the patient developed acute respiratory distress syndrome (ARDS) due to pneumonia, requiring mechanical ventilation and antibiotics.

The decision was made to start V-V ECMO to support the patient during the positioning of an Amplatzer Stent in the bronchopleural fistula. Extracorporeal membrane oxygenation was performed with a 23 Fr/55 cm Peripheral Cannula (Medtronic) in the left femoral vein and with a 25 Fr/38 cm Multihole Venous Cannula (Medtronic) in the right femoral vein. Since the beginning of ECMO support, issues with venous drainage thus restricting ECMO flow below 1.8 L/min with negative pressure exceeding −60 mm Hg have persisted for a suspected retroperitoneal hematoma associated with femoral cannulation. Consequently, it was not possible to administer continuous anticoagulation.

In the initial 24 hours, TEG alteration necessitated procoagulant infusion (2 grams Fibrinogen and 2000 IU Human Prothrombin Complex). A gradual improvement in coagulation parameters was noted following the administration of 2 units of FFP and 4 units of RBC.

On second day of ECMO, the procedure was carried out successfully.

Over the next 48 hours, the ECMO flow remained consistently low (max = 1.0 L/min) and due to persistent anemia and guided by laboratory test and TEG results, the patient received 5 units RBC transfusions and additional procoagulant factor (1 gram Fibrinogen and 2000 IU Human Prothrombin Complex). Heparin was not administered due to the clinical condition. These interventions preceded the weaning from ECMO on the fifth day.

Case 3

A 68 year old male was admitted to the Emergency Room due to fever in June 2023. The patient's medical history included Ascending Aorta replacement due to Aortic Dissection in 2020.

Transesophageal echocardiography (TEE) revealed endocarditis in the aortic bioprosthesis, a periprosthetic abscess, and significant mitral valve insufficiency with a severe left ventricular dysfunction (ejection fraction 18%). The patient underwent a Bentall procedure with a homograft and mitral valve repair.

Unsuccessful weaning from extracorporeal circulation required V-A ECMO assistance using a 25 Fr/55 cm Multihole Venous Cannula (Maquet) in right femoral vein and a 17 Fr/15 cm Arterial Cannula (Maquet) in the right axillary artery.

During the first 24 hours after surgery, there was persistent bleeding (above 3,500 ml) raising suspicion of disseminated intravascular coagulation (DIC). The patient received 15 units RBC, 4 units PLT, 5 units FFP, 4,000 IU Human Prothrombin Complex, 3 grams fibrinogen supplementation, and 2 mg recombinant factor VIIa.

No continuous heparin infusion started due to the clinical condition.

Additionally, echocardiography revealed a left ventricular spontaneous echocardiography contrast (L-V SEC), necessitating the bedside placement of an Impella CP (Abiomed, MA) for further management.

Despite these efforts, the patient encountered complications, leading to two surgical revisions for bleeding and cardiac tamponade (2 and 5 days, respectively).

On the eighth day, the patient was weaned from ECMO and continued LV support with Impella.

Results

All the data collected during ECMO support in the three cases are presented in Table 1.

Case 1 underwent ECMO for 17 days, whereas cases 2 and 3 were shorter term (4 and 7 days, respectively). Oxygenator replacement was not required in any patient. Notably also, all three cases were managed without continuous intravenous heparin due to their critical bleeding balance.

As shown in Table 1, mean paO_2 post-oxygenator was consistently above 100 mm Hg and mean $paCO_2$ post-oxygenator consistently below 45 mm Hg. Membrane FiO_2 did never exceed 75%. In both V-A ECMO, AF *versus* BF ratio consistently remained close to 1:1 (case 1 BF: 4.3 ± 1.4 L/min with AF 3.9 ± 1.5 L/min; case 3 BF: 2.8 ± 0.9 L/min with AF 2.7 ± 0.6 L/min), whereas in V-V ECMO the ratio was within 1:2 (BF: 1.5 ± 0.3 L/min AF: 3.5 ± 1.2 L/min).

There was no evidence of excessive operating pressure in the device, with a pressure drop consistently below 28 mm Hg and a maximum peak resistance value of 7 Δmm Hg/L/min (within the boundaries required by the device).

Cases 1 and 3 required PLT transfusions (4 units each) due to low PLT counts ($28 \pm 22 \times 10^9$/L and $47 \pm 26 \times 10^9$/L, respectively).

All three patients required RBC transfusions due to low Hb levels, and FFP to counter bleeding.

Discussion

In this article, we sought to assess the performance of Nautilus* Smart ECMO Module in a series of patients with hemostatic disorders.

Table 1. Description of the Extracorporeal Membrane Oxygenation Treatment in Each Patient Including Coagulation-Related Measurements and Oxygenator Performance Metrics

	Case 1	Case 2	Case 3
Period (days)	17	4	7
Continuous anticoagulation use	No	No	No
Oxygenator replacement (nr)	0	0	0
Use of procoagulant factors	Yes	Yes	Yes
BFR (L/min)	5, 3 ± 1, 4	1, 5 ± 0, 3	2, 8 ± 0, 9
FGF (L/min)	3, 9 ± 1, 5	3, 5 ± 1, 2	2, 7 ± 0, 6
Membrane FiO_2 (%)	65, 3 ± 7, 5	47, 0 ± 7, 2	53, 3 ± 6, 7
Pressure IN oxygenator (mm Hg)	202, 8 ± 46, 4	32, 4 ± 14, 2	167, 7 ± 45, 6
Pressure OUT oxygenator (mm Hg)	181, 2 ± 42, 4	23, 5 ± 12, 6	151, 0 ± 40, 3
Pressure drop (mm Hg)	20, 5 ± 7, 9	8, 8 ± 3, 5	17, 0 ± 5, 2
R (Δmm Hg/L/min)	4, 9 ± 1, 7	5, 5 ± 1, 5	6, 0 ± 0, 9
PO_2 pre-oxygenator (mm Hg)	45, 4 ± 4, 8	43, 1 ± 4, 3	38, 1 ± 3, 0
PCO_2 pre-oxygenator (mm Hg)	45, 9 ± 6, 7	51, 5 ± 5, 1	44, 4 ± 8, 1
PO_2 post-oxygenator (mm Hg)	167, 0 ± 55, 4	220, 6 ± 62, 7	173, 6 ± 68, 6
PCO_2 post-oxygenator (mm Hg)	40, 5 ± 4, 3	36, 8 ± 5, 4	37, 2 ± 7, 3
PO_2 patient (mm Hg)	102, 0 ± 31, 3	89, 8 ± 17, 3	137, 7 ± 56, 7
PCO_2 patient (mm Hg)	39, 2 ± 6, 6	45, 9 ± 7, 0	39, 3 ± 8, 6
Hemoglobin (gr/dl)	9, 8 ± 0, 9	10, 2 ± 0, 7	9, 5 ± 1, 0
aPTT (sec)	75, 1 ± 21, 2	37, 9 ± 3, 2	51, 7 ± 10, 3
ATIII (%)	75, 2 ± 15, 5	73, 3 ± 11, 3	81, 5 ± 23, 6
DDs (μg/ml)	19,966 ± 10,476	24,930 ± 10,110	15,337 ± 10,189
PLT (10^9/L)	28 ± 22	216 ± 95	47 ± 26
FIB (mg/dL)	231 ± 71	528 ± 154	229 ± 51
RBC (units for patient)	18	9	15
PLT (units for patient)	4	0	4
Plasma (units for patient)	4	2	5

Value are presented as numbers are mean ± SD.

aPTT, activated partial thromboplastine time; ATIII, antithrombin III; BFR, blood flow ratio; Dds, D-dimers; FGF, fresh gas flow; FIB, fibrinogen; Membrane FIO_2, fractional inspired of oxygen; PCO_2, partial pressure carbon dioxide; PLT, platelet; PO_2, partial pressure oxygen; R, resistance of oxygenator; RBC, red blood cells.

Current literature provides limited insights into the management of ECMO oxygenators in the context of coagulation disorders[4] and there isn't evidence of using specific ECMO device in patients with hemostatic disorders.

In our institution, we use various types of ECMO oxygenators based on factors such as diagnosis, predictive length of stay, and considerations regarding current availability of device.

In the specific, in our clinical practice, we used the Nautilus Smart ECMO for managing all the patients expected to require prolonged ECMO assistance (*eg*, cardiogenic shock, post-cardiotomy ECMO, veno-venous ECMO) and we tried this device in patients that involved in hemostatic alteration, such as those encountered in postcardiotomy procedures which may require high-dose procoagulant infusion or contraindication to anticoagulation.[5]

In our experience, the administration of heparin is guided by TEG[6] and aPTT ratio[7] with a specific protocol, but in such cases is difficult to manage the delicate balance between providing adequate anticoagulation[8,9] to prevent circuit thrombosis and maintaining an effective level of coagulation[10,11] to prevent bleeding complications.[12] The right balance becomes crucial to ensuring the longevity and optimal function of the oxygenator.

Even in patients who discontinued anticoagulation administration[13] due to bleeding or HIT[14,15] maintaining a careful balance in aPTT and TEG management proves to be protective for the efficacy of oxygenators.

We encounter ECMO scenarios involving disrupted coagulation, necessitating extraordinary interventions that may deviate from the standard management.

More specifically, the device was used in three patients where anticoagulation was contraindicated.

Our goal is not to focus on length of stay (only case 3 lasted 17 days), but to highlight the performance of the device under specific stressors, including the absence of continuous anticoagulation with large infusion of procoagulants or inability to maintain BF in absence of anticoagulation infusion (case 2).

We evaluated the device under high-flow conditions, particularly in case 1 where a flow rate of 7 L/min was attained, prompted by a septic shock requiring elevated doses of vasoconstrictors to address a severe state of vasodilation.

Our assessment shows that the device has good gas exchange, maintaining favorable levels of pO_2 and pCO_2 post-oxygenator relative to AF and membrane FiO_2. Furthermore, the device effectively manages operating pressures with consistently low-pressure drops and minimal peak resistance values across all three considered cases.

Limitation

A few limitations must be considered. First, conducting statistical analyses in this patient population is not easy because of the heterogeneous nature of the patients who undergo ECMO. Second, this experience has a very small sample size and results cannot be generalized to other uses of ECMO. Finally, and linked to the first point, a systematic approach cannot be used to treat these patients and so it is hard to define a protocol.

The Extracorporeal Life Support Organization (ELSO) Anticoagulation Guidelines emphasize the necessity of "anticoagulation in adult patients to prevent circuit clotting," but as highlighted in hemorrhage and thrombosis paragraph "in postcardiotomy patients, where bleeding is difficult to control,

the unfractionated heparin (UFH) may be held up to 12 hours or longer until bleeding is controlled."

"Thrombosis and hemorrhagic management during ECMO should be tailored to the individual patient, and new developments in circuit materials may allow for more restrictive anticoagulation strategies to be developed."[4]

Based on the preview guidelines, we treated hemostatic disorders patients with tailored anticoagulation strategy, evaluating the performance of the Nautilus Smart Oxygenator.

In our initial experience, we observed that the device was able to provide an adequate performance under different conditions of flow in patients requiring procoagulant therapy.

However, prospective studies with larger sample sizes are required to ratify our preliminary observations.

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