Venous or Arterial Thromboses after Venoarterial-Extracorporeal Membrane Oxygenation Support: Frequency and Risk Factors

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Tweet: Vascular complications –cannula-associated deep vein thrombosis, leg ischemia or delayed arterial stenosis– are frequent after VA-ECMO removal, and should be systematically sought

ABSTRACT

Background: Although venous thrombosis following venovenous-extracorporeal membrane oxygenation (ECMO) is well described, vascular complications occurring after venoarterial-ECMO (VA-ECMO) removal have not yet been thoroughly described. Our aim was to evaluate the frequency of vascular (arterial and venous) complications after VA-ECMO removal and try to identify risk factors associated with them.

Methods: Retrospective analysis of data prospectively collected in two ICUs. Consecutive patients successfully weaned-off VA-ECMO during 1 year were screened for cannula-associated deep-vein thrombosis (CaDVT) or arterial complications (arterial thrombosis/stenosis) using Doppler ultrasonography.

Results: From November 2018 to November 2019, 107 patients (median (IQR) age 54 (42-63) years old and median (IQR) days on ECMO support 8 (2-5)) were successfully weaned-off VA-ECMO and included. CaDVT occurred in 44 (41%) patients and arterial complications in 15 (14%) (nine acute leg ischemia, one arteriovenous femoral fistula, and five late femoral stenosis). Multivariable analysis retained longer duration of ECMO support (OR, 1.12 per day; 95% CI, 1.02-1.22), and infection occurring on ECMO (OR, 3.03; 95% CI, 1.14-8.03) as independent risk factors for CaDVT whereas older age (odds ratio (OR), 0.97 per year; 95% confidence interval (CI), 0.94-0.99) and prior anticoagulation use (OR 0.21; 95% CI, 0.06-0.68) were protective factors for CaDVT. No risk factors for arterial complications were identified.

Conclusions: In patients requiring VA-ECMO support, vascular complications occurred frequently after its removal, especially CaDVT. Arterial complications, either early leg ischemia or late arterial stenosis, were observed less often. Strategies aimed at preventing CaDVT after VA-ECMO remain to be determined.

Venoarterial-extracorporeal membrane oxygenation (VA-ECMO) is used to support patients with heart failure refractory to conventional therapies [1]. The technique exposes the patient's circulating blood to the synthetic surfaces of the circuit that can lead to thrombosis, with subsequent activation of the coagulation cascade, platelets, leukocytes and complement, inducing thrombin generation and hypercoagulability [2]. Moreover, the use of intravascular devices is a known risk factor for developing deep-vein thrombosis (DVT), especially for intensive care unit (ICU) patients [3]. All those changes might contribute to higher thrombosis rates seen in these patients. Whereas the bleeding risks have been widely described [4], the risk of developing cannula-associated DVT (CaDVT) has only been studied in patients after venovenous (VV)-ECMO, with frequencies ranging from 15 to 80% [5]. Although some authors found a relationship between CaDVT and the anticoagulation level [6], the results were not homogeneous across studies [7–9].

Because patients on VA-ECMO may receive higher anticoagulation levels than those on VV-ECMO [10], the risk of developing DVT might theoretically be lower but, to date, is unknown. Moreover, the frequency of arterial thrombosis/leg ischemia in VA-ECMO patients after decannulation remains to be determined. Therefore, we designed this study to evaluate the frequencies of venous or arterial thromboses in VA-ECMO patients after decannulation, and to try to identify risk factors associated with those events.

MATERIALS AND METHODS

Patients

All consecutive patients who received VA-ECMO and were successfully weaned-off it in two ICUs between November 2018 and November 2019 were included. Patients who had less than 48 hours of ECMO run, died on-ECMO or those not screened for cannula-related thrombosis were excluded. All the following information was collected prospectively: ICU-admission Simplified Acute Physiology Score (SAPS) II and Sequential Organ-Failure Assessment (SOFA) score; local infectious complications (ie, cannula infection and cannula-related cellulitis) during and after ECMO; ECMO parameters (indication, duration of ECMO support, type of insertion, cannula sizes); anticoagulation parameters (days on heparin, daily-heparin dose, activated partial thromboplastin time (aPTT), anti-Xa activity, fibrinogen, platelets, use of antiplatelet agents); evolution after decannulation (existence of thrombosis, anticoagulation regimen, hemorrhagic or thrombotic complications, thrombosis evolution under treatment), length of ICU stay, hospital mortality.

ECMO Implantation, Anticoagulation and Weaning

The cannulation technique used was outflow via the femoral vein and inflow via the femoral artery with systematic reperfusion catheter to prevent limb ischemia; when venoarterial–venous-ECMO (VAV-ECMO) was required, another inflow cannula was inserted into the right internal jugular vein. Usual diameter ranges were: 15-19 Fr for the arterial cannula and 21-29 Fr for the venous cannula. ECMO was implanted percutaneously under ultrasound guidance by trained cardiovascular surgeons as first-line choice or surgically, if necessary [11].

All patients received the same anticoagulation protocol, as previously described [4,12]. After a heparin bolus (5000 IU) at ECMO initiation, all patients were continuously infused with unfractionated heparin (UFH). The heparin dose was adapted, at least once daily, according to the aPTT (expressed as patient-/normal-value ratio, targeting 1.5–2-fold the normal-control value) and clinical tolerance; heparin was stopped when bleeding occurred and restarted once it was controlled. Antithrombin 3 was not routinely measured. The need for heparin discontinuation was defined as any bleeding (at the ECMO implantation site, central or arterial lines, tracheal secretions, ear, nose and throat), with or without hemodynamic impact or hemoglobin decline, judged meaningful by the patient's treating physician. Anticoagulant overdose was defined as an aPTT > 2.5, corresponding to an absolute value of ≥80 s.

The membrane oxygenator and its circuitry were checked daily by experienced perfusionists and changed when: fibrin deposition or thrombi had deleterious effects on blood oxygenation; platelet count (< 20 giga/L) or blood fibrinogen (< 1.5 g/L) decreased markedly; or intravascular hemolysis (twice-measured free-plasma hemoglobin > 200 mg/L and no other cause of mechanical hemolysis found). No systematic circuit change was scheduled.

According to our local protocol, ECMO was removed after a successful weaning test by a cardiac surgeon [13]. For percutaneous ECMO implantation, the vessels were manually compressed after decannulation during 60 min. In case of persistent bleeding, a surgical correction was performed. When ECMO had been implanted surgically, it was also removed surgically.

Thrombosis Diagnosis and Treatment

The primary objective of the study was to determine the CaDVT frequency after decannulation. Occurrence of arterial complications post-decannulation was also evaluated.

CaDVT was routinely assessed by experienced ICU physicians with duplex ultrasonography within the 24 hours following ECMO withdrawal. CaDVT diagnosis was based on vein incompressibility, absence of flow and thrombus presence for peripheral veins (i.e., femoral and jugular), and on thrombus presence in the inferior vena cava [14]. The femoral vein and inferior vena cava were systematically screened for thrombosis in all patients and the jugular vein when needed. When a CaDVT was identified, clinical symptoms and obstruction of the vein (arbitrarily split in 2 categories; obstruction ≤50% of the vessel lumen and obstruction >50% of the vein lumen) were noted. For inferior vena cava thrombus, thrombus length was noted. Anticoagulation with continuous UFH infusion was started in the ICU for a clinically significant thrombus, as defined by the treating physician, then switched to oral anticoagulation according to physician's choice. Thrombus persistence was verified regularly in the ICU and at the discretion of the medical team caring for the patient. Anticoagulation was stopped when the thrombus was no longer present on duplex ultrasonography. Pulmonary embolism (PE) was diagnosed on computed-tomography (CT) images obtained when clinically suspected but was not routinely ordered.

In the case of a clinically suspected complication post-decannulation, arterial thrombotic events were sought and diagnosed with duplex ultrasonography or CT scan. The treatment was chosen in accordance with the surgical team and could include surgical intervention and systemic anticoagulation.

All hemorrhagic and arterial or venous thrombotic events, from decannulation until hospital discharge, were recorded for all patients.

Ethics

In accordance with French law, and as confirmed by the Ethics Committee of the Société de Réanimation de Langue Française (registration number CE SRLF 19-20), informed consent for demographic, physiologic and hospital-outcome data analyses was not obtained because this observational study did not modify existing diagnostic or therapeutic strategies. Nonetheless, patients and/or relatives were informed about the anonymous data collection and told that they could decline inclusion. This database is registered with the Commission Nationale l'Informatique et des Libertés (CNIL, registration no. 1950673).

Statistical Analyses

Results are expressed as median (IQR) or n (%). Between-group comparisons were analyzed using Student's *t*-test or the Mann-Whitney *U*-test according to variable's distribution, ie, normal or not for continuous variables. Between-group differences were assessed with chi-square test or Fisher's exact test for nominal variables. A logistic-regression model was used to examine the univariable association of CaDVT and patients' characteristics or ICU events. Thereafter, multivariable logistic-regression model using backward-stepwise variable elimination (with the variable exit threshold set at $P > 0.05$) tested the factors that were significant in the univariable analyses ($P \leq 0.10$). Variables included in the model were age (per year increase), prior anticoagulation therapy, days on ECMO support (per day), infection on ECMO support, highest fibrinogen level during ECMO run (per g/L increase), postcardiotomy reason for ECMO and highest platelets level (per Giga/L increase). Between-variable interactions were sought in the models; variables strongly associated with other(s) were not included in the multivariable model. All reported *P* values are two-sided and $P <$

176 0.05 was considered significant. Comparisons were computed using SPSS Version 23 (IBM
177 SPSS, Chicago, IL).

RESULTS

Patient Characteristics

Between November 2018 and November 2019, 107 patients were successfully weaned-off ECMO and all were included in the study. Their median age was 54 (42-63) years and median time on ECMO support was 8 (2-15) days. The main indications for ECMO were acute on chronic cardiac failure (35.5%) and postcardiotomy care (31.8%). VAV-ECMO hook-up was used for five patients. Their baseline characteristics, course on ECMO and outcomes are reported in Table 1.

CaDVT and Arterial Complications

Among the 107 patients, 44 (41%) developed CaDVT (Fig. 1). The most frequent CaDVT location was the inferior vena cava (38 patients, including one patient with extension into a subhepatic vein, followed by seven in the femoral vein. Mean ± SD inferior vena cava thrombus length was 3.4 ± 1.4 cm, with minimal and maximal size of 1 and 7 cm, respectively. Seven patients had a cannula in the right internal jugular vein, five because of VAV-ECMO lines and two because of a return cannula in the pulmonary artery (venoarterial–pulmonary-ECMO) for right ventricular support after left ventricular assist-device–implantation. Among them, three were diagnosed with jugular vein CaDVT. Multiple thromboses were found in four of the 44 (9%): two patients had inferior vena cava and femoral vein CaDVTs, one had inferior vena cava and jugular vein CaDVTs and one had bilateral femoral vein thromboses, for a total of 48 CaDVTs, among which 19 (40%) were large, defined as > 50% lumen obstruction. All inferior vena cava and jugular vein thromboses were asymptomatic, whereas 43% of patients with femoral vein CaDVTs had unilateral swelling.

Arterial complications were diagnosed in 15 (14%) of the 107 patients. Ten patients had early symptoms: seven had acute leg ischemia treated with thrombectomy, two experienced femoral or iliac dissection and one developed a femoral arteriovenous fistula. Five patients had late symptoms (that appeared 4–30 days after ECMO removal), all five had CT-scan–diagnosed femoral or iliac artery stenosis.

Patients' outcomes are reported in Table 1. Among the patients with CaDVTs, 37 were treated with anticoagulation therapy, 27 had favorable outcomes with duplex ultrasonography showing thrombus disappearance, three died shortly after ECMO withdrawal and seven were lost to follow-up. Anticoagulation was administered for 7 to > 60 days. Two CaDVT-group patients were diagnosed with PE after ECMO decannulation: one had distal PE and favorable outcome after anticoagulation therapy, the other had proximal PE and died in-ICU of septic and hemorrhagic shock. The hemorrhagic complication and in-hospital–mortality rates were the same for patients with CaDVT or without.

CaDVT Risk Factors

CaDVT-associated factors are reported in **Tables 1** and **2**. CaDVT-group patients were younger and less frequently received pre-ECMO anticoagulant therapy, whereas severity scores at admission and ECMO start, and history of malignancy or thromboembolic disease were similar for the two groups. Time on ECMO was significantly longer for patients who developed CaDVT. Hemostasis parameters were similar for patients with CaDVT or without, except for highest fibrinogen level during the ECMO run that was higher in patients with CaDVT than those without. The median aPTT ratio and median percentage of days with aPTT in the therapeutic zone (ie, 1.5–2-fold the normal-control value), the total UFH dose received,

days on UFH or the median platelet count did not differ between groups. Patients who developed CaDVT after ECMO removal more frequently had an infection during the ECMO run than those without CaDVT, whereas the infection rate before ECMO implantation and after ECMO removal did not differ between patients with CaDVT or without. The cannula-related–infection rate was doubled for patients with CaDVT than those without ($P = 0.06$).

Multivariable analysis retained ECMO runtime and concurrent infection as independent risk factors significantly associated with CaDVT, whereas older age and prior anticoagulant use were protective risk factors (**Table 3**).

Risk Factors for Arterial Complications

Clinical and laboratory parameters as a function of arterial complications or not are given in Tables 4 and 5; none was associated with having an arterial complication in our population.

DISCUSSION

The results of this study showed that arterial thrombosis and CaDVT were frequent in VA-ECMO–treated patients, with the latter occurring in 41% of patients and being more frequent than the former. Also, several risk factors for developing CaDVT in this population were identified, namely: infection on ECMO support, longer duration of ECMO support, while older age and anticoagulant therapy prior to ECMO support were protective factors. To the best of our knowledge, vascular complications in adult patients after weaning-off VA-ECMO have not been examined previously; all earlier studies included only patients given VV-ECMO support and focused on DVT [7]. Our 41% CaDVT rate for VA-ECMO is in agreement with VV-ECMO DVT rates for those series, which ranged from 18% to 80%.

Pathogenesis and risk factors for CaDVT

The exact pathogenesis of venous thrombosis in ECMO patients is not fully understood: the origin of thrombus is probably the cannula itself, a thrombogenic surface that may activate coagulation cascade. Venous stasis due to reduction in venous diameter may also play a role. We were able to identify, in our study, specific risk factors for CaDVT. First, we found that infection on ECMO was a major risk factor for CaDVT. Infection induces inflammatory processes that might have enhanced thrombogenic activity in these patients and local (cannula-related) infection might have played a role by locally increasing thrombogenicity [15]. Infection has not previously been specifically described as a risk factor for CaDVT; one study reported a higher CaDVT rate when bacterial pneumonia-related acute respiratory distress syndrome was the indication for ECMO, as compared to other situations requiring ECMO; ~~,~~ but other nosocomial infections have not been investigated [9].

Second, and as found by others [6], ECMO duration was longer for the CaDVT group. That finding might be explained by a longer cannulation time being associated with a higher risk of stasis and, thus, thrombosis formation.

We also found that prior anticoagulation therapy had a protective effect against CaDVT. In addition to ECMO, some patients had another indication for anticoagulation, mostly atrial fibrillation or mechanical valve prosthesis, conditions that could have influenced anticoagulation level and therefore CaDVT occurrence [16]. Although we were unable to establish any direct relationship between coagulation parameters during ECMO course and the risk of developing CaDVT, two studies reported a protective effect of anticoagulation [6, 8,9]. These differences might be partly explained by the difficult evaluation of anticoagulation level in ECMO patients, since these latter experienced potentially multiple hemostasis disorders (induced by the ECMO itself and/or by associated-organ failures, antiplatelet agent use…) [17].

Interestingly, developing a CaDVT did not impact mortality. The ICU length of stay was longer for CaDVT patients but that excess is probably explained by their longer ECMO durations.

Arterial complications after ECMO removal

Another study originality was examining arterial complications following VA-ECMO, although small number of events in our study precluded identification of any risk factors associated with arterial complications. We found that the arterial complication rate was lower than that of CaDVT, however, because most events were clinically apparent, we could have missed some clinically less obvious episodes. Pertinently, some of those events could happen immediately after ECMO removal (leading to leg ischemia), but also later, with arterial

stenosis. It is important that intensivists be aware of the potential latency of this rare complication, to follow their patients after decannulation and actively look for it, in particular in patients who might need repeated vascular procedures such as chronic heart failure or heart transplant patients. Regardless of the type of arterial complication, they often required more aggressive treatment than CaDVT, involving interventional radiologists and/or surgeons.

Potential implications of our results

Several implications of our results that could help clinicians taking care of those patients should be discussed. Firstly, physicians should monitor venous thrombosis during ECMO course and immediately after ECMO removal. Indeed, although our data don't allow knowing whether or not monitoring venous thrombosis before ECMO removal should be interesting, it seems logical to do so: if there is venous thrombosis around cannula before ECMO removal, the likelihood of having venous thrombosis after ECMO removal is very high. Moreover, due to the high rate of CaDVT, systematic screening for CaDVT after ECMO removal should be recommended.

The second implication refers to treatment of CaDVT, although this latter is not standardized. Venous thrombectomy during decannulation should be avoided, since this procedure may injured endothelium and increase the risk of venous thrombus formation. According to guidelines [18], a 3-month anticoagulation regimen is recommended for catheter-related DVT. Our practice and recommendation is to start anticoagulation in the ICU, when the thrombosis is considered clinically significant and the bleeding risk is acceptable, taking into account that VA-ECMO patients have a higher risk of bleeding at the decannulation site than those on VV-ECMO. We then regularly monitor the thrombus with ultrasounds and stop anticoagulation

when is disappears. This approach seemed to be safe, since the hemorrhagic complication rate after ECMO decannulation was the same for no-CaDVT and CaDVT groups.

The last implication refers to arterial complications following ECMO removal. Indeed, arterial complications occurring during or early after ECMO removal is usually obvious and easy to diagnose since physicians are aware of potential acute leg ischemia; whereas complication occurring late after ECMO removal may be less obvious for clinicians. They should be aware that arterial stenosis may occur late after ECMO removal and systematically screen their patient to look for it.

Study limitations

Our study has several limitations that should be addressed. Firstly, we include patients after ECMO removal and focused our study on vascular complications after ECMO removal. Therefore, we didn't retrieve vascular complications occurring during ECMO support. Secondly, the retrospective design of our study exposes to inherent bias of such studies. However, all data were collected prospectively, so few data are missing. Moreover, all consecutive patients were included. Third, the use of ultrasound to diagnose venous thrombosis–and in particular inferior vena cava thrombosis– may be disputable. Fourth, no pre-ECMO evaluations were available for our patients; therefore, we cannot exclude that some patients might have had preexisting vascular lesions, especially femoral artery stenosis. However, we think that is unlikely, because these lesions were not present shortly after decannulation and only appeared on follow-up images. Moreover, it is highly unlikely that some patients with preexisting femoral stenosis could have undergone VA-ECMO with a femoral cannula without any clinical manifestation. Fifth, the thrombosis rate might have been underestimated because CaDVT was diagnosed ultrasonographically; in particular

extension of femoral thrombosis to iliac veins, which are difficult to evaluate in the ICU setting. Similarly, some patients with asymptomatic arterial complications may have been missed. Sixth**,** follow-up was not standardized and thrombosis persistence was evaluated at different times for each patient depending on the patient's therapeutic pathway. Seventh, we didn't perform specific coagulation test, and didn't monitor antithrombin 3 levels during ECMO course, whereas coagulation factors levels may be altered during ECMO and may have play a role in venous thrombosis by inducing prothrombotic state [19]. However, a recent small randomized controlled trial failed to demonstrate any beneficial effect of antithrombin supplementation during ECMO run [20]. Finally, PE might have also been underdiagnosed because CT scans were only ordered when clinical signs were present [21].

Conclusion

In conclusion, vascular complications after VA-ECMO removal are frequent. CaDVT was the most frequent and should be actively sought in every patient after VA-ECMO explantation, especially patients with prolonged ECMO runs, or when an on-ECMO infection occurred. Arterial complications were less frequent, could occur early after ECMO withdrawal (acute ischemia) or later (arterial stenosis). Further studies are needed to evaluate the precise duration of anticoagulation in patients with CaDVT.

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Author contribution: FB and CEL drafted the study design, analyzed the results and drafted the manuscript. All authors participated in the data collection, final manuscript preparation and agreed with the latest manuscript.

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367 **TABLE 1** Characteristics of the Study Population According to CaDVT Status after VA-
368 ECMO Removal

Characteristic	All (n = 107)	CaDVT		*P* Value
		No (n = 63)	Yes (n = 44)	
Age, year	54 (42-63)	58 (45-67)	51 (38-60)	0.02
Male sex	72 (67.3)	39 (61.9)	33 (75)	0.16
Body mass index, kg/m^2	25.3 (22-28)	25.7 (22.6-29.4)	24.2 (21-27.1)	0.26
Comorbidities				
Cancer	10 (9.3)	8 (12.7)	2 (1.9)	0.15
Hemopathy	2 (1.9)	0	2 (4.5)	0.17
Venous thromboembolic disease	4 (3.7)	3 (4.8)	1 (2.3)	0.64
Heart failure	49 (45.8)	31 (49.2)	18 (40.9)	0.39
Chronic inflammatory disease	2 (1.9)	2 (3.2)	0	0.51
Venous insufficiency	3 (2.8)	3 (4.8)	0	0.27
Anticoagulation therapy	29 (27.1)	22 (34.9)	7 (15.9)	0.03
Severity scores				
SAPS II at admission	49 (37-71)	49 (37-73)	52.5 (36.5-70.7)	0.95
SOFA at admission	10 (7-13)	10 (7-13)	12 (8-15)	0.28
SOFA at ECMO start	12 (9-14)	11 (10-13)	12 (8-15)	0.44
Reason for ECMO				
Acute coronary syndrome	22 (20.6)	12 (19.0)	10 (22.7)	0.64
Acute on chronic heart failure	38 (35.5)	20 (31.7)	18 (40.9)	0.33
Myocarditis	7 (6.5)	3 (4.8)	4 (9.1)	0.44
Septic shock	3 (2.8)	1 (1.6)	2 (4.5)	0.57
Pulmonary embolism	1 (0.9)	1 (1.6)	0	1
Cardiac arrest	24 (22.4)	14 (22.2)	10 (22.7)	0.95
Postcardiotomy	34 (31.8)	26 (41.3)	8 (18.2)	0.01
Percutaneous cannulation	90/105 (85.7)	54/63 (85.7)	36/42 (85.7)	1
Venous cannula diameter, n/n (%)				0.96

< 25 Fr	9/100 (9)	5/60 (8.3)	4/40 (10)	
25 Fr	81/100 (81)	49/60 (81.7)	32/40 (80)	
> 25 Fr	10/100 (10)	6/60 (10)	4/40 (10)	
Days of ECMO support	8 (2-15)	7 (4-10)	10 (7-16)	0.001
Events during ICU stay				
Use of aspirin	34 (31.8)	23 (36.5)	11 (25)	0.21
Use of ≥ 2 antiplatelet agents	23 (21.5)	14 (22.2)	9 (20.5)	0.83
Infection before ECMO start[a]	31/106 (29.2)	16/63 (25.4)	15/43 (34.9)	0.29
Pulmonary	30/106 (28.6)	5/63 (7.9)	11/43 (25)	0.02
Other	15/106 (14.1)	5/63 (17.5)	4/43 (9.3)	0.27
Infection on ECMO[a]	47 (43.9)	20 (31.7)	27 (61.4)	0.002
Pulmonary	30 (28.6)	12 (19)	18 (40.9)	0.017
Cannula-related	22 (20.6)	9 (14.3)	13 (29.5)	0.06
Other	9 (8.4)	4 (6.3)	5 (11.4)	0.48
Infection after ECMO removal[a]	42/102 (41.2)	25/61 (41)	17/41 (41.5)	0.96
Pulmonary	22/102 (21.6)	13/61 (21)	9/41 (21.9)	1
Cannula-related	16/102 (15.6)	9/61 (14.8)	7/41 (15.9)	1
Other	14/102 (13.7)	10/61 (16.3)	4/41 (9.7)	0.39
Heart transplant	34 (31.8)	20 (31.7)	14 (31.8)	0.97
Heparin-induced thrombocytopenia	1/106 (2.3)	0/62	1/44 (2.3)	0.42
Oxygenator change	17/106 (16.3)	8/62 (12.9)	9/42 (21.4)	0.25
Outcomes				
Hemorrhagic complications	30/104 (28.8)	12/61 (27.9)	18/43 (29.5)	0.86
ICU length of stay, days	20 (12-28)	20 (10-24)	24 (13-35)	0.047
Hospital mortality	17 (15.9)	7 (11.1)	10 (22.7)	0.11

Results are expressed as median (IQR) or n (%). CaVDT = cannula-associated deep-vein thrombosis; VA-ECMO = venoarterial-extracorporeal membrane oxygenation; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ-Failure Assessment; ICU = intensive care unit.

[a] Whatever the site of infection

TABLE 2 Blood-Coagulation Parameters on VA-ECMO Support According to CaDVT Status after Its Removal

Characteristic	All (n = 107)	CaDVT		*P* Value
		No (n = 63)	Yes (n = 44)	
Daily UFH dose, IU	8004 (4614-13429)	7695 (3087-13663)	8301 (5403-12810)	0.75
Days on UFH therapy, %[a]	90.6 (66.6-100)	88.8 (66.6-100)	100 (66.6-100)	0.45
aPTT ratio	1.49 (1.32-1.72)	1.48 (1.34-1.71)	1.50 (1.25-1.72)	0.81
Days with aPTT ratio < 1.2, %[a]	20 (0-40)	20 (0-43)	21.5 (8-40)	0.57
Days with aPTT ratio ≥ 1.2 and < 1.5, %[a]	30.7 (20-50)	33.3 (22-50)	27.5 (17-59)	0.59
Days with aPTT ratio ≥ 1.5 and < 2, %[a]	23 (0-33)	25 (0-38)	18 (0-32)	0.25
Days with aPTT ratio ≥ 2, %[a]	0 (0-22)	0 (0-20)	2 (0-23)	0.18
Days with anti-Xa activity < 0.2 IU/mL, %[a]	50 (25-75)	50 (25-67)	53.9 (34-80)	0.21
Days with anti-Xa activity ≥ 0.2 and < 0.5 IU/mL, %[a]	0 (0-16,7)	0 (0-23)	0 (0-15.9)	0.78
Days with anti-Xa activity ≥ 0.5 IU/mL, %[a]	0 (0-0)	0 (0-0)	0 (0-0)	0.32
Days with unknown anti-Xa activity, %[a]	25 (0-50)	25 (0-50)	25 (3-43)	0.69
Fibrinogen, g/L	3.82 (3.08-5.07)	3.58 (3-5)	4.2 (3.4-5.3)	0.07
Lowest fibrinogen level	2.2 (1.7-3.3)	2.2 (1.67-2.87)	2.35 (1.77-3.42)	0.34
Highest fibrinogen level	5.5 (4.5-7)	5.15 (4.37-6.6)	6.55 (4.5-7.5)	0.034
Days with fibrinogen < 2 g/L, %[a]	0 (0-11.1)	0 (0-16.7)	0 (0-7.3)	0.18
Days with fibrinogen 2 ≥ and < 4 g/L, %[a]	47.4 (0.14-0.66)	50 (14.3-66.7)	40 (14.5-67.6)	0.43

Days with fibrinogen ≥ 4 g/L, % [a]	44.4 (0.1-0.75)	33.3 (8.3-75)	51.3 (12.5-75)	0.27
Platelets, Giga/L	110 (82-142)	113 (85.8-140)	100 (79.2-152)	0.72
Lowest platelet count,	62 (43-95)	70.5 (46-96)	55 (41-92)	0.22
Highest platelet count,	188 (142-235)	182 (142-217)	207 (140-250)	0.17
Days with platelets < 150, % [a]	85.7 (0.6-1)	87.5 (66.7-100)	82.6 (50-100)	0.63
Days with platelets ≥ 150 and < 400, % [a]	12.5 (0-37.5)	12.5 (0-31)	13.4 (0-40)	0.95
Days with platelets ≥ 400, % [a]	0 (0-0)	0 (0-0)	0 (0-0)	0.09

Results are expressed as median (IQR). VA-ECMO = venoarterial-extracorporeal membrane oxygenation; CaVDT = cannula-associated deep-vein thrombosis; UFH = unfractionated heparin; IU = international unit; aPTT = activated partial thrombin time.

[a]Expressed as the ratio of the percentage of days/the total number of days on ECMO.

TABLE 3 Multivariable Analysis of Factors Associated with CaDVT after VA-ECMO

Parameter	Odds Ratio (95% CI)	*P* Value
Age, per year	0.97 (0.94-0.99)	0.02
Prior anticoagulation therapy	0.21 (0.06-0.68)	0.009
Days on ECMO support, per day	1.12 (1.02-1.22)	0.02
Infection on ECMO support	3.03 (1.14-8.03)	0.02

CaDVT = cannula-associated deep-vein thrombosis; C = confidence interval; VA-ECMO = venoarterial-extracorporeal membrane oxygenation.

Variables entered into the model were age (per year increase), prior anticoagulation therapy, days on ECMO support (per day), infection on ECMO support, highest fibrinogen level during ECMO run (per g/L increase), postcardiotomy reason for ECMO and highest platelets level (per Giga/L increase).

TABLE 4 Characteristics of the Study Population According to Arterial Complication Status after VA-ECMO Removal

Characteristic	All (n = 107)	Arterial Complication		*P* Value
		No (n = 92)	Yes (n = 15)	
Age, year	54 (42-63)	56.5 (44-62)	50 (20-67)	0.27
Male sex	72 (67.3)	64 (69.6)	8 (53.3)	0.21
Body mass index, kg/m^2	25.3 (22-28)	25.3 (22-28.7)	25.1 (22-27.1)	0.92
Comorbidities				
Cancer	10 (9.3)	9 (9.8)	1 (6.7)	1
Hemopathy	2 (1.9)	1 (1.1)	1 (6.7)	0.26
Venous thromboembolic disease	4 (3.7)	4 (4.3)	0	1
Heart failure	49 (45.8)	45 (48.9)	4 (26.7)	0.16
Chronic inflammatory disease	2 (1.9)	2 (2.2)	0	1
Venous insufficiency	3 (2.8)	3 (3.3)	0	1
Anticoagulation therapy	29 (27.1)	27 (29.3)	2 (13.3)	0.35
Severity scores				
SAPS II at admission	49 (37-71)	48 (36-70)	63 (47-74)	0.14
SOFA at admission	10 (7.25-13)	10 (7-13)	12 (8-14)	0.53
SOFA at ECMO start	12 (9-14)	11 (9-14)	12 (10-15)	0.45
Reason for ECMO				
Acute coronary syndrome	22 (20.6)	19 (20.7)	3 (20)	1
Acute on chronic heart failure	38 (35.5)	36 (39.1)	2 (13.3)	0.08
Myocarditis	7 (6.5)	5 (5.4)	2 (13.3)	0.25
Septic shock	3 (2.8)	3 (3.3)	0	1
Pulmonary embolism	1 (0.9)	1 (1.1)	0	1
Cardiac arrest	24 (22.4)	20 (21.7)	4 (26.7)	0.74
Postcardiotomy	34 (31.8)	29 (31.5)	5 (33.3)	1
Percutaneous cannulation	90/105 (85.7)	78/90 (86.7)	12/15 (80)	0.49
Arterial cannula diameter, n/n (%)				0.65
< 17 Fr	10/101 (9.9)	8/89 (9)	2/12 (16.7)	
17 Fr	77/101 (76.2)	69/89 (77.5)	8/12 (66.7)	

> 17 Fr	14/101 (13.9)	12/89 (13.5)	2/12 (16.7)	
Days of ECMO support	8 (2-15)	8 (5-13)	8 (4-11)	0.49
Events during ICU stay				
Use of aspirin	34 (31.8)	29 (31.5)	5 (33.3)	1
Use of ≥2 antiplatelet agents	23 (21.5)	20 (21.7)	3 (20)	1
Infection before ECMO start	31/106 (29.2)	24/91 (26.4)	7/15 (46.7)	0.13
Pulmonary	16/106 (15)	13/91 (14.3)	3/15 (20)	0.7
Other	15/106 (14)	11/91 (12)	4/15 (26.7)	0.22
Infection on ECMO	47 (43.9)	41 (44.6)	6 (40)	0.79
Pulmonary	30 (28)	26 (28.3)	4 (26.7)	1
Cannula-related	22 (20.6)	21 (22.8)	1 (6.7)	0.15
Other	9 (8.4)	7 (7.6)	2 (13.3)	0.61
Infection after ECMO removal	42/102 (41.2)	33/88 (37.5)	9/14 (64.3)	0.06
Pulmonary	22/102 (21.6)	18/88 (20.5)	4/14 (28.5)	0.5
Cannula-related	16/102 (15.6)	9/88 (10.2)	7/14 (50)	0.001
Other	14/102 (13.7)	13/88 (14.8)	1/14 (7.1)	0.69
Heart transplant	34 (31.8)	31 (33.7)	3 (20)	0.38
Heparin-induced thrombocytopenia	1/106 (2.3)	0/91	1/15 (6.7)	0.14
Oxygenator change	17/104 (16.3)	17/89 (19.1)	0/15	0.12
Outcomes				
Hemorrhagic complications	30/104 (28.8)	25/89 (28)	5/15 (33.3)	0.62
ICU length of stay, days	20 (12-28)	20 (12-28)	21 (17-50)	0.16
Hospital mortality	17 (15.9)	16(17.4)	1 (6.7)	0.32

Results are expressed as median (IQR) or n (%). VA-ECMO = venoarterial-extracorporeal membrane oxygenation; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ-Failure Assessment; ICU = intensive care unit.

TABLE 5 Hemostasis Parameters on VA-ECMO Support According to Arterial Complication Status after Its Removal

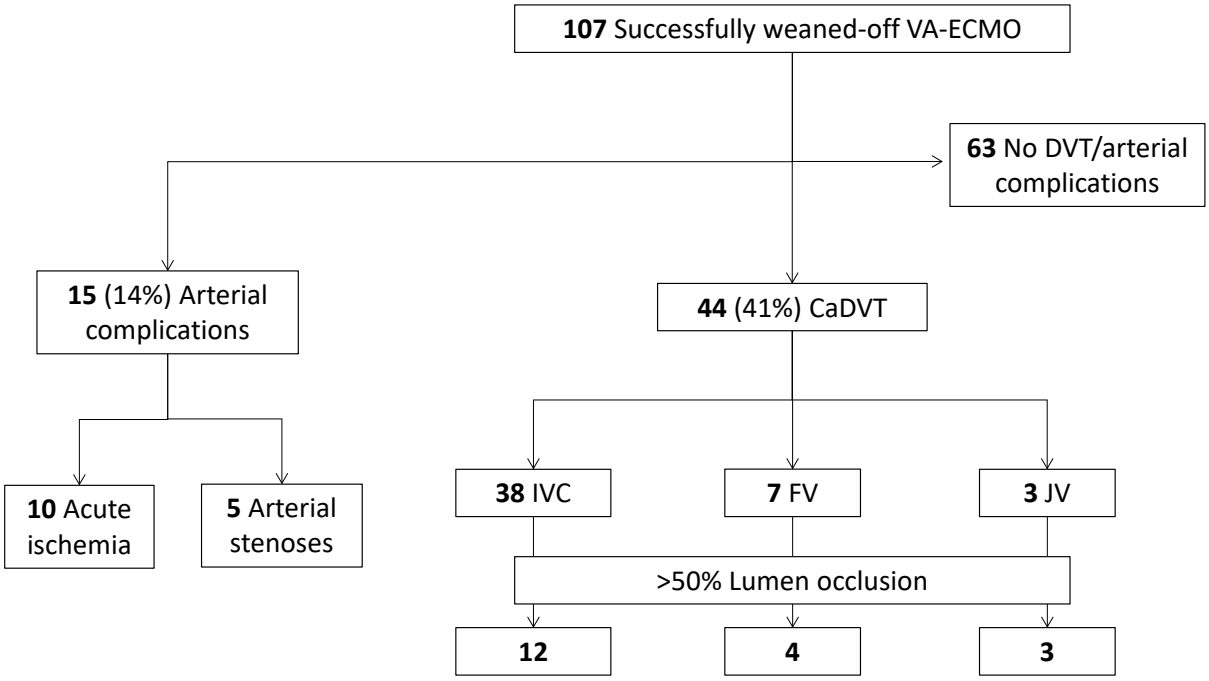
Parameter	All (n = 107)	Arterial Complication		*P* Value
		No (n = 92)	Yes (n =15)	
Daily UFH dose, IU	8004 (4614-13429)	8231 (4620-13330)	7613 (3105-16942)	0.93
Days on UFH therapy, %[a]	90.6 (66.6-100)	100 (66.6-100)	77 (50-100)	0.16
aPTT ratio	1.49 (1.32-1.72)	1.49 (1.33-1.72)	1.47 (1.25-1.73)	0.16
Days with aPTT ratio < 1.2, %[a]	20 (0-40)	20 (0-40)	12.5 (0-44)	0.55
Days with aPTT ratio ≥1.2 and < 1.5, %[a]	30.7 (20-50)	29 (19-50)	41 (25-60)	0.36
Days with aPTT ratio ≥1.5 and < 2, %[a]	23 (0-33)	23 (0-33)	25 (0-42)	0.92
Days with aPTT ratio ≥ 2, %[a]	0 (0-22)	0 (0-21.7)	0 (0-28.6)	0.70
Days with anti-Xa activity < 0.2 IU/mL, %[a]	50 (25-75)	50 (25-78)	36.3 (25-50)	0.15
Days with anti-Xa activity ≥ 0.2 and < 0.5 IU/mL, %[a]	0 (0-16,7)	0 (0-16.5)	0 (0-28.6)	0.55
Days with anti-Xa activity ≥ 0.5 IU/mL, %[a]	0 (0-0)	0 (0-0)	0 (0-14.3)	0.19
Days with unknown anti-Xa activity, %[a]	25 (0-50)	25 (0-50)	25 (0-60)	0.75
Fibrinogen, g/L	3.82 (3.08-5.07)	3.8 (3-5.14)	4.15 (3.15-4.47)	0.92
Lowest fibrinogen level,	2.2 (1.7-3.3)	2.2 (1.7-3.3)	2.5 (1.6-3.5)	0.73
Highest fibrinogen level,	5.5 (4.5-7)	5.4 (4.45-7)	6 (4.9-7)	0.81
Days with fibrinogen < 2, %[a]	0 (0-11)	0 (0-11)	0 (0-9)	0.30

Days with fibrinogen ≥2 and < 4, % [a]	47.4 (0.14-0.66)	46 (15-66)	54 (8-81)	0.46
Days with fibrinogen ≥ 4, % [a]	44.4 (0.1-0.75)	42 (10-75)	45 (9-85)	0.89
Platelets, Giga/L	110 (82-142)	106 (81-141)	118 (89-165)	0.26
Lowest platelet count	62 (43-95)	61 (42-91)	81 (52-109)	0.08
Highest platelet count	188 (142-235)	188 (140-233)	187 (145-262)	0.91
Days with platelets < 150, % [a]	85.7 (0.6-1)	83 (60-100)	87.5 (67-100)	0.51
Days with platelets ≥150 and < 400, % [a]	12.5 (0-37.5)	12.5 (0-37.5)	12.5 (0-33)	0.70
Days with platelets ≥ 400, % [a]	0 (0-0)	0	0	

Results are expressed as median (IQR). VA-ECMO = venoarterial-extracorporeal membrane oxygenation; CaVDT = cannula-associated deep vein thrombosis; UFH = unfractionated heparin; IU = international unit; aPTT = activated partial thrombin time.

[a]Expressed as the ratio of the percentage of days/the total number of days on ECMO.

Figure 1 – Study flow chart. VA-ECMO = venoarterial extracorporeal membrane oxygenation; DVT = deep-vein thrombosis; CaDVT = cannula-associated DVT; IVC = inferior vena cava; FV = femoral vein; JV = jugular vein.



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