Prevalence and Risk Factors for Thrombotic Complications Following Venovenous Extracorporeal Membrane Oxygenation: A CT Scan Study

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Objectives: The aims of this study were to: 1) analyze the cannula-associated deep vein thrombosis frequency after venovenous extracorporeal membrane oxygenation using a CT scan and 2) identify the associated risk factors for cannula-associated deep vein thrombosis.

Design: Retrospective observational analysis at a single center.

Setting: Tertiary referral university teaching hospital.

Patients: Patients under venovenous extracorporeal membrane oxygenation with a femorofemoral or femorojugular cannulation admitted for acute respiratory distress syndrome or primary graft dysfunction after pulmonary transplantation. CT scan was performed within 4 days after decannulation.

Interventions: None.

Measurements and Main Results: We included 105 of 228 patients screened. Bacterial pneumonia was the main indication of venovenous extracorporeal membrane oxygenation (46.7%). CT scans were performed at a median of 2 days (1–3 d) after decannulation. Cannula-associated deep vein thrombosis was found in 75 patients (71.4%) despite it having a mean activated partial thromboplastin time ratio of 1.60 ± 0.31. Femorofemoral cannulation induced femoral cannula-associated deep vein thrombosis more frequently than femorojugular cannulation (69.2% vs 63.1%, respectively; $p = 0.04$). Seventeen of the 105 patients (16.2%) had a pulmonary embolism. Multivariate logistic regression analysis showed that higher the percentage of thrombocytopenia less than 100 G/L during extracorporeal membrane oxygenation period, lower the risk for developing cannula-associated deep vein thrombosis (hazard ratio, 0.98; 95% CI, 0.98–1.00; $p = 0.02$).

Conclusions: Cannula-associated deep vein thrombosis after venovenous extracorporeal membrane oxygenation is a frequent complication. This plead for a systematic vascular axis imaging after venovenous extracorporeal membrane oxygenation. Thrombocytopenia is associated with a reduction in the occurrence of thrombotic events. (*Crit Care Med* 2019; XX:00–00)

Key Words: acute respiratory distress syndrome; anticoagulant; cannula; complication; deep vein thrombosis; extracorporeal membrane oxygenation

Critically ill patients have an increased risk for deep vein thrombosis (DVT), with an incidence from 8% to 40% (1). The occurrence of DVT in ICUs is associated with longer durations of mechanical ventilation and of ICU and hospital lengths of stay, as well as increased in-hospital mortality (2). Extensive literature reports incidences for central venous catheter-related DVT up to 22% and 42% in the femoral and jugular sites, respectively (3, 4), due to coagulation cascade activation induced by nonbiological materials (5). Venovenous extracorporeal membrane oxygenation (ECMO) is mainly used to support patients who suffer from severe acute respiratory distress syndrome (ARDS) (6). Thrombotic and hemorrhagic events are the main complications of venovenous ECMO (7).

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However, few studies have investigated their incidence and risk factors. Furthermore, most studies include both venovenous and venoarterial ECMOs. Thrombotic events suffer from a lack of a definition and include arterial thrombotic events. Few studies have investigated the occurrence of deep vein thromboses associated with the use of venovenous ECMO, and a wide range for the frequency of cannula-associated DVT (CaDVT), from 18.1% to 85.4%, has been reported (8–11). The main diagnostic method for CaDVT is sonography, which does not allow exhaustive exploration of vascular axes, particularly the inferior vena cava and the superior vena cava. Furthermore, anticoagulation recommendations during venovenous ECMO are based on expert conferences due to a lack of evidence from research.

The main objective of this study was to evaluate the frequency of venovenous ECMO CaDVT using CT scan.

MATERIALS AND METHODS

This study was retrospectively designed, but all the information needed to complete the datasheet were obtained prospectively. This study was performed at a 14-bed ICU of a teaching hospital and was conducted according to French ethical law. According to our Institutional Review Board, information and consent were not required due to the retrospective and noninterventional nature of the study. Patient information was anonymized before analysis.

From a patient data registry, we selected all patients who required venovenous ECMO for an ARDS or primary graft dysfunction after lung transplantation. Venoarterial ECMO were not included due to the low use over the study period (< 4 per year). Double venovenous ECMO cannulation, femorojugular or femorofemoral, was performed. It is our policy that the CT scan is routinely performed after ECMO retrieval occurs. Patients who underwent a thoraco-abdominopelvic CT scan with iodinated contrast injection within 4 days after decannulation of venovenous ECMO, including jugular and femoral vascular axes, were retained for analysis. Only one CT scan was performed for each patient. A first interpretation was done just after CT scan was completed. The first radiologist was the one who was on call the day of the CT scan. He/she was not necessarily specialized in vascular radiology. A second radiologist presenting advanced experience in DVT analysis reevaluated all the CT scans blinded for the first radiologist analysis. The second radiologist could contradict the findings of the first radiologist. In case of disagreement between the two radiologists, the results of the first radiologist was given to the second radiologist, and the final interpretation was left to the discretion of the second radiologist. The cannulation was performed by a cardiac-surgeon using percutaneous cannulation (Seldinger technique). Decannulation without a vascular suture in the absence of major leakage but with a skin suture was performed by a vascular surgeon. Direct compression of the cannulation site was performed for 10 minutes, followed by the placement of a noncircular compressive dressing for 24 hours. The ECMO material was the same throughout the study period (see **supplemental data**, Supplemental Digital Content 1, http://links.lww.com/CCM/F140). The anticoagulation was protocolized without modification of practices over the study period. In our center, in case of a history of heparin-induced thrombocytopenia, venovenous ECMO was contraindicated due to the exclusive use of heparin-bonded circuits. An unfractionated heparin (UFH) bolus was administered just before the cannulation was performed unless preexisting bleeding disorder or thrombocytopenia less than 70 G/L were presented. Patients were treated with continuous UFH after cannulation at an initial dosage of 10 to 20 international units (IU)/kg/hr. The anticoagulation was guided by the activated partial thromboplastin time (APTT) and was titrated to have an APTT ratio between 1.2 and 1.5 in accordance with French recommendations (12) except if a full systemic anticoagulation was indicated. The APTT was measured 4 to 6 hours after each modification of the UFH infusion dose. A research of heparin-platelet factor 4 immunoassay associated with functional assay was recommended during the study period in case of thrombocytopenia. If positive, heparin was substituted for danaparoid sodium and titrated to have an anti-Xa activity between 0.2 and 0.4 IU/mL. Decannulation was considered as soon as possible. Heparin was stopped in the case of clinically significant persistent bleeding and thrombocytopenia less than 70 G/L. Heparin recovery was left to the discretion of the clinician. Only after decannulation was performed, a prophylactic dose of low molecular weight heparin (LMWH) was used in the absence of CaDVT. All patients with CaDVT were treated with full systemic anticoagulation by UFH with the goal of achieving an APTT ratio between 2 and 3 (except in cases of patients with thrombocytopenia < 50 G/L or hemorrhagic syndrome), followed by a LMWH or vitamin K anticoagulant treatment for at least 3 months and a CT scan or sonography at 3 months. The venovenous ECMO placement and removal, anticoagulation strategy and CT scan procedure was protocolized and did not change throughout the study period.

To assess the quality of anticoagulation, the mean APTT ratio was calculated as the mean APTT ratio value of all APTT ratios measured during the venovenous ECMO period. The same procedure was performed to assess the platelet count, fibrinogen level, and prothrombin ratio. We calculated the percentage of the APTT ratios between two thresholds or greater than a determinate threshold, defined as the number of APTT ratios according to the chosen threshold(s) divided by the total number of APTT ratios achieved times 100. The same operation was performed for the platelet count, fibrinogen level, and prothrombin ratio.

The main objective of the present study was to determine the frequency of CaDVT diagnosed by CT scan with iodinated contrast injection.

Definition

DVT was defined as low-attenuating partial or complete filling defects surrounded by enhanced blood seen on at least two consecutive axial images. CaDVT was defined as DVT at one of the cannulation sites. Jugular CaDVT was defined as a

thrombus in the internal jugular vein or in the superior vena cava, and femoral CaDVT was defined as a thrombus in the femoral vein or in the inferior vena cava. Femoral or iliac vein thrombosis and jugular or subclavian vein thrombosis were considered as a proximal thrombosis from the cannulation site. Thrombosis located in the vena cava were considered as a distal thrombosis from the cannulation site. Other thrombosis was defined as a thrombus in a noncannulated vein for ECMO or that within a pulmonary artery which is defined as pulmonary embolism.

Control Group

The control group consisted of 32 patients admitted for ARDS without the use of venovenous ECMO throughout the study period and who had a central venous catheter and CT scan with iodinated contrast injection within a similar period of time.

Statistics

Descriptive statistics included the percentages for categorical variables and the mean (± SD) or median (interquartile ranges) for continuous variables according to the distribution. Comparisons between the two groups according to the presence of CaDVT (CaDVT group vs no CaDVT group) for continuous variables were made using the Student *t* test or the Mann-Whitney *U* test, according to the variable distribution. Comparisons between the two groups for categorical variables were made using the Pearson chi-square test or Fisher exact test. A multinomial logistic regression procedure was performed to identify factors associated with the presence of CaDVT. The no CaDVT group was used as the reference group. All of the variables with a p value of less than 0.20 (history of DVT, ARDS related to bacterial pneumonia, % platelet count < 100 G/L, % fibrinogen level < 1.0 g/L, and % APTT ratio < 1.2) were included in the model. The Cohen's kappa was calculated to evaluate the reliability agreement between the two radiologists regarding the diagnosis of thrombosis. A p value of less than 0.05 was considered significant. The statistical analysis was conducted using SPSS Version 20.0 (IBM SPSS, Chicago, IL).

RESULTS

Between January 2013 and December 2017, 228 patients had a venovenous ECMO and 105 were included in this study (see flow chart in **Fig. 1**). The characteristics of the patients are presented in **Table 1**. The main indication of venovenous ECMO was bacterial pneumonia. Venovenous ECMO cannulation was femorofemoral for 26 patients (24.8%) and femorojugular for 79 patients (75.2%). The median duration of venovenous ECMO cannulation was 10 days (6–16 d). CT scans were performed at a median of 2 days (1–3 d) after decannulation.

Seventy-five of the 105 patients (71.4%) had a CaDVT. The distribution of CaDVT by site and type of cannulation is presented in **Figure 2**. When all CaDVT were considered, there was no statistically significant difference between femorofemoral cannulation and femorojugular cannulation ($p = 0.78$). In contrast, for femoral CaDVT, femorofemoral cannulation induced CaDVT more frequently than did femorojugular cannulation (69.2% vs 63.1%, respectively; $p = 0.04$) (Fig. 2).

Considering proximal or distal location, 70 of 75 patients (93.3%) had a proximal thrombosis, 35 (46.7%) a distal thrombosis, and 29 (38.7%) had both proximal and distal thrombosis. Seventeen of the 105 patients (16.2%) had a pulmonary embolism diagnosed by the CT scan. In 10 patients, the pulmonary embolism was associated with a CaDVT, and in one patient, it was associated with central venous catheter-related DVT. Six patients had a pulmonary embolism without any other thrombosis. Sixteen patients (15.2%) had a central venous catheter-related DVT, and a CaDVT was presented in 12 (75%) of these 16 patients.

CT scan for the 32 control group patients not receiving ECMO was conducted at 12 ± 4 days, and a similar rate of central venous catheter-related DVT compared with the venovenous ECMO study population was shown

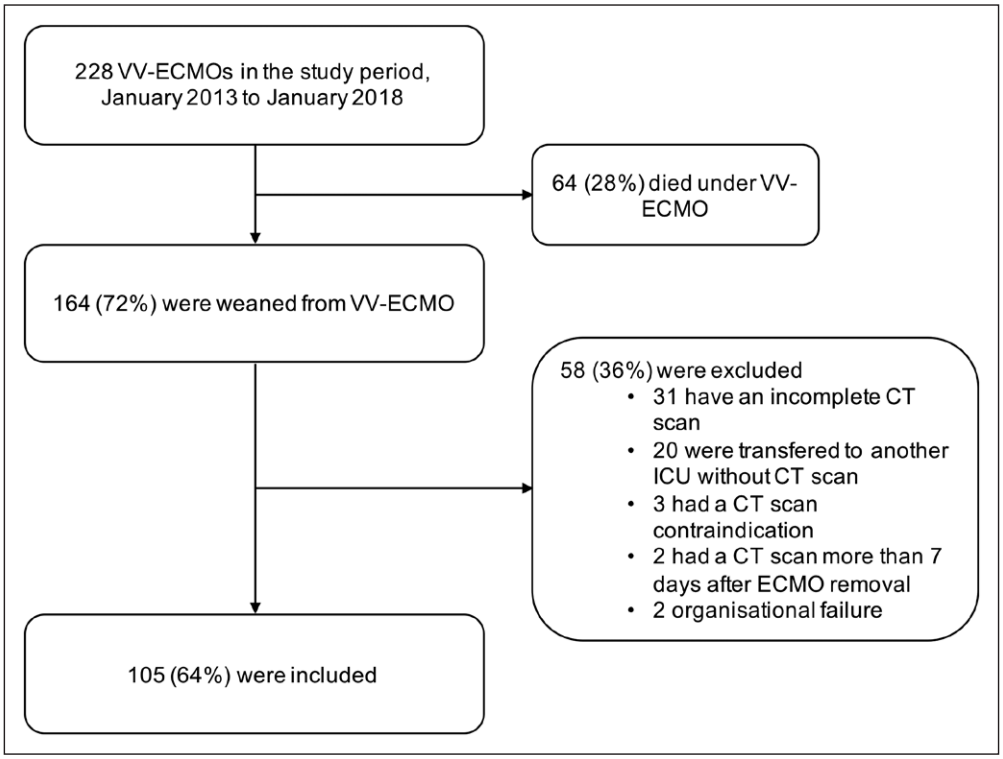

Figure 1. Flow chart. VV-ECMO = venovenous extracorporeal membrane oxygenation.

TABLE 1. Baseline Characteristics of Patients and Outcomes

Characteristics	All (*n* = 105)	CaDVT Group (*n* = 75)	No CaDVT Group (*n* = 30)	*p*
Age, yr, mean (SD)	48.0 (16.0)	47.3 (14.9)	47.9 (17.6)	0.86
Male sex, *n* (%)	71 (67.6)	52 (69.3)	19 (63.3)	0.55
Pregnancy, *n* (%)	1 (0.09)	0 (0)	1.0 (3.3)	0.29
Body mass index, kg/m^2, mean (SD)	26.9 (7.5)	26.7 (7.7)	27.4 (7.1)	0.65
Sequential Organ Failure Assessment, mean (SD)	10.0 (4.0)	9.5 (3.9)	9.9 (3.2)	0.64
Simplified Acute Physiology Score 2, mean (SD)	46.0 (13.0)	45.8 (13.0)	46.2 (12.6)	0.89
Comorbidities, *n* (%)				
Diabetes	11 (10.5)	9 (12.0)	2 (6.7)	0.73
Immunodeficiency	32 (30.5)	22 (29.3)	10 (33.3)	0.69
Chronic respiratory dysfunction	33 (31.4)	23 (30.7)	10 (33.3)	0.79
Chronic renal dysfunction	0 (0.0)	–	–	–
Chronic cardiac dysfunction	4 (3.8)	2 (2.7)	2 (6.7)	0.32
Cirrhosis	3 (2.9)	2 (2.7)	1 (3.3)	1.00
Malignant solid tumor	16 (15.2)	12.0 (16.0)	4.0 (13.3)	0.73
Malignant hemopathy	5 (4.8)	4 (5.3)	1 (3.3)	1.00
History of deep vein thrombosis, *n* (%)	5 (4.8)	2 (2.7)	3 (10.0)	0.14
Indication for venovenous ECMO, *n* (%)				
ARDS related to bacterial pneumonia	49 (46.7)	38 (50.7)	11 (36.7)	0.19
ARDS related to viral pneumonia[a]	17 (16.2)	10 (13.3)	7 (23.3)	0.21
ARDS related to extrapulmonary sepsis	10 (9.5)	6 (8.0)	4 (13.3)	0.47
Pulmonary transplantation[b]	29 (27.6)	20 (26.7)	9 (30.0)	0.73
Interhospital transfer by ECMO mobile unit, *n* (%)	56 (53.3)	38 (50.7)	18 (60.0)	0.39
Antiplatelet agent continued during ECMO, *n* (%)	8 (7.6)	7 (9.3)	1 (3.3)	0.44
Number of days of venovenous ECMO, median (IQR)	10 (6–16)	10 (5–17)	8 (6–14)	0.50
Number of days in ICU before venovenous ECMO, median (IQR)	1 (0–6)	1 (0–6)	1 (0–5)	0.69
Number of days of ICU stay, median (IQR)	30 (20–42)	32 (22–42)	25 (17–43)	0.31
Number of days of invasive mechanical ventilation, median (IQR)	28 (18–42)	30 (20–42)	25 (14–44)	0.37
Number of ventilator-free days assessed to day 28, median (IQR)	0 (0–6)	0 (0–5)	0 (0–12)	0.63
Number of ventilator-free days assessed to day 90, median (IQR)	48 (0–68)	49 (0–67)	40 (0–74)	0.94
Number of days of venovenous ECMO free days assessed to day 28, median (IQR)	18 (11–23)	18 (11–23)	18 (12–22)	0.99
Number of days of venovenous ECMO free days assessed to day 90, median (IQR)	80 (70–85)	80 (72–85)	78 (25–84)	0.35
Mortality, *n* (%)				
At ICU discharge	25 (23.8)	18 (24.0)	7 (23.3)	0.94
At day 90	26 (24.8)	19 (25.3)	7 (23.3)	0.83
In-hospital	30 (28.6)	23 (30.7)	7 (23.3)	0.45

ARDS = acute respiratory distress syndrome, CaDVT = cannula-associated deep vein thrombosis, ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.

[a]Influenzae virus except one adenovirus and one varicella.

[b]One patient underwent venovenous ECMO as a bridge-to-lung transplantation.

Dashes denote that no patient was available for statistical analysis in this subgroup of patient.

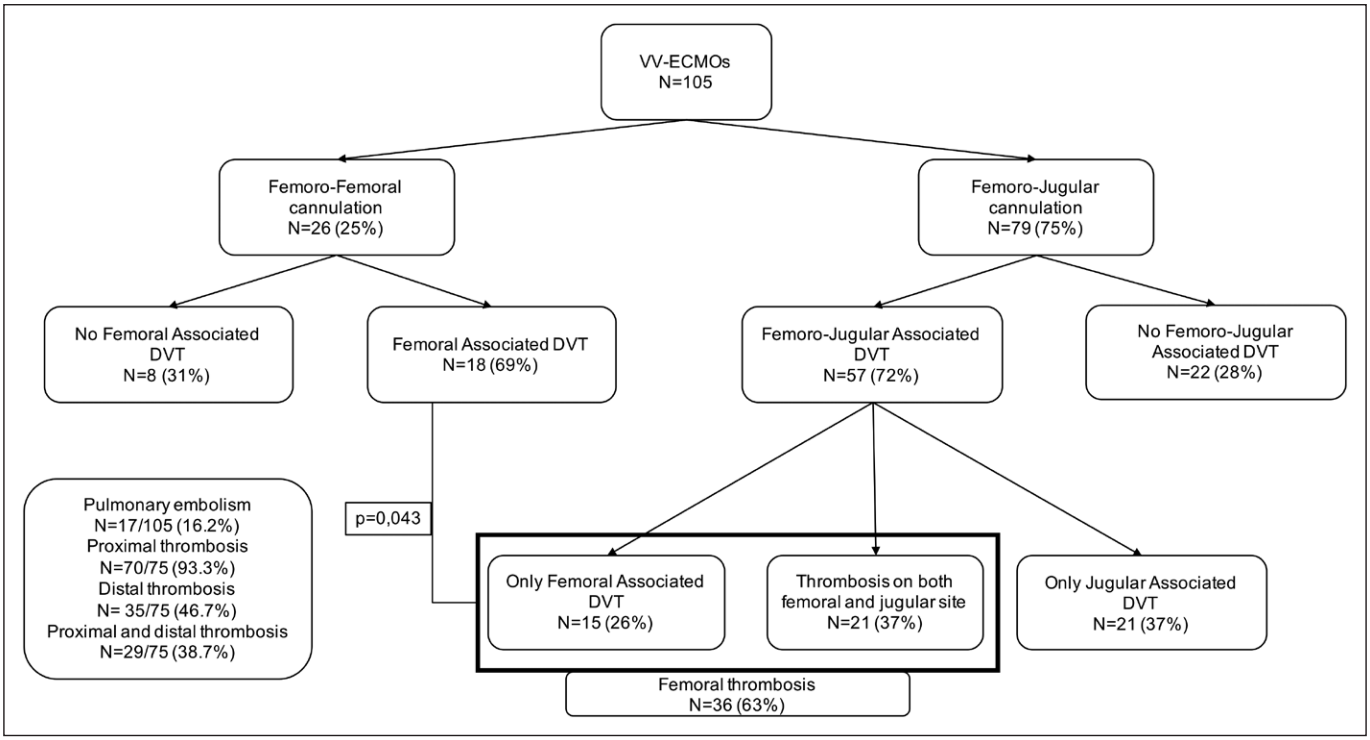

Figure 2. Cannula-associated deep vein thrombosis location. DVT = deep vein thrombosis, VV-ECMO = venovenous extracorporeal membrane oxygenation.

for them (15.6% vs 15.2%, respectively; $p = 1.00$). The rate of pulmonary embolism tended to be higher in the venovenous ECMO population than in the control group (16.2% vs 3.1%, respectively; $p = 0.07$).

Agreement between the two radiologists was very high for all CT scan examinations, and Cohen's kappa coefficient for this analysis was 0.95 ± 0.32 ($p < 0.001$).

The main clinical outcomes are presented in Table 1. The median duration of venovenous ECMO was not statistically significantly different between the two groups (10 d [5–17 d] in the CaDVT group vs 8 d [6–14 d] in the no CaDVT group; $p = 0.50$). The mean number of patients requiring ECMO circuit replacement was significantly higher in the CaDVT group than in the no CaDVT group (38.7% vs 16.7%; $p = 0.04$) (**Table S1**, Supplemental Digital Content 2, http://links.lww.com/CCM/F141). All circuit replacement ($n = 34$) were performed because of hemolysis, except of one patient (2.9%) due to circuit thrombosis. There was no difference between the CaDVT and no CaDVT groups regarding mortality evaluated either upon ICU discharge, at day 90, or in-hospital. The ICU length of stay and duration of mechanical ventilation duration were not statistically significantly different between the two groups (Table 1).

The blood coagulation parameters are presented in **Table 2**. All APTT ratio, prothrombin, and fibrinogen analysis results were not statistically different between the CaDVT and no CaDVT groups. The percentage of APTT ratio less than 1.2 was slightly higher in the no CaDVT group than in the CaDVT group (15% vs 9.4%; $p = 0.051$). A heparin-induced thrombocytopenia (HIT) test was performed in 45 patients. Two patients had a laboratory-confirmed HIT, but the result was returned the day after decannulation for the first patient, and 2 days before decannulation for the second patient. The heparin was substituted for danaparoid sodium. These two patients had a CaDVT. The mean platelet count was significantly lower in the no CaDVT group than in the CaDVT group (108 ± 59 vs 146 ± 68 G/L; $p = 0.01$). The percentage of the platelet count less than 100 G/L was higher in the no CaDVT group than in the CaDVT group (59.5% vs 42.2%, respectively; $p = 0.03$) (Table 2). Platelet transfusion requirements were higher in the no CaDVT group than in the CaDVT group (0.3 [0.1–0.5] vs 0.05 [0–0.3], respectively; $p = 0.02$) (**Table S2**, Supplemental Digital Content 3, http://links.lww.com/CCM/F142). There was no difference regarding blood products transfusion requirements and hemorrhagic complications between the two groups (Table S2, Supplemental Digital Content 3, http://links.lww.com/CCM/F142). There was no difference regarding canula size between the two groups (**Table S3**, Supplemental Digital Content 4, http://links.lww.com/CCM/F143).

Multivariate logistic regression analysis including history of DVT, ARDS related to bacterial pneumonia, percentage of platelet count less than 100 G/L, percentage of fibrinogen level less than 1.0 g/L, and percentage of APTT ratio less than 1.2 during ECMO period showed the percentage of thrombocytopenia less than 100 G/L led to a significantly decreased risk for developing a CaDVT (hazard ratio [HR], 0.98; 95% CI, 0.98–1.00; $p = 0.02$) (**Table 3**).

DISCUSSION

We showed that cannula-related DVT after venovenous ECMO is a common complication since 71.4% of the

TABLE 2. Blood Coagulation Parameters During Venovenous Extracorporeal Membrane Oxygenation

Variables	All ($n = 105$)	CaDVT Group ($n = 75$)	No CaDVT Group ($n = 30$)	p
Mean APTT ratio	1.60 (0.31)	1.60 (0.31)	1.61 (0.32)	0.82
% APTT ratio between (1.2 and 1.5)	52.5 (21.3)	54.0 (21.9)	49.0 (19.3)	0.28
% APTT ratio > 1.5	35.5 (22.8)	35.3 (22.5)	36.0 (23.8)	0.88
% APTT ratio < 1.2	11.0 (13.3)	9.40 (12.4)	15.0 (14.9)	0.05
% APTT ratio ≥ 1.8	20.0 (18.6)	20.2 (19.0)	19.4 (17.9)	0.85
% APTT ratio ≥ 3	3.4 (6.1)	2.9 (6.0)	4.6 (6.5)	0.21
Mean prothrombin ratio	66.8 (11.0)	66.8 (10.9)	66.8 (11.4)	1.00
% Prothrombin ratio < 50%	11.3 (17.1)	11.1 (17.3)	11.7 (16.6)	0.89
% Prothrombin ratio < 40%	2.8 (7.3)	2.2 (6.2)	4.2 (9.5)	0.30
% Prothrombin ratio < 30%	1.1 (4.3)	0.7 (2.2)	2.1 (7.3)	0.30
Mean platelet	134.9 (67.4)	145.9 (67.8)	107.5 (58.9)	0.01
% Platelet count < 100 G/L	47.1 (36.0)	42.2 (34.3)	59.5 (37.8)	0.03
% Platelet count < 50 G/L	8.4 (18.0	5.5 (14.0)	15.5 (24.2)	0.04
Mean fibrinogen level (g/L)	4.4 (1.8)	4.4 (1.8)	4.2 (1.7)	0.70
% Fibrinogen level < 1.5 g/L	4.0 (8.5)	4.2 (8.8)	3.3 (7.7)	0.61
% Fibrinogen level < 1.0 g/L	0.8 (3.0)	1.0 (3.5)	0.1 (0.9)	0.06
% Fibrinogen level ≤ 0.5 g/L	0.03 (0.29)	0.04 (0.34)	0.0 (0.00)	0.53
% Fibrinogen level ≥ 6 g/L	24.0 (29.1)	25.5 (29.8)	20.1 (27.3)	0.39

APTT = activated partial thromboplastin time, CaDVT = cannula-associated deep vein thrombosis.

APTT ratio is provided as times over the baseline value.

Mean APPT ratio, mean prothrombin ratio, mean platelet level and mean fibrinogen level are expressed as the mean (SD). Mean denotes the arithmetic mean of all measures completed during the venovenous extracorporeal membrane oxygenation period.

% aPTT denotes the percentage of APTT between two thresholds or greater than a given threshold, defined by the number of APTT according to the chosen threshold(s) divided by the total number of aPTT achieved times 100. The same was done for % prothrombin ratio, % fibrinogen level, and % platelet count. These data are provided as the mean percentage (SD).

patients in the current study developed a CaDVT. The type of cannulation (femorofemoral or femorojugular) was not statistically significantly different for all CaDVT. Specifically, for femoral CaDVT, femorofemoral cannulation induced CaDVT more frequently than did femorojugular cannulation (69.2% vs 63.1%).

Few studies have investigated the frequency of CaDVT after venovenous ECMO and high frequency variability is reported. In a study including 103 patients, Cooper et al (8) found a CaDVT frequency of 18.1%. Trudzinski et al (9) found a frequency of CaDVT of 47.1% among 51 patients. The population consisted of 54% ARDS patients and 46% bridge-tolung transplantation patients. Menaker et al (10) found a frequency of 85.4% in 48 patients with pulmonary ARDS. Menaker et al (10) found a frequency of 85.4% in 48 patients with pulmonary ARDS (11). Despite the high level of CaDVT shown in our population, the frequency of central venous catheter-related DVT was in accordance with data in the literature suggesting a significant prothrombogenic role of venovenous ECMO cannulas.

Femorofemoral and femorojugular cannulation are the two most common types of cannulation. Three studies also used a bicaval dual-lumen cannula (8, 9, 11). The rate of thrombosis according to the cannulation site is variable. Menaker et al (10) found a higher frequency in the jugular site (75.6% vs 48.1%), whereas Cooper et al (8) showed a higher frequency in the femoral site (10.4% vs 0%). Two studies found a similar overall frequency between the jugular and femoral sites (9, 11).

The diagnostic method that is mainly used for CaDVT in studies is ultrasonography (8–11), performed between 1 and 4 days after decannulation. Ultrasonography probably underestimates the prevalence of CaDVT due to the limitations of ultrasound for pelvic and inferior and superior vena cava location (13). Indeed, Trudzinski et al (9) found a vena cava thrombosis rate of 51.7% after autopsy. Two studies used a CT scan for CaDVT diagnosis, but it concerns only 20.7% and 3.5% of patients in each study (9, 11).

The management of anticoagulation during the venovenous ECMO period is a real challenge to maintain a balance between thrombotic risk and hemorrhagic risk. Bleeding under

TABLE 3. Multivariable Analysis

Variables	All ($n = 105$)	CaDVT Group ($n = 75$)	No CaDVT Group ($n = 30$)	Univariate p	Multivariate Hazard Ratio (95% CI)	Multivariate p
History of deep vein thrombosis, *n* (%)	5 (4.8)	2 (2.7)	3 (10.0)	0.139	0.18 (0.02–1.45)	0.11
Acute respiratory distress syndrome related to bacterial pneumonia, *n* (%)	49 (46.7)	38 (50.7)	11 (36.7)	0.194	1.66 (0.62–4.46)	0.32
% Platelet count < 100 G/L, mean (SD)	47.1 (36.0)	42.2 (34.3)	59.5 (37.8)	0.025	0.98 (0.97–1.00)	0.02
% Fibrinogen level < 1.0 g/L, mean (SD)	0.8 (3.0)	1.0 (3.5)	0.1 (0.9)	0.057	1.25 (0.85–1.83)	0.26
% Activated partial thromboplastin time ratio < 1.2, mean (SD)	11.0 (13.3)	9.40 (12.4)	15.0 (14.9)	0.052	0.97 (0.94–1.00)	0.06

CaDVT = cannula-associated deep vein thrombosis.

% Activated partial thromboplastin time (aPTT) ratio < 1.2 denotes the percentage of APTT ratios below 1.2 and is defined by the number of APTT ratios below 1.2 divided by the total number of aPTT achieved times 100. The same procedure was repeated for the % fibrinogen level with a chosen threshold at 1.0 g/L, and for % platelet count with a chosen threshold at 100 G/L.

venovenous ECMO is recognized as a poor prognostic factor (7, 14, 15). UFH anticoagulation monitored by APTT is the recommended and predominantly used method. In our study, intensity of anticoagulation measured by the APTT was not associated with CaDVT, despite an adequate mean APTT ratio at 1.6, which is close to the upper bound of French recommendation range (APTT ratio of 1.2–1.5) (12) and anticoagulation target in the ECMO to rescue acute lung injury in severe ARDS (EOLIA) study reflecting a widespread anticoagulation practice (16). The target range of anticoagulation used in other studies is closed to that of our practice. Cooper et al (8) used an APPT ratio target between 1.5 and 2, Trudzinski et al (9) used an APTT target greater than 50 seconds, Menaker et al (10) and Fisser et al (11) used an APTT target between 45 and 55 seconds. Insufficient anticoagulation was appreciated using the percentage of APTT ratio less than 1.2. Surprisingly, the percentage of APTT ratio less than 1.2 was slightly higher in the no CaDVT group than in the CaDVT group (15% vs 9.4%; $p = 0.051$) (Table 2). Additionally, 41.9% of patients had a significant bleeding during venovenous ECMO period (Table S2, Supplemental Digital Content 3, http://links.lww.com/CCM/F142). This result probably reflects the high risk of bleeding in the cohort and the difficult balance between pro and anticoagulant demand. Conversely, a higher level of anticoagulation (estimated using the percentage of APTT ratio > 1.8 or ≥ 3) was not associated with a lower frequency of CaDVT. Despite this, two studies found an association between the APTT value and CaDVT with a protective effect of the percentage of APTT greater than 50 seconds (9, 11). APTT monitoring for UFH use assumes that the patient's baseline APTT is comparable to that of the control, which is imprecise as APTT levels in critically ill patients vary from the normal control levels and could be insufficient for an accurate monitoring. This may explain the difficulties in demonstrating an association between the APTT and CaDVT. Furthermore, anticoagulation interruption during bleeding events or in case of thrombocytopenia less than 70 G/L might increase the risk of thrombosis. Other biological tests to monitor anticoagulation, such as anti-Xa and antithrombin activity, have been proposed, but published studies have discordant results on the reduction of thrombotic events (17–22). Reliability of anti-Xa test in case of hemolysis is compromised, and 39% of patients had a hemolysis diagnosed during the venovenous ECMO period (23). Thromboelastometry and thromboelastography suffer from a significant difficulty in interpretation, which is mainly due to the heparin effect on platelets (5). Combination of coagulation tests should be investigated.

Two patients had a HIT associated with a CaDVT, but the test was performed only in 45 of 105 patients. However, this result seems to be consistent with the frequency of HIT reported in other studies (24, 25). In our study, patients with higher percentage of platelet count less than 100 G/L during ECMO period have a significant lower risk for developing a CaDVT, with a HR of 0.98 (0.97–1.00) ($p = 0.02$). Only one study investigating DVT after venovenous ECMO report platelet transfusion rate and no statistical difference was found (9). Obviously, larger studies are needed to ensure these results.

The venovenous ECMO duration was not associated with CaDVT, one study found the venovenous ECMO duration as a risk factor for CaDVT (9). The number of circuits and oxygenator replacements was higher in the CaDVT group than in the no CaDVT group. This may indicate an increased prothrombotic activity in patients who develop CaDVT. This result is not reported in other studies, but the global frequency is slightly higher than in the EOLIA study (32.4% vs 27%) (16).

In-hospital mortality increased from 24% to 30.7% in the CaDVT group, while it was stable at 23.3% in the no CaDVT group. Despite lacking statistical significance, this result suggests a possible impact on the mortality of thrombotic events related to venovenous ECMO, which is consistent with other studies (26).

There are some limitations of this study. Its retrospective nature is intrinsically susceptible to have a biased selection. The main limitation is that CT scan was not performed in all patients during the study period, and patients who died under venovenous ECMO were obviously not scanned. We report CaDVT prevalence only in venovenous ECMO survivors, thus probably underestimating the global prevalence of CaDVT since deceased patients could have had a thrombotic cause of death. This bias is encountered in the other studies (8, 10, 11), except for autopsy series (9). Furthermore, 58 patients were excluded mainly due to nonperformed or incomplete CT scan, or a transfer in another ICU (Fig. 1). Furthermore, some types of venous thrombosis such as popliteal venous thrombosis have not been explored with the CT scan. Finally, the CT scan delay performed at a maximum of 4 days following venovenous ECMO may have missed CaDVT due to thrombus migration. We cannot exclude that patients had an insufficient anticoagulation because of APTT monitoring, but this limitation is shared with other studies and need further investigations with a higher power. The impact of CaDVT on the length of stay, morbidity, and mortality remains to be studied.

CONCLUSIONS

To the best of our knowledge, this is the first study to describe the CaDVT prevalence after venovenous ECMO using CT scan in such a large cohort of patients. CaDVT after venovenous ECMO is a common event, as 71.4% of survivors had a CaDVT. Anticoagulation recommendations seem to have a moderate impact on the thrombotic risk of cannulated vessels. We show that thrombocytopenia during venovenous ECMO has a protective effect on CaDVT. Further investigations are needed to improve thromboprophylaxis and achieve more reliable anticoagulation monitoring for the prevention of CaDVT. Our results suggest the interest in the systematic imaging of all cannulated vessels after venovenous ECMO.

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