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

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1 Venous or Arterial Thromboses after Venoarterial-Extracorporeal

2 Membrane Oxygenation Support: Frequency and Risk Factors

3

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34

35

36 **Tweet:** Vascular complications –cannula-associated deep vein thrombosis, leg ischemia or

37 delayed arterial stenosis– are frequent after VA-ECMO removal, and should be systematically

38 sought

39

40 ABSTRACT

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

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

50 **Results:** From November 2018 to November 2019, 107 patients (median (IQR) age 54 (42-
51 63) years old and median (IQR) days on ECMO support 8 (2-5)) were successfully weaned-
52 off VA-ECMO and included. CaDVT occurred in 44 (41%) patients and arterial
53 complications in 15 (14%) (nine acute leg ischemia, one arteriovenous femoral fistula, and
54 five late femoral stenosis). Multivariable analysis retained longer duration of ECMO support
55 (OR, 1.12 per day; 95% CI, 1.02-1.22), and infection occurring on ECMO (OR, 3.03; 95%
56 CI, 1.14-8.03) as independent risk factors for CaDVT whereas older age (odds ratio (OR),
57 0.97 per year; 95% confidence interval (CI), 0.94-0.99) and prior anticoagulation use (OR
58 0.21; 95% CI, 0.06-0.68) were protective factors for CaDVT. No risk factors for arterial
59 complications were identified.

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

64

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

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

83

84

85 MATERIALS AND METHODS

86 Patients

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

99

100 ECMO Implantation, Anticoagulation and Weaning

101 The cannulation technique used was outflow via the femoral vein and inflow via the femoral
102 artery with systematic reperfusion catheter to prevent limb ischemia; when venoarterial-
103 venous-ECMO (VAV-ECMO) was required, another inflow cannula was inserted into the
104 right internal jugular vein. Usual diameter ranges were: 15-19 Fr for the arterial cannula and
105 21-29 Fr for the venous cannula. ECMO was implanted percutaneously under ultrasound
106 guidance by trained cardiovascular surgeons as first-line choice or surgically, if necessary ¹¹.

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

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

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

127

128 **Thrombosis Diagnosis and Treatment**

129 The primary objective of the study was to determine the CaDVT frequency after
130 decannulation. Occurrence of arterial complications post-decannulation was also evaluated.
131 CaDVT was routinely assessed by experienced ICU physicians with duplex ultrasonography
132 within the 24 hours following ECMO withdrawal. CaDVT diagnosis was based on vein
133 incompressibility, absence of flow and thrombus presence for peripheral veins (i.e., femoral
134 and jugular), and on thrombus presence in the inferior vena cava ¹⁴. The femoral vein and
135 inferior vena cava were systematically screened for thrombosis in all patients and the jugular
136 vein when needed. When a CaDVT was identified, clinical symptoms and obstruction of the
137 vein (arbitrarily split in 2 categories; obstruction $\leq 50\%$ of the vessel lumen and obstruction
138 $> 50\%$ of the vein lumen) were noted. For inferior vena cava thrombus, thrombus length was
139 noted. Anticoagulation with continuous UFH infusion was started in the ICU for a clinically
140 significant thrombus, as defined by the treating physician, then switched to oral
141 anticoagulation according to physician's choice. Thrombus persistence was verified regularly
142 in the ICU and at the discretion of the medical team caring for the patient. Anticoagulation
143 was stopped when the thrombus was no longer present on duplex ultrasonography. Pulmonary
144 embolism (PE) was diagnosed on computed-tomography (CT) images obtained when
145 clinically suspected but was not routinely ordered.

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

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

152

153 **Ethics**

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

161

162 **Statistical Analyses**

163 Results are expressed as median (IQR) or n (%). Between-group comparisons were analyzed
164 using Student's *t*-test or the Mann-Whitney *U*-test according to variable's distribution, ie,
165 normal or not for continuous variables. Between-group differences were assessed with chi-
166 square test or Fisher's exact test for nominal variables. A logistic-regression model was used
167 to examine the univariable association of CaDVT and patients' characteristics or ICU events.
168 Thereafter, multivariable logistic-regression model using backward-stepwise variable
169 elimination (with the variable exit threshold set at $P > 0.05$) tested the factors that were
170 significant in the univariable analyses ($P \leq 0.10$). Variables included in the model were age
171 (per year increase), prior anticoagulation therapy, days on ECMO support (per day), infection
172 on ECMO support, highest fibrinogen level during ECMO run (per g/L increase),
173 postcardiotomy reason for ECMO and highest platelets level (per Giga/L increase). Between-
174 variable interactions were sought in the models; variables strongly associated with other(s)
175 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).

178 RESULTS

179 Patient Characteristics

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

186 CaDVT and Arterial Complications

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

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

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

214

215 **CaDVT Risk Factors**

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

224 days on UFH or the median platelet count did not differ between groups. Patients who
225 developed CaDVT after ECMO removal more frequently had an infection during the ECMO
226 run than those without CaDVT, whereas the infection rate before ECMO implantation and
227 after ECMO removal did not differ between patients with CaDVT or without. The cannula-
228 related–infection rate was doubled for patients with CaDVT than those without ($P = 0.06$).
229 Multivariable analysis retained ECMO runtime and concurrent infection as independent risk
230 factors significantly associated with CaDVT, whereas older age and prior anticoagulant use
231 were protective risk factors (**Table 3**).

232

233 **Risk Factors for Arterial Complications**

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

236

237

238 **DISCUSSION**

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

248

249 **Pathogenesis and risk factors for CaDVT**

250 The exact pathogenesis of venous thrombosis in ECMO patients is not fully understood: the
251 origin of thrombus is probably the cannula itself, a thrombogenic surface that may activate
252 coagulation cascade. Venous stasis due to reduction in venous diameter may also play a role.
253 We were able to identify, in our study, specific risk factors for CaDVT. First, we found that
254 infection on ECMO was a major risk factor for CaDVT. Infection induces inflammatory
255 processes that might have enhanced thrombogenic activity in these patients and local
256 (cannula-related) infection might have played a role by locally increasing thrombogenicity ¹⁵.
257 Infection has not previously been specifically described as a risk factor for CaDVT; one study
258 reported a higher CaDVT rate when bacterial pneumonia-related acute respiratory distress
259 syndrome was the indication for ECMO, **as** compared to other situations requiring ECMO; ⁵
260 but other nosocomial infections have not been investigated ⁹.

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

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

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

277

278 **Arterial complications after ECMO removal**

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

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

290

291 **Potential implications of our results**

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

300 The second implication refers to treatment of CaDVT, although this latter is not standardized.
301 Venous thrombectomy during decannulation should be avoided, since this procedure may
302 injured endothelium and increase the risk of venous thrombus formation. According to
303 guidelines¹⁸, a 3-month anticoagulation regimen is recommended for catheter-related DVT.
304 Our practice and recommendation is to start anticoagulation in the ICU, when the thrombosis
305 is considered clinically significant and the bleeding risk is acceptable, taking into account that
306 VA-ECMO patients have a higher risk of bleeding at the decannulation site than those on VV-
307 ECMO. We then regularly monitor the thrombus with ultrasounds and stop anticoagulation

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

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

316

317 **Study limitations**

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

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

342

343 **Conclusion**

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

350

351

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354 Healthcare, outside the scope of the submitted work. M.S. reports lecture fees from Maquet,
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357

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

361

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366

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

Characteristic	All (n = 107)	CaDVT		<i>P</i> 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

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

373 ^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 \geq 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 \geq 150 and $<$ 400, % ^a	12.5 (0-37.5)	12.5 (0-31)	13.4 (0-40)	0.95
Days with platelets \geq 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.

^aExpressed 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)	<i>P</i> 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

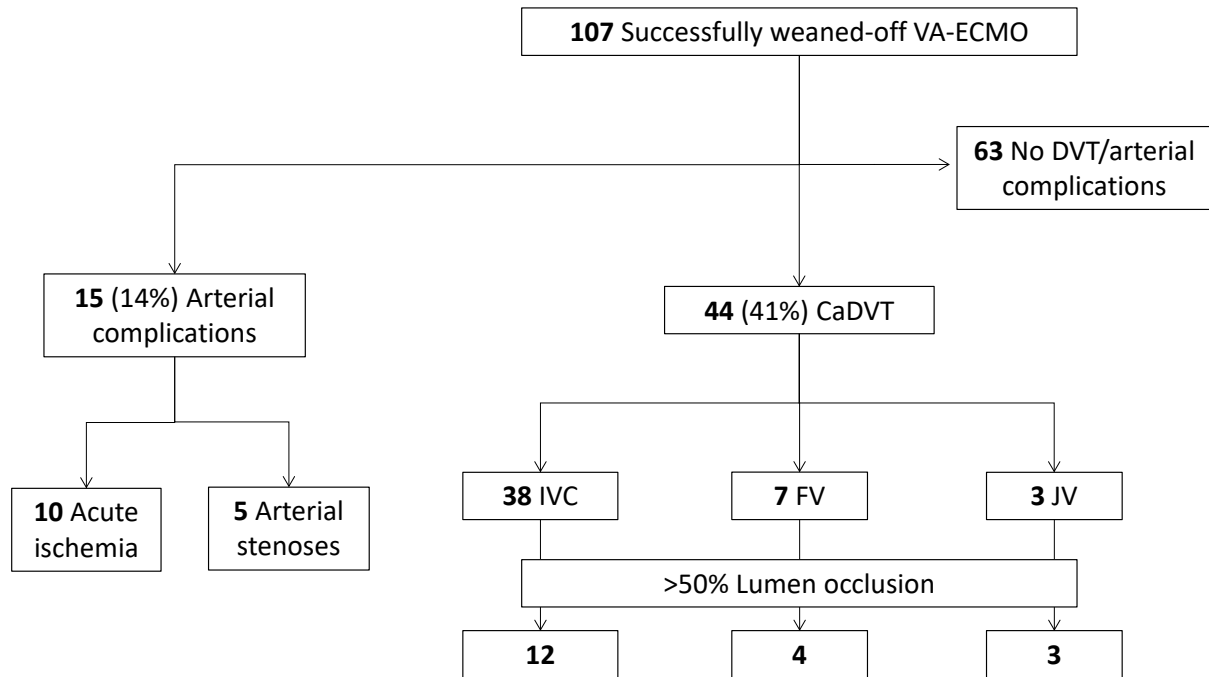
Parameter	All (n = 107)	Arterial Complication		P Value
		No (n = 92)	Yes (n =15)	
Daily UFH dose, IU	8004 (4614-13429)	8231 (4620-13330)	7613 (3105-16942)	0.93
Days on UFH therapy, % ^a	90.6 (66.6-100)	100 (66.6-100)	77 (50-100)	0.16
aPTT ratio	1.49 (1.32-1.72)	1.49 (1.33-1.72)	1.47 (1.25-1.73)	0.16
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.

^aExpressed 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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