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Brain Injury during Venovenous Extracorporeal Membrane Oxygenation

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Abstract

Purpose: The frequency of neurological events and their impact on patients receiving venovenous-extracorporeal membrane oxygenation (VV-ECMO) are unknown. We therefore study the epidemiology, risk factors and impact of cerebral complications occurring in VV-ECMO patients.

Methods: Observational study conducted in a tertiary referral center (2006–2012) on patients developing a neurological complication (ischemic stroke or intracranial bleeding) while on VV-ECMO versus those who did not, and systematic review on this topic.

Results: Among 135 consecutive patients having received VV-ECMO, 18 (15 assessable) developed cerebral complications on ECMO: cerebral bleeding in 10 (7.5%), ischemic stroke in 3 (2%) or diffuse microbleeds in 2 (2%), occurring after respective medians (IQR) of 3 (1–11), 21 (10–26) and 36 (8–63) days post-ECMO onset. Intracranial bleeding was independently associated with renal failure at intensive care unit admission and rapid $PaCO_2$ decrease at ECMO initiation, but not with age, comorbidities or hemostasis disorders. Seven (70%) patients with intracranial bleeding and one (33%) with ischemic stroke died versus 40% of patients without neurological event. Systematic review found comparable intracranial bleeding rates (5%).

Conclusions: Neurological events occurred frequently in patients on VV-ECMO. Intracranial bleeding, the most frequent, occurred early and was associated with higher mortality. Because it was independently associated with rapid hypercapnia decrease, the latter should be avoided at ECMO onset, but its exact role remains to be determined. These findings may have major implications for the care of patients requiring VV-ECMO.

Abstract word count: 237 words

The use of venovenous-extracorporeal membrane oxygenation (VV-ECMO) to treat patients with refractory acute respiratory distress syndrome (ARDS) has increased in recent years [1, 2]. Among complications occurring during ECMO support, neurological injury is important because it may be associated with increased mortality and long-term functional sequelae. In the landmark observational study on VV-ECMO for refractory ARDS complicating H1N1v2009 influenza, most deaths were attributed to cerebral hemorrhage [3]. To date, only two studies have specifically investigated neurological complications of ECMO support and both showed high numbers of brain injuries [4, 5]. However, those observational studies concerned patients receiving venoarterial-ECMO (VA-ECMO) and most subjects were included after cardiac surgery or cardiac arrest. VV-ECMO neurological complications have mostly been reported as case reports [6, 7].

Because no epidemiological data on neurological complications occurring during VV-ECMO are available, we undertook this retrospective study on information prospectively collected from a large series of VV-ECMO patients to describe the frequency, morbidity, mortality and risk factors of cerebral injury. We then conducted a systematic review of all reported neurological complications in VV-ECMO series.

METHODS

All patients admitted to our intensive care unit (ICU) from 2006 to 2012 who received VV-ECMO support were included. Because circulatory assistance of any type can be complicated by thromboembolic phenomena, particularly cerebral infarction due to embolism, we excluded patients having received a VA-ECMO (peripheral or central), a left ventricle assist device (VAD), a BiVAD or a total artificial heart before, during or after VV-ECMO run. Thus, patients switched from VA-ECMO to VV-ECMO or from VV- to VA-ECMO were excluded. Clinical information on medical history, clinical and biological parameters at ICU

admission and during the stay was collected prospectively. In particular, any events occurring during ECMO support were prospectively recorded in the ICU's database.

We defined clinical neurological complication as any clinical event occurring during ECMO course. It included any clinical sign suggestive of stroke (hemiplegia, mydriasis, anisocoria, asymmetry on clinical examination), but also confusion, delirium, seizures, coma despite sedation withdrawal. Patients were categorized according to the presence or not of brain injury on brain imaging (i.e. no brain damage, ischemic stroke, intracranial bleeding and microbleeds) and groups were compared.

ECMO Circuit

The extracorporeal system consisted of polyvinyl chloride tubing, a membrane oxygenator (QuadroxBioline, Jostra-Maquet, Orléans, France, or Eos ECMO, Sorin, Milan, Italy), a centrifugal pump (Rotaflow, Jostra-Maquet, or Revolution, Sorin), and drainage and reinfusion cannulae (Biomedicus Carmeda, Medtronic, Boulogne-Billancourt, France, or Edwards Lifesciences, Irvine, CA). An oxygen–air blender (Sechrist Industries, Anaheim, CA) was used to ventilate the membrane oxygenator. All patients had two-site cannulation and all cannulae were inserted percutaneously. The drainage cannula was inserted into the femoral vein (extending into the inferior vena cava) and the reinfusion cannula was inserted into the internal jugular vein (extending into the right atrium).

Patient Management under ECMO

All patients had a blood gas analysis in the 2 hours preceding ECMO start (blood gas analysis pre-ECMO) and in the 2 hours following ECMO start (blood gas analysis post-ECMO).

All patients had the same protocol for anticoagulation. A heparin bolus (5000 IU) was injected at ECMO initiation; then all patients were continuously infused with unfractionated

heparin. The heparin dose was adapted at least once daily according to activated partial thrombin time (aPTT) value (targeting 1 to 1.5-fold the control value) and clinical tolerance; heparin was stopped when bleeding occurred and restarted once it was controlled. Bleeding leading to heparin withdrawal was defined as any clinical bleeding judged significant by the physician in charge of the patient (at ECMO site, central or arterial lines, tracheal secretions, ear nose and throat) with or without hemodynamic impact, with or without decrease in haemoglobin level. Anticoagulant overdose was defined biologically as an aPTT (patient/control) ratio >2.5, corresponding to an absolute value of ≥80 s.

Membrane oxygenator and circuitry were checked daily by experienced perfusionists and were changed when fibrin deposition or thrombi had deleterious effects on blood oxygenation, platelet count (<20,000/ml) or blood fibrinogen level (<1.5 g/L) decreased significantly, or significant intravascular hemolysis (free plasma haemoglobin> 200 mg/L at 2 time points and no other cause of mechanical hemolysis) appeared. No systematic circuit change was scheduled.

Daily routine neurologic examinations were performed in our patients by the physicians and the nurses in charge of the patient. Physicians performed at least once daily neurologic examination after sedation withdrawal, including Glasgow coma scale calculation, response to verbal orders or pain, tendon reflexes, brainstem reflexes and plantar reflex, eye opening and pupils' examination. Size of pupils and their light reactivity were assessed by the nurse in charge of the patient every 4 hours. Moreover, when an unexpected event occurred (such as seizures, delirium confusion, no awakening after sedation withdrawal…), this was registered in the medical chart. Once a neurologic symptom was observed (including but not restricted to change in neurological exam, mydriasis, anisocoria, seizures, delirium, confusion, coma despite sedation withdrawal…) within 6 hours a cerebral CT scan was performed.

Literature Review

We conducted a systematic MEDLINE-Database literature review through the PubMed search engine with a global search strategy applying prespecified selection and outcome (occurrence of neurological complication and mortality) criteria using the terms ECMO, venovenous-ECMO and extracorporeal oxygenation. Details on methodology and the results of this review are presented in an Online Supplemental Data.

Statistical Analyses

Data are expressed as medians [25^{th}–75^{th} percentile interquartile range (IQR)] or means (± standard deviation (SD)), as appropriate. Between-group comparisons were analyzed using Student's *t*-test or the Mann-Whitney *U*-test for continuous variables, chi-square test for categorical variables. For dichotomous variables, the median value was chosen for the cut-off to separate the variable into two categories. To examine the univariable impact of patients' clinical characteristics and ICU events on the development of cerebral bleeding, a logistic-regression model tested each characteristic. Thereafter, multivariable analysis with a Cox regression model compared the factors that were significant in the univariable analysis. The analysis was run using backward-stepwise variable elimination (with the variable-exit threshold set at $P > 0.05$). Risk factors achieving $P \leq 0.10$ in our univariable analysis and parameters previously reported to be strongly associated with intracranial bleeding were entered into the model. Interactions were tested in the model; variables strongly associated with other(s) were not included in the multivariable model. The final model included renal failure on admission, PaO2 change and PaCO2 change. In a sensitivity analysis, lowest platelets count, lowest fibrinogen level and lowest prothrombin time were added to the final

model for intracranial bleeding. Two other endpoints were investigated using Cox regression model: ICU mortality without intracranial bleeding, and a composite endpoint; intracranial bleeding or ICU mortality. Analyses were computed with StatView v5.0 (SAS Institute Inc, Cary, NC) and SPSS v11.5 (SPSS Inc, Chicago, IL) software. $P < 0.05$ defined significance.

Ethics

In accordance with the ethical standards of our hospitals institutional review boards (Committee for the Protection of Human Subjects), informed consent for demographic, physiological and hospital-outcome data analyses was not obtained because this observational study did not modify existing diagnostic or therapeutic strategies.

RESULTS

During the study period, 135 patients required VV-ECMO support. Table 1 reports their baseline characteristics. For 23 of those 135 patients, a cerebral event could not be ruled out because they died before neurological examination could be performed or had preexisting neurological disease. A clinical neurological symptom appeared in 25 (19%) during VV-ECMO support (Figure 1). Three of those 25 were clinically brain dead, confirmed by electroencephalogram, and did not undergo cerebral imaging; therefore, hemorrhagic stroke could not be excluded.

Brain imaging was obtained for the remaining 22 patients (computed-tomography (CT) scan for 21 and magnetic resonance imaging (MRI, performed after ECMO removal) for one), and five other patients without any clinical signs underwent cerebral CT scans (for one of them with traumatic brain injury, the CT scan was obtained for follow-up) (Figure 1). Cerebral-imaging findings as a function of clinical neurological feature(s) are given in Table 2. Cerebral-imaging sequences for 10 patients were normal; 10 patients had intracranial

bleeding, either intraparenchymal hematoma (n = 9) or subarachnoid hemorrhage (n = 1); three patients had ischemic strokes; two patients had diffuse microbleeds and two patients had brain edema (for the latter, the neurological injury preceded ECMO: one suffered traumatic brain injury 7 days before ECMO with cerebral edema before ECMO; the other had prolonged cardiac arrest 2 days pre-ECMO and cerebral edema was attributed to cerebral anoxia).

Thus, 18 (13%, 95% CI 7.3–18.7%) of the 135 patients had a cerebral complication that occurred while on ECMO (three brain deaths without imaging, 10 intracranial bleeds, three ischemic strokes and two diffuse microbleeds). Table 1 gives patients' characteristics as a function of the type of neurological event occurring on ECMO or not. Patients with such complications were older and more frequently had renal failure at ICU admission (especially patients with intracranial bleeding) than those without these events. Other parameters did not differ between groups, although patients with intracranial bleeding tended to have higher mortality and shorter time from ECMO onset to neurological complications.

Patients with Intracranial Bleeding

Because the predominant neurological event was intracranial bleeding, we specifically analyzed those 10 patients to attempt to identify risk factors associated with this complication. Figure 2 reports the pH, $PaCO_2$ and PaO_2 changes between just before and after starting ECMO in patients with and without intracranial bleeding. Comparing patients without to those with cerebral bleeding, respectively, the latter had higher PaO_2 increases just after ECMO onset (medians [IQR]: 20 [4.7–52] vs. 58 [19–214] mmHg; $P = 0.04$), a not significant $PaCO_2$ decrease just after ECMO initiation (–24 [–15 to –38] vs. –33 [–28 to –38] mmHg; $P = 0.06$) but no pH change difference just after starting ECMO (0.17 [0.09–0.26] vs. 0.26 [0.12–0.29]; $P = 0.26$).

Table 3 reports the factors associated with intracranial bleeding. Renal failure at ICU admission, PaO_2 increase just after ECMO initiation >50 mmHg and $PaCO_2$ decrease just after ECMO onset <–27 mmHg were the only factors significantly associated with brain hemorrhage in the univariable analysis, whereas the Cox analysis retained renal failure at ICU admission and $PaCO_2$ decrease as the only factors independently associated with intracranial bleeding. Absolute baseline values of PaO2 and PaCO2 were not associated with intracranial bleeding. Age, female sex and mechanical ventilation duration pre-ECMO showed a trend towards association with intracranial bleeding. Hemostasis disorders were not associated with intracranial bleeding in uni-or-multivariable analyses (sensitivity analysis not shown). Table 4 lists the hemostasis-parameter values 3 days before brain injury. These patients' heparin doses were low, as were their aPPT values and anti-Xa activity, and none had profound thrombopenia or low fibrinogen levels.

Same risk factors were associated with an increased risk of both death and the composite endpoint (Online Supplement, Tables E1 and E2). Among them, $PaCO_2$ change and lowest prothrombin time during EMCO, but not renal failure, were associated with ICU mortality (Online Supplement, Tables E1 and E2).

DISCUSSION

We report here the largest study to date of neurological complications during VV-ECMO. We found that 25 of our 135 patients (19%) experienced a clinical neurological event, with 18 (13%, 95% CI 7.3–18.7%) of those neurological injuries occurring on VV-ECMO. Cerebral bleeding was the predominant complication, manifesting as coma or mydriasis. Intriguingly, it was not associated with hemostasis disorders or anticoagulant use: platelet counts, prothrombin time, aPPT and fibrinogen levels while on ECMO were similar among patients

with and without cerebral hemorrhage, and heparin doses during the 3 days preceding cerebral bleeding were low, without overdose. The only factors independently associated with brain hemorrhage were renal failure at ICU admission and acute $PaCO_2$ changes at ECMO initiation.

Our results are in accordance with the literature on neurological complications occurring in ECMO patients (Table 5). Kasirajan *et al*. reported 18.9% intracranial bleeding for their series of 74 VA-ECMO patients. In that study, cerebral bleeding was independently associated with female sex and thrombocytopenia. Mateen *et al*. retrospectively studied 87 VA-ECMO patients and found a high rate of neurological injury, including stroke, intracranial bleeding and brain death [5]; the 10 brains examined at autopsy revealed more neurological sequelae than would have been predicted by clinical findings alone. However, that study included VA-ECMO patients after cardiac surgery or cardiac arrest. The authors of the largest study that included 23,951 patients given ECMO support reported 10.9% neurological complications [13]. Ischemic stroke, cerebral bleeding and seizure frequencies were 4.1%, 3.6% and 4.1%, respectively, but, as underlined by the authors themselves, they mixed adults, children and newborns, and were unable to distinguish patients receiving VV- and/or VA-ECMO [13]. The cerebral bleeding frequency for VV-ECMO patients observed in the systematic review (see online supplement) was 5%, similar to ours. However, this systematic review has several limitations: first, among the 16 studies reporting neurological complications of ECMO, most of them mixed VV- and VA-ECMO. Thus, the exact cerebral complication frequency of VV-ECMO is difficult to calculate precisely. Another limitation is that most previous studies reported only cerebral bleeding and no other neurological complications, e.g. ischemic stroke. Lastly, unlike our investigation, those studies had not been designed to evaluate factors associated with neurological complications.

The pathophysiology of VA-ECMO– or VV-ECMO–associated brain injury probably

differs. In VA-ECMO patients, brain damage could reflect the pre-ECMO clinical context (low blood pressure and cerebral blood flow, hypoxia, acidosis, electrolyte disturbances, and/or hemostasis disorders related to hepatic failure frequently observed in cardiogenic shock), reperfusion injury at ECMO implantation, the ECMO process itself (embolic stroke from the arterial cannula) and/or hemostasis disorders induced by the ECMO circuit. To date, the exact mechanism of brain damage is not fully understood and probably includes a combination of all those factors.

In VV-ECMO patients, a combination of factors also probably leads to neurological complications, even though some of these factors are not strictly the same. Whereas disorders created by the ECMO circuit and the oxygenator (hemolysis, thrombocytopenia, fibrinolysis, acquired von Willebrand syndrome [14]) are the same in VA- and VV-ECMO, pre-ECMO factors and ECMO-induced metabolic changes could differ. The pre-ECMO factors include hypoxia, hypercapnia, respiratory acidosis and parameters associated with acute respiratory failure before starting support. VV-ECMO specificities include abrupt O_2 and CO_2 changes at ECMO onset [15, 16]. Because CO_2 is involved in the regulation of cerebral blood flow [17, 18], sudden CO_2-level changes (from hypercapnia to normocapnia or hypocapnia) at ECMO initiation could have induced sudden cerebral blood-flow changes that could have precipitated brain damage. Recently, Muellenbach et al. reported that patients receiving vvECMO treatment were at risk for a decrease in cerebral regional tissue oxygen saturation at ECMO initiation, and that this decreased is linked to PaCO2 change. This could be involved in the pathogenesis of brain injury of ECMO patients [19, 20]. In our study, the acute $PaCO_2$ change was independently associated with cerebral bleeding and one can hypothesize that these abrupt changes may have facilitated brain hemorrhages. Although we have no definite proof of this association, we think it should be taken into account when initiating VV-ECMO and in our ICU we have now changed our practice by trying to avoid too rapid hypercapnia

correction. It could be achieved by starting with a low sweep gas flow and progressively increasing it over time. Even though PaO_2 change was not independently associated with cerebral bleeding, it can be recommended not to correct it too quickly by starting with a low fraction of inspired oxygen and increasing it slowly over time. However, because rapid decrease in PaCO2 leads to vasoconstriction, the relationship between PaCO2 change and cerebral bleeding is difficult to understand. We cannot exclude that ECMO-induced alkalosis have caused microbleeds or excessive local flow with altered brain blood barrier and bleeding.

Surprisingly, hemostasis disorders were not associated with intracranial bleeding herein. However, because lowest prothrombin time while on ECMO was strongly associated with an increased risk of mortality, the lack of association between lowest prothrombin time and intracranial bleeding could be an indirect effect of the increased mortality among patients presenting this risk factor. Moreover, because our patients' platelet function was not explored, we cannot exclude that those with intracranial haemorrhage might have had platelet dysfunction. Our patients received relatively low dose of heparin, but this is explained by our anticoagulation policy; we target an aPTT ratio of 1 to 1.5, and stop heparin when clinical bleeding occurs. Although hemostasis disorders could have played a role, the mechanism of cerebral bleeding in those patients is probably multifactorial, including vascular injury due to underlying disease severity, disorders created by the ECMO circuit (hemolysis, fibrinolysis…), rapid PaO_2 and $PaCO_2$ changes and other, as yet unknown, factors. Future studies should investigate the precise mechanisms that could precipitate neurological complications, particularly controllable factors like PaO_2 and $PaCO_2$ changes.

Our study has several limitations. First, this was a single-center study and, although we included many VV-ECMO patients, not many developed neurological events. Thus, our results, particularly the role of rapid gas exchange parameter changes in cerebral bleeding,

will have to be confirmed by larger studies. Moreover, because the delivery of ECMO is so variable from centre to centre (devices used, techniques employed; management of anticoagulation and transfusion, thresholds for addressing hypoxemia, and so on), these results would be difficult to extrapolate to other centres. Second, although it is our policy to carefully check hemostasis parameters in patients on VV-ECMO, we did not examine hemostasis, specifically thrombosis and fibrinolysis, with thromboelastogram, D-dimer or other tests [21]. Because it is well-known that ECMO patients have primary hemostasis disorders (e.g., acquired von Willebrand disease [14]), we cannot exclude the possibility of unrecognized hemostasis disorders that might explain the high intracranial bleeding frequency. Third, because it was difficult to assess neurological status at ICU admission, it is possible that, at least in some patients, neurological complications may have preceded ECMO and that ECMO aggravated them. However, albeit impossible to demonstrate, it is not likely, since our policy is to carefully check daily for clinical signs of brain involvement, in particular at ICU admission. Fourth, because 23 patients could not be evaluated before dying and because we also cannot exclude that some patients might have had an undetected neurological injury, we may have underestimated the exact frequency of brain injury, as in most studies published to date and reporting neurological outcomes. Fifth, because neuroimaging was not performed in all patients, we could have underestimated the frequency of neurological injury (missing subclinical events). Sixth, we found no direct association between hemostasis disorders and intracranial bleeding, but lowest prothrombin time while on ECMO was strongly associated with ICU mortality. This lack of association between lowest prothrombin time and intracranial bleeding could be an indirect effect of the increased mortality among patients presenting this risk factor. Lastly, we identified 2 conditions associated with cerebral bleeding during ECMO, but their relationships with brain haemorrhage remain unknown: are they causative factors or merely coincidental? Moreover,

we explored only the blood gas change at ECMO start, not during the whole ECMO course. We therefore cannot be sure that rapid change of PaO2/PaCO2 could have occurred after several hours or days and could have play a role in brain injury. Future studies should explore these possibilities.

In conclusion, neurological complications are frequent in patients on VV-ECMO. Intracranial bleeding, the most frequent event, occurred early during ECMO and was associated with high mortality. The precise roles of sudden O_2- and CO_2-level changes need to be more precisely evaluated, not only for the sake of knowledge, but mainly because they might have major implications in the care of patients requiring VV-ECMO.

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Conflicts of Interest: Alain Combes is the primary investigator of the EOLIA, NCT07470703, a randomized trial of VV-ECMO supported in part by MAQUET. Alain Combes has received honoraria for lectures by MAQUET, BAXTER, and ALUNG. Other authors declare that they have no conflict of interest related to the purpose of this manuscript.

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Figure Legends

Figure 1. Flow chart of the study. VV-ECMO, venovenous-extracorporeal membrane oxygenation**.**

Figure 2. Gas exchange parameter changes at the start of venovenous-extracorporeal membrane oxygenation (VV-ECMO) in the 10 patients with intracranial bleeding (hatched boxes) and the remaining 125 (white boxes). (*A*) Absolute pH change defined as post-ECMO-onset pH – pre-ECMO pH. (*B*) Absolute $PaCO_2$ change defined as post-ECMO-onset $PaCO_2$ – pre-ECMO $PaCO_2$. (*C*) Absolute PaO_2 change defined as post-ECMO-onset PaO_2 – pre-ECMO PaO_2. The horizontal lines inside the box plots are the medians, the lower and upper limits of the box correspond to the 25^{th} and 75^{th} percentile interquartile ranges, the T-bars represent the 10^{th} and 90^{th} percentile interquartile ranges, and the circles are outliers.

Table 1. Admission Characteristics, Hemostasis Disorders during VV-ECMO and Patient Outcomes According to Brain Damage

Characteristic	No Brain Damage (*n = 117*)	Patients with Brain Damage		
		Intracranial Bleeding (*n = 10*)	Microbleeds (*n = 2*)	Ischemic Stroke (*n = 3*)
Age, yr[a]	44 ± 14	49 ± 12	54 ± 4	59 ± 6
Male sex, n (%)	79 (68)	5 (50)	2 (100)	1 (33)
Body mass index, kg/m^2	26 [24–31]	23 [21–27]	22 [21–22]	26 [25–47]
McCabe & Jackson comorbidity score ≥2, n (%)	41 (35)	2 (20)	0	1 (33)
ICU-admission SAPS II score	69 ± 14	71 ± 12	61 ± 1	71 ± 9
H1N1v2009 influenza-related ARDS, n (%)	18 (15)	1 (10)	0	0
Duration of MV before ECMO, days	5 [1–10]	8 [4–11]	5 [3–7]	11 [9–17]
Organ failure at ECMO start[b]				
Cardiovascular	30 (25)	2 (20)	1 (50)	0
Hepatic	25 (23)	4 (40)	0	0
Renal[a]	48 (41)	8 (80)	0	2 (67)
Hematological	15 (13)	1 (10)	0	0
Neurological	94 (80)	8 (80)	1 (50)	3 (100)
Gas exchange values pre-ECMO				
Arterial pH	7.26	7.18 [7.07–	7.16 [7.16–	7.36 [7.32–

	[7.16–7.34]	7.29]	7.17]	7.40]
$PaCO_2$	59 [49–73]	74 [57–94]	57 [53–60]	58 [53–63]
PaO_2	55 [47–68]	68 [66–75]	86 [42–129]	61 [55–67]
Gas exchange value post-ECMO				
Arterial pH	7.44 [7.37–7.50]	7.41–7.36–7.45]	7.43 [7.38–7.48]	7.52 [7.35–7.57]
$PaCO_2$	34 [28.9–38.7]	32 [30–47]	31 [20–41]	36 [26–37]
PaO_2	78 [66–118]	154 [101–257]	140 [42–237]	84 [63–125]
Hemostasis disorders during ECMO[c]				
Platelet count, $\times 10^9$/L	46 [30–85]	59 [26–77]	100 [76–125]	109 [50–177]
Patients with platelets <20 $\times 10^9$/L, n (%)	20 (17)	2 (20)	0	0
Patients with platelets <10$\times 10^9$/L, n (%)	7 (6)	0	0	0
Prothrombin time, % of the standard value	53 [37–64]	46 [39–70]	62 [43–80]	50 [29–60]
Patients with PT <30%, n (%)	18 (15)	1 (10)	0	1 (33)

Patients with PT <20%, n (%)	13 (11)	0	0	0
Fibrinogen, g/L	2.5 [1.6–3.9]	2.3 [1.6–4.6]	3.2 [0.5–5.5]	2.2 [0.7–3.9]
Patients with fibrinogen <1.5 g/L, n (%)	26 (22)	2 (20)	1 (50)	1 (33)
Patients with fibrinogen <1 g/L, n (%)	16 (14)	1 (10)	1 (50)	1 (33)
Anticoagulant overdose, n (%)	15 (13)	0	0	0
Days of ECMO before neurological event[d]	–	3 [1–11]	36 [8–63]	21 [11–26]
Total duration of ECMO support, days	10 [6–25]	3.5 [2–6]	29 [3–54]	15 [7–29]
ICU length of stay, days	18 [8–30]	3.5 [2–22]	36 [8–63]	16 [5–40]
Mortality, n (%)	45 (38)	7 (70)	0	1 (33)

Results are expressed as mean ± SD, number (%) or median [27th–75th percentile interquartile range].

Abbreviations: SAPS, Simplified Acute Physiology Score; VV-ECMO, venovenous-extracorporeal membrane oxygenation; MV, mechanical ventilation; ARDS, acute respiratory distress syndrome; PT, prothrombin time; ICU, intensive care unit.

[a]$P < 0.05$ for between-group comparisons.

[b]Organ failure was deemed present when the corresponding Sepsis-related Organ Failure Assessment score was >2.

[c]Worst value before or during ECMO.

[d]Time of neurological event was calculated using the date of cerebral imaging

Table 2. Cerebral Imaging Findings and Their Corresponding Clinical Features in the 22 Patients

	Cerebral Imaging Findings				
Clinical Picture	**Intracranial Bleeding (*n = 10*)**	**Ischemic Stroke (*n = 3*)**	**Microbleeds (*n = 2*)**	**Cerebral Edema (*n = 2*)**	**Normal (*n = 10*)**
Mydriasis	6	1	–	–	–
Coma	2	–	2	–	3
Brain death	–	–	–	1	–
Hemiplegia	1	1	–	–	–
Confusion	1	–	–	–	1
Seizures	–	1	–	–	1
Oculomotor paralysis	–	–	–	–	1
None	–	–	–	1	4

Table 3. Univariable and Multivariable Analyses of Factors Associated With Intracranial Bleeding (Excluding Microbleeds) on VV-ECMO

	Univariable Analysis	**Cox Analysis**
Factor	**OR [95% CI]**	**HR [95% CI]**
Age >46 yr	1.91 [0.51–7.10]	
Female sex	2.02 [0.55–7.41]	
SAPS II score at ICU admission ≥70	1.16 [0.32–4.19]	
Body mass index >26	0.47 [0.1–1.96]	
McCabe & Jackson comorbidity score ≥2	0.46 [0.09–2.24]	
MV duration before ECMO >5 days	1.68 [0.45–6.24]	
Organ failure at ECMO initiation[a]		
Cardiovascular	0.73 [0.15–3.60]	
Hepatic	2.74 [0.69–10.95]	
Renal	5.80 [1.18–28.47]	6.13 [1.29–28.57]
Hematological	0.81 [0.09–6.83]	
Neurological	1.05 [0.21–5.25]	
Gas exchange change		
Arterial pH >0.2[b]	2.34 [0.61–8.89]	
PaO_2 >50 mmHg[b]	4.44 [1.16–17.03]	
$PaCO_2$ <–27 mmHg[b]	5.95 [1.20–29.52]	6.02 [1.28–28.57]
Renal replacement therapy	1.26 [0.34–4.68]	
Hemostasis disorders during ECMO		
Platelets $<20 \times 10^9$/L	1.31 [0.26–6.62]	
Prothrombin time <30%[c], n (%)	0.52 [0.06–4.33]	
Fibrinogen, <1.5 g/L	0.76 [0.15–3.76]	

Anticoagulant overdose	–

Abbreviations: SAPS, Simplified Acute Physiology Score; ICU, intensive care unit; MV, mechanical ventilation; VV-ECMO, venovenous-extracorporeal membrane oxygenation.

[a] Organ failure was deemed present when the corresponding Sepsis-related Organ Failure Assessment score was >2.

[b] Defined as the post-ECMO pH, $PaCO_2$ or PaO_2value – the pre-ECMO pH, $PaCO_2$ or PaO_2 value.

[c] Expressed as percentage of the standard value**.**

Table 4. Hemostasis Parameters of Patients on Venovenous-Extracorporeal Membrane Oxygenation with Intracranial Bleeding During the 3 Days Before the Brain Haemorrhage

Parameter	**Patients with Intracranial Bleeding (*n = 10*)[a]**
aPTT, patient-to-normal value ratio[b]	1.14 [1.1–1.7]
Anti-Xa activity, IU/L[b]	0.1 [0.1– 0.1]
Platelet count, $\times 10^9$/L[c]	84 [29–135]
Fibrinogen, g/L[c]	2.65 [2–5.6]]
Heparin dose, IU/24 h[b]	2,750 [0–10,000]

Abbreviation: aPTT, activated partial thrombin time.

[a]Values are expressed as median [25th–75th interquartile range].

[b]Highest value.

[c]Lowest value.

Table 5. Studies on Neurological Injuries in Patients on ECMO Support Included in the Systematic Review

Reference	Study Design	No. of Patients	Clinical Outcome		Hemostasis Disorders	Anticoagulant Use	ECMO–Brain Injury Interval
			Neurological Complications	Deaths			
Kolla [22]	Cohort	100: 65 VV-ECMO; 11 VA-ECMO; 34 with both	10 (10%)[a]:		NR	NR	NR
			2 ischemic strokes	2/2			
			2 cerebral hemorrhages	2/2			
			6 brain deaths	6/6			
Linden [23]	Cohort	17: 8 VV-ECMO; 7 VA-ECMO; 2 with both	3 (18%) [a]:		NR	NR	NR
			1 cerebral edema	1/1			
			1 cerebral bleeding	1/1			
			1 ischemic stroke	1/1			
Mols [24]	Cohort	62: all VV-ECMO	2 (3%):				
			1 cerebral bleeding	1/1			
			1 brain death	1/1			
Hemmila [25]	Cohort	255: 168 VV-ECMO; 47 VA-	37 (15%) [a]:		NR	NR	NR
			14 ischemic strokes	11/14			

		ECMO; 40 with both	9 brain deaths 7 cerebral bleeds 7 seizures	9/9 6/7 4/7			
Brogan [26]	Registry	1473: 703 VV-ECMO; 297 VA-ECMO; 50 with both; 423 unknown	136 (9%) [a]: 64 cerebral strokes or bleeds 72 brain deaths	 51/64 72/72	NR	NR	NR
Peek [27]	RCT	90 VV-ECMO arm: 65 received it	NR	4/90 died of neurological disorders	NR	NR	NR
Davies [3]	Cohort	68 with H1N1 flu: 63 VV-ECMO; 5 VA-ECMO	6 (9%) cerebral bleeds	6/6	NR	NR	NR
Noah [28]	Cohort	69 VV-ECMO for H1N1 flu	8 (12%) cerebral bleeds	8/8	NR	NR	NR

Patroniti [29]	Cohort	60: 59 VV-ECMO; 1 VA-ECMO	2 (3%) [a]: 1 (2%) cerebral bleeding 1 NR	1/1	NR	NR	2 days NA
Pham [30]	Cohort	123:107 VV-ECMO; 16 VA-ECMO	5 cerebral bleeds (4%) [a]	5/5	NR	NR	NR
Lindskov [31]	Cohort	124: 110 VV-ECMO; 14 VA-ECMO	NR	9 fatal cerebral infarcts with hemorrhage	NR	NR	NR
Michaels [32]	Cohort	12: 7 VV-ECMO; 5 VA-ECMO	3 ischemic strokes 1 ischemic brain injury	3/3 1/1	NR	NR	NR
Roch [33]	Cohort	85: 77 VV-ECMO; 8 VA-ECMO	2 (2%) cerebral bleeds [a]	2/2	NR	NR	NR
Ng [34]	Cohort	31 VV-ECMO	1 (3%) cerebral bleeding	1/1	NR	NR	NR
Kon [35]	Cohort	55 VV-ECMO	4 cerebral bleeds	NR	NR	NR	NR
Gray [36]	Cohort	353[b]: 262 VV-	16 cerebral bleeds or infarctions [a]	14/16	NR	NR	NR

								ECMO; 91 VA-ECMO	

Abbreviations: VA, venoarterial; VV, venovenous; ECMO, extracorporeal membrane oxygenation; NR, not reported; RCT, randomized–controlled trial.

[a] Because the authors of these studies did not differentiate between VV- and VA-ECMO patients, the exact frequency of neurological complications occurring on VV-ECMO cannot be calculated.

[b] 353 adults received ECMO support for acute respiratory distress syndrome among a series 2000 adults and pediatric patients who received VA- or VV-ECMO for cardiac or respiratory reasons.

Figure 1

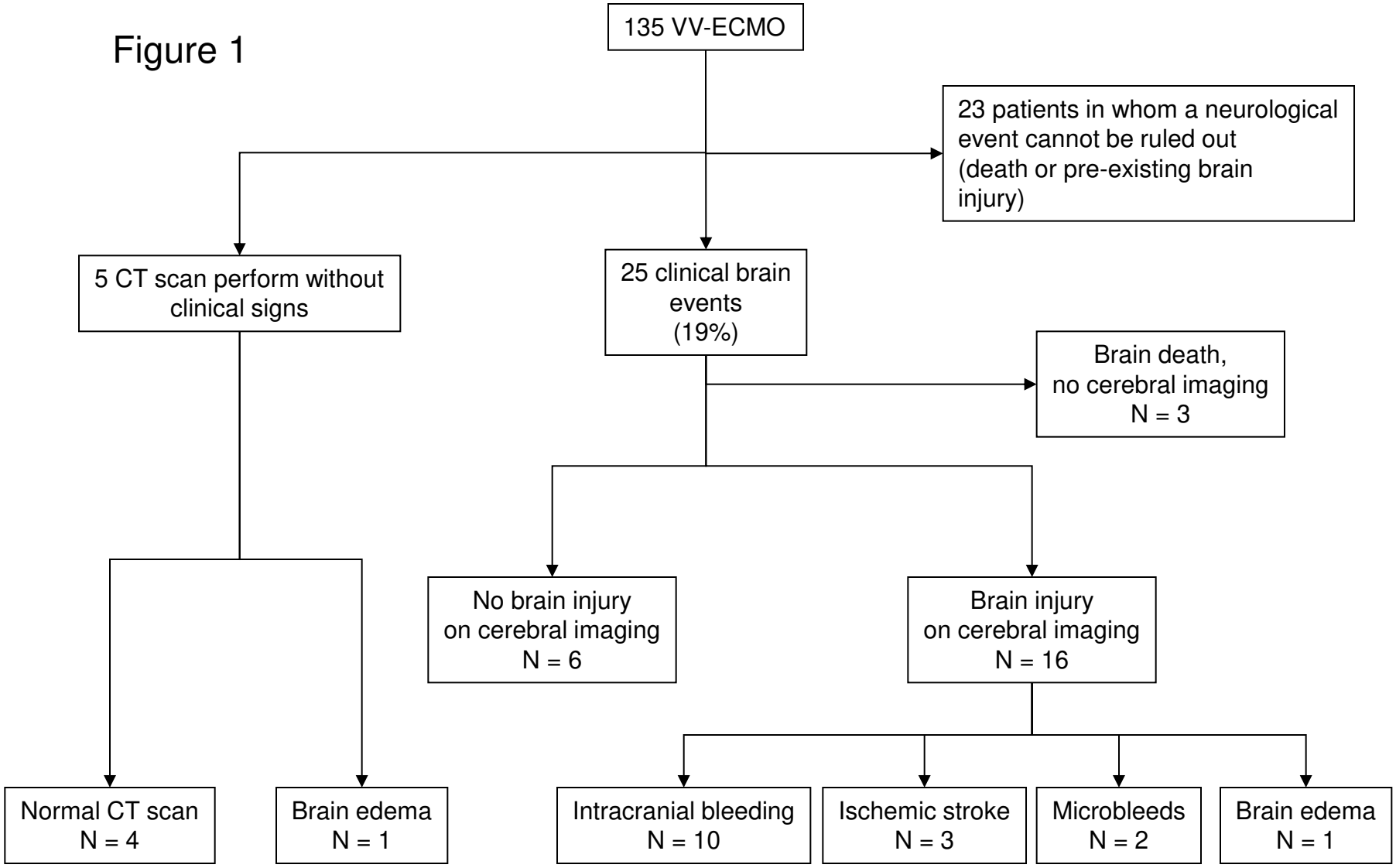
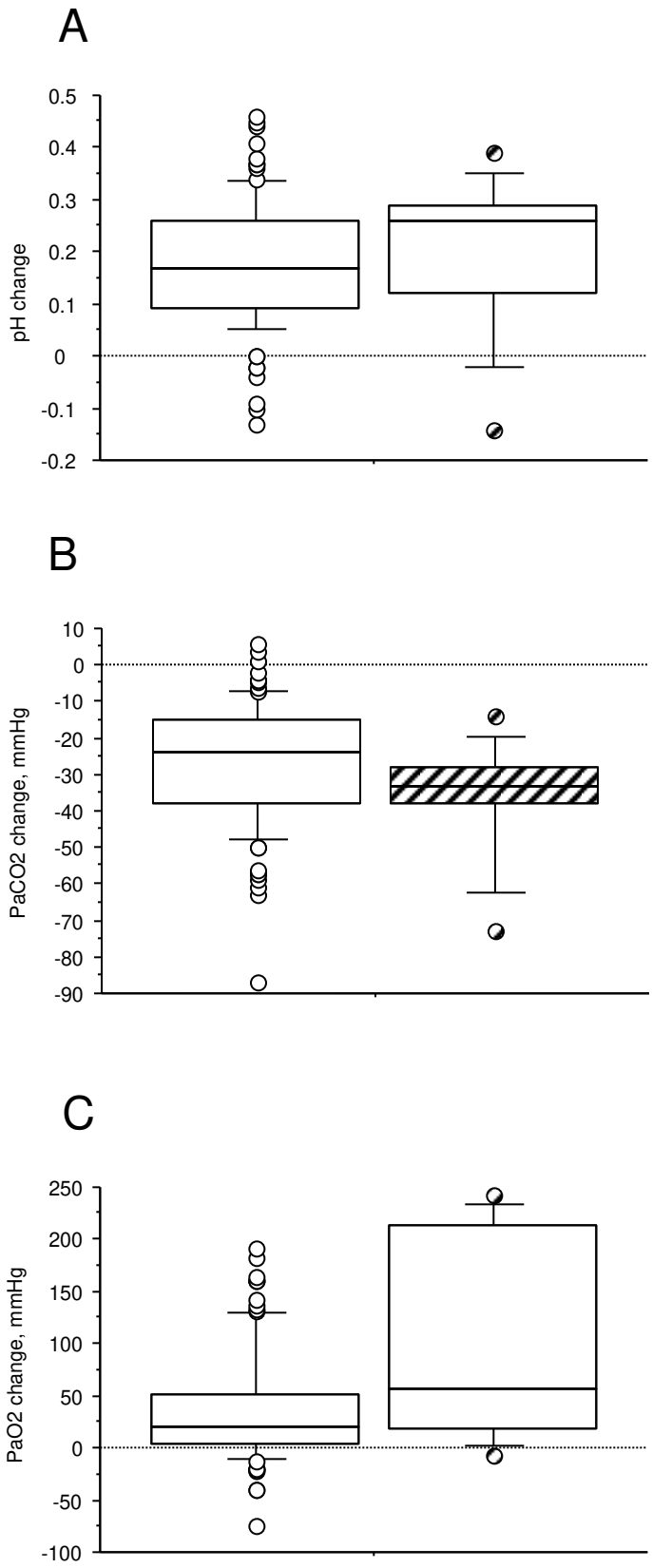

135 VV-ECMO
23 patients in whom a neurological event cannot be ruled out (death or pre-existing brain injury)
5 CT scan perform without clinical signs
25 clinical brain events (19%)
Brain death, no cerebral imaging N = 3
No brain injury on cerebral imaging N = 6
Brain injury on cerebral imaging N = 16
Normal CT scan N = 4
Brain edema N = 1
Intracranial bleeding N = 10
Ischemic stroke N = 3
Microbleeds N = 2
Brain edema N = 1

Figure 2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0.4
0.3
0.2
0.1
0
-0.1
-0.2
pH change
B
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
PaCO2 change, mmHg
C
250
200
150
100
50
0
-50
-100
PaO2 change, mmHg