Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Two-dimensional speckle-tracked RV longitudinal strain has been suggested as a method to overcome some of the difficulties associated with the conventional quantitative parameters and, although showing promise in research settings, has not yet found widespread use in clinical practice.

During the pandemic, critical care echocardiography, delivered by clinicians at the bedside, has been essential for the management of critically ill patients with COVID-19. In such a setting, focused intensive care echocardiography often does not include the ability to measure quantitative parameters and is reliant on answering qualitative questions; *is the RV dilated or not?*[6] *Is there RV dysfunction or not*? We have heard anecdotal reports of quantitative echocardiography (such as that offered by an accredited echocardiography service) not being available in "red-zone" (COVID) intensive care units due to concerns regarding staff safety.

We agree with Isgro et al. that there is a need for large-scale prospective echocardiography data in COVID-19 patients. To this end we are conducting a multicenter prospective transthoracic echocardiographic study, to explore the incidence of RV dysfunction in critically ill patients ventilated with COVID-19 (COVID-RV), which currently is recruiting in 12 Scottish intensive care units.[7] Given the difficulties in RV assessment described, the presence of RVD for this study includes the qualitative parameters of RV dilatation, interventricular septal flattening, and a *subjective* description of "dysfunction." These measures previously have been demonstrated to be associated without outcome in patients with acute respiratory distress syndrome.[8,9] The use of quantitative parameters, including speckle- racked longitudinal strain, will be explored off-line as secondary outcomes and will help provide further mechanistic insights.

Isgro et al. highlighted the need for prospective studies of RV protection in patients with COVID-19. We applaud this aim, and like them, we believe such an approach could lead to meaningful patient benefit. We urge, however, that any research forming such a study, or indeed when describing appropriate inclusion criteria for a trial, should include an echocardiographic definition of RVD that is sufficiently pragmatic to empower the bedside clinician to make the diagnosis.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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Neurologic Injury in Patients With COVID-19 Who Receive VV-ECMO Therapy: A Cohort Study

To the Editor:

THROMBOTIC AND BLEEDING events have been implicated in the progression of coronavirus disease 2019 (COVID-19).[1,2] This dysregulation of coagulation has been associated with poor prognoses.[3,4] Neurologic sequelae, such as ischemic stroke and intracranial hemorrhage (ICH), have been reported in patients with COVID-19 at rates of 0.9%-to-2.3% and 0.9%, respectively.[5,6,7,8] Limited data exist on neurologic events in patients with COVID-19 in the intensive care unit who require extracorporeal membrane oxygenation (ECMO) due to severe acute respiratory distress syndrome (ARDS).

We retrospectively reviewed adult patients with COVID-19 supported by ECMO at our tertiary care center. Inclusion criteria were (1) a positive polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and (2) cannulation for venovenous (VV) ECMO support. Patient demographics, past medical history, adverse events during hospitalization, laboratory values on day one of ECMO, ECMO variables, and outcomes were obtained through electronic medical records. Neurologic events, such as ischemic stroke, hypoxic ischemic brain injury, ICH, and cerebral microbleed (CMB), were identified based on computed

tomography (CT) and magnetic resonance imaging (MRI) reports conducted anytime during ECMO support up to five days after decannulation. ICHs were defined as any hemorrhages visualized on a CT scan, and CMBs were defined as hemorrhages <5 mm, visualized on susceptibility-weighted imaging or gradient-recalled echo MRI.[9] Both CMBs and ICHs were defined as hemorrhagic neurologic events. Bleeding events were categorized as in the gastrointestinal tract, at the cannulation site, and at the tracheostomy site. This study was approved by the institutional review board. All patients who require ECMO in our center receive neurocritical care consultation and standardized neuromonitoring protocol.[10] All patients received a heparin bolus at the time of cannulation and heparin infusion before and during ECMO therapy, with an activated partial thromboplastin time (aPTT) goal of 50-to-65 seconds. Comparisons of demographic and clinical variables were performed using Fisher's exact test or Mann-Whitney U test as appropriate. A p value < 0.05 was considered significant.

Of 16 patients (median age, 51 years [interquartile range (IQR), 38-57], male: 81%) with VV-ECMO support, four (25%) had neurologic events. The clinical characteristics and ECMO variables of the four patients on ECMO who had neurologic events are shown in Table 1. Neurologic events included four hemorrhagic neurologic events in two patients with ICH only, one patient with CMB only, and one patient with both ICH and CMB. Among the three patients with ICH, two had subarachnoid hemorrhages and one had an intraventricular hemorrhage. There were no ischemic strokes. Excluding the patient with CMB only, which was detected on MRI four days after ECMO decannulation, the median number of days from ECMO cannulation to ICH was three days. Figure 1 shows CT without contrast imaging for the three patients who experienced ICH. All three patients with ICHs were managed by discontinuing heparin upon CT detection of a neurologic event. These patients' laboratory values on the first day of ECMO are shown in Table 2.

The four patients who experienced neurologic events during ECMO support were compared with those that did not to better understand the differences between the two groups (Table 3). Patients with neurologic events tended to be older, albeit non-significantly, with a median age of 55.5 years (IQR, 50-59) versus 47 years (IQR, 36-54). Although not statistically significant, patients with neurologic events had more bleeding events while on ECMO (100% *v* 75%), compared with those without neurologic events. These patients also were less likely to have received remdesivir (0% *v* 42%), interleukin 6 (IL-6) inhibitors (25% *v* 75%), and steroids (0% *v* 33%). Ventilation and ECMO variables were similar between the groups. All 16 patients were proned, received neuromuscular blockade, and underwent mechanical ventilation. Not surprisingly, patients with neurologic events had a longer hospital stay (55.5 *v* 41 days). Nineteen percent (three of 16) died within 30 days, and this mortality rate was similar regardless of whether the patient experienced a neurologic event. Patients with neurologic events were significantly more likely to have lower platelet counts and higher D-dimer values versus those without.

Table 1
Clinical Characteristics and ECMO Variables

Case	Age (y)/Sex	Past Medical History	Bleeding History	Type of Neurological Injury	SOFA Score	Apache II Score	Days on Mechanical Ventilation	Days From Admission to ECMO	Days From ECMO Cannulation to Neurological Event	Days On ECMO	Cannula Site	Cannula Size, F	P:F Ratio at Time of Cannulation	ECMO Flow (L/min)
1	58/female	DM, CAD, HL, HTN	GI	SAH	9	18	37	6	0	13	Right IJ	32	58	5
2	60/female	DM, HL, HTN	Cannulation site	CMB	11	28	29	6	33	29	Right IJ	32	67	6.2
3	47/male	-	Cannulation site	SAH	10	16	40	4	3	15	Right IJ/FEM	22/25	62	6.6
4	53/male	-	Cannulation site, tracheostomy	Intraventricular hemorrhage, CMB	9	16	45	5	12	22	Right IJ	32	59	5

Abbreviations: AC, assist control; CAD, coronary artery disease; CMB, cerebral microbleed; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; FEM, femoral; GI, gastrointestinal; HL, hyperlipidemia; HTN, hypertension; IJ, internal jugular; PC, pressure control; P:F, pressure of arterial oxygen to fraction of inspired oxygen; SAH, subarachnoid hemorrhage; SOFA, Sequential Organ Failure Assessment.

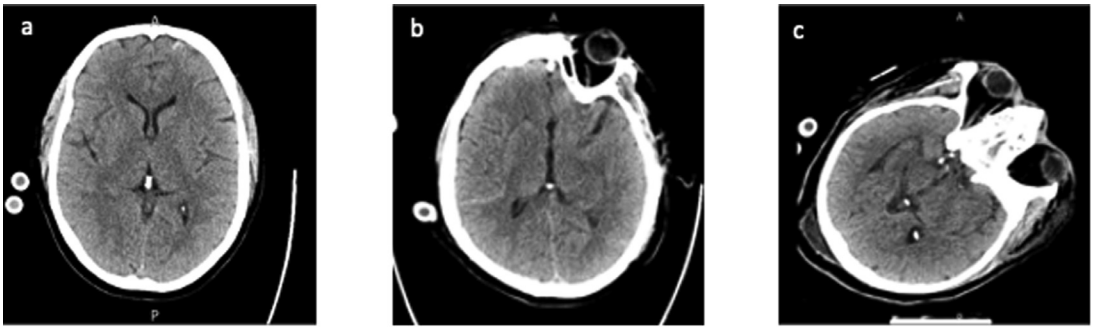

Fig 1. Neuroimaging (CT without contrast) of intracranial hemorrhage in patients with COVID-19 on ECMO. (A) CT of patient one showed 5 mm linear hyperdensity within the cortex of the left frontal lobe along the anterior/inferior parafalcine region, compatible with subarachnoid hemorrhage. (B) CT of patient three showed hyperdensity in the right Sylvian fissure, compatible with subarachnoid hemorrhage. (C) CT of patient four showed subtle hyperdensity within the posterior horn of the right lateral ventricle, concerning for minimal intraventricular hemorrhage. CT, computed tomography.

Table 2
Laboratory Findings on Day 1* of ECMO Therapy

Case	pH	PCO_2	PO_2	Platelet Count, K/cu mm	IL-6, pg/mL	LDH, U/L	Ferritin, ng/mL	CRP, mg/dL	Medications
1	7.35	48	105	177	-	643	5924	22.5	Pressors, hydroxychloroquine
2	7.37	33	65	101	-	751	705	38.1	Pressors
3	7.37	38	62	114	231	920	1845	6.5	Pressors, tocilizumab
4	7.46	37	77	149	1359	476	1503	31.1	Pressors, convalescent plasma

* Values measured on ECMO day 1 closest to time of ECMO cannulation.Abbreviations: CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; IL-6, interleukin-6; LDH, lactate dehydrogenase.

Table 3
Comparison Between Patients on ECMO With and Without Neurologic Complications

	All patients (N = 16)	No Neurologic Event (n = 12)	Neurologic Event (n = 4)	p Value*
Demographic/past medical history				
Age, y, median (IQR)	51 (38-57)	47 (36-54)	55.5 (50-59)	0.129
Sex, male, n (%)	13 (81)	11 (92)	2 (50)	0.136
Race, n (%)				0.118
African American	5 (31)	2 (17)	3 (75)	
Hispanic	10 (63)	9 (75)	1 (25)	
BMI, kg/m^2, median (IQR)	31.9 (29.4-35.5)	32.4 (30.5-35.5)	29.4 (29.1-34.8)	0.363
Smoker, n (%)	1 (6)	0 (0)	1 (25)	0.250
Hypertension, n (%)	7 (44)	5 (42)	2 (50)	1.000
Diabetes mellitus, n (%)	6 (38)	4 (33)	2 (50)	0.604
Hyperlipidemia, n (%)	4 (25)	2 (17)	2 (50)	0.245
Coronary artery disease, n (%)	1 (6)	0 (0)	1 (25)	0.250
Medications				
Neuromuscular blockade, n (%)	16 (100)	12 (100)	4 (100)	1.000
Inhaled nitric oxide, n (%)	14 (88)	10 (83)	4 (100)	1.000
Vasopressors, n (%)	12 (75)	8 (67)	4 (100)	0.516
Hydroxychloroquine, n (%)	2 (13)	1 (8)	1 (25)	0.450
Remdesivir, n (%)	5 (31)	5 (42)	0 (0)	0.245
IL6 inhibitor, n (%)	10 (63)	9 (75)	1 (25)	0.118
Steroids, n (%)	4 (25)	4 (33)	0 (0)	0.516
Convalescent plasma, n (%)	5 (31)	4 (33)	1 (25)	1.000
Ventilation				
Proned, n (%)	16 (100)	12 (100)	4 (100)	1.000
Airway pressure release ventilation, n (%)	9 (56)	7 (58)	2 (50)	1.000
Mechanical ventilation, n (%)	16 (100)	12 (100)	4 (100)	1.000
P:F ratio at time of cannulation, median (IQR)	60.5 (53.5-64)	60.5 (51-64)	60.5 (58.5-64.5)	0.627
Pre-ECMO ventilation, median (IQR)	6.5 (4.5-7)	7 (4.5-8)	5.5 (4.5-6.5)	0.387
Pre-tracheostomy ventilation, median (IQR)	14 (13-20)	14 (12-20)	15.5 (14-19)	0.509
Mechanical ventilation support time, d, median (IQR)	40 (25-51.5)	41 (20.5-60.5)	38.5 (33-42.5)	0.808

(*continued*)

Table 3 (*continued*)

	All patients (N = 16)	No Neurologic Event (n = 12)	Neurologic Event (n = 4)	p Value*
ECMO Variables				
Support time, day, median (IQR)	27 (15-33)	24 (13-41)	29 (25-30)	0.626
Cannulation site, RIJ, n (%)	12 (75)	9 (75)	3 (75)	1.000
Speed, rpm, median (IQR)	3855 (3508-3943)	3883 (3450-3993)	3830 (3658-3873)	0.716
Flow, L/min, median (IQR)	5 (4.7-5.9)	5 (4.4-5.7)	5.6 (5-6.4)	0.180
Sweep, L/min, median (IQR)	5.3 (4-7.5)	5.3 (4.3-7)	5.5 (3.5-7.5)	0.712
AC, n (%)	14 (88)	11 (92)	3 (75)	0.450
Adverse events and complications, n (%)				
Acute kidney injury	7 (44)	5 (42)	2 (50)	1.000
Bleeding event	13 (81)	9 (75)	4 (100)	0.529
Thrombotic event	6 (38)	4 (33)	2 (50)	0.604
Pneumonia	12 (75)	9 (75)	3 (75)	1.000
Sepsis	4 (25)	3 (25)	1 (25)	1.000
Right ventricular dysfunction	5 (31)	4 (33)	1 (25)	1.000
Outcomes				
Hospitalization time, d, median (IQR)	51 (36-66)	41 (24-77)	55.5 (43.5-69)	0.695
Tracheostomy on ECMO, n (%)	14 (88)	10 (83)	4 (100)	0.550
Death within 30 d of hospital admission, n (%)	3 (19)	2 (17)	1 (25)	0.673
Laboratory values, median (IQR)†				
WBC, K/cu mm	13.2 (9.0-17.8)	13.2 (9.5-17)	13.7 (9.0-19.3)	0.904
Hemoglobin, g/dL	11.2 (9.2-11.9)	11.4 (9.3-12.6)	9.0 (7.6-10.7)	0.129
Hematocrit, %	33.8 (29.8-38.9)	35.5 (31.3-39.3)	28.9 (24.9-34.2)	0.069
Platelets, K/cu mm	281 (174-332)	297 (239-341)	132 (108-163)	0.005
Creatinine, mg/dL	1.0 (0.8-1.6)	1.0 (0.7-1.5)	1.5 (1.2-2.9)	0.160
Lactate, mmol/L	2.2 (1.4-3)	1.8 (1.3-2.9)	3.2 (2-4.2)	0.129
AST, U/L	60 (45-78)	54 (39-73)	81 (67-104)	0.052
ALT, U/L	43 (33-57)	41 (33-61)	44 (35-50)	1.000
Bilirubin (total), mg/dL	0.6 (0.4-1.3)	0.5 (0.4-1.4)	0.9 (0.5-1.3)	0.583
IL-6, pg/mL	290 (167-710)	290 (167-697)	795 (231-1,359)	0.346
LDH, U/L	558 (453-668)	515 (428-616)	697 (560-836)	0.115
Ferritin, ng/mL	1099 (785-1,906)	996 (608-1,906)	1674 (1,104-3,885)	0.396
CRP, mg/dL	17.2 (8.2-35.3)	14.3 (7-35.3)	26.8 (14.5-34.6)	0.467
D-dimer, mg/L	18 (4-30)	7 (3-20)	30 (27-30)	0.031
Fibrinogen, mg/dL	469 (322-717)	551 (396-675)	496 (165-768)	1.000
INR	1.1 (1-1.2)	1.1 (1-1.2)	1.25 (1.1-1.4)	0.342
PT, s	11.7 (11-13)	11.7 (10.8-12.6)	13.1 (11.2-14.9)	0.280
aPTT, s	48.9 (37.7-57.5)	42.8 (36.6-57.5)	51.1 (46.7-77.1)	0.240
pH	7.39 (7.37-7.44)	7.39 (7.37-7.44)	7.37 (7.36-7.42)	0.463
$PaCO_2$, mmHg	47 (38-50)	48 (45-52)	38 (35-43)	0.060
PaO_2, mmHg	70 (67-77)	70 (68-76)	71 (64-91)	0.952
$\Delta PaCO_2$, mmHg	36 (30-43)	39 (30-43)	33 (27-48)	0.557
ΔPaO_2, mmHg	7 (−18 to 13)	8 (−9 to 13)	−5 (−30 to 9)	0.228
Severity of illness, median (IQR)				
RESP score	1 (0-3)	1.5 (0.8-3)	0.5 (−0.5 to 1.3)	0.243
SOFA score	8 (6.5-9.5)	7 (6-8.5)	9.5 (9-10.5)	0.027
Apache II score	16 (11-20)	13 (10-20)	17 (16-23)	0.179

Abbreviations: AC, assist-control; ALT, alanine transferase; aPTT, activated partial thromboplastin time; AST, aspartate transferase; BMI, body mass index; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; IL-6, interleukin 6; INR, international normalized ratio; IQR, interquartile range; LDH, lactate dehydrogenase; P:F, pressure of arterial oxygen to fraction of inspired oxygen; PT, prothrombin time; RESP, Respiratory ECMO Survival Predication; RIJ, right internal jugular; SOFA, Sequential Organ Failure Assessment; WBC, white blood cells.

* Mann-Whitney U and Fisher's exact tests, as appropriate.

† Values measured on ECMO day 1 closest to time of ECMO cannulation.

Although not statistically significant, neurologic events also were associated with lower hemoglobin, hematocrit, and $PaCO_2$ values and higher creatinine, aspartate aminotransferase, IL-6, lactate dehydrogenase, ferritin, C-reactive protein, and aPTT values. An increased Sequential Organ Failure Assessment score on ECMO day one (median, 9.5 *v* 7) was significantly associated with neurologic events.

Our analysis provided several important findings. First, no patient had an ischemic stroke, and ICHs were common, with a rate of 25%. We hypothesized that the prevalence of neurologic events in patients with COVID-19 ARDS with ECMO support would be similar to other patients with ARDS with ECMO support. Several prior studies have reported that patients treated with VV-ECMO for

non–COVID-19-related respiratory failure are at higher risk for ICH than ischemic stroke.[11,12] The Extracorporeal Life Support Organization registry study reported that the rates of infarct and ICH in 983 patients with COVID-19 on ECMO were 0.7% and 6% ICHs, respectively.[13] Our data showed an ICH rate much greater than that of non–COVID-19 patients on ECMO.

In addition, severity of illness and coagulopathy may be important risk factors in ECMO-associated ICH. Although the pathophysiology of ICH in patients with COVID-19 likely is multifactorial, one hypothesis is that the cytokine-induced endothelial damage and breakdown of the blood brain barrier in patients with COVID-19 may increase risk of ICH.[14] Additionally, sepsis-induced coagulopathy may result in consumptive coagulopathy, exacerbating bleeding risk. Tang et al[4] reported high D-dimer and fibrin degradation product levels in patients with COVID-19 with severe pneumonia, suggestive of disseminated intravascular coagulation with enhanced fibrinolysis. Lersy et al[15] found that CMBs in patients with COVID-19 were associated significantly with high D-dimer levels. These findings were consistent with our study, showing significantly higher D-dimer levels and Sequential Organ Failure Assessment scores in patients with neurologic events versus those without (Table 3).

Lastly, lower platelet counts and higher aPTT values on ECMO day one were associated with neurologic events, indicating anticoagulation is an important factor in ECMO-associated ICH in patients with COVID-19. Lower hemoglobin values in these patients may indicate worsening coagulopathy, predisposing patients to bleeding events. Furthermore, ICHs may be related to an acquired von Willebrand syndrome due to the high sheer stress of the ECMO circuit.[16,17]

Caution should be taken in interpreting these findings, however, because this study had a small sample size, and our center has a rigorous standardized neuromonitoring protocol that may increase the sensitivity of the detection of neurologic events.[10] Diagnosis of neurologic event was only made upon imaging findings, and routine CT was not recommended without neurologic symptoms due to limited resources and a desire to avoid unnecessary exposures during the pandemic. Thus, only 12 of the 16 patients received a CT scan during ECMO, causing a selection bias. Although the absence of ischemic stroke is interesting, this diagnosis is more difficult to make than ICH due to poor sensitivity of CT scans for early ischemia. In the absence of comparative analysis with a control group, we cannot provide definitive evidence of COVID-19 infection conferring independent risk of neurologic events during ECMO support. However, our study still provided valuable information suggesting an increased ICH risk in patients with COVID-19 on ECMO. Future research is warranted to corroborate our findings and describe the risk factors for this critically ill population. Given the devastating outcome of neurologic events in patients with COVID-19 on ECMO, the utility of routine neuroimaging and reevaluation of anticoagulation strategy should be further explored.

Conflict of Interest

None.

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