Propofol-Infusion Syndrome in Traumatic Brain Injury: Consider the ECMO Option.

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Dear Editor,

Propofol-infusion syndrome (PRIS) is a life-threatening complication of prolonged (>48h) high-dose (>4mg/kg/h) propofol sedation. Mortality is high and traumatic brain-injured (TBI) patients are particularly at risk[1, 2]. Symptomatology is variable and management requires urgent discontinuation of propofol and aggressive supportive treatment[3]. Considering potential reversibility, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) may offer temporary cardiac support in PRIS-induced cardiogenic shock or arrest, although VA-ECMO is often withheld in trauma patients due to bleeding risks.

We present a single-center, retrospective, consecutive case-series (1/12/2015-1/12/2017) of four young TBI patients developing PRIS-induced refractory cardiogenic shock or arrest. All patients received VA-ECMO-support and survived with good neurological outcome and quality-of-life.

At hospital admission, all patients (23±6years, 2/4male, mean APACHE-II 18[range:9-26]) required intubation for reduced and deteriorating consciousness (GCS:9±2). Initial CT-brain documented mild intracranial hemorrhage in all *(Supplementary Table-1)*. Predicted 6-month unfavorable outcome was 18[range:9-34]% according to the TBI-IMPACT-Score. All patients received an external ventricular drain (EVD), analgo-sedation with propofol and opioids, and

goal-directed management of intracranial hypertension according to Brain Trauma Foundation guidelines. Propofol was administered at 4.6±0.6mg/kg/h average for a total of 6±1days.

All patients developed increasing vasopressor requirements, greenish discoloration of urine and mild rhabdomyolysis in the days preceding cardiogenic shock or arrest *(Supplementary Table-1&2)*. Consistent and dynamic ECG-changes started <24h before collapse, including progressive QRS-widening and STT-segment changes, which culminated in a sinusoidal ECG-pattern in two patients *(Figure-1)*. All patients developed type-1 Brugada pattern, prolonged QTc and episodes of ventricular tachycardia. Femoral-femoral VA-ECMO was initiated for refractory cardiac arrest (n=2), and for inotrope-resistant cardiogenic shock (n=2), 4-7days after ICU-admission, and propofol was discontinued. ECMO-circuits were heparin-coated and patients received 5000-IU heparin loading upon ECMO-cannulation. Two patients required left ventricular venting. Considering the bleeding risk in patients with TBI and EVD, no additional therapeutic anticoagulation was provided during the ECMO-run. Two patients required major extracranial surgery during ECMO-support. In the first 72h after discontinuation of propofol, progressive resolution of QRS-widening and type-1 Brugada patterns occurred, while prolonged diffuse STT-segment changes remained *(Figure-1)*. Patients were successfully weaned from ECMO after mean 3[range:1-5]days, and inotropic support could be stopped after mean 3[range:1-6]days. Median ICU-stay was 27[range:22-112]days. All patients survived with good neurological outcome (Cerebral Performance Category Scale:CPC-1) and functional independence (Barthel Index:20/20) with overall good self-reported quality-of-life (36-Item-Short-Form-Survey-Score) at mean 43[range:32-53]months after ICU-admission *(Supplementary Table-1)*.

We report the largest case-series of severe PRIS requiring VA-ECMO-support, resulting in full cardiac recovery with good neurological outcome and quality-of-life. A high index of suspicion, early recognition and timely discontinuation of propofol are crucial to prevent PRIS. Otherwise unexplained increasing vasopressor requirements, greenish urine discoloration and mild rhabdomyolysis were the earliest potential signs of looming PRIS throughout this case-series. Typical dynamic ECG-changes appeared a sensitive albeit late omen of impending cardiovascular collapse[4]. Given the swift reversibility, VA-ECMO should be strongly considered as bridge-to-recovery in selected patients with PRIS. Severe TBI with EVD inserted and mild intracranial hemorrhage should not be considered an absolute contra-indication for ECMO-initiation[5]. Anticoagulation should be individually tailored, taking intracranial bleeding risk into account.

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Figure-1: Dynamic PRIS-induced ECG-changes: Peak of hemodynamic instability was referenced as day 0. ECMO was initiated day 0 at 18h00. Typical type-1 Brugada patterns are indicated with red rectangles.

Supplementary Table-1: Detailed clinical, laboratory and electrocardiographic description of the individual PRIS-cases. Worst laboratory values 2 days before ECMO-initation and up to 5 days after ECMO-initiation are presented, *[Reference Values]*. [§]. TBI-IMPACT score was calculated according to the Core + CT + Lab model, *. Ischemic leg after ECMO-cannulation, [£]. Inotropic support: adrenaline or dobutamine, [@]. Laparotomy: partial resection ileum and caecum (ischemia), [$]. Amputation: upper leg (ischemia), [#]. Mini-thoracotomy: apical left ventricular vent, [&]. Laparotomy: segmental hepatectomy (laceration), [€]. SF-36 with higher scores indicating less disability.

Abbreviations: TBI = traumatic brain injury, ICB = intracranial bleeding, SDH = subdural hematoma, SAH = subarachnoid hemorrhage, IPH = intraparenchymatous hemorrhage, EDH = epidural hematoma, ICP = intracranial pressure, EVD = external ventricular drain, ND = not documented, VT = ventricular tachycardia, LVEF = left ventricular ejection fraction, AKI = acute kidney injury, ECPR = extracorporeal cardiopulmonary resuscitation, CAR = cardiogenic shock, Fem = femoral, Jug = jugular, CRRT = continuous renal replacement therapy, IHD = intermittent hemodialysis, IPPV = intermittent positive pressure ventilation, PEEP = positive end expiratory pressure, Pplat = plateau pressure, SAVE Score = survival after veno-arterial ECMO score, ICU = intensive care unit.

Supplementary Table-2: Detailed timeframe of vasopressor/inotrope doses and PRIS-related laboratory values in relation to hemodynamic collapse. *. Ischemic leg after ECMO-cannulation. ND = not documented.

Supplementary Table-3: Literature search on all currently published cases of ECMO-support in patient with traumatic brain injury. TBI = traumatic brain injury, ICH = intracranial hemorrhage, IPH = intraparenchymatous hemorrhage, EDH = epidural hematoma, FIM = functional independence measure. *. No further information.

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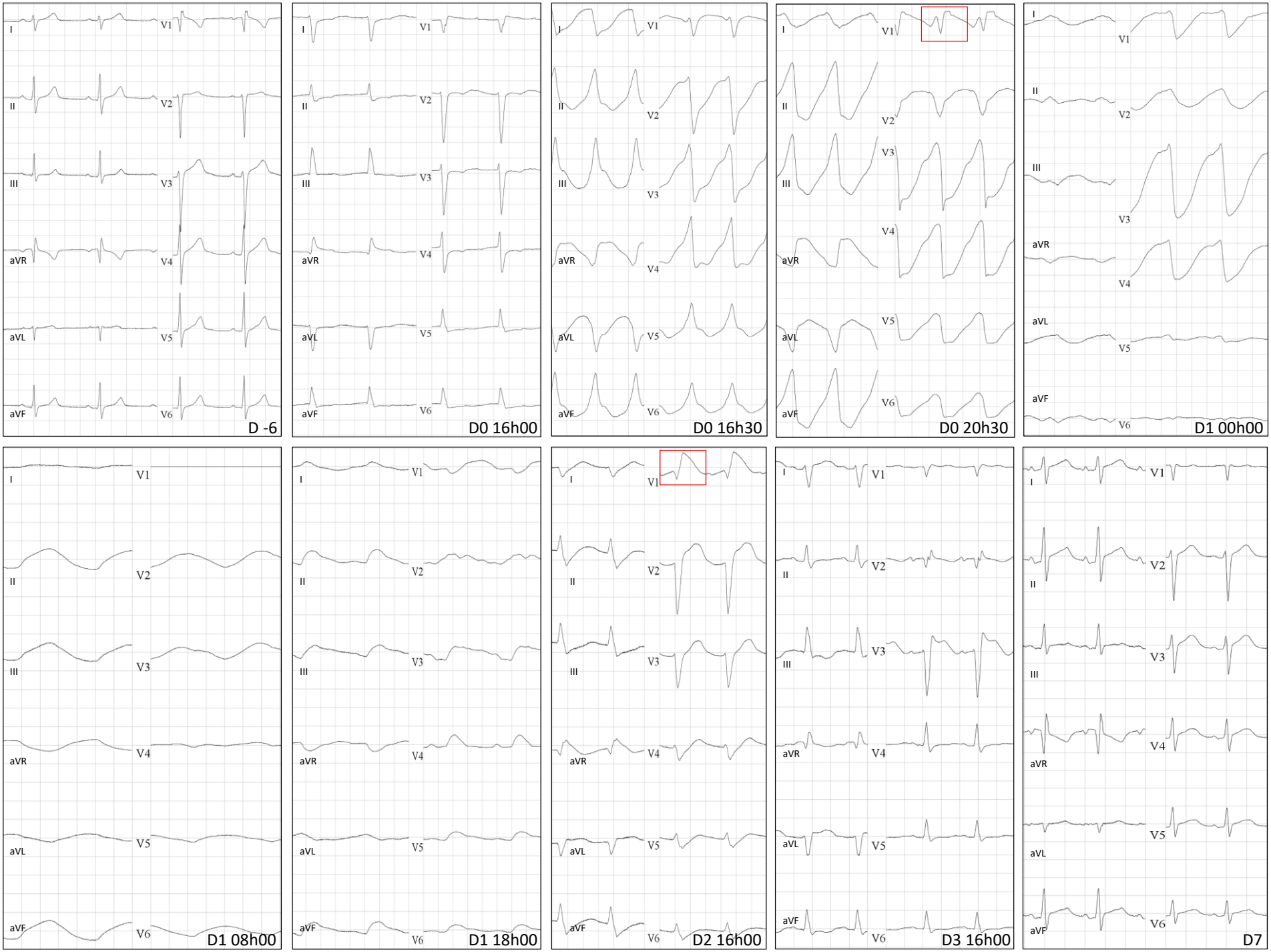
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SUPPLEMENTARY TABLES:

PATIENT	Case 1	Case 2	Case 3	Case 4
Age (y)	19	28	17	28
Sex	Male	Female	Female	Male
Weight (kg)	75	67	62	70
Body Mass Index (kg/m^2)	23.2	24	21.5	22.5
ADMISSION				
Admission diagnosis	Non-isolated TBI	Non-isolated TBI	Isolated TBI	Isolated TBI
Initial Glasgow Coma Scale (GCS)	8	10	6	10
APACHE II Score	24	9	26	12
TRAUMATIC BRAIN INJURY				
TBI IMPACT Score [§] -Predicted 6 month mortality -Predicted 6 month unfavorable outcome	 9% 13%	 16% 34%	 5% 9%	 8% 16%
Marshall CT Score	II	II	II	II
ICB	Minimal SAH	Mild SDH, mild SAH, mild IPH	Minimal IPH	Mild EDH, minimal SAH
ICP catheter during ECMO-run	EVD + bolt (Codman)	EVD + bolt (Codman)	EVD	EVD
Maximum ICP prior to ECMO-initiation (mmHg)	22	28	24	29
Maximum ICP after ECMO-initiation (mmHg)	21	25	24	23
PROPOFOL DOSING				
Average propofol dose (mg/kg/h)	4.7	3.8	5.1	4.8
Maximum propofol dose (mg/kg/h) and duration maximum propofol dose (hours)	4.8 106	4.5 32	6.5 78	6.3 38
Cumulative propofol dose (mg/kg)	604	365	735	686
Total duration propofol infusion (days)	6	4	7	5
Multimodal analgo-sedation prior collapse: -midazolam (dose, start prior collapse) -ketamine -opioids	 4.8mg/h (-2d) No Yes	 7.2mg/h (-5d) Yes Yes	 15mg/h (-6d) No Yes	 10.5mg/h (-4d) No Yes
ECG FINDINGS				
Brady-arrhythmia's	ND	ND	ND	ND
Tachy-arrhythmia's	Yes (VT)	Yes (VT)	Yes (VT)	Yes (VT)
Brugada pattern	Type 1	Type 1	Type 1	Type 1
Sinusoid pattern	Yes	Yes	ND	ND

QTc prolongation	Yes	Yes	Yes	Yes
LABORATORY VALUES				
Lowest pH and HCO3 (mmol/L) *[7,35-7,43; 22-29]*				
- Prior to ECMO-initiation	7.46 – 20.1	7.35 – 16.6	7.25 – 21.4	7.2 – 14.2
- After ECMO-initiation	7.09 – 11	7.06 – 11.3	7.3 – 22.4	7.41 – 22.1
Highest Lactate (mmol/L) *[0,5-2,2]*				
- Prior to ECMO-initiation	0.9	1.7	3.28	5.14
- After ECMO-initiation	13.9	16	1.7	2.7
Highest CKs (U/L) *[≤190]*				
- Prior to ECMO-initiation	5209	283	444	935
- After ECMO-initiation	235060 *	3091	19859	4376
Highest potassium (mmol/L) *[3,45-4,45]*				
- Prior to ECMO-initiation	4.6	5.0	5.88	5.48
- After ECMO-initiation	7.2	5.5	5.3	4.7
Highest triglycerides (mg/dL) *[≤150]*				
- Prior to ECMO-initiation	341	149	ND	ND
- After ECMO-initiation	196	166	271	243
Highest ALT (U/L) *[≤41]*				
- Prior to ECMO-initiation	104	35	15	23
- After ECMO-initiation	4857	113	203	72
Highest AST (U/L) *[≤37]*				
- Prior to ECMO-initiation	239	36	31	32
- After ECMO-initiation	14612 *	552	679	98
Highest hs-Troponin T (µg/L) *[≤0,013]*				
- Prior to ECMO-initiation	0.014	0.699	0.03	ND
- After ECMO-initiation	0.682	0.680	0.705	0.063
Highest Creatinin (mg/dL) *[0,67-1,17]*				
- Prior to ECMO-initiation	0.9	0.9	0.72	1.04
- After ECMO-initiation	1.67	2.91	1.45	1.15
CLINICAL FINDINGS				
Highest temperature (°C)	40	37.9	39.1	38.5
'Greenish' discoloration urine and Appearance before collapse (hours)	Yes -34	Yes -67	Yes -92	Yes -96
Noradrenaline requirements (µg/kg/min)				
- 72h prior to collapse	0.18	0.07	0.21	0.19
- 48h prior to collapse	0.24	0.17	0.51	0.36
- 24h prior to collapse	0.31	0.37	0.61	0.76
- Collapse & ECMO initiation	0.42	1.15	0.50	1.00
Duration inotropic support [£] (days)	6	3	1	3
Cardiac Failure	Yes	Yes	Yes	Yes
Cardiac arrest	Yes	Yes	Yes	No
Worst documented LVEF (%) by echocardiography	0	< 10	40	30
Pattern of systolic LV-dysfunction	Global	Global	Global	Global
Acute Kidney Injury Stage (KDIGO)	AKI 3	AKI 3	AKI 2	AKI 2
Duration CRRT (days)	21	5	0	0
Duration IHD (days)	15	0	0	0

EXTRACORPOREAL MEMBRANE OXYGENATION				
VA-ECMO indication and configuration and LV-vent	ECPR Fem-Fem Yes	ECPR FemJug-Fem Yes	CAR Fem-Fem No	CAR Fem-Fem No
ECMO retrieval	No	No	Yes	Yes
Duration VA-ECMO support (days)	3	5	1	3
ECMO therapeutic anticoagulation	No	No	No	No
LV venting technique	LV apical vent through mini-thoracotomy	LV apical vent through mini-thoracotomy	/	/
Surgery during ECMO-support	Laparotomy [@] Amputation [$] Thoracotomy [#]	Laparotomy [&] Thoracotomy [#]	No	No
Average ECMO Blood Flow (L/min)	3.8	3.8	2.4	3.4
Average ventilator Settings during ECMO-support				
- Ventilation mode	IPPV	IPPV	IPPV	IPPV
- Tidal Volume (mL)	470	375	324	453
- Frequency (/min)	18	11	11	14
- PEEP (cmH_20)	11	11	5	6
- FiO2 (%)	60	36	40	35
- Pplat (cmH_20)	26	23	17	17
SAVE Score	-4	2	-2	1
SAVE Score Estimated Survival Rate (%)	30-40	50-60	35-45	45-55
OUTCOME				
Duration ICU stay (days)	112	29	25	22
Duration hospital stay (days)	247	110	80	27
Survival to hospital discharge	Yes	Yes	Yes	Yes
Cerebral Performance Category Scale (CPC) at hospital discharge	CPC-1	CPC-1	CPC-1	CPC-1
36-Item Short Form Survey (SF-36) [€]				
- Months after admission	53	52	36	32
- Physical functioning	35%	100%	65%	95%
- Role limitations physical health	100%	25%	25%	100%
- Role limitations emotional problems	100%	67%	100%	100%
- Energy/fatigue	55%	40%	25%	45%
- Emotional well-being	92%	64%	60%	76%
- Social functioning	75%	63%	63%	100%
- Pain	78%	90%	23%	68%
- General health	55%	70%	55%	50%
Barthel Index	20/20	20/20	20/20	20/20
- Months after admission	53	52	36	32

Supplementary Table-1

	Timeframe in relation to collapse						
	-72h	**-48h**	**-24h**	**Immediately prior Collapse**	**+24h**	**+48h**	**+72h**
Noradrenaline (µg/kg/min)							
-Case1	0.18	0.24	0.31	0.42	0.18	0.11	0.13
-Case 2	0.07	0.17	0.37	1.15	1.00	0.30	0.1
-Case 3	0.21	0.51	0.61	0.50	0.17	0.15	0.05
-Case 4	0.19	0.36	0.76	1.00	0.76	0.07	0
Adrenaline (µg/kg/min)							
-Case1	0	0	0	0	0.36	0.27	0.22
-Case 2	0	0	0	0	0.60	0.20	0.05
-Case 3	0	0	0	0.1	0	0	0
-Case 4	0	0	0	0	0	0	0
Dobutamine (µg/kg/min)							
-Case1	0	0	0	0	0	0	0
-Case 2	0	0	0	0	0	0	0
-Case 3	0	0	0	10	0	0	0
-Case 4	0	0	0	0	4.8	4.8	2.4
pH *[7,35-7,43]*							
-Case1	7.58	7.47	7.36	7.16	7.38	7.46	7.54
-Case 2	7.43	7.44	7.43	7.38	7.51	7.53	7.46
-Case 3	7.38	7.40	7.38	7.37	7.46	7.5	7.51
-Case 4	7.52	7.40	7.40	7.20	7.44	7.41	7.48
HCO3 (mmol/L) *[22-29]*							
-Case1	26.7	25.5	23.8	16.5	17.8	29.5	24.4
-Case 2	22.7	23.4	21.2	17.4	27.4	26.3	29.5
-Case 3	21	22.9	24.2	23.6	27.8	25.7	28.4
-Case 4	20.3	16.6	19.9	14.2	25.1	22.7	25.7
Lactate (mmol/L) *[0,5-2,2]*							
-Case1	1.4	0.4	0.5	5.7	10	3.2	3.1
-Case 2	0.6	0.9	1.7	2.6	4.2	1.2	1.3
-Case 3	1.5	1.1	1.2	3.3	0.7	0.8	1.0
-Case 4	1.0	2.1	2.0	5.1	0.9	0.8	0.7
CK (U/L) *[≤190]*							
-Case1	ND	ND	5209	4347*	73670*	123500*	235060*

-Case 2	ND	ND	176	283	3091	ND	ND
-Case 3	ND	299	406	2999	12274	18442	18666
-Case 4	ND	935	ND	1775	2858	3201	4376
Creatinine (mg/dL) *[0,67-1,17]*							
-Case1	0.98	1.19	1.09	0.90	1.57	1.48	1.54
-Case 2	0.72	0.77	0.70	0.90	1.35	1.38	1.45
-Case 3	0.72	0.67	0.77	1.19	1.45	1.12	1.02
-Case 4	0.75	0.90	0.89	1.30	1.34	1.18	1.07
Potassium (mmol/L) *[3,45-4,45]*							
-Case1	3.6	4	2.8	4.4	6.6	5.1	4
-Case 2	4.4	4	3.9	5.5	3.9	3.9	3.7
-Case 3	3.6	3.1	4.4	5.4	4.1	3.5	3.5
-Case 4	3.2	3.1	3.4	5.5	4.0	3.8	3.6
ALT (U/L) *[≤41]*							
-Case1	99	99	93	104	1614	4857	4629
-Case 2	7	8	20	35	113	83	80
-Case 3	ND	15	ND	186	ND	203	179
-Case 4	20	23	ND	35	35	ND	47
AST (U/L) *[≤37]*							
-Case1	216	239	206	195	3261	14612	12696
-Case 2	12	18	36	70	552	352	261
-Case 3	ND	31	ND	657	ND	679	61
-Case 4	32	ND	ND	72	65	ND	98
Triglycerides (mg/dL) *[≤150]*							
-Case1	ND	ND	ND	341	168	101	ND
-Case 2	149	ND	105	149	73	88	91
-Case 3	ND	ND	ND	57	184	271	ND
-Case 4	ND	ND	ND	104	187	243	ND

Supplementary Table-2

	N	Age	Trauma	Neurosurgery	ECMO Support Mode	ECMO Support Duration	Anticoagulation	ICH progression during ECMO	PRIS	Survival	Neurological Outcome
Biscotti M, et al. (2015)[1]	Case 1	18y	Isolated TBI	No	VV-ECMO	13d	Yes	ND	No	Yes	No neurologic deficits
	Case 2	20y	Isolated TBI	No	VV-ECMO	6d	Yes	ND	No	Yes	No neurologic deficits
Leloup G, et al. (2011)[2]	1	27y	Non-Isolated TBI	ND	VV-ECMO	7d	ND	ND	No	Yes	No neurologic deficits
Stoll MC, et al. (2014)[3]	1	18y	Non-Isolated TBI	ND	VV-ECMO	7d	No	ND	No	Yes	ND
Menut R, et al. (2013)[4]	1	24y	Non-Isolated TBI	No	VA-ECMO	7d	Yes	No	No	Yes	No neurologic deficits
Reynolds HN, et al. (1999)[5]	1	16y	Non-Isolated TBI	No	VV-ECMO	7d	No	No	No	Yes	Moderate cognitive deficit
Anton-Martin P, et al. (2018)[6]	1	8y	Non-Isolated TBI	Decompression, evacuation IPH	VV-ECMO	7d	Yes	Yes	No	Yes	Mild cognitive deficit
Frickey N, et al. (2008)[7]	1	41y	Isolated TBI	No	VA-ECMO	12d	Yes	No	No	Yes	No neurologic deficits
Zhou R, et al. (2014)[8]	1	31y	Non-Isolated TBI	No	VA-ECMO	9h	Yes	No	No	Yes	No neurologic deficits
Messing J, et al. (2014)[9]	1	21y	Non-Isolated TBI	No	VV-ECMO	20d	Yes (Delayed: 5d after cannulation)	No	No	Yes	No neurologic deficits
Friesenecker BE, et al. (2005)[10]	1	34y	Non-Isolated TBI	Decompression, evacuation IPH	VV-ECMO	17d	Yes	Yes	No	Yes	GCS 11/15 at 6 mo
Yen TS, et al. (2008)[11]	1	21y	TBI *	Decompression, evacuation EDH	VA-ECMO	2d	No	No	No	Yes	No neurologic deficits
Muellenbach RM, et al. (2011,2012)[12, 13]	Case 1	53y	Non-Isolated TBI	No	VV-ECMO	8d	Yes (Delayed: 5d after cannulation)	No	No	Yes	FIM 68/126 at 4 mo
	Case 2	16y	Non-Isolated TBI	No	VV-ECMO	3d	Yes	No	No	Yes	No neurologic deficit

							(Delayed: 1d after cannulation)				
	Case 3	28y	Non-Isolated TBI	No	VV-ECMO	3d	Yes (Delayed: 2d after cannulation)	ND	No	Yes	FIM 61/126 after rehabilitation

Supplementary Table-3

ADDITIONAL SUPPLEMENTARY CONTENT:

Compliance with Ethical Standards:
The protocol and consent forms were approved by the institutional review board at University Hospitals Leuven (S64304). Written informed consent was provided by all patients. None of the authors reports potential conflicts of interest regarding this manuscript.

Overview of propofol use: 1/12/2015-1/12/2017:
This is a consecutive case series of all patients with PRIS requiring VA-ECMO-support, admitted to the department of Intensive Care Medicine from the University Hospitals Leuven, from 1/12/2015 till 1/12/2017. In this timeframe, a total of 3060 patients were treated with propofol in our department. Of those, only 271 patients (8.9%) received propofol for a total duration of more than 48 hours with a median propofol dose of 2.2 mg/kg/h (IQR 1.6-2.7 mg/kg/h). All discharge letters were screened for “Propofol Infusion Syndrome” and “PRIS”, resulting in four cases, all included in this case series.

Overview of ECMO use: 1/12/2015-1/12/2017:
This is a consecutive case series of all patients with PRIS requiring VA-ECMO-support, admitted to the department of Intensive Care Medicine from the University Hospitals Leuven, from 1/12/2015 till 1/12/2017. In this timeframe, a total of 136 ECMO-runs (both VA-ECMO and VV-ECMO) were performed in our department. Only 4 ECMO-runs were performed in patients with TBI (all cases included in this case series).

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