Neurological Complications of ECMO

Alain Combes, MD, PhD
Cardiology Institute, Hôpital Pitié-Salpêtrière, AP-HP
Inserm UMRS 1166, iCAN, Institute of Cardiometabolism and Nutrition
Sorbonne University, Paris, France
www.paris-tcsecmo.org
alain.combes@aphp.fr
Conflict of interest

• Principal Investigator: EOLIA trial
  • VV ECMO in ARDS
  • NCT01470703
  • Sponsored by MAQUET, Getinge Group

• Received honoraria from
  • MAQUET, XENIOS, GAMBRO, ALUNG
ECMO-associated Brain Injuries
Which Neurological Events under ECMO?
Which Neurological Events?

• Ischemic infarction
• Intracerebral hemorrhage
• Subarachnoid hemorrhage
• Seizures
• Diffuse microbleeds
• Anoxic encephalopathy
  • Cerebral edema
  • Brain death
• Drug toxicity
VV-ECMO
## Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome

### Table 3. Patient Outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>2009 Influenza A(H1N1)</th>
<th>All Infections (N = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Confirmed Infection (n = 53)</td>
<td>Suspected Infection (n = 15)</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d ICU</td>
<td>26 (16-35)</td>
<td>31 (15-38)</td>
</tr>
<tr>
<td>Hospital</td>
<td>35 (24-45)</td>
<td>40 (27-54)</td>
</tr>
<tr>
<td>Duration, median (IQR), d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival at ICU discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3 (27)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>4 (36)</td>
<td>2 (66)</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Intractable respiratory failure</td>
<td>3 (27)</td>
<td>1 (33)</td>
</tr>
</tbody>
</table>

ICH = 9%
3% died of intracranial hemorrhage
Neurologic Complications of ECMO: Report from the ELSO registry

Type of Neurologic Complications

- Brain death
- Seizures
- Cerebral Infarction
- Cerebral Hemorrhage

Rate of Neurologic Complications (%)

- Respiratory
- Cardiac
- ECPR

Crit Care Med, 2016
Neurologic Injury in Adults Supported With Veno-Venous Extracorporeal Membrane Oxygenation for Respiratory Failure: Findings From the Extracorporeal Life Support Organization Database

Lorrusso et al, Crit Care Med 2017

- 4,988 adults on VV ECMO for respiratory failure
- Neurologic injury was defined as
  - Brain death, seizures, stroke, and intracranial hemorrhage
- 426 neurologic complications reported in 356 patients (7%)
  - 43% intracranial hemorrhage
  - 24% brain deaths
  - 20% stroke
  - 14% seizure events
- In-hospital mortality with CNS complications (76% vs 39%; p < 0.001)
  - 80% in patients with intracranial hemorrhage
  - 68% in patients with stroke
  - 50% in patients with seizures
Neurologic Injury in Adults Supported With Veno-Venous Extracorporeal Membrane Oxygenation for Respiratory Failure: Findings From the Extracorporeal Life Support Organization Database

Lorrusso et al, Crit Care Med 2017
Neurologic Injury in Adults Supported With Veno-Venous Extracorporeal Membrane Oxygenation for Respiratory Failure: Findings From the Extracorporeal Life Support Organization Database

Lorrisso et al, Crit Care Med 2017
• Multivariate analysis of NI predictive factors
  • Pre-ECMO cardiac arrest
    • OR, 3.127; 95% CI, 1.788–5.469; p < 0.001
  • Hyperbilirubinemia during ECMO
    • OR, 2.370; 95% CI, 1.446–3.886; p = 0.001
  • Use of continuous veno-venous hemofiltration
    • OR, 2.331; 95% CI, 1.280–4.426; p = 0.006
Severe Respiratory Failure, Extracorporeal Membrane Oxygenation, and Intracranial Hemorrhage

Christopher J. A. Lockie, MBBS¹; Stuart A. Gillon, FFICM²; Nicholas A. Barrett, FCICM¹; Daniel Taylor, MBBS¹; Asif Mazumder, FRCR³; Kaggere Paramesh, MBBS³; Katie Rowland, MBBS¹; Kathleen Daly, PhD¹; Luigi Camporota, PhD¹; Christopher I. S. Meadows, FFICM¹; Guy W. Glover, FFICM¹; Nicholas Ioannou, FFICM¹; Christopher J. Langrish, FFICM¹; Stephen Tricklebank, FFICM¹; Andrew Retter, MBBS¹; Duncan L. A. Wyncoll, FFICM¹

**Objectives:** For patients supported with veno-venous extracorporeal membrane oxygenation, the occurrence of intracranial hemorrhage is associated with a high mortality. It is unclear whether intracranial hemorrhage is a consequence of the extracorporeal intervention or of the underlying severe respiratory pathology. In a cohort of

**Patients:** Patients admitted between December 2011 and February 2016.

**Intervention:** None.

**Measurements and Main Results:** Three hundred forty-two patients were identified: 250 managed with extracorporeal support and 92

*Crit Care Med, 2017*
382 patients identified from Severe Respiratory Failure Centre Database

- 40 patients excluded
  - no admission CT (n= 34)
  - Traumatic brain injury (n= 3)
  - low flow extra-corporeal carbon dioxide removal (ECCO₂R) (n=3)

342 Severe Respiratory Failure patients

- 250 patients treated with Veno-venous ECMO
  - 41 patients with evidence of ICH
  - 209 patients with no evidence of ICH

- 92 patients treated with conventional ventilation
  - 7 patients with evidence of ICH
  - 85 patients with no evidence of ICH
<table>
<thead>
<tr>
<th>Prevalence and Type of ICH</th>
<th>Extracorporeal Membrane Oxygenation</th>
<th>Conventional</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of ICH, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>41/250 (16.4)</td>
<td>7/92 (7.6)</td>
<td>48/342 (14.0)</td>
</tr>
<tr>
<td>Diagnosis at admission CT</td>
<td>35/250 (14)</td>
<td>5/92 (5.4)</td>
<td>40/342 (11.7)</td>
</tr>
<tr>
<td>Diagnosis made on “repeat” imaging for altered neurology</td>
<td>6/250 (2.4)</td>
<td>2/92 (2.1)</td>
<td>8/345 (2)</td>
</tr>
<tr>
<td>Type of ICH, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenchymal large</td>
<td>8/41 (19.5)</td>
<td>0 (7)</td>
<td>8/48 (16)</td>
</tr>
<tr>
<td>Parenchymal petechial</td>
<td>16/41 (39)</td>
<td>5/7 (71)</td>
<td>21/48 (44)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>23/41 (56)</td>
<td>3/7 (43)</td>
<td>26/48 (53)</td>
</tr>
<tr>
<td>Subdural</td>
<td>1/41 (2)</td>
<td>0 (7)</td>
<td>1/48 (2)</td>
</tr>
<tr>
<td>&gt; 1 type</td>
<td>15/41 (37)</td>
<td>1/7 (14)</td>
<td>16/48 (32)</td>
</tr>
</tbody>
</table>

*Crit Care Med, 2017*
<table>
<thead>
<tr>
<th>Survival</th>
<th>ICH</th>
<th>No ICH</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival in veno-venous ECMO patients, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival to ECMO decannulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH diagnosed at admission</td>
<td>27/35 (77.1)</td>
<td></td>
<td>0.522</td>
</tr>
<tr>
<td>Overall ICH(^a)</td>
<td>33/41 (80.5)</td>
<td>170/208 (81.7)</td>
<td>0.851</td>
</tr>
<tr>
<td>Survival to ICU discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH diagnosed at admission</td>
<td>24/35 (68.6)</td>
<td></td>
<td>0.189</td>
</tr>
<tr>
<td>Overall ICH(^a)</td>
<td>28/41 (68.3)</td>
<td>162/206 (78.6)</td>
<td>0.151</td>
</tr>
<tr>
<td>Survival at 6 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH diagnosed at admission</td>
<td>24/35 (68.6)</td>
<td></td>
<td>0.350</td>
</tr>
<tr>
<td>Overall ICH(^a)</td>
<td>28/41 (68.3)</td>
<td>155/204 (76.0)</td>
<td>0.302</td>
</tr>
<tr>
<td>Survival in conventional patients, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival ICU discharge</td>
<td>5/7 (71.4)</td>
<td>68/85 (79)</td>
<td>0.590</td>
</tr>
<tr>
<td>Survival at 6 mo</td>
<td>4/7 (57.1)</td>
<td>62/81 (76.5)</td>
<td>0.250</td>
</tr>
</tbody>
</table>

*Crit Care Med, 2017*
<table>
<thead>
<tr>
<th>Survival</th>
<th>ICH</th>
<th>No ICH</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival in veno-venous ECMO patients, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Survival to ECMO decannulation</td>
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<tr>
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<td></td>
<td>0.022</td>
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<td>0.851</td>
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<td>4/7 (57.1)</td>
<td>62/81 (76.5)</td>
<td>0.250</td>
</tr>
</tbody>
</table>

*Crit Care Med, 2017*

No Impact on Mortality
Factors independently associated with intracranial hemorrhage

• Duration of ventilation pre-ECMO
  • Odds ratio, 1.13 [95% CI, 1.03–1.23]; $p = 0.011$

• Admission fibrinogen (g/L)
  • Odds ratio, 0.73 [0.57–0.91]; $p = 0.009$

• ECMO not an independent risk factor
  • Odds ratio, 3.29 [0.96–15.99]; $p = 0.088$
Predictors of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation: an observational cohort study

Alexander Fletcher Sandersjöö¹,²*, Jiri Bartek Jr.¹,²,³, Eric Peter Thelin²,⁴, Anders Eriksson⁵, Adrian Elmi-Terander¹, Mikael Broman⁵,⁶ and Bo-Michael Bellander¹,²

253 ECMO patients, 63% VV-ECMO
54 (21%) had ICH during ECMO
Predictors of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation: an observational cohort study

Alexander Fletcher Sandersjöö¹,²*, Jiri Bartek Jr.¹,²,³, Eric Peter Thelin²,⁴, Anders Eriksson⁵, Adrian Elmi-Terander¹, Mikael Broman⁵,⁶ and Bo-Michael Bellander¹,²

1 month mortality with ICH 81% vs. 28%
6 months mortality with ICH 85% vs. 33%
<table>
<thead>
<tr>
<th>Variables</th>
<th>ICH cohort (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral hemorrhage</td>
<td>41 (76%)</td>
</tr>
<tr>
<td>Hematoma volume (mL)(^a)</td>
<td>22.8 (6.24–56.7)</td>
</tr>
<tr>
<td>Subdural hemorrhage</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hematoma volume (mL)(^a)</td>
<td>25.0 (range N/A)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>12 (22%)</td>
</tr>
<tr>
<td>Fisher grade</td>
<td>2 (2–4)</td>
</tr>
<tr>
<td>Variable</td>
<td>Univariate $p$ value</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Pre-admission antithrombotic therapy</td>
<td>0.014</td>
</tr>
<tr>
<td>Platelet count</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0.043</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.020</td>
</tr>
<tr>
<td>Spontaneous extracranial hemorrhage</td>
<td>0.031</td>
</tr>
</tbody>
</table>
Brain injury during venovenous extracorporeal membrane oxygenation

135 VV-ECMO patients

25 clinical events (19%)

5 CT scan performed Without clinical signs

23 patients for whom neurologic event cannot be ruled out

Death, pre-existing neurologic injury

Intensive Care Med, 2016
Brain injury during venovenous extracorporeal membrane oxygenation

25 clinical brain events (19%)

5 CT scan performed
Without clinical signs

22 CT scan performed

Brain death, no cerebral imaging
N = 3

22 CT scan performed

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
CT-scan in 27 patients

- Bleeding: N = 10 (7.5%)
- Ischemic stroke: N = 3 (2%)
- Edema: N = 2 (1.5%)
- Normal: N = 10

Microbleeds: N = 2
CT-scan in 27 patients

27 patients

- **Bleeding**
  - N = 10 (7.5%)
  - 3 (1-11) days after ECMO
  - 7 deaths (70%)

- **Stroke**
  - N = 3 (2%)
  - 21 (10-26) days after ECMO
  - 1 death (33%)

- **Edema**
  - N = 2 (1.5%)
  - 1 anoxia, 1 trauma both before ECMO
  - 2 deaths (100%)

- **Microbleeds**
  - N = 2 (1.5%)

- **Normal**
  - N = 10

*Intensive Care Med, 2016*
## Brain injury during venovenous extracorporeal membrane oxygenation

*Intensive Care Med*, 2016

<table>
<thead>
<tr>
<th>Worst value during ECMO</th>
<th>Bleeding N = 10</th>
<th>No Bleeding N = 123</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets, 10^3/mm^3</td>
<td>58.5 (26-77)</td>
<td>47 (28-94)</td>
</tr>
<tr>
<td>Patients with platelets &lt;20, n (%)</td>
<td>2 (20)</td>
<td>20 (16)</td>
</tr>
<tr>
<td>Patients with platelets &lt;10, n (%)</td>
<td>0</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>45 (39-70)</td>
<td>50 (24-63)</td>
</tr>
<tr>
<td>Patients with PT &lt;30%, n (%)</td>
<td>1 (10)</td>
<td>22 (18)</td>
</tr>
<tr>
<td>Patients with PT &lt;20%, n (%)</td>
<td>0</td>
<td>16 (13)</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>2.2 (1.6-4.6)</td>
<td>2.4 (1.4-3.8)</td>
</tr>
<tr>
<td>Patients with fibrinogen &lt;1.5, n (%)</td>
<td>2 (20)</td>
<td>30 (24)</td>
</tr>
<tr>
<td>Patients with fibrinogen &lt;1, n (%)</td>
<td>1 (10)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Anticoagulant overdose, n (%)</td>
<td>0</td>
<td>16 (13)</td>
</tr>
</tbody>
</table>
Higher PaO2 increase AND PaCO2 decrease just after ECMO initiation in patients with brain injury
Brain injury during venovenous extracorporeal membrane oxygenation

- Independent factors associated with brain hemorrhage
  - Renal SOFA >2 at ECMO initiation
  - $\Delta$PaCO2 > −27 mmHg
    - Before/after ECMO onset

*Intensive Care Med, 2016*
Diffuse Cerebral Microbleeds
• 4 consecutive patients with VA or VV ECMO
• No awakening
• All had diffuse cerebral microbleeds on MRI
• All were clinically prognosticated to have a very bad outcome
Diffuse Cerebral Microbleeds after Extracorporeal Membrane Oxygenation Support

American Journal of Respiratory and Critical Care Medicine Volume 191 Number 5 | March 1 2015

- Etiologies of microbleeds
  - Arteriolopathy
    - Cerebral small vessel disease, amyloid angiopathy
  - Diffuse emboli
    - Endocarditis, fat emboli

- No precise explanation in our patients
  - Role of severe hypoxia?
  - Microembolism?

- Neurologists and intensivists should be aware of this rare complication of ECMO support
  - Diffuse brain microbleeds in ECMO patients
  - Not a reason for limitation of active treatments
The Pattern of Brain Microhemorrhages After Severe Lung Failure Resembles the One Seen in High-Altitude Cerebral Edema

Sebastian Riech, Crit Care Med 2015

Mountain climber

Severe ARDS
Cerebral microemboli detected by transcranial doppler in patients treated with extracorporeal membrane oxygenation

M. Marinoni 1, M. L. Migliaccio 1, S. Trapani 1, M. Bonizzoli 1, L. Gucci 1, G. Cianchi 1, A. Gallerini 1, L. Tadini Buoninsegni 1, A. Cramaro 1, S. Valente 2, M. Chiostri 2 and A. Peris 1

1Neuromusculoskeletal and Sensory Organs Department, Careggi Teaching Hospital, Florence, Italy
2Intensive Care Unit of Heart and Vessels Department, Careggi Teaching Hospital, Florence, Italy

42 VV and 11 VA ECMO patients
Microembolic signals in
26% of VV ECMO and in 82% of VA ECMO patients
Conclusion

• ECMO might improve the outcomes of severe ARDS patients
  • By preventing hypoxia-induced brain sequelae?

• Neurologic Events are frequent in ECMO patients
  • Get a brain CT scan if CT needed for other reasons

• Brain Hemorrhages more frequent with VV?
  • Not associated with hemostasis disorders
  • Role of rapid CO$_2$ change? Longer time on support?
  • Increased intracerebral pressure due to return cannula?
  • Need for less anticoagulants in these patients...