Brain Injury during Venovenous Extracorporeal Membrane Oxygenation

Charles-Edouard Luyt, Nicolas Bréchot, Pierre Demondion, Tamara Jovanovic, Guillaume Hékimian, Guillaume Lebreton, Ania Nieszkowska, Matthieu Schmidt, Jean-Louis Trouillet, Pascal Leprince, Jean Chastre, and Alain Combes

ONLINE DATA SUPPLEMENT

Methods

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. We also searched the references of identified studies. Randomized–controlled trials, observational studies and case series reporting on adult VV-ECMO patients with their outcomes, particularly their neurological events, were eligible. Studies on children or newborns, those without any outcome information, especially about neurological complications, were excluded.

Two authors (C.-E.L. and N.B.) independently reviewed the retrieved abstracts and assessed eligibility. A third author (G.H.) determined eligibility in the case of disagreement. The following data were extracted: study design, participants' characteristics, ECMO type (VV or VA), outcome data (neurological complications, mortality, mortality of patients with

neurological complications), hemostasis disorders and anticoagulation use.

Results

Systematic Review

Among the 8,647 search strategy-identified citations, 8,615 failed to meet screening eligibility, mostly because they concerned only VA-ECMO patients, reported no neurological events or described pediatric series. Among the 38 studies extracted for full-text analysis, 16 met the inclusion criteria and were subsequently analyzed in detail (Table 5): 15 cohort studies and one randomized–controlled trial [1-16]. All but five [4, 6, 10, 14, 15] reported both VA- and VV-ECMO. The randomized–controlled trial reported only neurological injury-related deaths without specifying the cerebral complications [4] and one cohort study reported only fatal brain complications [13]. Three studies reported the use of roller pump rather than centrifugal pumps [1, 2, 11, 14], but we decided to include them because the results were similar. Five studies in which more than a third of the patients had received VA-ECMO were not used to calculate frequency of neurological complications [1-3, 13, 16]. The cerebral bleeding frequency in the remaining eight studies was 5% (29/553). Including our population in that analysis did not change the results: 39/688 (6%) patients had cerebral bleeding. Brain-injury–related mortality was very high: all 28 patients with cerebral bleeding and available data died (Table 5). None of the studies evaluated hemostasis disorders or anticoagulation use and only one reported the ECMO-initiation-to-cerebral-bleeding interval (2 days) [10]. Only five studies reported neurological complications other than cerebral bleeding [1-3, 11, 16], but because VA-ECMO patients represented more than one-third of those studied populations, no conclusions could be drawn about neurological complications other than cerebral bleeding.

Table E1. Univariable and Multivariable Analyses of Factors Associated With Death on VV-ECMO

Factor	Univariable Analysis OR [95% CI]	Cox Analysis HR [95% CI]
Age >46 yr	5.9 [2.8–12.6]	5.9 [2.2–15.7]
Female sex	0.7 [0.4–1.5]	
SAPS II score at ICU admission ≥70	1.8 [0.9–3.6]	
Body mass index >26	1.04 [0.5–2.1]	
McCabe & Jackson comorbidity score ≥2	3.5 [1.7–7.4]	2.8 [1.1–7.4]
MV duration before ECMO >5 days	2.4 [1.2–4.8]	3.3[1.2–8.9]
Organ failure at ECMO initiation[a]		
Cardiovascular	0.8 [0.4–1.8]	
Hepatic	1.5 [0.7–3.5]	
Renal	0.9 [0.5–1.9]	
Hematological	0.8 [0.3–2.5]	
Neurological	0.6 [0.3–1.5]	
Gas exchange change		
Arterial pH >0.2[b]	1.7 [0.7–3.8]	
PaO_2 >50 mmHg[b]	0.8 [0.3–1.8]	
$PaCO_2$ <–27 mmHg[b]	2.9 [1.3–6.4]	3.1 [1.2–8.4]
Renal replacement therapy	1.5 [0.8–3.0]	
Hemostasis disorders during ECMO		
Platelets $<20 \times 10^9$/L	0.5 [0.2–1.3]	
Prothrombin time <30%[c], n (%)	5.3 [1.9–14.5]	7.4 [1.7–32.3]
Fibrinogen, <1.5 g/L	0.7 [0.3–1.5]	

Anticoagulant overdose	1.5 [0.5–4.2]

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 E2. Univariable and Multivariable Analyses of Factors Associated With Death or Intracranial Bleeding on VV-ECMO

Factor	Univariable Analysis OR [95% CI]	Cox Analysis HR [95% CI]
Age >46 yr	5.5 [2.6–11.6]	5.5 [2.2–13.7]
Female sex	0.9 [0.5–1.9]	
SAPS II score at ICU admission ≥70	1.7 [0.9–3.4]	
Body mass index >26	0.9 [0.4–1.7]	
McCabe & Jackson comorbidity score ≥2	3.5 [1.6–7.3]	
MV duration before ECMO >5 days	2.2 [1.1–4.5]	2.7 [1.1–6.9]
Organ failure at ECMO initiation[a]		
Cardiovascular	0.9 [0.4–1.9]	
Hepatic	1.9 [0.8–4.4]	
Renal	1.02 [0.5–2.04]	
Hematological	1.02 [0.4–2.9]	
Neurological	0.7 [0.3–1.7]	
Gas exchange change		
Arterial pH >0.2[b]	1.9 [0.8–4.3]	
PaO_2 >50 mmHg[b]	0.9 [0.4–2.2]	
$PaCO_2$ <–27 mmHg[b]	3.2 [1.4–7.1]	3.8 [1.5–9.7]
Renal replacement therapy	1.6 [0.8–3.1]	
Hemostasis disorders during ECMO		
Platelets $<20 \times 10^9$/L	2.1 [0.8–5.3]	
Prothrombin time <30%[c], n (%)	4.7 [1.7–12.9]	5.9 [1.5–23.8]
Fibrinogen, <1.5 g/L	1.3 [0.6–2.8]	

Anticoagulant overdose	1.3 [0.5–3.8]

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**.**

REFERENCES

1. Kolla S, Awad SS, Rich PB, Schreiner RJ, Hirschl RB,Bartlett RH (1997) Extracorporeal life support for 100 adult patients with severe respiratory failure. Ann Surg 226: 544-64; discussion 565-6.
2. Linden V, Palmer K, Reinhard J, Westman R, Ehren H, Granholm T,Frenckner B (2000) High survival in adult patients with acute respiratory distress syndrome treated by extracorporeal membrane oxygenation, minimal sedation, and pressure supported ventilation. Intensive Care Med 26: 1630-7.
3. Brogan TV, Thiagarajan RR, Rycus PT, Bartlett RH,Bratton SL (2009) Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. Intensive Care Med 35: 2105-14.
4. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK,Elbourne D (2009) Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 374: 1351-63.
5. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, Forrest P, Gattas D, Granger E, Herkes R, Jackson A, McGuinness S, Nair P, Pellegrino V, Pettila V, Plunkett B, Pye R, Torzillo P, Webb S, Wilson M,Ziegenfuss M (2009) Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA 302: 1888-95.
6. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, Harvey C, Cordingley JJ, Price S, Vuylsteke A, Jenkins DP, Noble DW, Bloomfield R, Walsh TS, Perkins GD, Menon D, Taylor

BL,Rowan KM (2011) Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA 306: 1659-68.

7. Patroniti N, Zangrillo A, Pappalardo F, Peris A, Cianchi G, Braschi A, Iotti GA, Arcadipane A, Panarello G, Ranieri VM, Terragni P, Antonelli M, Gattinoni L, Oleari F,Pesenti A (2011) The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks. Intensive Care Med 37: 1447-57.
8. Pham T, Combes A, Roze H, Chevret S, Mercat A, Roch A, Mourvillier B, Ara-Somohano C, Bastien O, Zogheib E, Clavel M, Constan A, Marie Richard JC, Brun-Buisson C,Brochard L (2103) Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med 187: 276-85.
9. Roch A, Hraiech S, Masson E, Grisoli D, Forel JM, Boucekine M, Morera P, Guervilly C, Adda M, Dizier S, Toesca R, Collart F,Papazian L (2014) Outcome of acute respiratory distress syndrome patients treated with extracorporeal membrane oxygenation and brought to a referral center. Intensive Care Med 40: 74-83.
10. Ng GW, Leung AK, Sin KC, Au SY, Chan SC, Chan OP,Wu HH (2014) Three-year experience of using venovenous extracorporeal membrane oxygenation for patients with severe respiratory failure. Hong Kong Med J 20: 407-12.
11. Hemmila MR, Rowe SA, Boules TN, Miskulin J, McGillicuddy JW, Schuerer DJ, Haft JW, Swaniker F, Arbabi S, Hirschl RB,Bartlett RH (2004) Extracorporeal life support for severe acute respiratory distress syndrome in adults. Ann Surg 240: 595-605; discussion 605-7.
12. Lindskov C, Jensen RH, Sprogoe P, Klaaborg KE, Kirkegaard H, Severinsen IK, Lorentsen AG, Folkersen L, Ilkjaer S,Pedersen CM (2013) Extracorporeal membrane

oxygenation in adult patients with severe acute respiratory failure. Acta Anaesthesiol Scand 57: 303-11.

13. Michaels AJ, Hill JG, Bliss D, Sperley BP, Young BP, Quint P, Shanks TR, Dalthorp J, Long WB,Morgan LJ (2013) Pandemic flu and the sudden demand for ECMO resources: a mature trauma program can provide surge capacity in acute critical care crises. J Trauma Acute Care Surg 74: 1493-7.
14. Mols G, Loop T, Geiger K, Farthmann E,Benzing A (2000) Extracorporeal membrane oxygenation: a ten-year experience. Am J Surg 180: 144-54.
15. Kon ZN, Dahi S, Evans CF, Byrnes KA, Bittle GJ, Wehman B, Rector RP, McCormick BM, Herr DL, Sanchez PG, Pham SM,Griffith BP (2015) Long-Term Venovenous Extracorporeal Membrane Oxygenation Support for Acute Respiratory Distress Syndrome. Ann Thorac Surg.
16. Gray BW, Haft JW, Hirsch JC, Annich GM, Hirschl RB,Bartlett RH (2015) Extracorporeal life support: experience with 2,000 patients. ASAIO J 61: 2-7.