Intensive Care Med (2019) 45:1040–1042
https://doi.org/10.1007/s00134-019-05570-9

LETTER

Prone positioning and extracorporeal membrane oxygenation for severe acute respiratory distress syndrome: time for a randomized trial?

Christophe Guervilly[1,2*], Eloi Prud'homme[1], Vanessa Pauly[2], Jérémie Bourenne[3], Sami Hraiech[2,4], Florence Daviet[1], Mélanie Adda[1], Benjamin Coiffard[1,2], Jean Marie Forel[1,2], Antoine Roch[1,2,4], Nicolas Persico[4] and Laurent Papazian[1,2]

Dear Editor,

The recently published EOLIA study [1] has failed to demonstrate a 20% increase in survival in patients with very severe acute respiratory distress syndrome (ARDS) using a strategy of early application of veno-venous extracorporeal membrane oxygenation (vvECMO) as compared with low-volume, low-pressure ventilation in combination with rescue therapies including prone positioning (PP), inhaled nitric oxide and neuromuscular blockers. Early, prolonged and repeated sessions of prone positioning (PP) are associated with a substantial outcome benefit in ARDS patients, with a PaO_2/FiO_2 ratio < 150 mmHg [2]. In the EOLIA trial, there was a difference in the use of PP between the two arms, with 90% of the patients in the control group turned to PP before and/or after randomization, and only 66% of the patients in the ECMO group.

Therefore, we have performed a retrospective observational study to compare outcomes of severe ARDS patients under vvECMO according to the use of PP or lack thereof during their ECMO run in order to assess the potential justification for further randomized clinical trials.

A flow chart, ECMO criteria, management of vvECMO and mechanical ventilation are described in the ESM. We have compared patients with a combination of PP during ECMO (prone ECMO group) to those maintained in supine position (ECMO alone group). See statistical details in the ESM.

During the study period, 168 patients were supported by vvECMO for severe ARDS and were included in the analysis. The main pre-ECMO characteristics and outcomes are presented in Table 1. Among the patients, 91 (54%) were placed at least once in prone position during the ECMO run, whereas 77 (46%) were maintained in supine position during ECMO. Patients in the prone ECMO group were more frequently turned to PP before ECMO. Patients underwent a mean of three PP sessions, with a range from 1 to 17. Patients in the prone ECMO group were more likely to be weaned from ECMO. Accordingly, 30-day, 60-day and 90-day survival rates were significantly higher.

To reduce the risk of bias (indication for PP, severity of illness), we duplicated the comparisons with matching according to age, sex, SOFA, prior duration of mechanical ventilation and prior PP before ECMO. We also found a higher rate of ECMO weaning and better survival rates in a comparative matched study of 50 pairs of patients (see ESM). However, we cannot exclude residual confounding factors that overestimate the effect.

Aside from its positive effects on oxygenation, PP can reduce ventilator-induced lung injury in ARDS patients under ECMO [3, 4]. A further randomized controlled trial should be performed in patients with severe ARDS supported by vvECMO with implementation of

*Correspondence: christophe.guervilly@ap-hm.fr
[1] Medical Intensive Care Unit North Hospital, APHM, Marseille, France
Full author information is available at the end of the article

Table 1 Demographic characteristics, pre-ECMO treatments, ECMO and mechanical ventilation settings and outcomes of patients

	All patients ($n=168$)	ECMO alone ($n=77$)	Prone ECMO ($n=91$)	*P* value
Age (years), mean ± SD	51 ± 14	53 ± 13	49 ± 15	0.13
Male sex, *n* (%)	118 (70)	52 (67)	66 (72)	0.48
SOFA score at cannulation, mean ± SD	10 ± 4	11 ± 4	10 ± 4	0.27
Mechanical ventilation before ECMO (days), mean ± SD	5 ± 6	6 ± 7	5 ± 5	0.32
PaO_2 to FiO_2 ratio before ECMO (mmHg), mean ± SD	67 ± 20	67 ± 19	67 ± 21	0.94
Prone position before ECMO, *n* (%)	108 (64)	39 (50)	69 (76)	0.001
iNO before ECMO, *n* (%)	62 (37)	31 (40)	31 (34)	0.44
Mobile ECMO team, *n* (%)	118 (70)	52 (67)	66 (72)	0.48
Mechanical ventilation settings the first day of ECMO, mean ± SD				
Tidal volume (mL)	175 ± 60	167 ± 52	180 ± 63	0.15
Plateau airway pressure (cm H_2O)	24 ± 4	24 ± 4	24 ± 4	0.44
PEEP (cmH_2O)	15 ± 3	14 ± 4	15 ± 3	0.36
Driving pressure (cmH_2O)	10 ± 4	10 ± 4	10 ± 4	0.92
Respiratory rate (cycles/min)	11 ± 2	11 ± 2	11 ± 2	0.95
Respiratory system compliance (mL/cmH_2O)	21 ± 11	21 ± 11	22 ± 12	0.54
Inspired fraction of oxygen (%)	75 ± 24	74 ± 24	76 ± 25	0.63
ECMO settings, the first day of ECMO, mean ± SD				
ECMO blood flow (L/min)	4.2 ± 0.7	4.1 ± 0.7	4.3 ± 0.7	0.17
Sweep gas flow (L/min)	5 ± 2	5 ± 2	5 ± 2	0.80
Membrane lung fraction of oxygen (%)	100	100	100	1
Number of prone session during ECMO, mean ± SD	1.5 ± 2.5	–	3 ± 3	–
ECMO weaning, *n* (%)	103 (61)	39 (50)	64 (70)	0.009
Duration of ECMO (days), mean ± SD	15 ± 13	9 ± 8	20 ± 14	< 0.001
ECMO free days at day 60, mean ± SD	22 ± 23	19 ± 25	24 ± 22	0.30
Ventilator-free days at day 60, mean ± SD	15 ± 19	13 ± 20	16 ± 18	0.19
ICU length of stay (days), mean ± SD	29 ± 25	20 ± 18	36 ± 28	< 0.001
30-day survival, *n* (%)	98 (58)	33 (43)	65 (71)	< 0.001
60-day survival, *n* (%)	88 (52)	31 (40)	57 (62)	0.004
90-day survival, *n* (%)	82 (49)	29 (38)	53 (58)	0.008

Values are expressed as mean ± SD, proportions as *n* (%)

ECMO extracorporeal membrane oxygenation, *SOFA* sepsis-related organ failure assessment, *iNO* inhaled nitric oxide, *ICU* intensive care unit, *PEEP* positive end-expiratory pressure

systematic PP in one arm. Such a trial would be faced with predictable challenges related to the small number of centres trained in prone-positioning of patients on ECMO and the relatively low percentage of eligible patients after exclusion of contraindications for PP. Determining the best timing and duration of PP in ECMO requires further investigation.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05570-9) contains supplementary material, which is available to authorized users.

Author details

[1] Medical Intensive Care Unit North Hospital, APHM, Marseille, France. [2] CERESS, Center for Studies and Research On Health Services and Quality of Life EA3279, Aix-Marseille University, Marseille, France. [3] Medical and Emergency Resuscitation, La Timone 2 University Hospital, Aix-Marseille University, Marseille, France. [4] Emergency Department, North Hospital, APHM, Marseille, France.

Acknowledgements

The authors would like to thank all the ICU nursing staff and the perfusionist's team.

Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical statement

According to the French legislation, because of the retrospective design of the study, no inform consent is warranted. The study was registered by the French authority Commission Nationale Informatique et Libertés under the number: CIL/APHM 2018-44.

Publisher's Note

Accepted: 13 February 2019
Published online: 5 March 2019

References

1. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A, EOLIA Trial Group, REVA, and ECMONet (2018) Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 378:1965–1975
2. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L, PROSEVA Study Group (2013) Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 368:2159–2168
3. Gattinoni L, Taccone P, Carlesso E, Marini JJ (2013) Prone position in acute respiratory distress syndrome. rationale, indications, and limits. Am J Respir Crit Care Med 188:1286–1293
4. Albert RK, Keniston A, Baboi L, Ayzac L, Guérin C, Proseva Investigators (2014) Prone position-induced improvement in gas exchange does not predict improved survival in the acute respiratory distress syndrome. Am J Respir Crit Care Med 189:494–496