Editorial

In acute respiratory distress syndrome, is extracorporeal membrane oxygenation an adjuvant for "everyone"?

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The first publication from the LUNG SAFE Investigators and the ESICM Trials Group was published in the spring 2016 (1). The primary outcome variable was the incidence of acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU) according to the Berlin definition (2). The results showed the incidence for ARDS to be 10.4% over four weeks in the five continents cohort of more than 29,000 critically ill patients from 50 countries. An interesting and important finding was the indication of under-recognition of ARDS. The study has been commented and criticized for bias on several points including deductions on under-recruitment (3). The consequence for the patient of missed or delayed diagnose increase morbidity and risk for death from late commencement or not being offered supportive and adjunct therapies at all. In patients with mild ARDS 80%, moderate 65%, and severe 39% were never offered any adjunctive therapy. In the cohort recognized, positive end expiratory pressure (PEEP) was higher, more patients were submitted to prone therapy, inhaled vasodilators, neuromuscular blockade, and extracorporeal membrane oxygenation (ECMO). This editorial focuses on the approach in ECMO treatment.

Our clinical assumption, that the more severe ARDS patient is more likely to be identified was acknowledged by the LUNG SAFE study (1). Late or missed identification of the patient in the early assessment may lead to a more severe course of illness. Lung driven inflammation escalates and trigger apoptosis and vicious circles for further organ failures, e.g., acute kidney injury. This subjects the patient to a more dangerous situation and demands for more intense and extreme organ and life support.

In resuscitation algorithms for severe systemic inflammation/sepsis volume replacement is one important cornerstone. However, too ambitious fluid resuscitation form edema due to capillary leakage. Continued fluid accumulation after the resuscitation phase carry worse outcome (4). Any, and all organ systems may be affected by this interstitial permeability syndrome (5): lung, brain, intestines/viscera (abdominal compartment syndrome), subcutaneous tissue, etc. Interstitial edema has impacts on diffusion distances and interstitial pressures in the lung as well as peripheral tissues. Furthermore, the area of the respiratory membrane decreases from intra-alveolar fluid, atelectasis, pus, etc. Different parts of the lung exhibit heterogeneity concerning hypoxemic vasoconstriction, alveolar dead space, shunting, compression of capillaries and airways, clotting from coagulation activation, etc.

In this complex pathophysiology lung management is performed using the common concept today known as protective lung ventilation (high PEEP, restricted tidal volumes, limited inspiratory pressures/plateau pressures,

inverse ratio breathing, recruitment manoeuvers, and permissive hypercapnia). High PEEP, sometimes >20 cmH_2O is used keep the lung open, i.e., as a measure to prevent de-recruitment. On top of PEEP, the tidal volume is applied for ventilation to clear carbon dioxide. Increased ventilator pressure has disadvantages, exposing the heterogenous lung for increased stress and strain. Besides the risk of inducing ventilator induced injury, secondary effects on circulation, etc. (6). A physiologic reality, in clinical practice often forgotten is entrapment of interstitial fluid in the lung exposed to airway pressures above 15 cmH_2O due to impairment of lymph drainage from the lung (7).

During these circumstances, methods for extracorporeal life (ECLS) support allow for applications of lung rest settings or ultraprotective mechanical ventilation and potentially less ventilator-induced lung injury (8). To provide full gas exchange ECMO may be applied (9). The extracorporeal circuit is composed of a blood pump, a membrane lung (ML) (oxygenator, artificial lung), and vascular access(es) large enough to promote a blood flow sufficient for oxygenation and carbon dioxide removal. Blood flows needed are commonly 4–4.5 L/min, with a range from a minimum of 2 to >7 L/min depending on patient mass and metabolic demand (i.e., oxygen consumption). The deoxygenated blood is drained from the patient's venous circulation, oxygenated in the ML and then pumped back to the patient's circulation via a cannula implanted in a major vein [venovenous (VV) ECMO]. Thus, lung support is provided. In VV there is no by-pass flow which means that the native cardiac output (CO) enforces total oxygen delivery. Therefore, echocardiography is a valuable tool in assessing cardiac function. In case of need for concomitant cardiac support, e.g. cytotoxic cardiac failure in the septic patient, or right ventricular failure (from secondary pulmonary hypertension in ARDS) (6), blood is drained and oxygenated as above but returned to the arterial side often via a femoral artery [venoarterial (VA)]. It should be noted that in VA ECMO a by-pass situation is created and cannulae etc. should be dimensioned to support patient's whole need for CO. In severe ARDS the risk for conversion from VV to VA ECMO may be approximately 20% (unpublished data). Hence, both VV and VA are synonymous with respiratory (r) ECMO. It is all about the individual patient's need for organ support.

In this context, extracorporeal carbon dioxide removal ($ECCO_2R$) should be mentioned. The method may support ventilation, i.e., CO_2 clearance if correctly dimensioned. It may thus be used as a mean to facilitate ultraprotective lung ventilation. The method provides CO_2 exchange via an extracorporeal pump-less device where flow is promoted by the patient's own arterial blood pressure via a drainage cannula in a femoral artery and return cannula in a femoral vein, arteriovenous (AV) $ECCO_2R$, (PECLA), or a pump-driven circuit (drainage via a larger vein with the return to the venous side, venovenous (VV) $ECCO_2R$ (9). In both devices, a ML is part of the circuit for CO_2 exchange. To clear a significant part of the CO_2 produced by an adult the blood flow needs to be 1–1.5 L/min, i.e. three to four times of that accomplished by the recently introduced $ECCO_2R$ devices used with the conventional renal replacement devices. The oxygen transfer is limited by the lower flows used for $ECCO_2R$, and, therefore needs remained lung function. No benefit has been shown on mortality and morbidity for $ECCO_2R$ in ARDS patients (10). The risk for bleeding and thromboembolic complications considered, this technology with hitherto limited proven effect, widespread use should be discouraged awaiting results in future trials.

The incidence for acute respiratory failure (ARF) fulfilling the ARDS criteria in the LUNG SAFE cohort varied between continents from 0.27 to 0.57 cases/ICU bed per study period. If true differences existed could not be clarified due to unknown population sizes served. Data from Spain indicated an annual incidence for ARDS of 7.2/100,000 (11), Sweden 7 (12), Australia and New Zealand 28 (13), and the United States 1.3–22 (14). These data are based on definitions preceding the Berlin criteria (2).

In the most severe cases of ARDS, where ECMO was implemented the incidence in France was reportedly 1.0/100,000 per year (15), Sweden 0.34 [data extracted from the Swedish Intensive Care Registry (12) between 2012 and 2017], and for Germany 2.4–3.5 (16). The high German incidences are influenced by the inclusion criteria for ECMO, they coincide with the total regional/national resources available, and economical incentives, etc., further discussed below. For the LUNG SAFE cohort, a comparison could not be made, but the more severe the ARDS the higher the frequency for ECMO. According to the guidelines concerning adult rECMO developed by the Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI, USA, www.elso.org) (17), treatment is indicated at PaO_2/FiO_2 ratios <100 mmHg. This criterion was only fulfilled by the ECMO patients in the severe ARDS group constituting 48 individuals (2.0%) of the 2,377 ARDS patients treated with invasive ventilation. In moderate ARDS (PaO_2/FiO_2 <150), ECMO may be considered. Twenty-seven (1.1%)

patients from the moderate ARDS cohort (PaO_2/FiO_2 149, 95% CI: 147–150), and one patient with mild ARDS were on ECMO support. In comparison to international data the LUNG SAFE numbers fall in reasonable coherence with the international (15), Spanish (11) and Swedish data reported (12). Concerning Germany, the incidence was substantially higher (16). At the 9th Joint Scandinavian Conference in Cardiothoracic Surgery in Helsinki 2017, data from Germany (82 million people) was referred: 2,200 annual VV runs with a surprisingly low survival rate, 38%. However, survival from high-volume German centers was reported 70%. The large study by Karagiannidis *et al.* (16), on data from the German Federal Statistical Office between 2007 and 2014, showed a survival of 42% for VV, and 34% for VA ECMO. Twenty-five percent commenced on VV ECMO died within 48 hours, and 70% of all short-term (<4–6 days) patients died. The database design did not allow for separation in age groups (survival for children in general higher), center-volume to outcome, indications, diagnose, etc. Provision of ECMO is not regulated in Germany contributing to an open market for low-volume and less experienced centers to operate. Hence, the question arises if too many are doing too few and not in patient's best interest? Would more lives have been saved if treated at another/larger center? Were there a center-limitation to only perform VV ECMO when VA was the only adequate regimen? Were these individuals in fact exposed to a treatment worse than the illness itself if continued with conventional critical care? Herein lays an ethical dilemma.

Contemporary knowledge emphasizes that center-volume matters for both patient outcome, and for resources and costs spent. Concerning neonatal and pediatric ECMO, for increased survival at least 20–30 annual respiratory runs are needed (18,19). Adult centers performing >30 runs have an Odds ratio for death of 0.6 (95% CI: 0.52–0.76) compared to low-volume centers (<6 runs per year) (20). For In the adult population, the ECMO Net position paper (15) on adult rECMO proposed a minimum of at least 12 respiratory runs per year. An annual total minimum of at least 20 ECMO treatments (including cardiac, etc.) is required for a reasonable learning curve and to maintain competence. Respiratory ECMO should be consolidated to high-volume centers for best value of resources spent on this patient population. This means reduced costs, decreased morbidity and increased survival. Consolidation of rECMO requires mobile ECMO expert services for assessment, implantation of cannulae and commencement of ECMO treatment at the referring hospital for a safe transport on ECMO back to the high-volume center (21,22). Such transport services are on-call 24/7, and best organized integrated into a high-volume ECMO center serving an adult population of 8–15 million at a regional or national level.

It may be expected that rECMO is a uniform treatment offered at different hospitals. However, a survey conducted by support of EuroELSO (European chapter of ELSO) in 2015–2016 revealed several differences between the 53 participating European centers (23). Eighty percent of the EuroELSO member centers performed at least 20 annual runs (high-volume centers), 77% offered mobile ECMO cervices and 72% applied adjunctive rescue therapies before ECMO. Of the non-member centers, 39% reported an annual volume >20, 41% offered transport services, and 41% adjunctive therapies before ECMO. The member centers preferred awake patients on ECMO which was not the case for the non-members. If the heterogeneity between centers could be compared with different outcomes was not the scope of the survey. The investigators concluded that adult rECMO should be performed at high-volume ECMO centers, which confirmed the statement from ECMO Net.

Do high-volume centers offer "the same ECMO"? That does not seem to be the case. In a comparative multi-centric study from five high-volume European ECMO centers (24), data from 48 patients with primary ARDS from bacterial pneumonia treated with VV ECMO were investigated. Inclusion followed the ELSO Guidelines (17). At admission, all center cohorts were similar concerning age, mean SOFA score (10.8–14.8) and ventilator settings (PEEP 9.7–12.3 cmH_2O, PIP 33–35 cmH_2O). At one center the bi-caval dual lumen cannula dominated. The most common configuration was two single lumen cannula (SLC) in a femoral-jugular flow direction. One center applied jugulo-femoral SLC mode. After commencement of ECMO driving pressure (PIP-PEEP) was reduced at all centers. However, some centers increased PEEP (open lung), others decreased PEEP as a measure of providing lung rest (8). The resulting tidal volumes varied probably due to different approaches to sedation. Regarding the management of ECMO the blood flows were different but kept rather constant during the treatment period. The management of the weaning processes was performed in at least three different ways (25). One participant extubated the patients before weaning and offered non-invasive ventilation support. Mean days on ECMO ranged from 8.1 to 19.7 days, and survival was 92% (24).

The LUNG SAFE study conducted during February–March in the northern, and June–August in the southern

hemisphere, i.e., during the respective influenza season, indicated that 25–60% of all ICU beds during the 4 weeks study period were occupied by patients diagnosed with ARDS according to the Berlin criteria. Under-recognition of ARDS or not has been discussed by others (3). However, based on earlier published data, the more severe ARDS cases in need of ECMO seemed to be identified with less missed cases in the LUNG SAFE cohort. The incidence of ECMO in severe ARDS was within the expected range after a rough estimate was made by the author of this editorial based on the frequency of patients offered ECMO. Survival from ECMO was not reported, but a paper from the LUNG SAFE Investigators and the ESICM Trials Group on the ECMO population is reported to come.

From several investigations and expert groups' opinion referred to in this editorial, it cannot be emphasized enough, the importance of regional and national infrastructures supporting the management of all ECMO patients at high-volume ECMO centers (15,16,18-20,23). Any center offering ECMO services should be a complete high-volume ECMO center, i.e., have substantial experience in both VV and VA rECMO. Each region/nation should organize a 24/7 mobile ECMO transport service program (15,21,22). High-volume centers may collaborate in networks, even across national borders to serve large populations in times of pandemic or high seasonal load. Low-volume centers may also be part of such network, i.e., the Hub-and-Spoke model (15). This would increase transparency and clinical experience would spread from the more experienced providers and promote development towards more uniform management of methods for ECLS in best interest for the future (ARDS) patients. Until more clinical research data has been presented it is advocated that acknowledged centers should be ELSO Center of Excellence in Life Support since this is the only "quality indicator" today. The organization is submitted to peer reviewed by ELSO, and reporting to the international ELSO Registry is mandated which allow for quality follow-up, research and development for the ECLS community whole.

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Footnote

Conflicts of Interest: LM Broman was a contributor of study data to the LUNG SAFE study which however does not affect the offspring of this Editorial. LM Broman is a member of the independent research consortium European ECMO Advisory Board, the EuroELSO Scientific Committee, the EuroELSO Working Group for Innovation and Technology on ECLS and ECMO, the ELSO Workgroups for Adult ECMO, Pediatric ECMO, and ELSO Registry Committee. LM Broman is also a member of the Medical Advisory Board of Eurosets Srl, Medolla, Modena, Italy.

References

1. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315:788-800.
2. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA 2012;307:2526-33.
3. Villar J, Schultz MJ, Kacmareket RM. The LUNG SAFE: a biased presentation of the prevalence of ARDS! Critical Care 2016;20:108.
4. O'Connor ME, Prowle JR. Fluid Overload. Crit Care Clin 2015;31:803-21.
5. Siddall E, Khatri M, Radhakrishnan J. Capillary leak syndrome: etiologies, pathophysiology, and management. Kidney Int 2017;92:37-46.
6. Boissier F, Katsahian S, Razazi K, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. Intensive Care Med 2013;39:1725-33.
7. Frostell CG. Lung lymph drainage. Acta Anaesthesiol Scand Suppl 1991;95:55-7; discussion 58-9.
8. Fanelli V, Ranieri MV, Mancebo J, et al. Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. Crit Care 2016;20:36.
9. Conrad SA, Broman LM, Taccone FS, et al. The Extracorporeal Life Support Organization Maastricht Treaty for Nomenclature in Extracorporeal Life Support: A Position Paper of the Extracorporeal Life Support Organization. Am J Respir Crit Care Med 2018. [Epub ahead of print].
10. Taccone FS, Malfertheiner MV, Ferrari F, et al. EuroELSO Workgroup "Innovation on ECMO and ECLS". Extracorporeal CO2 removal in critically ill patients: a

systematic review. Minerva Anestesiol 2017;83:762-72.
11. Villar J, Blanco J, Añón JM, et al. ALIEN Network. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. Intensive Care Med 2011;37:1932-41.
12. Swedish Intensive Care Registry (SIR). Available online: http://www.icuregswe.org
13. Bersten AD, Edibam C, Hunt T, et al. Australian and New Zealand Intensive Care Society Clinical Trials Group. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. Am J Respir Crit Care Med 2002;165:443-8.
14. Goss CH, Brower RG, Hudson LD, et al. ARDS Network. Incidence of acute lung injury in the United States. Crit Care Med 2003;31:1607-11.
15. Combes A, Brodie D, Bartlett R, et al. The International ECMO Network (ECMONet). Position Paper for the Organization of Extracorporeal Membrane Oxygenation Programs for Acute Respiratory Failure in Adult Patients. Am J Respir Crit Care Med 2014;190:488-96.
16. Karagiannidis C, Brodie D, Strassmann S, et al. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. Intensive Care Med 2016;42:889-96.
17. Guidelines for ECMO transport. Extracorporeal Life Support Organization (ELSO), Ann Arbor, MI, USA, [Accessed 2018 May 2]. Available online: https://www.elso.org/Portals/0/ELSO%20Guidelines%20For%20Adult%20Respiratory%20Failure%201_4.pdf
18. Karamlou T, Vafaeezadeh M, Parrish AM, et al. Increased extracorporeal membrane oxygenation center case volume is associated with improved extracorporeal membrane oxygenation survival among pediatric patients. J Thorac Cardiovasc Surg 2013;145:470-5.
19. Freeman CL, Bennett TD, Casper TC, et al. Pediatric and neonatal extracorporeal membrane oxygenation: does center volume impact mortality? Crit Care Med 2014;42:512-9.
20. Barbaro RP, Odetola FO, Kidwell KM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. Am J Respir Crit Care Med 2015;191:894-901.
21. Ericsson A, Frenckner B, Broman LM. Adverse Events during Inter-Hospital Transports on Extracorporeal Membrane Oxygenation. Prehosp Emerg Care 2017;21:448-55.
22. Broman LM. Inter-hospital transports on extracorporeal membrane oxygenation in different health-care system. J Thorac Dis 2017;9:3425-9.
23. Pappalardo F, Montisci A, Scandroglio A, et al. VV ECMO in Europe: are we all speaking the same language? Minerva Anestesiol 2017;83:424-5.
24. Malfertheiner MV, Broman LM, Belliato M, et al. Management strategies in venovenous extracorporeal membrane oxygenation: a retrospective comparison from five European centres. Crit Care Resusc 2017;19:76-81.
25. Broman LM, Malfertheiner MV, Montisci A, et al. Weaning from venovenous extracorporeal membrane oxygenation: how I do it. J Thorac Dis 2018;10:S692-7.

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