Intensive Care Med (2017) 43:1869–1871
DOI 10.1007/s00134-017-4930-x

EDITORIAL

Do we need randomized clinical trials in extracorporeal respiratory support? We are not sure

Jean-Louis Vincent[1*] and Laurent J. Brochard[2,3]

Introduction

It is difficult to say we do not need a clinical trial, especially on a controversial topic like extracorporeal respiratory support in respiratory failure. The use of these techniques has increased tremendously over the last few years, such that they are now probably overused [1]. Better definition of the indications for extracorporeal respiratory support would be welcome, as would more insight into optimal practice. Whether such questions can be answered by randomized controlled trials (RCTs) remains debatable, however, largely because of issues related to variability in protocol and practice (Table 1).

Variability in goals

When considering extracorporeal respiratory support in respiratory failure, we need to define its purpose. Is it a rescue therapy to prevent death from hypoxemia? Or a technique to maintain oxygenation while avoiding unnecessary pressures? Or could it simply limit inflammation in the lungs and the subsequent release of inflammatory mediators into the circulation? Or all of these possibilities? RCTs of extracorporeal support in severe respiratory failure may, therefore, have different comparators and different outcome measures.

Variability in techniques

The first RCT of extracorporeal respiratory support in acute respiratory failure was designed to demonstrate that extracorporeal membrane oxygenation (ECMO) could reduce mortality in severe acute respiratory distress syndrome (ARDS) [2]. The study was well designed but really compared mechanical ventilation alone to ECMO plus (virtually) the same mechanical ventilatory conditions. Both arms had a mortality rate of around 90%. One may argue that the results from this study are now outdated, because ECMO technology has improved considerably over the years, but this also applies to the more lung-protective way in which we deliver mechanical ventilation. The subsequent RCT on extracorporeal CO_2 removal ($ECCO_2R$) in ARDS was conducted in 1994 by Morris et al. [3] who did not have extensive expertise in the use of the technique.

Variability in overall management

It would be reductionist to consider that an RCT of extracorporeal respiratory support would be only about the technique. One cannot separate the effects of this sophisticated technique from other aspects of the overall management of these complex patients. This point is illustrated by the CESAR trial [4], in which transfer to a specialized institution with ECMO facilities resulted in better outcomes; this was probably due to better overall management as well as the use of ECMO. We therefore need to answer (and define) several crucial questions first, such as what type of ventilation should we provide during ECMO? When and how should we allow spontaneous breathing? Should we allow patient mobilization? Could we use biomarkers to be sure that we safely rest the lungs?

Variability among centers

Along the same lines, the level of expertise in extracorporeal respiratory support can vary substantially from one institution to another and even among team

*Correspondence: jlvincent@intensive.org
[1] Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium
Full author information is available at the end of the article
For contrasting viewpoints, pleasego to doi:10.1007/s00134-017-4826-9 and doi:10.1007/s00134-017-4933-7.

Springer

Table 1 Randomized controlled trials on extracorporeal respiratory support in respiratory failure: some hurdles

	Hurdle
End points	
Mortality	Defining entry criteria for optimal severity Ethical aspects of randomizing life-saving therapy Variability in end-of-life approach
Ventilator-induced lung injury	Hard to measure (Small) benefit vs (small) risks
Comfort	Minimally invasive techniques not yet ready (Small) benefit versus (small) risks
Logistics	
Technical aspects	Various ECMO techniques in use Many unresolved issues about anticoagulation, respirator management, infection control, etc.
Center effects	Variability in expertise and patient recruitment
Other management aspects	Variability in other aspects of general patient management

members in the same institution. Other aspects of management, including mechanical ventilation conditions, anticoagulation, drug management, catheter maintenance, management of infections, and sedation, also vary. Overall patient management and technology are continuously improving, making it difficult to interpret the results of RCTs, which often take years to design and execute [5]. The suggestion that ECMO should only be conducted in expert centers [6] is also based on a wish to harmonize practice in the context of clinical trials and high-quality research.

Variability in populations and predictable outcome

Regardless of the question raised, acute respiratory failure encompasses many different diseases and patients with various associated types of organ failure and comorbidities. Hence, patient populations in such trials can be very heterogeneous, with some patients destined to do better or worse regardless of treatment. In other words, the real potential for mortality reduction may be much smaller than often postulated (and calculated). This is one of the reasons why many trials in the ICU are overly optimistic and frequently overestimate the expected treatment effects, leading to inconclusive trials [7].

If the end point is not survival, but a marker (still to be found!) of ventilator-induced lung injury (VILI), it may be difficult to show a difference in this outcome because the lung damage attributable to mechanical ventilation is now probably limited and has to be weighed against the side effects of extracorporeal systems, including bleeding. Perhaps a difference in patient comfort could be considered as an outcome if simple extracorporeal systems could replace endotracheal intubation and invasive mechanical ventilation, but such simple, safe, and affordable systems are not yet available.

Equipoise

One can argue that a life-saving therapy (e.g., cardiac defibrillation in patients with ventricular fibrillation) cannot be studied in an RCT, as the control group would be deprived of a chance of survival. During an influenza epidemic, would relatives of a patient about to die from respiratory failure agree for him/her to be randomized? Interestingly, when researchers tried to perform propensity matching on a cohort of patients with H1N1-induced ARDS in order to compare patients who were or were not treated with ECMO, they were not able to match a substantial number of the ECMO patients [8]: the unmatched ECMO patients were younger and more hypoxemic (and also had better survival). The fact that one could hardly find any young, very hypoxemic patients who did not receive ECMO in this setting likely reflects a strong feeling among clinicians that these patients should absolutely receive ECMO.

Conclusion

Although RCTs of extracorporeal respiratory support are a priori desirable, all the above factors boil down to a risk of negative RCTs to be added to our already long list of negative clinical trials in critical care medicine. The consequences of negative clinical trials are frequently that the intervention is abandoned. So, if our RCT of extracorporeal respiratory support in respiratory failure is negative, should we abandon the technique? After all, the first study by Zapol et al. [2] was negative, but advances in knowledge and technology led us to revisit the use of the technique. If the results of such a trial show no difference, perhaps improvements would be needed before starting all over again… but then the story may never end. Better knowledge and technological improvements may make extracorporeal support a moving target…

Author details
[1] Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium. [2] Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada. [3] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada.

Compliance with ethical standards

Conflicts of interest
JLV has no conflicts of interest to declare. LB has received research grants and/or equipment for his research laboratory from Maquet (NAVA), Covidien (PAV), Air Liquide (helium, CPR), Fisher Paykel (high flow), General Electric (lung volume; ultrasound), and Philips (sleep).

Received: 24 August 2017 Accepted: 31 August 2017
Published online: 25 September 2017

References

1. Karagiannidis C, Brodie D, Strassmann S, Stoelben E, Philipp A, Bein T, Muller T, Windisch W (2016) Extracorporeal membrane oxygenation: evolving epidemiology and mortality. Intensive Care Med 42:889–896
2. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Peirce EC, Thomas AN et al (1979) Extracorporeal membrane oxygenation in severe acute respiratory failure: a randomized prospective study. JAMA 242:2193–2196
3. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF Jr, Weaver LK, Dean NC, Thomas F, East TD et al (1994) Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 149:295–305
4. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F et al (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 374:1351–1363
5. Frieden TR (2017) Evidence for health decision making—beyond randomized, controlled trials. N Engl J Med 377:465–475
6. Combes A, Brodie D, Bartlett R, Brochard L, Brower R, Conrad S, De Backer D, Fan E, Ferguson N et al (2014) Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. Am J Respir Crit Care Med 190:488–496
7. Djulbegovic B, Kumar A, Magazin A, Schroen AT, Soares H, Hozo I, Clarke M, Sargent D, Schell MJ (2011) Optimism bias leads to inconclusive results—an empirical study. J Clin Epidemiol 64:583–593
8. Pham T, Combes A, Roze H, Chevret S, Mercat A, Roch A, Mourvillier B, Ara-Somohano C, Bastien O et al (2013) 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 187:276–285