

What about prognostic outcome parameters in patients with acute respiratory distress syndrome (ARDS) treated with veno-venous extracorporeal membrane oxygenation (VV-ECMO)?

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Provenance: This is an invited Editorial commissioned by the Editorial Board Member Prof. Federico Pappalardo (Department of Anesthesia and Intensive Care, Advanced Heart Failure and Mechanical Circulatory Support Program, San Raffaele Scientific Institute and San Raffaele Vita-Salute University, Milan, Italy).

Comment on: Bonizzoli M, Lazzeri C, Cianchi G, *et al.* Serial Lactate Measurements as a Prognostic Tool in Venovenous Extracorporeal Membrane Oxygenation Support. *Ann Thorac Surg* 2017;103:812-8.

Burrell AJC, Lubnow M, Enger TB, *et al.* The impact of venovenous extracorporeal membrane oxygenation on cytokine levels in patients with severe acute respiratory distress syndrome: a prospective, observational study. *Crit Care Resusc* 2017;19:37-44.

Submitted May 17, 2018. Accepted for publication May 25, 2018.

doi: 10.21037/jtd.2018.05.172

View this article at: <http://dx.doi.org/10.21037/jtd.2018.05.172>

The acute respiratory distress syndrome (ARDS) remains a clinically relevant disease and causes high morbidity and mortality (1). Various treatment approaches exist to cope with the most critical patient courses. In the last decades therapeutic options for primary or secondary pulmonary failures were enlarged by the increasing spread and use of ECMO. The rate of treatments of severe respiratory failure with veno-venous extracorporeal membrane oxygenation (VV-ECMO) is rapidly increasing counting more than 15,600 adult treatments in the Extracorporeal Life Support Organization Registry in February 2018. In the treatment of ARDS, the VV-ECMO is a meanwhile established therapeutic approach despite ongoing discussion regarding evidence (2). Although there are consented parameters for indication of VV-ECMO (2), we are still lacking suitable prognostic parameters, that give us an arbitration about the potential success of ECMO treatment and about outcome of treated patients.

Treatment options for the severe ARDS

Conventional treatment modalities for ARDS range from supportive care by prone positioning, lung-protective ventilation, nitric oxide inhalation, and administration of

intravenous steroids in addition to a causal anti-infective therapy. Especially lung protective ventilation demonstrated an impressive impact on survival by preserving barrier properties of the alveolar endothelium and alveolar epithelium and downregulating also pro-inflammatory pathways resulting in lower plasma cytokine levels (IL-6, IL-8, TNF-alpha) (1). But despite these therapeutic approaches patients may suffer from arterial hypoxemia and hypercarbia. The initiation of VV-ECMO therapy, which is still a high risk and complex therapy, may be life-saving in severe ARDS. The risk-to-benefit ratio of ECMO in this setting has not yet been fully elucidated and evidence and recommendations especially for less severe forms of acute respiratory failure are lacking in the literature (2).

Control of inflammation during VV-ECMO in patients with ARDS: a valuable target?

In addition to a pronounced arterial hypoxemia and hypercarbia, patients with ARDS may present a massive systemic inflammatory response that might induce multiple organ dysfunction syndrome (3,4). Cytokine levels and pro-inflammatory mediators correlate in height with the degree of organ failure (5).

Understanding the inflammatory response mechanisms of patients with ARDS who undergo VV-ECMO are important and several therapeutic strategies for ARDS like lung-protective ventilation try to mitigate the ventilator-induced lung injury as a major factor of ventilator-attributable injury (6). Additionally, the inflammatory response to the pathogen, increasing tidal volume may also increase cytokine levels (7). A pathogen-induced inflammatory activation may result in an overwhelming inflammatory response. Several pro-inflammatory cytokines play important roles in the acute pulmonary inflammation process and the development of inflammatory lung diseases, in particular for ARDS (8). Fueled by the release of endogenous inflammatory mediators, an uncontrolled exuberant systemic inflammatory response with detrimental effects and organ damage can occur (9).

A recent study conducted by Burrell *et al.* described a cytokine decrease after initiation of VV-ECMO in patients with severe ARDS (10). The study differed ARDS with pulmonary and extrapulmonary origin and observed higher interleukin-6 (IL-6) and IL-8 plasma levels for the extrapulmonary ARDS. High IL-6 plasma levels correlate with high mortality rates (11). Increased IL-6 levels are also known to be associated to the trans-signaling pathway, which is associated with vascular leakage, followed by capillary leakage (12). This may induce a vicious circle resulting in tissue edema, hypoxia and cell death. Therefore, IL-6 is also relevant for the capillary leakage. Consequently, it is related to the integrity of the endothelial glycocalyx and finally to the endothelial barrier function (12). Preservation of an intact glycocalyx and an endothelial barrier function may play an important role for treatment strategies of severe ARDS.

Kellum *et al.* observed the highest mortality risk in septic pneumonia patients with highly elevated pro-inflammatory IL-6 and anti-inflammatory IL-10 plasma levels (11). The IL-10 levels were not stated in the study of Burrell *et al.* (10), but it would be interesting, if this subgroup (with highest IL-6 and highest IL-10 levels) had the worst prognosis of all included patients too. Consequently, the interaction of pro- and anti-inflammatory mediators must be seen as an important determinant for the courses of patients and should be focused in research to find strategies for early recognition and treatment.

In line to previous studies, Burrell *et al.* confirmed that normalization of highly elevated cytokine plasma levels was associated with better outcome in the VV-ECMO treated ARDS patients (10).

Because infections may induce organ damage due to the virulent pathogen, the cascade and pathways of signaling must be focused for further investigations to determine the intervals for cytokine monitoring. As shown by the steep decline in the first 24 hours after the start of VV-ECMO in the study by Burrell and colleagues, the most interesting phase is the initial phase and the immune processes are still unclear. Understanding the innate immune response mechanisms might be the key for treatment approaches.

Why do highly activated cytokine genes remain activated after fighting the pathogen associated infection?

What fuels the release and re-release of cytokines during the high-inflammatory period?

To break this vicious circle as quick as possible seems to be a valuable task for successful treatment. The question is still open if VV-ECMO per se induce the cytokine level decline in the study of Burrell and colleagues. In addition, it could be of interest to identify patient-individual specific conditions and circumstances which trigger enduring cytokine release. Probably, knowing the high-risk patient population and breaking the vicious circle of cytokine release as quick as possible seem to be essential for successful treatment approaches.

However, there are several aspects influencing cytokine plasma levels for the treatment of ARDS patients apart of the initiation of the VV-ECMO therapy itself:

- (I) Patients with ARDS due to infection are treated with antibiotics and/or antimycotics which may have a relevant impact on the pathogen load and the subsequent immune response.
- (II) Septic shock treatment protocols may include administration of corticosteroid medication, which also modulates the immune response.
- (III) Prone position combined with reduction of invasive ventilation itself reduces cytokine plasma levels.

To escape this vicious circle, early recognition of clinical situations, maintaining circulation and sufficient oxygenation are essential. Coping with excessive cytokine plasma levels is discussed to be a valuable target to mitigate and to prevent detrimental consequences of exuberant systemic inflammatory processes, organ damage, failure and death. Central questions for future investigations in the context of ARDS, ECMO, and cytokine plasma levels are:

- (I) Does VV-ECMO treatment itself reduce cytokine plasma levels and improve survival or is it a side-effect of the multi-therapeutic treatment approach with causative or pathogen-focused therapy according to established guidelines?

- (II) Are cytokines suitable targets for treatment?
- (III) Can we improve survival of patients with overwhelming inflammatory response by implementing additional cytokine reducing strategies?

The initiation of an extracorporeal circuit like ECMO therapy itself is associated with a complex and often unpredictable inflammatory reaction similar to the systemic inflammatory response syndrome (13) and this mechanism is triggered by the activation of inflammatory and coagulative cascades due to contact to foreign surfaces in the extracorporeal circuit (9). A massive uncontrolled release of pro-inflammatory cytokines, followed by leucocyte activation may lead to endothelial injury, disrupted microcirculation and as a consequence organ dysfunction (13). This has formed the basis for potential therapeutic interventions aimed at curbing the inflammatory process.

However, these interventions have to be assessed in the light of results of Burrell *et al.* (10), which showed a clear decline in cytokines levels within 24 hours by the implementation of ECMO and the associated reduction of aggressiveness of ventilator use alone.

On the one hand, inflammation is caused by the pathogenic agent and the host response and on the other hand, the release of inflammatory markers is triggered by therapy related invasive ventilation (5,7) or the ECMO treatment itself (13).

The mentioned study suggests positive effects of ECMO treatment in this context and the presented data suggest that in particular patients with high cytokine levels may benefit from VV-ECMO therapy. It could be argued that the reduction of positive end-expiratory pressure (PEEP), driving pressure and tidal volume reduces cytokine levels (significant for PEEP). Data also suggest that the higher the cytokine levels, the more beneficial the patients ECMO therapy. An interesting point for further investigations could be a detailed workup of the cytokine levels course during the first 24 hours after initiation of the VV-EVMO therapy, which reflects the highest decline of cytokine levels. The stated IL-6 levels in the study were at a moderate median of 1,338 pg/mL. The time course for the subgroup of patients with the highest IL-6 levels and highest associated mortality rate could show if there is an additional option for cytokine controlling strategies. This patient subgroup represents a high-risk group, which may predominantly profit from an early and aggressive anti-inflammatory treatment. The condition of a high inflammatory process consists several aspects of intensive care medicine and shock treatment

which have anti-inflammatory potential. Ideally this subgroup of sickest patients might profit from a fast cytokine reduction in particular. Removal of excessive plasma cytokines with a cytokine adsorbent device is discussed controversially as a therapeutic approach in clinical situations of overwhelming inflammatory responses (12) and several studies describe sufficient control of exuberant inflammation (14-17). Even if the harmful side effects of additional cytokine removal devices actually seem to be low, the question is not answered yet, if an additional cytokine removing device is helpful at all and how patients can be identified who benefit such a treatment approach.

Lactate clearance: a helpful prognostic parameter in VV-ECMO treated patients?

Suitable prognostic factors or appropriate markers of treatment efficacy in patients with ARDS during VV-ECMO are lacking. In a recently published study of Bonizzoli *et al.* (18) on patients with ARDS and VV-ECMO, the authors investigated serial measured lactate values before and up to 72 hours of VV-ECMO treatment for risk stratification. Lactate clearance was observed to be a prognostic factor in VV-ECMO treated patients with severe ARDS and especially reduced lactate clearance at 72 hours after initiation of the VV-ECMO therapy was demonstrated as an independent predictor of mortality.

Measurements of lactate are commonly used for a broad spectrum of critically ill patients and well established for cardiocirculatory shock and sepsis (19,20). Therapeutic approaches of severe shock and severe ARDS include VV-ECMO therapy which is able to stabilize oxygen supply, to diminish oxygen deficiency and to reduce carbon dioxide. The mismatch between oxygen delivery and oxygen consumption is associated with increased lactate levels as a result of anaerobic metabolism when glycolysis proceeds via pyruvate to lactate in absence of oxygen (21). Actually, serial lactate measurements and lactate clearance rates are important parameters monitored on intensive care units and are considered to be markers of shock severity and to have a predictive power for shock management (22). Hyperlactatemia is mainly considered to be of hypoxic origin in critically ill patients with tissue hypoxia and cannot be sustained over time without cell death due to lower energy production by anaerobic metabolism compared to aerobic metabolism (21).

Lactate levels at the bedside can easily be measured and serial lactate levels or lactate clearance have been well

investigated in critically ill patients especially in the cardiac setting for prognostic assessment (22). The influence of supportive therapies like VV-ECMO are so far not well elucidated regarding serial lactate measurements or lactate clearance for its prognostic potential. While VV-ECMO is increasingly used for severe ARDS, clinical tools for outcome prognosis and risk stratification are not well established. Serial lactate measurements or calculations of lactate clearance are well-established prognostic tools. A significant context between higher lactate clearance rates and improved survival was described for patients with ARDS from 12 to 72 hours which indicates lactate clearance as a predictor of mortality (23). Even treatment with veno-arterial ECMO and serial lactate measurements or lactate clearance showed an unclear and heterogenous picture and has not proven to be a reasonable predictive tool.

Only a few data on patients with VV-ECMO regarding lactate courses are available. The study of Bonizolli and colleagues (18) on patients with ARDS undergoing VV-ECMO therapy described the course of lactate levels before and during the extracorporeal treatment as a valuable tool with predictive potential. Bonizolli *et al.* suggested hypoperfusion and a worsening lung function to be the main sources of increased lactate concentrations as seen in the non-survivor group. Norepinephrine dosages, hemodynamics, renal and hepatic functions were similar in both groups. ECMO flow rates were higher in the non-survivor group despite equal oxygen and carbon dioxide partial pressures. In conclusion, the authors suggested that the remaining lung function was more compromised in the non-survivor group. Moreover, the survivor and non-survivor group showed significant differences for age, SOFA score, and body mass index, which should be taken into account. In particular, the time of mechanical ventilation before initiation of VV-ECMO differed significantly. Thus, the longer period of compromised gas exchange may still be an expression of an accumulated metabolic deficiency appearing as worse lactate clearance. The study stated that lactate clearance rate of 72 hours should be considered as an independent predictor of intensive care unit mortality and that patients with reduced lactate clearance rates have a higher risk of dying.

However, it has to be considered that the lung itself is regarded to be a major source of lactate and the magnitude of lung injury correlates with lactate levels (24). Accordingly, lactate levels need to be evaluated and compared very carefully—especially for patients with varying degrees of ARDS before any conclusions can be drawn. Even if lactate

clearance might stay in close context with mortality in VV-ECMO treated patients, further investigations are needed for evaluation of the efficacy of serial lactate measurements, to identify the mechanisms of lactate release and search for other suitable prognostic outcome parameters during VV-ECMO and severe ARDS.

At the end of the day, we are still looking for helpful parameters that enable us to judge the efficacy of a complex treatment in ARDS patients and even may serve as prognostic but also pragmatic tools in the field of VV-ECMO treatment. Monitoring effects on inflammatory and metabolic activity as integrative parameters of immune system and organ function may show us a step toward this direction.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Datzmann T, Träger K. What about prognostic outcome parameters in patients with acute respiratory distress syndrome (ARDS) treated with venovenous extracorporeal membrane oxygenation (VV-ECMO)? *J Thorac Dis* 2018;10(Suppl 17):S2057-S2061. doi: 10.21037/jtd.2018.05.172