EJAIC

Eur J Anaesthesiol Intensive Care Med 2022; **2:**1(e0012)

OPEN

CASE REPORT

Indications for extracorporeal membrane oxygenation in coronavirus disease 2019: is the Berlin definition still adequate to adjust therapeutic interventions? A case report

Anna Rau, Onnen Moerer and Martin Sebastian Winkler

Eur J Anaesthesiol Intensive Care Med 2022, **2**:1(e0012)

Published online 8 December 2022

Introduction

Our medical centre, serving a rural area in Germany, specialises in acute respiratory distress syndrome (ARDS) and venovenous extracorporeal membrane oxygenation (vv-ECMO) therapy. We were confronted with a drastic increase of ARDS patients in the past 2.5 years and treated 106 ECMO patients with an in-hospital mortality of 56%. The international registry of the Extracorporeal Life Support Organization (ELSO) reports 14 717 coronavirus disease 2019 (COVID-19) ECMO treatments with an ICU mortality of 47% in June 2022.[1] Although ECMO survival rates can be regarded as a success, approximately 50% of patients die. This is reason enough to question our current practice of allocating ECMO resources on the basis of existing ARDS guidelines and criteria, and whether we need to adapt our strategies to include evolving evidence and patient characteristics.[2]

In this context, we present a COVID-19 case and discuss measured inflammatory and respiratory factors potentially defining an ideal interventional window for vv-ECMO.

Medical history

A 62-year-old male, high-risk patient with obesity grade III (BMI: 46.3), a history of arterial hypertension, atrial fibrillation and chronic rheumatoid arthritis was treated for 18 days in our ICU in March and April 2021.

Clinical course

Before admission to our centre, the patient was treated for COVID-19 pneumonia for 7 days in a small, nontertiary hospital. Due to progressive respiratory insufficiency, the patient was intubated and transferred to our ICU 24 h later with the diagnosis of moderate-to-severe ARDS according to the Berlin definition, with a p_aO_2/F_iO_2 ratio before ECMO therapy of 116 mmHg [66 to 191] (median [min to max]).[2] Our standardised protocol for COVID-19 includes monitoring of various inflammatory markers such as interleukin-6 (IL-6), D-dimers, procalcitonin (PCT) and C-reactive protein (CRP) as well as continuous measurement of other variables as previously described such as respiratory effort by calculation of mechanical power in Joules min^{-1} and various other respiratory parameters, such as driving pressure.[3] We were surprised by the rapid and progressive impairment of ventilatory parameters, which were accompanied by the inflammatory reaction represented by IL-6 levels (Fig. 1a). We interpreted this as an 'inadequate host-response' with peak IL-6 levels expressing the most vulnerable phase of SARS-CoV-2-infected lungs. Moreover, the supposed peak inflammatory response was associated with increasing respiratory effort, reflected by high mechanical power and driving pressures (Fig. 1a). We defined a hypothetical window of intervention and considered potential measures to overcome this critical phase. As therapeutic options to influence the patient's 'host-response', and suppress the pro-inflammatory response were both limited, we considered ECMO in order to lessen the respiratory stress even though the p_aO_2/F_iO_2 was not expressly indicative. We were aware of the ECMO-specific risks, such as bleeding, but decided to cannulate vv-ECMO on day 8 when a peak inflammatory phase was anticipated. This strategy was successful and the power applied to the lungs could be immediately

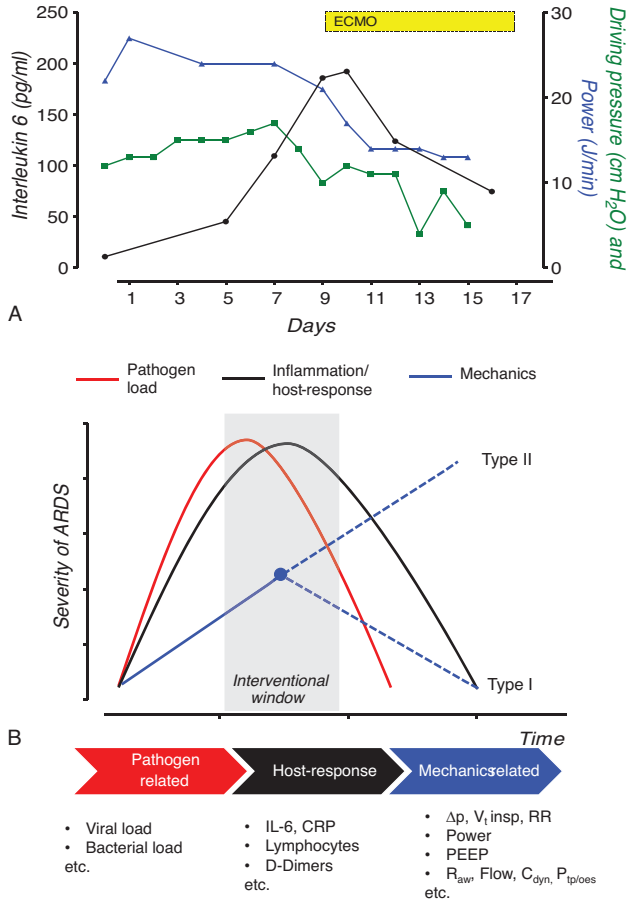
From the Department of Anaesthesiology and Intensive Care Medicine, University Medical Center Göttingen, University of Göttingen, Germany

Correspondence to Anna Rau, MD, Klinik für Anaesthesiologie, Universitätsmedizin Göttingen, Robert-Koch-Straße 40, D-37075 Göttingen, Germany. Tel: +49 551 3967744; e-mail: anna.rau2@med.uni-goettingen.de

DOI:10.1097/EA9.0000000000000012

EJAIC

Fig. 1 (a) ICU course of a patient with severe coronavirus disease 2019.



IL-6 levels (black line) left *y*-axis, mechanical parameters, power ($J\,min^{-1}$, blue line) and driving pressure (cmH_2O, green line) right *y*-axis, over time in ICU (*x*-axis). Rising IL-6 levels are accompanied by increasing driving pressure, a surrogate marker for declining pulmonary compliance. The respiratory effort as measured by mechanical power was high with a potential to further damage the inflamed lung. We identified a hypothetical interventional window: peak inflammation plus peak mechanical stress. ECMO was used as a protective strategy to eliminate mechanical stress. The success is indicated by declining power and driving pressure. (b) Model of parameters contributing to ARDS severity. ARDS pathogenesis and progression from mild-to-severe depend mainly on three factors theoretically related to the pathogen and the inflammatory host response. The patient compensates by increasing the respiratory effort, which is measured by mechanical power, respectively, the energy applied to the lung. The identification of a 'turning point' is problematic and challenging; hypothetically defined as a decline in respiratory effort together with the inflammatory response and pathogen load. In this type 1, patient lung compliance is preserved. Type 2 is defined as a low compliant lung with increasing respiratory effort and mechanical stress. The diagnostic challenge is identification of a therapeutic intervention window. Here, many dynamic parameters may help to identify pathogen related factors such as viral load, the host response by immune monitoring and mechanical stress by calculation of mechanical power, driving pressure and various other parameters. Δ*p*, driving pressure; ARDS, acute respiratory distress syndrome; C_{dyn}, dynamic compliance; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; Il-6, interleukin-6; PEEP, positive end expiratory pressure; $P_{tp/oes}$, transpulmonary, oesophageal pressure; R_{aw}, airway resistance; RR, respiratory rate; V_t insp, inspiratory tidal volume.

reduced (Fig. 1a). Furthermore, we were able to extubate the patient after 3 days using ECMO to eliminate CO_2 and thus reduce spontaneous respiratory effort. The ECMO was discontinued after 9 days, and the patient discharged with minor oxygen support. The informed consent to publication was obtained from the legal representative before discharge.

Discussion

We demonstrate a successful therapeutic intervention by ECMO therapy to avoid damage to the lung even though the p_aO_2/F_iO_2 according to the current Berlin definition was not continuously indicative. ECMO allowed us to procure better physiological conditions at a time when the inflammation was suspected to be most severe. This case is consistent with other observations and demonstrates that being able to cease harmful mechanical ventilation through the use of ECMO may terminate a vicious circle.[4] This vicious circle includes an inadequate host response together with an overwhelming pro-inflammatory, intraparenchymal process that causes hypoxaemic lung failure necessitating increased compensatory mechanical stress. This understanding is crucial for both concepts of either self-inflicted (P-SILI), host-mediated lung injury, or ventilator induced lung injury (VILI), a iatrogenic-induced lung injury.[3,5]

COVID-19 is a new disease entity allowing us to study the kinetics of this vicious circle from the beginning of mild infection to severe ARDS. In this regard, COVID-19 is a prime example of a time-dependent interaction of pathogen, host and mechanical factors that determine clinical severity.[4] Three considerations may help to identify patients at risk: the disease progression is driven by the viral/pathogen load, the inflammatory host response[4] and mechanical parameters[3] (Fig. 1b). This complexity is inadequately reflected by the traditional Berlin definition, which has a focus on p_aO_2/FiO_2.[2,6] The usefulness of precise host-response monitoring to classify patients is even more important as hypoxaemia is a hallmark of all patients presenting with severe COVID-19. In this pandemic, we have gained new experiences, highlighting the field of immune monitoring in order to characterise the host response better; also applicable to other forms of sepsis-induced ARDS.

In addition, we should acknowledge that different COVID-19 phenotypes exist with variable mechanical parameters, which have been described earlier, leading to therapeutic recommendations.[6] The main differences that concern the lung compliance and the mechanical energy applied to the lungs (type 1: high C and low power vs. type 2: low C and high power). The PRoVENT-COVID-19 collaboration confirmed that a comparatively homogenous population converts over time to a heterogenous cohort, with mechanical power being the most discriminatory parameter of the two phenotypes.[7] It is imperative to identify these clinical phenotypes and adjust individual treatment algorithms,

such as noninvasive oxygenation strategies for patients with high pulmonary compliance, and tracheal intubation and ECMO for patients with reduced pulmonary compliance.[6] Furthermore, we should be aware that all interventions may be harmful. In this context, Lebreton *et al.*[8] has recently shown that a delay in ECMO commencement in intubated COVID-19 patients is an independent risk factor of not surviving. The risk of death significantly increased when ECMO therapy became indicated after more than 3 days of invasive MV.[8] The delay between intubation and ECMO cannulation, as a survival factor, presents a strong argument for early cannulation to allow protective ventilatory strategies to maintain high compliance by reducing the mechanical power.

Conclusion

COVID-19-related lung failure is unique and complex, such that a single well established physiological parameter is not sufficient to reflect the dynamic, time critical progression from infection to ARDS. The interventional window should, therefore, include parameters that describe more factors. Deviation from certain thresholds may justify escalating therapy, including invasive ECMO therapy even before intubation, and even before the Berlin definition informs us that p_aO_2/F_iO_2 is below 100. In this context, 'bridging-ECMO' allows time for the host to eliminate the pathogen and control the inflammatory response under the best protective ventilatory conditions.

Acknowledgements relating to this article

Assistance with the study: none.

Financial support and sponsorship: the publication of the case report was supported by the open access publication fund of University of Göttingen. Within the last 36 months OM received honoraria for industry sponsored lectures on congress and webinars by Getinge and CSL Behring.

Conflicts of interest: MW received unrestricted funding from SARTORIUS Ag-Lung research. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Presentation: none.

This manuscript was handled by Dan Longrois.

References

1 Registry Dashboard of ECMO-Supported COVID-19 Patient Data. Ann Arbor, USA. Extracorporeal Life Support Organization. 2022. Available at: https://www.elso.org/Registry/Full COVID-19RegistryDashboard.aspx. [Accessed 04 July 2022]

2 The ARDS Definition Task ForceRanieri VM, Rubenfeld GD, *et al.* . Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012; **307**:2526–2533.

3 Marini JJ, Rocco PRM, Gattinoni L. Static and dynamic contributors to ventilator-induced lung injury in clinical practice. pressure, energy, and power. *Am J Respir Crit Care Med* 2020; **201**:767–774.

4 Osuchowski MF, Winkler MS, Skirecki T, *et al.* The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med* 2021; **9**:622–642.

5 Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017; **195**:438–442.

6 Gattinoni L, Chiumello D, Caironi P, *et al.* COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020; **46**:1099–1102.

7 Bos LDJ, Sjoding M, Sinha P, *et al.* Longitudinal respiratory subphenotypes in patients with COVID-19-related acute respiratory distress syndrome: results from three observational cohorts. *Lancet Respir Med* 2021; **9**:1377–1386.

8 Lebreton G, Schmidt M, Ponnaiah M, *et al.* Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. *Lancet Respir Med* 2021; **9**:851–862.