Intensive Care Med (2021) 47:1494–1496
https://doi.org/10.1007/s00134-021-06523-x

LETTER

Standardized liberation trials in patients with COVID-19 ARDS treated with venovenous extracorporeal membrane oxygenation: when ready, let them breathe!

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Dear Editor,

Venovenous (VV) extracorporeal membrane oxygenation (ECMO) has proven to be useful in the management of patients with severe acute respiratory distress syndrome (ARDS) associated with coronavirus disease 2019 (COVID-19) [1]. Due to its invasive nature, timely liberation from ECMO should become a priority when it is no longer needed for gas exchange or to attenuate ventilator induced lung injury. Current liberation strategies are variable [2–4] and may lead to both under-recognition of readiness or unsafe initiation of liberation attempts.

We designed a single-center, retrospective cohort study of adult patients treated with VV ECMO for COVID-19 ARDS at Toronto General Hospital between May and October 2020. The objective of the study was to assess the feasibility of adopting a standardized liberation protocol. We introduced an alternative approach to liberation, incorporating a daily assessment of eligibility for ECMO liberation trials. Entry criteria included 12 h of treatment for ARDS, no neuromuscular blockade, hemodynamic stability, reasonable ventilation parameters, and extracorporeal blood flow ≤ 5 L/min and sweep gas flow (SGF) ≤ 4 L/min (Supplementary material Table 1). Readiness for liberation was assessed by conducting standardized liberation trials (SLTs) (Fig. 1—Panel A and supplementary material Tables 2 and 3). SLTs consisted in interrupting SGF (i.e., 4–0 L/min), emulating spontaneous breathing trials. For successful SLTs, patients would be maintained off SGF until decannulation (usually within 24 h). In failed SLTs, patients would continue to be trialed daily. Differences in ventilatory, hemodynamic and blood gas parameters were collected and compared between SLT outcomes using Mann–Whitney *U* test.

We performed 61 SLTs in 31 patients, with 19 SLTs (31%) leading to decannulation (Supplementary material Table 4—Fig. 1). Seventy-three percent of decannulated patients were liberated from higher SGF than usual practice (SGF ≥ 2 L/min), with 63% requiring ≤ 2 SLTs (Fig. 1—Panel B). At trial termination, failed SLTs had different respiratory mechanics, ventilatory ratio and worse oxygenation (Fig. 1—Panel C and supplementary material Table 5). Median time to SLT failure was 0.25 h (IQR 0.25–1.5). The most common reasons for failing were hypoxemia (40%) and increased work of breathing (36%).

The rate of SLT related complications was 3% (respiratory acidosis and atrial fibrillation). Two patients (10%) failed decannulation [5]. One patient was recannulated and ultimately decannulated after treating for a new ventilator associated pneumonia. Four patients (23%) died after decannulation (two died of non-respiratory causes, one died of unrelated pulmonary hemorrhage, one died of respiratory failure and sepsis [decannulation failure]). Median time to death was 7.5 days (IQR 6–13) (Supplementary material Figs. 3 and 4). All remaining decannulated patients were subsequently extubated (median 11 days, IQR 2–25).

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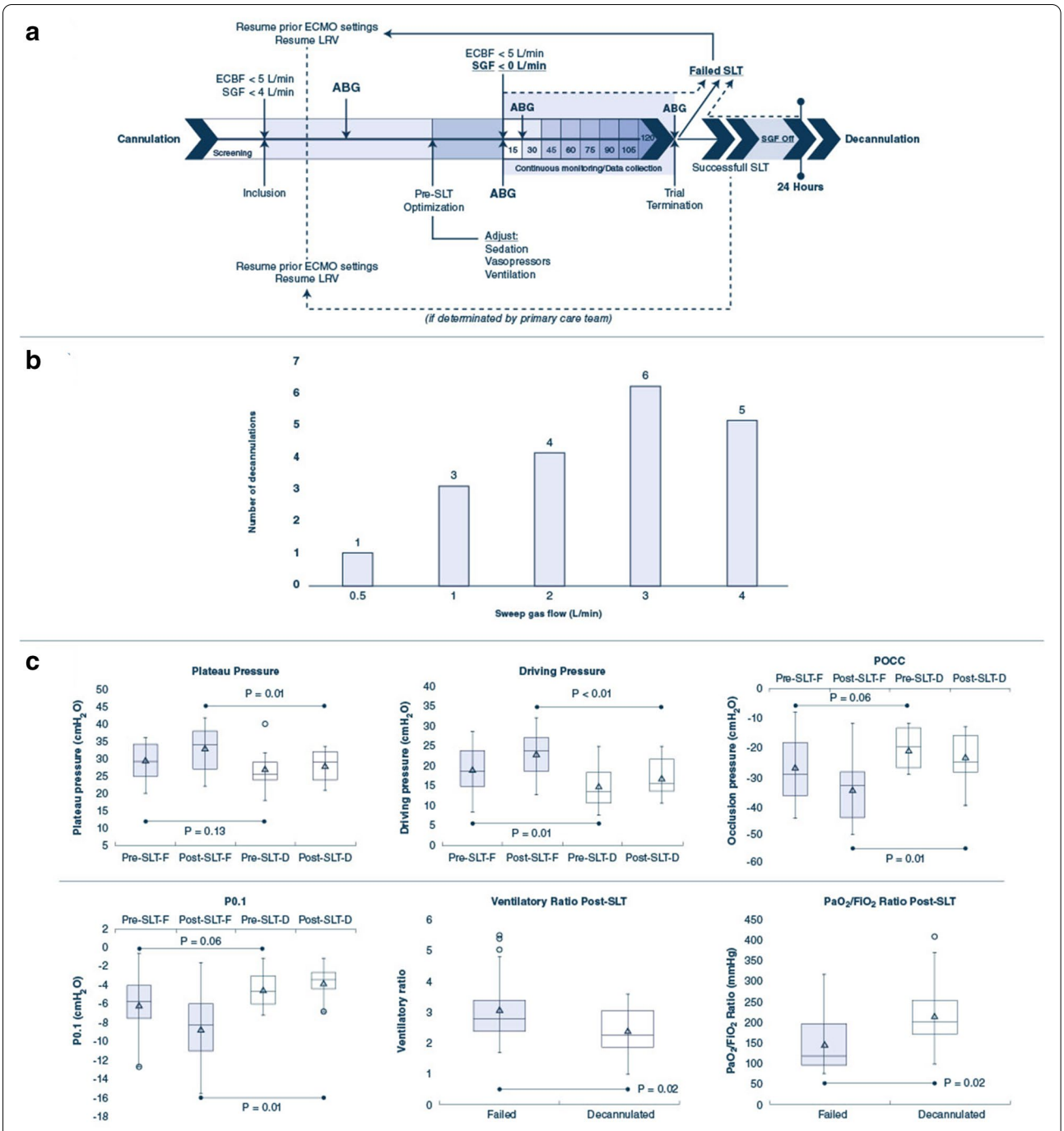

Fig. 1 **A** Protocol schematic. *SLT* standardized liberation trial, *ECMO* extracorporeal membrane oxygenation, *LRV* lung rest ventilation, *LPV* lung protective ventilation, *ABG* arterial blood gas, *ECBF* extracorporeal blood flow, *SGF* sweep gas flow. **B** Number of decannulation performed as a function of the sweep gas flow rate at the start of the standardized liberation trial. **C** Changes in physiologic parameters during standardized liberation trials. Gray box plots represent failed trials. White box plots represent trials that led to decannulation. Boxes encompass values between the 25th and 75th percentile. The horizontal line within the box represents the median. The triangles represents the mean. Whiskers account for the 10th and 90th percentiles. *Pre-SLT-F* pre standardized liberation trial values in failed trials, *Pre-SLT-D* pre standardized liberation trial values in trials that led to decannulation, *Post-SLT-F* post standardized liberation trial values in failed trials, *Post-SLT-D* post standardized liberation trial values in trials that led to decannulation, *POCC* occlusion pressure. Occlusion pressure is measured by performing an expiratory hold during inspiration in mechanical ventilation. The maximal negative deflection in the airway pressure tracing represents the occlusion pressure, and is a surrogate of respiratory effort. The ventilatory ratio is a marker of impaired ventilation, and is calculated by the following formula: VR = [Minute ventilation (ml/min) × $PaCO_2$]/ Predicted body weight × 100 × 37.5

We developed and tested a standardized liberation protocol incorporating defined entry criteria and pragmatic liberation trials to identify patients with enough lung recovery to be liberated from ECMO. Given the small sample size and exploratory nature of our study, we did not explore the utility of collected variables for predicting successful decannulation. Although hypothesis generating, early identification of patients ready to be liberated may potentially allow for shorter duration of support, reducing ECMO related costs and complications. The limitations of the study include its retrospective observational nature, small population and single center distribution. We did not capture duration of sedation or paralysis, however, all patients needed to be off paralysis for at least 24 h prior to a SLT. As no universal definition of successful decannulation exists, we were unable to fully explore the safety of incorporating SLTs to clinical practice. Further research into liberation from ECMO is needed. Extrapolating from research on liberation from mechanical ventilation, where a systematic assessment demonstrated superiority to clinical judgement and preference, it is intuitive to think that protocolized approaches to liberation form ECMO will follow a similar path.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06523-x.

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RT-P: conceptualization, methodology, data collection, analysis, manuscript preparation. PT: conceptualization, data collection, review and editing. AS: conceptualization, methodology, data storage, review and editing. LDS: conceptualization, methodology, review and editing. EF: conceptualization, methodology, analysis, review and editing.

Funding
Not applicable.

Availability of data and material
Not applicable.

Code availability
Not applicable.

Declarations

Conflicts of interest
EF reports personal fees from ALung Technologies, Baxter, Boehringer-Ingelheim, GE Healthcare, and MC3 Cardiopulmonary outside the submitted work. No conflicts of interest/competing interests for all other remaining authors.

Ethics approval
This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University Health Network (REB 20-6142) approved this study.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Publisher's Note

Received: 1 July 2021 Accepted: 30 August 2021
Published online: 16 September 2021

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