Outcomes of Patients Denied Extracorporeal Membrane Oxygenation during the COVID-19 Pandemic in Greater Paris, France

To the Editor:

Venovenous extracorporeal membrane oxygenation (ECMO) was considered early in the pandemic to rescue the most severe forms of coronavirus disease (COVID-19)–associated acute respiratory distress syndrome (ARDS). The 90-day survival of these patients was 60–64% in the largest cohorts of studies published to date (1, 2). To prevent a shortage of resources and avoid compassionate use and futility, an ECMO hub-and-spoke network organization was created in Greater Paris, France. Guidelines for ECMO indications and management were developed by a task force and disseminated by the regional health administration. These criteria did not change during the study period. All ECMO indications were validated by the Pitié-Salpêtrière Hospital ECMO team. Patients being considered for ECMO had to fulfill EOLIA (ECMO to Rescue Acute Lung Injury in Severe ARDS) trial ARDS severity criteria (3) despite the optimization of mechanical ventilation, a trial of prone positioning, and the use of neuromuscular-blocking agents. Contraindications for ECMO were age >70 years (case-by-case discussion for those aged 65–70 yr), serious comorbidities (including immunosuppression, chronic lung diseases, and extreme obesity), multiple organ failure, and ongoing mechanical ventilation for >10 days. Although our network organization and outcomes after ECMO have been described elsewhere (4), the outcome of patients denied ECMO is still unknown.

In this context, we prospectively collected the characteristics of all patients proposed for ECMO at the ECMO–COVID-19 hub between March 8, 2020, and June 3, 2020. At least two intensivists discussed each patient’s case and decided among the following: “ECMO, yes” (i.e., prompt cannulation by a local or a mobile ECMO team); “ECMO, no, not yet” because criteria for ECMO were not met; or “ECMO, no, never,” because of an anticipated poor prognosis despite ECMO (5). When an “ECMO, no, not yet” decision was made, advice to optimize patients’ management and mechanical ventilation settings were given, with a possibility to reevaluate later ECMO indication.

Patients’ characteristics among the three groups were compared by ANOVA. Kaplan–Meier survival curves were computed and compared using log-rank tests. Follow-up started from the decision to initiate ECMO or not. The study was approved by the local ethical committee, Comité d’Éthique de la Recherche de Sorbonne University (CER-SU-2020-69).

Of the 575 cases from 75 centers submitted to the ECMO–COVID-19 hub, 302 (53%) patients met eligibility criteria and received ECMO (4), of whom 12 received ECMO after an initial “ECMO, no, not yet” decision. These 12 patients were included in the “ECMO, yes” group. ECMO was denied to 273 (48%) patients after a first call, of which 15 had too many missing data and 12 received ECMO secondarily (i.e., they were included in the “ECMO, yes” group for the analysis). Reasons for ECMO refusals in the 162 (66%) “ECMO, no, never” patients were mechanical ventilation >10 days (n = 68), age >65 years (n = 53), multiple organ failure (n = 32), immunosuppression (n = 23), or severe disability due to extreme obesity (n = 16). For 35 of 68 patients, mechanical ventilation >10 days was the only reason for being denied ECMO, whereas 27 of 53 patients were denied only because of being aged >65 years. “ECMO, no, not yet” was advised for 84 (34%) patients. Characteristics and outcomes of patients are provided in Table 1. Briefly, “ECMO, yes” patients were younger, had a shorter time between intubation and ECMO–COVID-19 hub call, and had a higher Respiratory ECMO Survival Prediction score than patients denied ECMO (P < 0.01). Compared with the two other patient groups, “ECMO, no, not yet” patients significantly lower driving pressure and higher PaO2/FIO2 ratio and lung static compliance (both P < 0.01). They also were more frequently on renal replacement therapy. Ninety-day survival (Figure 1) was obtained for 233 of 246 patients denied ECMO (i.e., 83 “ECMO, no, not yet” and 150 “ECMO, no, never”) patients and was not different between “ECMO, yes” and “ECMO, no, not yet” patients (49% vs. 46%; log-rank test, P = 0.93). However, the 90-day survival of “ECMO, no, never” patients was significantly lower than the two other groups (14%; log-rank test, P < 0.001). Compared with “ECMO, no, not yet” and “ECMO, no, never” patients, “ECMO, yes” patients had a significantly longer stay in the ICU (median [interquartile range], 30 [17–47] d vs. 24 [15–37] d and 16 [10–26] d, P < 0.01) and longer duration of mechanical ventilation (median [interquartile range], 28 [15–44] d vs. 22 [13–32] d and 16 [9–26] d, P < 0.01), respectively.

Our study reports the characteristics and outcomes of patients with COVID-19 with severe ARDS referred for ECMO decision during the first wave of the pandemic in Greater Paris. A similar 90-day survival was observed for patients who received ECMO and those for whom ECMO was not yet indicated. Alternatively, patients considered not suitable for ECMO had a very low 90-day survival.

The decision to initiate ECMO in patients with severe ARDS remains complex, especially in the context of a pandemic with a shortage of resources and ICU beds and of a new disease, for which...
mid-term and long-term outcomes are still unknown. Ideally, the decision should be based on scientific evidence and the ability to identify patients more likely to benefit from ECMO. The similar survival rate observed in “ECMO, yes” and “ECMO, no, not yet” patients is reassuring and validates a posteriori the restrictive ECMO selection criteria that we defined for patients with COVID-19. However, a sizeable proportion of patients in the “ECMO, no, not yet” group may have received ECMO before the pandemic (3), and we cannot exclude that early ECMO may have improved their outcomes. The very low survival rate of “ECMO, no, never” patients is in agreement with series evaluating outcome predictors of patients with COVID-19 and severe ARDS (6). These patients were older, had more comorbidities, had spent more days on mechanical ventilation, and had signs of more severe lung disease. Although not all of them died, the probability of ECMO saving many lives in this group is obviously lower. The substantial proportion of ECMO refusal that occurred only because of mechanical ventilation >10 days could advocate for an earlier call to the ECMO center, although we cannot ensure that criteria for ECMO initiation had already been met in the days preceding the call.

Our study has some limitations. Data were collected mainly on the day of the call to the ECMO–COVID-19 hub, with no information regarding complications and organ dysfunction that occurred during the ICU stay in patients who were denied ECMO.
Our study also took place during the first wave of the pandemic in France. The management of patients with COVID-19 in later phases of the pandemic, with more frequent use of dexamethasone and tocilizumab and more frequent and longer recourse to noninvasive ventilation strategies before intubation, may have changed the outcomes of our three patient groups (7–9).

In conclusion, the Greater Paris ECMO hub-and-spoke network, which first defined criteria for ECMO and then regulated and centralized ECMO indications during the COVID-19 pandemic, appropriately selected patients who were more likely to benefit from the technique (10).

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: The authors thank Drs. Petra Bahroum, Lucie Lefèvre, Antoine Troger, and Jeremy Arzoine for their care of ECMO patients during the COVID-19 crisis.

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Dysanapsis and the Spirometric Response to Inhaled Bronchodilators

To the Editor:

Chronic obstructive pulmonary disease (COPD) and asthma are major sources of morbidity and mortality. Inhaled bronchodilators are a cornerstone of disease management, but treatment is not equally effective in all patients (1, 2). Identifying factors associated with bronchodilator efficacy may expand opportunities for precision medicine and, critically, identify patient subgroups for which new therapies are urgently needed.

The airway tree is the target of inhaled therapies. Using computed tomography (CT), we have demonstrated that variation in native airway tree caliber relative to lung size (i.e., dysanapsis) is common in the general population (3), extends to the peripheral airways (4), and is associated with COPD risk (3). Although computational fluid dynamic studies of particle deposition (5) suggest that dysanapsis may modify inhaled pharmacotherapy efficacy, in vivo evidence is lacking.

This study evaluated whether dysanapsis quantified by CT is associated with the spirometric response to a standardized dose of inhaled bronchodilator.

Methods

Participants. The COLD (Canadian Obstructive Lung Disease) prevalence study used census data to recruit a random sample of noninstitutionalized adults ≥40 years old from nine communities (2005–2009). In 2010–2014, the ongoing CanCOLD (Canadian Cohort Obstructive Lung Disease) study enrolled COLD participants with COPD, and representative random subsets of COLD nonsmoking and smoking participants without COPD matched on age and sex (6). Data from the baseline CanCOLD visit were included in this analysis. Institutional review board approval was obtained, and all participants provided written informed consent.

CT assessment of dysanapsis. Full-inspiration CT was performed on helical scanners according to a standardized protocol. Airway lumen diameters at 19 standard anatomic locations (trachea-to-subsegments) and total lung volume were measured from CT images using Apollo Software (VIDA Diagnostics) by trained readers unaware of other participant information. Trained readers achieved a minimum training set interrater intraclass correlation of 0.9 (3).

Dysanapsis was quantified as the mean of airway lumen diameters in centimeters divided by the cube root of total lung volume in cubic centimeters (airway-to-lung ratio). Lower values of airway-to-lung ratio indicate smaller airway tree-to-lung size, and higher values indicate larger airway tree-to-lung size. Secondary dysanapsis measures were percent-predicted airway tree caliber calculated from reference equations that account for age, sex, height, and lung volume (3), and the mean of airway lumen diameters in centimeters.

Lung function. Spirometry was performed before and 15 minutes after inhalation of 200 µg of salbutamol (albuterol) that was administered from a metered-dose inhaler with spacer device (100 µg/actuation) (7). Participants were instructed not to use regular inhaled medications 6–24 hours before spirometry depending on medication class. Spirometric COPD was defined by post-bronchodilator FEV1/FVC <0.7 (1). Bronchodilator-associated change in FEV1 (ΔFEV1) and FEV1/FVC (ΔFEV1/FVC) were calculated as post-bronchodilator minus prebronchodilator values.

Other variables. Age, sex, cigarette smoking status, and regular inhaled medication use were self-reported. Clinical diagnoses of asthma and COPD corresponded to an affirmative response to

Supported by NIH/NHLBI grant R01-HL130506, Canadian Institute of Health Research (CIHR) grant PJT-162335, and a Canadian Lung Association/CIHR Catalyst Grant. M.V. was supported by Vanier Canada Graduate Scholarship. CanCOLD (Canadian Cohort Obstructive Lung Disease) was supported by the Canadian Respiratory Research Network; industry partners: AstraZeneca Canada Ltd.; Boehringer Ingelheim Canada Ltd.; GlaxoSmithKline Canada Ltd.; and Novartis. Researchers at Research Institute of the McGill University Health Centre Montreal and iCAPTURE Centre Vancouver led the project. Previous funding partners are the CIHR (CIHR/Rx&D Collaborative Research Program Operating Grant 93326); the Respiratory Health Network of the Fonds de la recherche en santé du Québec; industry partners: Almirall; Merck Nomedco; Pfizer Canada Ltd.; and Theratechologies.

Author Contributions: Concept and design: W.C.T., J.B., M.V., and B.M.S. Drafting of the manuscript: M.V. and B.M.S. Statistical analysis: M.V. and B.M.S. Obtained funding: W.C.T., J.B., and B.M.S. Acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content: all authors. B.M.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Originally Published in Press as DOI: 10.1164/rccm.202107-1574LE on July 15, 2021