



Longitudinal Cytokine Profiling in Patients with Severe COVID-19 on Extracorporeal Membrane Oxygenation and Hemoadsorption

To the Editor:

Early in the coronavirus disease (COVID-19) pandemic, the description of a cytokine storm associated with the most severe forms of the disease elicited consideration of anticytokine therapies. However, more recent data showed that inflammatory cytokine concentrations in patients with critical COVID-19 are markedly lower than those reported in patients with sepsis or acute respiratory distress syndrome (ARDS) unrelated to COVID-19 (1). In the most severe forms of COVID-19, which required extracorporeal membrane oxygenation (ECMO), concerns were raised about the potential harm of ECMO itself (2, 3), which may increase serum and BAL fluid IL-6 and TNF- α concentrations (4) although significantly higher mortality had been associated with higher serum IL-6 in patients with COVID-19 (5). Apart from this, TNF- α and IL-8 concentrations rose rapidly during the first 2 hours of ECMO in a neonatal porcine ECMO model (6). Although estimated 60-day survival of ECMO-rescued patients with COVID-19 was similar to that of studies published in the past 2 years on ECMO for severe ARDS (7), the contribution of ECMO itself to the cytokine release syndrome observed in some patients with COVID-19 remains a matter of debate.

CytoSorb (CytoSorbents Europ) is a hemoadsorption cartridge containing polystyrene divinylbenzene beads coated with polyvinylpyrrolidone designed to remove cytokines from the blood. Small case series have suggested that cytokine removal with this device, which can be simply connected to the ECMO circuit, may improve the outcomes of patients with severe ARDS or cardiac surgery patients (8).

In this context, we studied 22 patients with COVID-19 on ECMO. The first consecutive 11 patients were included prospectively with a CytoSorb adsorber being combined to ECMO. During that period, four patients on ECMO were not included because a pre-ECMO sample was not possible. Then, 11 noncontemporaneous ECMO patients without CytoSorb (i.e., control group) were subsequently included. All of these patients were included without any selection based on clinical criteria, elevated concentrations of IL-6, or other biomarkers of inflammation. Whole blood was collected before ECMO, 4 hours after ECMO start without CytoSorb adsorber, and after 12 and 48 hours of CytoSorb and ECMO or after 12 and 48

hours on ECMO alone in the control group, respectively. We used highly sensitive classical or digital multiplex ELISA technologies to directly analyze combined cytokine production profiles (IL-1 β , IL-6, IL-8, IL-22, IL-10, IL-17A, IL-18, GM-CSF, IFN- α , IFN- γ , TNF- α , and IFN- β) in serum of patients at these different time points. Serum samples were also obtained at the same time points in 11 control patients (i.e., patients with COVID-19 on ECMO who did not receive CytoSorb). We compared cytokine profiles in patients with ECMO and CytoSorb (CytoSorb group) or ECMO alone (control group) between 1) before and after 4 hours on ECMO (i.e., direct impact of the ECMO) and 2) 4 and 48 hours on ECMO. Comparisons were performed by using a Wilcoxon test for nonparametric variables (SPSS version 21.0; IBM Corporation). The study was performed at the Pitié Salpêtrière Hospital and approved by the local ethical committee, Comité d'Ethique de la Recherche of Sorbonne University (#CER-SU-2020-21 and -31).

Twenty-two patients on ECMO who had COVID-19 (11 with ECMO and CytoSorb) were included, with 16 male patients, a median (range) age of 49 (33–65) years, Simplified Acute Physiology Score (SAPS) II of 46 (17–92), and time between intubation and ECMO start of 3 (1–11) days. The 48-hour study period was completed for 8/11 patients with CytoSorb and all control group patients. Before ECMO, only IL-1 β was significantly lower in the CytoSorb group compared with the control group ($P = 0.022$). Concentrations of IL-6, IL-8, and IL-18 were very high in all patients and were higher than serum concentrations of other cytokines tested. Importantly, serum cytokine concentrations, specifically those of IL-6, did not increase after 4 hours on ECMO (Figures 1A and 1B). Furthermore, IL-10 and IFN- γ concentrations decreased after 48 hours of CytoSorb treatment ($P = 0.008$ and $P = 0.02$, respectively). IL-6 concentrations also decreased from baseline concentrations, although the difference did not reach statistical significance ($P = 0.08$) (Figure 1B). Other cytokine concentrations were not altered by hemoabsorption. However, IL-6, IL-8, and IL-10 concentrations also significantly decreased in the 48 hours after ECMO initiation in the 11 patients who did not receive CytoSorb (Figure 1A). The eight 60-day survivors in the CytoSorb group were on ECMO for 25 (6–56) days, whereas the seven survivors of the control group spent 20 (1–42) days on ECMO.

Our findings suggest that ECMO itself does not exacerbate cytokine release in patients with COVID-19, contrary to what was previously suggested (2). Our results also question the actual impact of the CytoSorb treatment to decrease serum concentrations of IL-10, IFN- γ , and IL-6 in this context. Indeed, a prompt switch to “ultraprotective” mechanical ventilation aiming to markedly reduce V_T and the driving pressure (9, 10) or the spontaneous evolution of the disease may explain the significant decrease of IL-6, IL-8, and IL-10 also observed in control subjects in the 48 hours after ECMO initiation (Figure 1A). However, cytokine adsorption was associated with a more pronounced decrease of serum IL-6 in a recent series of four patients with COVID-19 on ECMO (11). Although these preliminary results need confirmation in larger cohorts, it should be mentioned that the nonselective reduction of cytokines with the CytoSorb adsorber could lead to paradoxical effects. Indeed, decreasing cytokine concentrations of IL-10, which is believed to dampen inflammation (12), may exacerbate COVID-19-associated organ damage. On the other hand, the reduction of IFN- γ , the main driver of macrophage activation, could contribute to controlling hemophagocytic

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The study was partially supported by a clinical research program (PHRC N 2020 “Digital Covid”) funded by Assistance Publique-Hôpitaux de Paris.

Author Contributions: G.L., A.C., and M.S. designed the study and collected the data. K.D., P.Q., and G.G. performed the cytokine analyses. K.D. and P.Q. performed the statistical analysis. M.S. wrote the first draft of the manuscript. G.L., A.C., and G.G. provided critical revisions of the manuscript. All authors gave critical comments on the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202011-4140LE on March 16, 2021

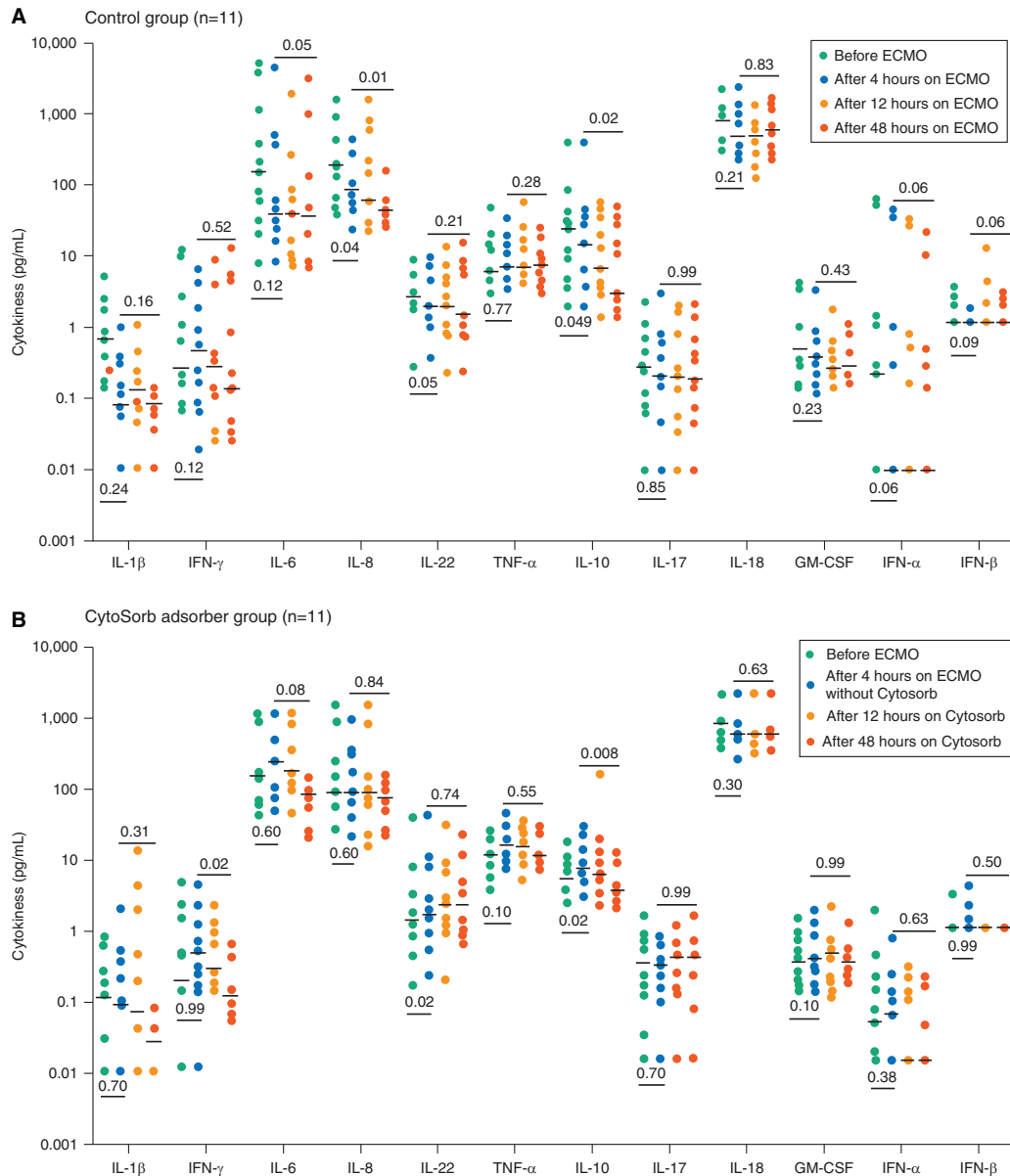


Figure 1. Cytokine production profiles in patients with coronavirus disease (COVID-19) (A) before and after 4, 12, and 48 hours on extracorporeal membrane oxygenation (ECMO) alone ($n = 11$), and (B) before and after 4 hours on ECMO and after 12 and 48 hours with the CytoSorb adsorber combined with ECMO ($n = 11$). Dots represent individual subjects; bars show the median. Statistical analyses were conducted using the Wilcoxon signed-rank test. Comparisons were performed between before ECMO and after 4 hours on ECMO as well as between after ECMO and either 48 hours on ECMO (control group) or 48 hours on CytoSorb (CytoSorb group).

lymphohistocytosis-like features associated with organ damage in some severe cases of COVID-19 pneumonia.

Our study has some limitations. First, the two groups were not randomly selected, and the control group was noncontemporaneous. Second, timing of initiation of CytoSorb was heterogeneous. We cannot rule out that the cytokine profile/response with CytoSorb could have been different if we had selected patients with a higher amount of inflammation before ECMO or if we had protocolized the timing of the CytoSorb initiation. Third, the number of patients included is small, which limits the interpretation and generalization

of our results. The ongoing randomized, multicenter controlled trial evaluating cytokine adsorption in patients with COVID-19 on ECMO (NCT04385771) may help to clarify whether this strategy improves the outcomes of these severe patients.

In conclusion, ECMO does not exacerbate cytokine release in patients with COVID-19, whereas IL-6, IL-8, and IL-10 decrease after 48 hours on ECMO with ultraprotective mechanical ventilation. To what extent combining a CytoSorb adsorber with ECMO could enhance the decrease of these cytokines and improve outcomes warrants further investigations. ■

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

Acknowledgment: The authors thank the doctors and nurses from the ICU department of Pitié-Salpêtrière Hospital who made this study possible, all members from the Cimi COVID-19 consortium, and particularly Christophe Parizot that took care of sample processing, clinical data mining, and biobanking for this part of the Cimi COVID-19 effort focused on patients on extracorporeal membrane oxygenation.

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Urban–Rural Mortality Disparities from Chronic Lower Respiratory Diseases in the United States, 1999–2019

To the Editor:

Chronic lower respiratory diseases, including chronic obstructive pulmonary disease (COPD) and asthma, comprised the fourth leading cause of death in the United States in 2018 (1). Total age-adjusted mortality rates (AAMRs) from chronic lower respiratory

Supported by NHLBI grant K08 HL146943.

Author Contributions: Conception and design: P.A.R., D.A.M., M.R.C., R.K., and S.S.K. Analysis and interpretation: P.A.R., B.K., J.B.P., D.A.M., and S.S.K. Drafting the manuscript for important intellectual content: P.A.R., M.R.C., R.K., and S.S.K.

Originally Published in Press as DOI: 10.1164/rccm.202011-4150LE on February 9, 2021