

High- versus Low-Flow Extracorporeal Respiratory Support in Experimental Hypoxemic Acute Lung Injury

*Original*

High- versus Low-Flow Extracorporeal Respiratory Support in Experimental Hypoxemic Acute Lung Injury / Brusatori, S.; Zinnato, C.; Busana, M.; Romitti, F.; Gattarello, S.; Palumbo, M. M.; Pozzi, T.; Steinberg, I.; Palermo, P.; Lazzari, S.; Maj, R.; Velati, M.; D'Albo, R.; Wassong, J.; Meissner, K.; Lombardo, F.; Herrmann, P.; Quintel, M.; Moerer, O.; Camporota, L.; Marini, J. J.; Meissner, K.; Gattinoni, L.. - In: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE. - ISSN 1535-4970. - 207:9(2023), pp. 1183-1193. [10.1164/rccm.202212-2194OC]

*Availability:*

This version is available at: 11583/2993698 since: 2024-10-25T13:40:31Z

*Publisher:*

NLM (Medline)

*Published*

DOI:10.1164/rccm.202212-2194OC

*Terms of use:*

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

*Publisher copyright*

(Article begins on next page)

# High- versus Low-Flow Extracorporeal Respiratory Support in Experimental Hypoxemic Acute Lung Injury

Serena Brusatori<sup>1\*</sup>, Carmelo Zinnato<sup>1\*</sup>, Mattia Busana<sup>1</sup>, Federica Romitti<sup>1</sup>, Simone Gattarello<sup>2</sup>, Maria Michela Palumbo<sup>1</sup>, Tommaso Pozzi<sup>1</sup>, Irene Steinberg<sup>1</sup>, Paola Palermo<sup>2</sup>, Stefano Lazzari<sup>2</sup>, Roberta Maj<sup>1</sup>, Mara Velati<sup>1</sup>, Rosanna D'Albo<sup>1</sup>, Jona Wassong<sup>1</sup>, Killian Meissner<sup>1</sup>, Fabio Lombardo<sup>1</sup>, Peter Herrmann<sup>1</sup>, Michael Quintel<sup>3</sup>, Onnen Moerer<sup>1</sup>, Luigi Camporota<sup>4</sup>, John J. Marini<sup>5</sup>, Konrad Meissner<sup>1</sup>, and Luciano Gattinoni<sup>1</sup>

<sup>1</sup>Department of Anesthesiology, University Medical Center Göttingen, Göttingen, Germany; <sup>2</sup>IRCCS San Raffaele Scientific Institute, Milan, Italy; <sup>3</sup>Department of Anesthesiology, Intensive Care and Emergency Medicine, Donau Isar Hospital Deggendorf, Deggendorf, Germany; <sup>4</sup>Department of Adult Critical Care, Guy's and St. Thomas' NHS Foundation Trust, Health Centre for Human and Applied Physiological Sciences, London, United Kingdom; and <sup>5</sup>Department of Pulmonary and Critical Care Medicine, University of Minnesota and Regions Hospital, St. Paul, Minnesota

ORCID IDs: 0000-0002-2867-4256 (C.Z.); 0000-0002-1626-1278 (M.B.); 0000-0001-5380-2494 (L.G.).

## Abstract

**Rationale:** In the EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial, oxygenation was similar between intervention and conventional groups, whereas  $\dot{V}_E$  was reduced in the intervention group. Comparable reductions in ventilation intensity are theoretically possible with low-flow extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R), provided oxygenation remains acceptable.

**Objectives:** To compare the effects of ECCO<sub>2</sub>R and extracorporeal membrane oxygenation (ECMO) on gas exchange, respiratory mechanics, and hemodynamics in animal models of pulmonary (intratracheal hydrochloric acid) and extrapulmonary (intravenous oleic acid) lung injury.

**Methods:** Twenty-four pigs with moderate to severe hypoxemia ( $\text{Pa}_{\text{O}_2}:\text{Fi}_{\text{O}_2} \leq 150$  mm Hg) were randomized to ECMO (blood flow 50–60 ml/kg/min), ECCO<sub>2</sub>R (0.4 L/min), or mechanical ventilation alone.

**Measurements and Main Results:**  $\dot{V}_{\text{O}_2}$ ,  $\dot{V}_{\text{CO}_2}$ , gas exchange, hemodynamics, and respiratory mechanics were measured and are presented as 24-hour averages. Oleic acid versus hydrochloric

acid showed higher extravascular lung water ( $1,424 \pm 419$  vs.  $574 \pm 195$  ml;  $P < 0.001$ ), worse oxygenation ( $\text{Pa}_{\text{O}_2}:\text{Fi}_{\text{O}_2} = 125 \pm 14$  vs.  $151 \pm 11$  mm Hg;  $P < 0.001$ ), but better respiratory mechanics (plateau pressure  $27 \pm 4$  vs.  $30 \pm 3$  cm H<sub>2</sub>O;  $P = 0.017$ ). Both models led to acute severe pulmonary hypertension. In both models, ECMO ( $3.7 \pm 0.5$  L/min), compared with ECCO<sub>2</sub>R (0.4 L/min), increased mixed venous oxygen saturation and oxygenation, and improved hemodynamics (cardiac output =  $6.0 \pm 1.4$  vs.  $5.2 \pm 1.4$  L/min;  $P = 0.003$ ).  $\dot{V}_{\text{O}_2}$  and  $\dot{V}_{\text{CO}_2}$ , irrespective of lung injury model, were lower during ECMO, resulting in lower  $\text{Pa}_{\text{CO}_2}$  and  $\dot{V}_E$  but worse respiratory elastance compared with ECCO<sub>2</sub>R ( $64 \pm 27$  vs.  $40 \pm 8$  cm H<sub>2</sub>O/L;  $P < 0.001$ ).

**Conclusions:** ECMO was associated with better oxygenation, lower  $\dot{V}_{\text{O}_2}$ , and better hemodynamics. ECCO<sub>2</sub>R may offer a potential alternative to ECMO, but there are concerns regarding its effects on hemodynamics and pulmonary hypertension.

**Keywords:** high-flow extracorporeal membrane oxygenation; low-flow extracorporeal CO<sub>2</sub> removal; acute respiratory distress syndrome;  $\dot{V}_{\text{O}_2}$ ;  $\dot{V}_{\text{CO}_2}$

(Received in original form December 1, 2022; accepted in final form February 21, 2023)

⊗ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern (dgern@thoracic.org).

\*These authors contributed equally to this work.

Supported by departmental sources, two grants for research in respiratory medicine from Sartorius AG, and one unconditional research grant from Estor.

Author Contributions: Study concept and design: M.B., F.R., and L.G. Acquisition, analysis, or interpretation of data: S.B., C.Z., M.B., F.R., S.G., M.M.P., T.P., I.S., P.P., S.L., R.M., M.V., R.D'A., J.W., K.M., F.L., P.H., L.C., J.J.M., and L.G. First draft of manuscript (writing committee): S.B., C.Z., S.G., and L.G. Critical revision for important intellectual content and final approval of manuscript: S.B., C.Z., M.B., F.R., S.G., M.M.P., I.S., P.P., S.L., R.M., M.V., R.D'A., F.L., P.H., M.Q., O.M., L.C., J.J.M., K.M., and L.G. Statistical analysis: S.B., C.Z., M.B., T.P., and L.G. Administrative, technical, or material support: L.C., P.H., M.Q., K.M., and O.M. Study supervision: L.G.

Correspondence and requests for reprints should be addressed to Luciano Gattinoni, M.D., Department of Anesthesiology, University Medical Center Göttingen, Robert Koch Straße 40, 37075 Göttingen, Germany. E-mail: gattinoniluciano@gmail.com.

Am J Respir Crit Care Med Vol 207, Iss 9, pp 1183–1193, May 1, 2023

Copyright © 2023 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.202212-2194OC on February 27, 2023

Internet address: www.atsjournals.org

## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** High-flow extracorporeal membrane oxygenation (ECMO) is indicated for the management of severely hypoxemic respiratory failure, by providing both oxygen supply and CO<sub>2</sub> removal. Low-flow extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) has been used to reduce the intensity of mechanical ventilation by decreasing the CO<sub>2</sub> load to be eliminated by the natural lung.

### What This Study Adds to the

**Field:** Our experimental model of pulmonary or extrapulmonary injury led to moderate to severe hypoxemia and pulmonary hypertension. High-flow ECMO provided immediate control of oxygenation and CO<sub>2</sub> removal, leading to a significant reduction in pulmonary vascular resistance and higher cardiac output. The reduction in  $\dot{V}_E$  in the ECMO group was associated with marked impairment in respiratory mechanics. The ECCO<sub>2</sub>R group, compared with the ECMO group, was characterized by persistently higher pulmonary hypertension. The higher doses of catecholamines required to control the worse hemodynamics led to marked increases in  $\dot{V}_{O_2}$  and  $\dot{V}_{CO_2}$ . Compared with ECMO, a more modest reduction in  $\dot{V}_E$  was associated with better respiratory mechanics. Despite the difference in extracorporeal blood flow, oxygenation becomes similar in the ECMO and ECCO<sub>2</sub>R groups after 4–8 hours.

Since the clinical introduction of extracorporeal membrane oxygenation (ECMO) by Hill and colleagues (1) and the first randomized trial testing its efficacy by Zapol and colleagues (2), the leading indication for ECMO has been the correction of severe refractory hypoxemia, rather than lung protection. When the H<sub>1</sub>N<sub>1</sub> pandemic made the clinical use of ECMO more

widespread (3, 4), the main indication was then, as it remains today, severe hypoxemia. Notably, the more recent EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial (5) used essentially the same inclusion criteria proposed by Zapol and colleagues more than 40 years ago.

Contemporaneously with Zapol and colleagues' study, we described the physiology of extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) in laboratory animal models, and we hypothesized that this technique could be used to allow lung rest and avoid the high V<sub>T</sub> and pressure traditionally used to ventilate patients with acute respiratory distress syndrome (ARDS) (6, 7). Unlike ECMO, the primary indication for ECCO<sub>2</sub>R is not oxygenation but the removal of carbon dioxide, which makes it possible to reduce the intensity of mechanical ventilation and its associated risk of lung injury (8).

However, randomized trials investigating ECMO and ECCO<sub>2</sub>R showed that Pa<sub>O<sub>2</sub></sub> was similar between the intervention group (i.e., ECMO or ECCO<sub>2</sub>R) and the respective control group (5, 9). Therefore, better oxygenation might not be the primary reason that explains the mortality reduction of ECMO; rather, that benefit more likely relates to the lower intensity of mechanical ventilation facilitated by the extracorporeal removal of CO<sub>2</sub>. Indeed, the EOLIA trial suggested that the patients who benefited the most from ECMO were those with less severe hypoxemia and hypercapnia.

Given that significant amounts of CO<sub>2</sub> can be removed by the less invasive (and lower blood flow requiring) ECCO<sub>2</sub>R method (10), we hypothesized that this technique might also be applied in patients with hypoxemia to facilitate adherence to lung protective strategies while maintaining viable oxygenation.

In this study, we induced lung injury in pigs to achieve moderate to severe hypoxemia by tracheal instillation of hydrochloric acid (HCl) or intravenous infusion of oleic acid (OA) to mimic direct or indirect lung injury, respectively. The animals were subsequently randomized to receive either high-blood flow ECMO or low-flow ECCO<sub>2</sub>R. Mechanical ventilation was adjusted to maintain the arterial Pa<sub>CO<sub>2</sub></sub> within a predefined range.

The hypothesis of this study was that in moderate or severe hypoxemic respiratory failure after experimental lung injury, extracorporeal support provided through low or high blood flow can achieve similar oxygenation, albeit through different mechanisms. Therefore, the aim of this study was to compare the effects of ECCO<sub>2</sub>R and ECMO on gas exchange, respiratory mechanics, and hemodynamics in lung-injured animals. The primary outcome was the difference in oxygenation between the two study groups.

## Methods

A detailed description is provided in the online supplement. After ethics committee approval (Niedersächsische Landesamt für Verbraucherschutz und Lebensmittelsicherheit 20/3464), animals were randomly assigned to lung injury by HCl (12 animals) or OA (12 animals); within each of these two groups, animals were randomly assigned to receive either ECCO<sub>2</sub>R or ECMO support (five animals per group) or no extracorporeal treatment (two animals per group) (*see* Figure E1 in the online supplement).

### Animal Preparation

Twenty-four female pigs were anesthetized, paralyzed, and mechanically ventilated in prone position, with V<sub>T</sub> of 8 ml/kg, positive end-expiratory pressure (PEEP) of 4 cm H<sub>2</sub>O, Fi<sub>O<sub>2</sub></sub> 40%, respiratory rate of 15 breaths/min, and inspiratory:expiratory ratio of 1:2. Each pig was instrumented with esophageal, central venous, pulmonary artery, and pulse index continuous cardiac output arterial catheters. The external jugular–right femoral and right femoral vein alone were cannulated for the ECMO and ECCO<sub>2</sub>R, respectively.

### Lung Damage Induction

With extracorporeal support already initiated but with zero sweep gas flow, pigs were ventilated protectively with V<sub>T</sub> of 6 ml/kg, PEEP of 10 cm H<sub>2</sub>O, Fi<sub>O<sub>2</sub></sub> of 40%, inspiratory:expiratory ratio of 1:2, and respiratory rate set to achieve Pa<sub>CO<sub>2</sub></sub> between 40 and 50 mm Hg. Lung damage was induced in steps of acid administration (intravenous OA for extrapulmonary, diffuse endothelial injury, or intratracheal HCl for

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at [www.atsjournals.org](http://www.atsjournals.org).

a direct pulmonary injury) until  $\text{PaO}_2:\text{FiO}_2 < 150$  mm Hg was achieved.

### Extracorporeal and Ventilatory Management during Treatment (23 h)

ECMO was performed with a blood: sweep gas flow ratio of 1:1 (blood flow 50–60 ml/kg/min) and ECCO<sub>2</sub>R with blood flow of 400 ml/min and sweep gas flow of 15 L/min. Unfractionated heparin was continuously infused, targeting an activated clotting time >250 seconds. In both treatment groups, natural lung ventilation was reduced by decreasing the respiratory rate. PEEP was increased to maintain a constant mean airway pressure. If plateau pressure exceeded 30 cm H<sub>2</sub>O,  $V_T$  was reduced accordingly. The four control animals were connected to ECMO or ECCO<sub>2</sub>R but with sweep gas flow kept at zero throughout the entire experiment. At the scheduled time (after the 23rd hour), extracorporeal support was suspended, and the animals were ventilated as baseline.

### Hemodynamic Management

Animals received a continuous infusion of Sterofundin ISO 2 ml/h (B. Braun). Additional crystalloids or colloids were administered if hemodynamic instability (mean arterial pressure < 60 mm Hg) or signs of hypoperfusion (increase in lactate) were observed. If no response to a fluid challenge was observed, catecholamine infusion was started.

### Outcome Measures

We measured variables related to metabolism, partitioned respiratory mechanics, and pulmonary and systemic hemodynamics. Gas tensions, electrolytes, and Hb concentration were measured in arterial, mixed venous, and pre- and postmembrane lung blood samples. Measurements were performed at baseline, after lung damage induction, during treatment, and after cessation of extracorporeal support. After euthanasia, lung weight and wet-to-dry ratios of lung, liver, kidney, bowel, and muscle were evaluated.

### Statistical Analysis

Data are reported as mean  $\pm$  SD. Variables recorded at baseline and after lung injury were compared within groups using Student's *t* test or the Wilcoxon-Mann-Whitney test. The differences among treatment groups within the two lung injury models were assessed using one-way ANOVA or the Kruskal-Wallis test, as

appropriate. *Post hoc* analyses were performed using Tukey's correction. A *P* value <0.05 was considered to indicate statistical significance. Analyses were performed using R for Statistical Computing 4.0 (<https://www.r-project.org/>).

## Results

### Lung Injury Models

Both the HCl and OA groups reached the target  $\text{PaO}_2:\text{FiO}_2$  ratio of <150 mm Hg in approximately 4 hours. The physiological characteristics at the target  $\text{PaO}_2:\text{FiO}_2$  ratio are reported in Table E1. As shown, HCl injury, compared with OA injury, resulted in worse respiratory mechanics, with higher plateau pressure, transpulmonary lung stress, lung elastance, and driving pressure. The hemodynamic and gas exchange variables were similar for the HCl and OA injury models, except for a higher  $\text{PaO}_2:\text{FiO}_2$  ratio in the HCl model ( $151 \pm 11$  vs.  $125 \pm 14$  mm Hg;  $P < 0.001$ ). Extravascular lung water was almost threefold greater in the OA group compared with the HCl group ( $1,424 \pm 419$  vs.  $574 \pm 195$  ml;  $P < 0.001$ ). The time courses of HCl and OA injuries in the absence of treatment are shown in Figures E2–E4. As shown, HCl control animals spontaneously improved gas exchange and respiratory mechanics over the first 8 hours and then remained stable throughout the experiment. In contrast, OA control animals remained severely hypoxemic and experienced progressively worsening respiratory mechanics. The OA control animals died before the end of the experiment, whereas no deaths occurred among the HCl control animals.

### Gas Exchange

**Oxygenation.** The average 24-hour  $\text{SaO}_2$  and  $\text{PaO}_2:\text{FiO}_2$  ratio were significantly lower during ECCO<sub>2</sub>R compared with ECMO treatment (*see* Table 1). Venous admixture was significantly higher in the ECMO group. The time courses for  $\text{SaO}_2$ ,  $\text{PaO}_2$ , pulmonary venous admixture, and  $\text{PaO}_2:\text{FiO}_2$  are presented in Figures 1 and E4A. As shown, in the HCl lung injury model, both  $\text{SaO}_2$  and  $\text{PaO}_2$  rapidly improved and became similar between ECCO<sub>2</sub>R and ECMO within 8 hours. Thereafter, these indicators remained stable until the end of the experiment. The control animals behaved similarly to those in the ECCO<sub>2</sub>R group. In the OA lung injury model,  $\text{SaO}_2$  and  $\text{PaO}_2$  rose rapidly and were

similar between the ECMO and ECCO<sub>2</sub>R groups after 4 ( $\text{PaO}_2$ ) and 8 ( $\text{SaO}_2$ ) hours. In the corresponding control animals without extracorporeal support, oxygenation remained severely impaired throughout the experiment.

**CO<sub>2</sub> clearance.** The average 24-hour values of  $\text{PaCO}_2$  in both HCl and OA models were significantly higher during ECCO<sub>2</sub>R compared with ECMO, because of lower CO<sub>2</sub> fraction eliminated by the membrane lung. This occurred despite significantly higher  $\dot{V}_E$ ,  $V_T$ , and respiratory rates required in the ECCO<sub>2</sub>R group to maintain  $\text{PaCO}_2$  within a clinically acceptable range (*see* Table 1 and Figure E5).

### Extracorporeal Treatment

**ECMO.** The details of ECMO treatment are reported in Table 2. As shown, ECMO blood flow was about 60% of cardiac output in both the HCl and OA groups. The mixed venous oxygen content, enriched by the oxygenated blood from the membrane lung, was about 90% during the entire experiment. The high mixed venous oxygen content explained the lower oxygen transfer by the natural lung. Indeed, ECMO provided about 85% of total  $\dot{V}_{\text{O}_2}$  and 65% of total CO<sub>2</sub> clearance in both groups. The time courses of membrane lung  $\dot{V}_{\text{O}_2}$  and  $\dot{V}_{\text{CO}_2}$  are shown in Figure E6.

**ECCO<sub>2</sub>R.** The details of ECCO<sub>2</sub>R treatment are reported in Table 2. As shown, ECCO<sub>2</sub>R blood flow represented about 10% of cardiac output in both the HCl and OA groups. The oxygen transfer provided by ECCO<sub>2</sub>R was negligible, and the mixed venous oxygen content was unaffected by ECCO<sub>2</sub>R treatment. Consequently, oxygen transfer occurred almost totally through the natural lung, while the CO<sub>2</sub> cleared by ECCO<sub>2</sub>R was about 40% of the total  $\dot{V}_{\text{CO}_2}$  in both groups. The time courses of membrane lung  $\dot{V}_{\text{O}_2}$  and  $\dot{V}_{\text{CO}_2}$  are shown in Figure E6.

**Respiratory mechanics.** The average 24-hour respiratory mechanics variables are detailed in Table 3. Compared with ECCO<sub>2</sub>R, ECMO was associated with greater impairment of plateau pressure, respiratory system and lung elastance, lung stress, and driving pressure. The time course of respiratory system elastance is presented in Figure 2B.

**Hemodynamics.** The average 24-hour hemodynamic variables are detailed in Table 3. As shown, in both the HCl and OA lung models, the ECCO<sub>2</sub>R group had greater hemodynamic compromise compared with the ECMO group. Indeed, in both lung injury models, pulmonary vascular

**Table 1.** Mean Values of Metabolic and Gas Exchange Variables during Extracorporeal Support According to Lung Injury Model

	Hydrochloric Acid				Oleic Acid			
	ECMO (n = 5)	ECCO <sub>2</sub> R (n = 5)	Control (n = 2)	P Value	ECMO (n = 5)	ECCO <sub>2</sub> R (n = 5)	Control (n = 2)	P Value
<b>Metabolism</b>								
Total $\dot{V}_{O_2}$ , ml/min	251 ± 41	344 ± 28*	340 ± 38*	<0.001	271 ± 44	352 ± 38*	401 ± 15*†	<0.001
Total $\dot{V}_{CO_2}$ , ml/min	205 ± 51	280 ± 45*	230 ± 65†	<0.001	186 ± 43	302 ± 49*	344 ± 14*†	<0.001
<b>Gas exchange</b>								
Arterial saturation, %	96 ± 2	96 ± 3	94 ± 7	0.150	96 ± 2	91 ± 9	68 ± 7*†	<0.001
Mixed venous saturation, %	94 ± 3	58 ± 9*	47 ± 12*†	<0.001	94 ± 3	51 ± 14*	31 ± 4*†	<0.001
Pa <sub>O<sub>2</sub></sub> :Fi <sub>O<sub>2</sub></sub> , mm Hg	321 ± 68	262 ± 52	270 ± 70*†	<0.001	334 ± 88	251 ± 117*	123 ± 19*†	<0.001
Pa <sub>O<sub>2</sub></sub> , mm Hg	118 ± 24	109 ± 21	108 ± 28	0.221	147 ± 52	124 ± 61	55 ± 4*†	<0.001
Pa <sub>CO<sub>2</sub></sub> , mm Hg	47 ± 5	53 ± 6*	50 ± 8	<0.001	44 ± 4	49 ± 5*	55 ± 5*†	<0.001
Pet <sub>CO<sub>2</sub></sub> , mm Hg	33 ± 10	44 ± 6*	42 ± 5*	<0.001	36 ± 5	45 ± 5*	42 ± 3*	<0.001
Pulmonary venous admixture, %	64 ± 18	13 ± 1*	15 ± 1*	<0.001	66 ± 13	19 ± 13*	49 ± 8*†	<0.001
Physiological dead space, %	67 ± 11	61 ± 4*	63 ± 7	0.018	63 ± 8	56 ± 4*	58 ± 4	<0.001
Respiratory rate, beats/min	12 ± 2	21 ± 5*	32 ± 2*†	<0.001	11 ± 3	21 ± 5*†	30 ± 1*†	<0.001
$\dot{V}_T$ per IBW, kg/m <sup>2</sup>	4.4 ± 1.2	5.3 ± 0.5*	5.5 ± 0.2*	<0.001	4.5 ± 0.6	5.4 ± 0.2*	5.6 ± 0.1*	<0.001
$\dot{V}_E$ , L/min	3.3 ± 1.0	7.1 ± 1.7*	11.5 ± 0.6*†	<0.001	3.5 ± 0.7	7.7 ± 2.1*	13.2 ± 0.6*†	<0.001
Alveolar ventilation, L/min	1.2 ± 0.5	2.8 ± 0.6*	3.9 ± 0.9*†	<0.001	1.3 ± 0.5	3.4 ± 0.9*	5.5 ± 0.5*†	<0.001

Definition of abbreviations: ECCO<sub>2</sub>R = extracorporeal CO<sub>2</sub> removal; ECMO = extracorporeal membrane oxygenation; IBW = ideal body weight; Pet<sub>CO<sub>2</sub></sub> = end-tidal Pa<sub>CO<sub>2</sub></sub>.

Differences among treatment groups within lung injury models were assessed using one-way ANOVA or the Kruskal-Wallis test, as appropriate. P values in boldface type denote statistical significance.

\*Significant comparison with respect to ECMO treatment group.

†Significant comparison with respect to ECCO<sub>2</sub>R treatment group.

resistance, cardiac output, stroke volume, and heart rate were significantly higher when applying ECCO<sub>2</sub>R compared with ECMO. The time course of pulmonary artery resistance is reported in Figure 2A. Significantly higher doses of epinephrine were required in the ECCO<sub>2</sub>R groups to maintain hemodynamics; these doses were positively associated with increased glycemia,  $\dot{V}_{O_2}$ , and  $\dot{V}_{CO_2}$  (see Figures E7–E11).

**Total  $\dot{V}_{O_2}$  and  $\dot{V}_{CO_2}$ .** An unexpected finding of this study was that the total  $\dot{V}_{O_2}$  and  $\dot{V}_{CO_2}$  were strongly associated with the type of extracorporeal support, irrespective of the injury model. Indeed, as shown in Table 1, the average 24-hour total  $\dot{V}_{O_2}$  was similar between the HCl and OA injury models but was markedly higher, for both models, in animals treated with ECCO<sub>2</sub>R compared with ECMO. The time course of total  $\dot{V}_{O_2}$  is represented in Figure 3A. As shown, total  $\dot{V}_{O_2}$  rose immediately after HCl and OA lung injury but decreased once ECMO was commenced, whereas it remained high during ECCO<sub>2</sub>R. Average 24-hour total  $\dot{V}_{CO_2}$  behaved similarly to total  $\dot{V}_{O_2}$ . Indeed, it was similar between the HCl and OA models and markedly higher in

animals treated with ECCO<sub>2</sub>R compared with ECMO. The time course of total  $\dot{V}_{CO_2}$  is shown in Figure 3B: it exhibited a trend similar to that of total  $\dot{V}_{O_2}$ , with an immediate increase after HCl and OA lung injuries but a decline during ECMO, whereas it remained high during ECCO<sub>2</sub>R.

The lower  $\dot{V}_{O_2}$  during ECMO compared with ECCO<sub>2</sub>R appeared significantly related, in various degrees, to lower pulmonary vascular resistance, higher mixed venous oxygen saturation, lower mixed venous P<sub>CO<sub>2</sub></sub>, and lower adrenaline doses (see Figures E12–E19).

**Anatomical findings.** Lung weight and wet-to-dry ratios of lung, liver, muscle, kidney, and bowel observed in both injury models treated with ECMO and ECCO<sub>2</sub>R are reported in Table 4. As shown, no differences were found in any of the variables except for lung weight, which tended to be higher in the HCl injury cohort treated with ECMO.

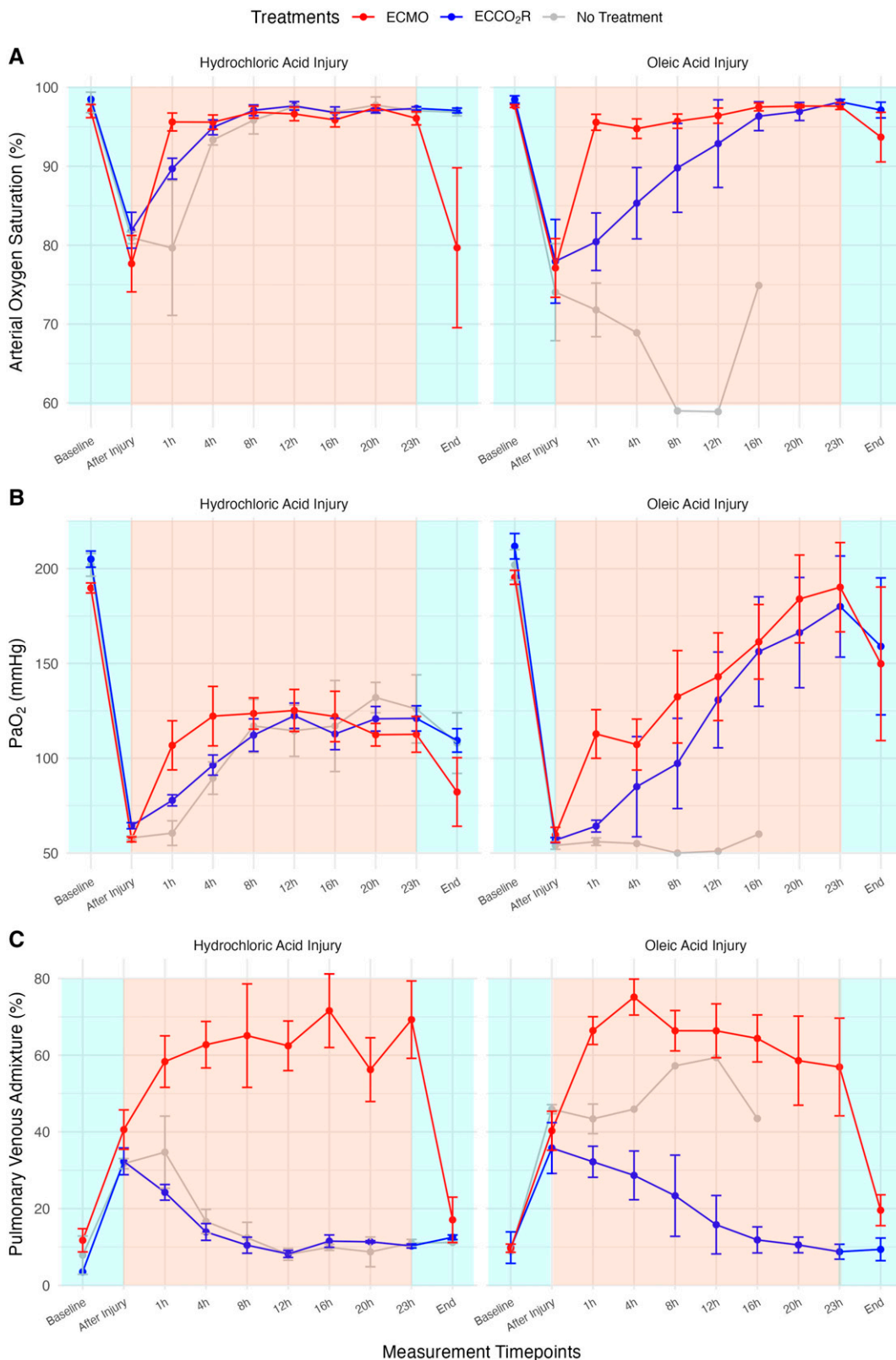
## Discussion

The main results of this study were as follows: 1) OA injury, compared with HCl

injury, was characterized by a more diffuse injury with worse oxygenation but better respiratory mechanics; 2) total  $\dot{V}_{O_2}$  was markedly lower during ECMO than during ECCO<sub>2</sub>R support; and 3) ECMO achieved better oxygenation, CO<sub>2</sub> removal, and hemodynamics in both injury models but resulted in worse respiratory mechanics compared with ECCO<sub>2</sub>R.

## Lung Injury Models

With intratracheal HCl, we aimed to mimic a direct lung injury from the alveolar side, while with intravenous OA, we aimed to mimic an indirect lung injury from the endothelial side. The physiological differences we observed between the two lung injury models confirm previous observations (11) of worse oxygenation and better respiratory mechanics in the OA model. Indeed, in the OA model, the threefold increase in extravascular lung water indicated a greater edema-induced shunt. Better oxygenation in the HCl model may have resulted from the patchy distribution of its injury pattern. Under these conditions, hypoxic vasoconstriction may divert blood flow to less injured and more functional lung regions.



**Figure 1.** (A–C) Time courses of SaO<sub>2</sub> (A), PaO<sub>2</sub> (B), and pulmonary venous admixture fraction (C) in hydrochloric acid (HCl)-treated and oleic acid (OA)-treated animals according to support method (ECMO in red, ECCO<sub>2</sub>R in blue, no treatment in gray). Values are represented as mean ± SE. “Baseline” refers to values measured before lung injury (light blue background), “After Injury” refers to values after HCl or OA administration

**Table 2.** Mean Values of Extracorporeal Support–related Variables according to Lung Injury Model

	Hydrochloric Acid				Oleic Acid			
	ECMO (n = 5)	ECCO <sub>2</sub> R (n = 5)	Control (n = 2)	P Value	ECMO (n = 5)	ECCO <sub>2</sub> R (n = 5)	Control (n = 2)	P Value
Blood flow, L/min	3.6 ± 0.5	0.4 ± 0.0*	2.0 ± 1.7 <sup>†</sup>	<b>&lt;0.001</b>	3.7 ± 0.4	0.4 ± 0.0*	3.2 ± 1.5 <sup>†</sup>	<b>&lt;0.001</b>
Blood flow as % of cardiac output	59 ± 11	8 ± 2*	42 ± 38 <sup>†</sup>	<b>&lt;0.001</b>	67 ± 13	9 ± 3*	69 ± 8 <sup>†</sup>	<b>&lt;0.001</b>
Sweep gas flow, L/min	4.0 ± 0.7	15.0 ± 0.0	—	<b>&lt;0.001</b>	3.6 ± 0.8	13.6 ± 1.5	—	<b>&lt;0.001</b>
Pin <sub>O<sub>2</sub></sub> , mm Hg	41 ± 3	51 ± 4*	36 ± 10 <sup>†</sup>	<b>&lt;0.001</b>	45 ± 5	47 ± 7	34 ± 5 <sup>†</sup>	<b>&lt;0.001</b>
Pout <sub>O<sub>2</sub></sub> , mm Hg	388 ± 35	114 ± 38*	36 ± 4 <sup>†</sup>	<b>&lt;0.001</b>	363 ± 43	129 ± 15*	37 ± 10 <sup>†</sup>	<b>&lt;0.001</b>
ṠO <sub>2NL</sub> , ml/min	30 ± 23	293 ± 51*	340 ± 3*	<b>&lt;0.001</b>	28 ± 13	330 ± 65*	401 ± 15 <sup>†</sup>	<b>&lt;0.001</b>
ṠO <sub>2ML</sub> , ml/min	235 ± 43	24 ± 3	—	<b>&lt;0.001</b>	242 ± 49	31 ± 7	—	<b>&lt;0.001</b>
ṠO <sub>2ML</sub> :total ṠO <sub>2</sub> , %	84 ± 6	6 ± 1	—	<b>&lt;0.001</b>	83 ± 6	7 ± 3	—	<b>&lt;0.001</b>
Pin <sub>CO<sub>2</sub></sub> , mm Hg	53 ± 5	53 ± 7	59 ± 8 <sup>†</sup>	<b>0.004</b>	51 ± 6	48 ± 8	69 ± 6 <sup>†</sup>	<b>&lt;0.001</b>
Pout <sub>CO<sub>2</sub></sub> , mm Hg	44 ± 5	11 ± 4*	60 ± 9 <sup>†</sup>	<b>&lt;0.001</b>	42 ± 4	16 ± 16	70 ± 5	<b>&lt;0.001</b>
ṠCO <sub>2NL</sub> , ml/min	63 ± 26	167 ± 31*	230 ± 65 <sup>†</sup>	<b>&lt;0.001</b>	67 ± 22	190 ± 44*	344 ± 14 <sup>†</sup>	<b>&lt;0.001</b>
ṠCO <sub>2ML</sub> , ml/min	147 ± 47	113 ± 26	—	<b>&lt;0.001</b>	119 ± 37	112 ± 61	—	0.547
ṠCO <sub>2ML</sub> :total ṠCO <sub>2</sub> , %	68 ± 13	41 ± 7	—	<b>&lt;0.001</b>	64 ± 10	36 ± 15	—	<b>&lt;0.001</b>

*Definition of abbreviations:* ECCO<sub>2</sub>R = extracorporeal CO<sub>2</sub> removal; ECMO = extracorporeal membrane oxygenation; Pin<sub>CO<sub>2</sub></sub> = Pa<sub>CO<sub>2</sub></sub> to the membrane lung; Pin<sub>O<sub>2</sub></sub> = Pa<sub>O<sub>2</sub></sub> to the membrane lung; Pout<sub>CO<sub>2</sub></sub> = Pa<sub>CO<sub>2</sub></sub> out of the membrane lung; Pout<sub>O<sub>2</sub></sub> = Pa<sub>O<sub>2</sub></sub> out of the membrane lung; ṠCO<sub>2NL</sub> = natural lung carbon dioxide removal; ṠCO<sub>2ML</sub> = membrane lung carbon dioxide removal; ṠO<sub>2ML</sub> = membrane lung oxygen production. Differences among treatment groups within lung injury models were assessed using one-way ANOVA or the Kruskal-Wallis test, as appropriate. P values in boldface type denote statistical significance.

\*Significant comparison with respect to ECMO treatment group.

<sup>†</sup>Significant comparison with respect to ECCO<sub>2</sub>R treatment group.

The less deranged respiratory mechanics of the OA model may be partially explained by a greater intratidal recruitability (12). Severe and sudden pulmonary hypertension characterized both models during injury development. Both models clearly differ from human ARDS but, taken together, may facilitate a better understanding of the varied physiological responses to lung injury, which may in part apply to the diverse clinical conditions of ARDS.

### Oxygenation

In our experimental setup, given the nearly constant Fi<sub>O<sub>2</sub></sub> throughout the study, the determinants of oxygenation during ECMO were 1) the amount of oxygen added to the mixed venous blood flowing through shunted areas; 2) the amount of shunt, which reflects the parenchymal lung condition; and 3) the amount of ṠO<sub>2</sub>, which is inversely related to Pa<sub>O<sub>2</sub></sub>:Fi<sub>O<sub>2</sub></sub> ratio (see Figures 1, 3 and E4A).

In ECMO-supported animals, the immediate increase in oxygenation was undoubtedly due to the addition of oxygen to the mixed venous blood (more than 80% of total ṠO<sub>2</sub>) (13). The further temporal evolution of oxygenation, unchanged in HCl injury and continuously improving in OA

injury, was likely due to the combined effect of changes in ṠO<sub>2</sub> and shunt. In HCl injury, the expected increase of Pa<sub>O<sub>2</sub></sub>:Fi<sub>O<sub>2</sub></sub> due to the progressive decrease in ṠO<sub>2</sub> was likely offset by worsening of the shunt fraction. In contrast, the decline in ṠO<sub>2</sub> observed after OA injury was associated with a decrease of shunt: this combination may account for a progressive increase in oxygenation (see Figures 1 and 3) (14, 15).

In ECCO<sub>2</sub>R, the increase of oxygenation is best explained by a decrease in shunt, as the extracorporeal addition of oxygen was almost negligible (about 7% of ṠO<sub>2</sub>), and ṠO<sub>2</sub> remained unmodified throughout the experiment. In HCl injury, rapid recovery of oxygenation (within 8 h of the initial injury) was likely due to the natural evolution of the model, as the HCl-injured animals without extracorporeal support behaved similarly. In contrast, in the OA group, the progressive improvement in oxygenation during ECCO<sub>2</sub>R can hardly be attributed to the natural history of the model, as OA-injured animals without extracorporeal support died with refractory hypoxemia. The explanation of oxygenation improvement with ECCO<sub>2</sub>R is not straightforward. However, it can be hypothesized that the maintenance of

hypoxic vasoconstriction and the reduced mechanical ventilation load may have contributed to the oxygenation increase.

### CO<sub>2</sub> Removal

Pa<sub>CO<sub>2</sub></sub> was a function of the amount of total ṠCO<sub>2</sub>, the amount of CO<sub>2</sub> removed by the membrane lung, the physiological dead space, and ṠE. In our study, the amount of CO<sub>2</sub> removed by ECMO and by ECCO<sub>2</sub>R was similar in both the HCl and OA groups. This would have allowed a similar decrease in ṠE, if the total ṠCO<sub>2</sub> had been similar between ECMO- and ECCO<sub>2</sub>R-treated animals (16); however, total ṠCO<sub>2</sub> was markedly higher in animals undergoing ECCO<sub>2</sub>R. The higher ṠCO<sub>2</sub> was associated, however, with higher ṠO<sub>2</sub> (Figure 3), indicating that the overall metabolic rate was about 20–30% higher with ECCO<sub>2</sub>R compared with ECMO. A possible explanation is the metabolic effects of the higher dose of epinephrine required to maintain hemodynamic status in the ECCO<sub>2</sub>R group (see the next section). Consequently, Pa<sub>CO<sub>2</sub></sub> increased significantly during ECCO<sub>2</sub>R compared with ECMO. To maintain Pa<sub>CO<sub>2</sub></sub> within a clinically acceptable range, these animals received

**Figure 1.** (Continued). before extracorporeal treatment (light blue background), “1h” to “23h” refer to values recorded during treatment (light pink background), and “End” refers to values measured 1 hour after extracorporeal treatment withdrawal while ventilating the pig with the same setting applied after injury (light blue background). ECCO<sub>2</sub>R = extracorporeal CO<sub>2</sub> removal; ECMO = extracorporeal membrane oxygenation.

**Table 3.** Mean Values of Respiratory Mechanics and Hemodynamic Variables during Extracorporeal Support According to Lung Injury Model

	Hydrochloric Acid				Oleic Acid			
	ECMO (n=5)	ECCO <sub>2</sub> R (n=5)	Control (n=2)	P Value	ECMO (n=5)	ECCO <sub>2</sub> R (n=5)	Control (n=2)	P Value
Respiratory mechanics								
Plateau pressure, cm H <sub>2</sub> O	31 ± 3	26 ± 2*	28 ± 4*	<b>&lt;0.001</b>	30 ± 4	25 ± 4*	28 ± 3	<b>&lt;0.001</b>
Mean airway pressure, cm H <sub>2</sub> O	18 ± 2	17 ± 2	16 ± 2	0.090	18 ± 2	16 ± 3*	18 ± 1	<b>&lt;0.001</b>
PEEP, cm H <sub>2</sub> O	13 ± 2	12 ± 1*	10 ± 0*†	<b>&lt;0.001</b>	13 ± 1	11 ± 1*	10 ± 0*†	<b>&lt;0.001</b>
Respiratory system elastance, cm H <sub>2</sub> O/L	68 ± 34	41 ± 6*	52 ± 10	<b>&lt;0.001</b>	59 ± 16	39 ± 9*	41 ± 4*	<b>&lt;0.001</b>
Lung elastance, cm H <sub>2</sub> O/L	57 ± 36	30 ± 7*	40 ± 7	<b>&lt;0.001</b>	47 ± 15	29 ± 11*	30 ± 5*	<b>&lt;0.001</b>
Stress, cm H <sub>2</sub> O	25 ± 5	19 ± 4*	22 ± 3*†	<b>&lt;0.001</b>	24 ± 4	18 ± 6*	21 ± 3	<b>&lt;0.001</b>
Driving pressure, cm H <sub>2</sub> O	18 ± 3	14 ± 2	19 ± 4*†	<b>&lt;0.001</b>	17 ± 4	14 ± 3	17 ± 2†	<b>0.008</b>
Mechanical power, J/min	9.3 ± 3.0	18.7 ± 3.7*	28.4 ± 7.1*†	<b>&lt;0.001</b>	10.1 ± 2.6	19.6 ± 8.4*	41.0 ± 3.7*†	<b>&lt;0.001</b>
Extravascular lung water, ml	1,167 ± 359	501 ± 123*	431 ± 88*	<b>&lt;0.001</b>	1,320 ± 550	1,093 ± 223	2,018 ± 514*†	<b>&lt;0.001</b>
Hemodynamics								
Mean arterial pressure, mm Hg	73 ± 11	64 ± 8*	67 ± 10	<b>&lt;0.001</b>	70 ± 12	63 ± 15	51 ± 8*	<b>0.004</b>
Central venous pressure, mm Hg	8 ± 2	9 ± 3*	8 ± 2	<b>0.034</b>	7 ± 3	8 ± 3	5 ± 1*†	0.059
Systemic vascular resistance, dynes/s/cm <sup>5</sup>	784 ± 155	758 ± 187	876 ± 152	0.093	872 ± 251	890 ± 355	667 ± 211	0.243
Mean pulmonary pressure, mm Hg	33 ± 5	34 ± 8	31 ± 7	0.346	30 ± 10	32 ± 9	39 ± 7	0.073
Pulmonary vascular resistance, dynes/s/cm <sup>5</sup>	242 ± 60	304 ± 102*	280 ± 130	<b>0.024</b>	239 ± 96	361 ± 216*	467 ± 134*	<b>0.001</b>
Pulmonary artery occlusion pressure, mm Hg	13 ± 2	12 ± 4	13 ± 3	0.304	12 ± 4	11 ± 3	9 ± 3	0.191
Cardiac output, L/min	6.3 ± 1.4	5.4 ± 1.3*	5.0 ± 0.8*	<b>0.002</b>	5.7 ± 1.3	4.8 ± 1.5*	5.5 ± 0.6	<b>0.042</b>
Stroke volume, ml	69 ± 19	56 ± 20*	53 ± 22*	<b>0.008</b>	67 ± 14	52 ± 20*	37 ± 13*	<b>&lt;0.001</b>
Heart rate, beats/min	114 ± 31	136 ± 45*	147 ± 39*	<b>0.013</b>	107 ± 40	146 ± 47*	181 ± 18*	<b>&lt;0.001</b>
Fluid administered, L	6.9 ± 2.1	9.7 ± 2.2*	9.4 ± 2.1*	<b>&lt;0.001</b>	8.9 ± 2.1	8.1 ± 3.2	8.2 ± 3.8	0.460
Cumulative noradrenaline, µg/kg/min	0.1 ± 0.1	0.4 ± 0.2*	0.1 ± 0.1†	<b>&lt;0.001</b>	0.3 ± 0.3	0.4 ± 0.4	0.8 ± 0.4	0.205
Cumulative adrenaline, µg/kg/min	0.01 ± 0.01	0.09 ± 0.08*	0.00 ± 0.00*†	<b>&lt;0.001</b>	0.09 ± 0.09	0.10 ± 0.08	0.80 ± 0.30*†	<b>&lt;0.001</b>

Definition of abbreviations: ECCO<sub>2</sub>R = extracorporeal CO<sub>2</sub> removal; ECMO = extracorporeal membrane oxygenation; PEEP = positive end-expiratory pressure.

Differences among treatment groups within lung injury models were assessed using one-way ANOVA or the Kruskal-Wallis test, as appropriate. P values in boldface type denote statistical significance.

\*Significant comparison with respect to ECMO treatment group.

†Significant comparison with respect to ECCO<sub>2</sub>R treatment group.

higher  $\dot{V}_E$  (in terms of both respiratory rate and  $V_T$ ) while still adhering to a lung protective strategy.

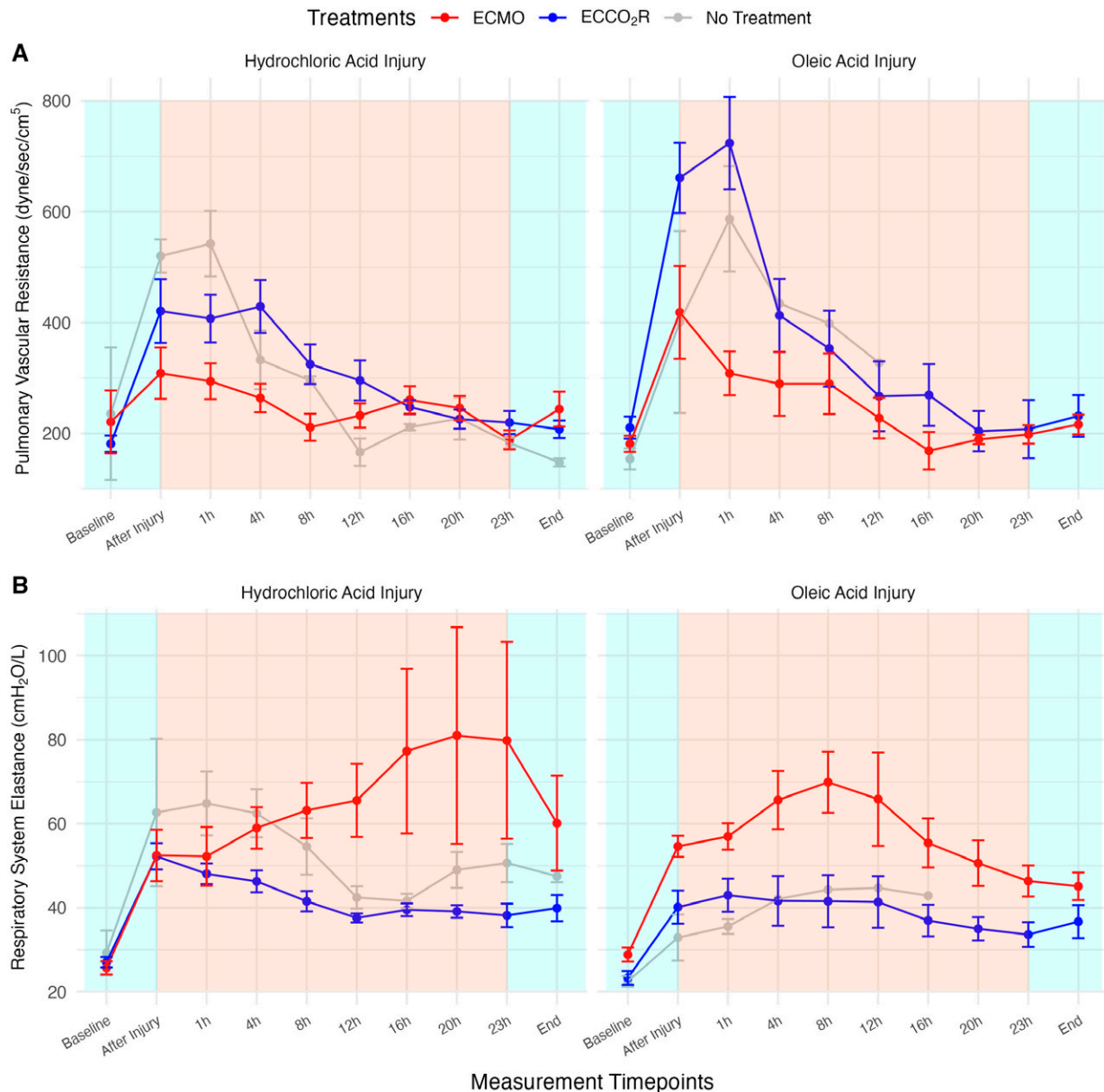
### Hemodynamics

The primary hemodynamic derangements after HCl and OA injuries were pulmonary hypertension, tachycardia, and hypotension,

which required resuscitation with fluids and catecholamines. After extracorporeal support commencement, however, the hemodynamic impairment persisted during ECCO<sub>2</sub>R, with higher pulmonary vascular resistance and lower cardiac output and mean systemic arterial pressure. The maintenance of pulmonary vasoconstriction in the presence

of low mixed venous oxygen saturation may account for this hemodynamic pattern. In contrast, the high mixed venous oxygen saturation during ECMO likely dampened the hypoxic vasoconstriction mechanism, leading to less hemodynamic impairment. In addition, several other factors may have contributed to the higher pulmonary





**Figure 2.** (A and B) Time courses of total pulmonary vascular resistance (A) and respiratory system elastance (B) in hydrochloric acid (HCl)-treated and oleic acid (OA)-treated animals according to method of support (ECMO in red, ECCO<sub>2</sub>R in blue, no treatment in gray). Values are represented as mean  $\pm$  SE. “Baseline” refers to values measured before lung injury (light blue background), “After Injury” refers to values after HCl or OA administration before extracorporeal treatment (light blue background), “1h” to “23h” refer to values recorded during treatment (light pink background), and “End” refers to values measured 1 hour after extracorporeal treatment withdrawal while ventilating the pig with the same setting applied after injury (light blue background). ECCO<sub>2</sub>R = extracorporeal CO<sub>2</sub> removal; ECMO = extracorporeal membrane oxygenation.

pressures and pulmonary vascular resistance in ECCO<sub>2</sub>R, such as lower mixed venous pH and higher mixed venous PCO<sub>2</sub> (see Figures E17–E19).

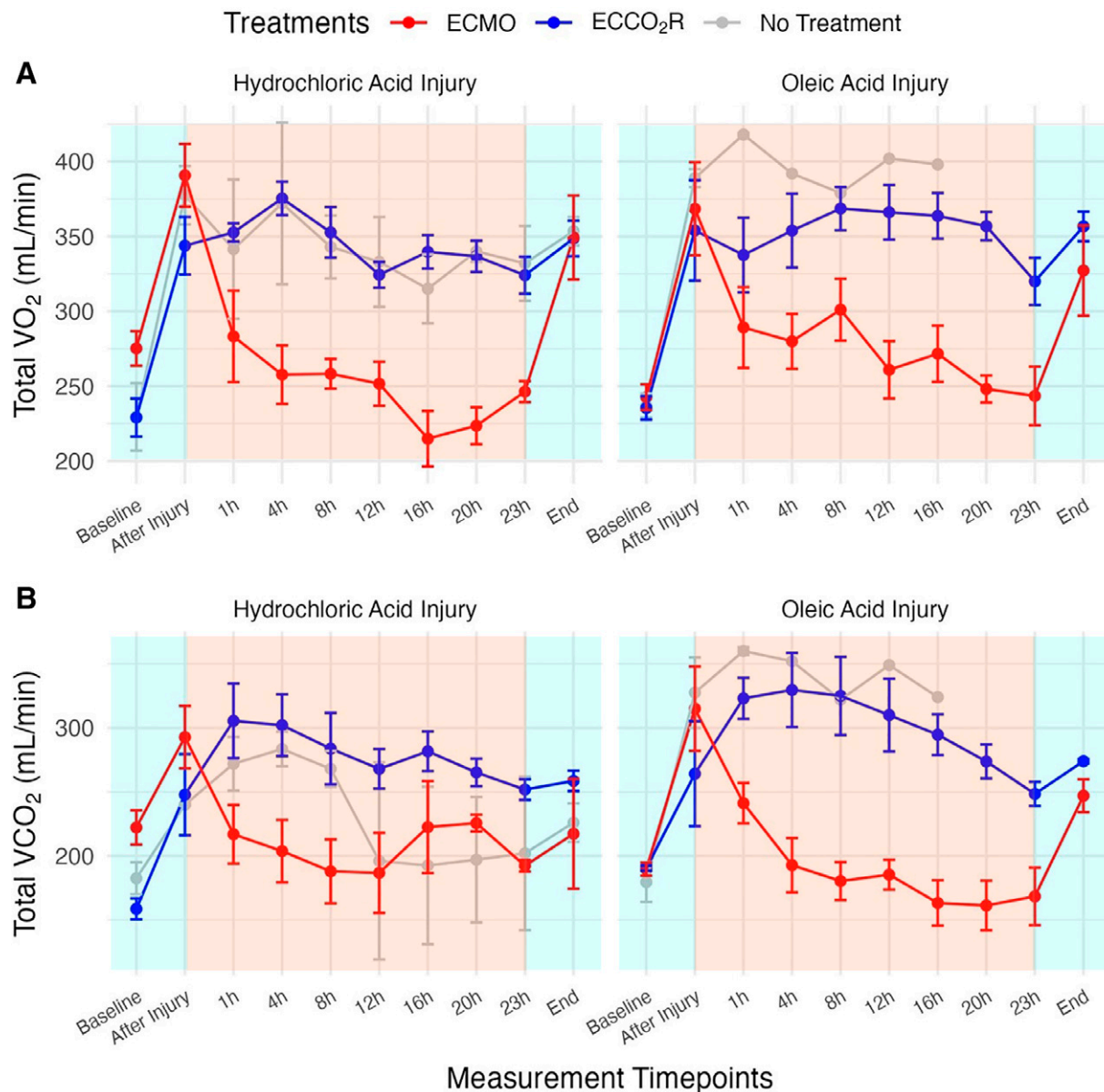
The different hemodynamic patterns during ECMO and ECCO<sub>2</sub>R likely account for the remarkable differences in  $\dot{V}O_2$  and  $\dot{V}CO_2$  we found in this study. Indeed, the cumulative dose of vasoactive drugs during ECCO<sub>2</sub>R (but not during ECMO) was

associated with an increase in  $\dot{V}O_2$  (see Figure E9) (17).

### Respiratory Mechanics

The animals in ECMO group experienced significantly greater impairment of respiratory and lung mechanics compared with their ECCO<sub>2</sub>R counterparts. Indeed, the *hyperprotective* mechanical ventilation applied in ECMO-treated animals was

associated with increased elastance, and a remarkable association was found between the  $\dot{V}_T$  or  $\dot{V}_E$  delivered and the changes in respiratory system elastance (see Figure E20). These findings are consistent with our previous observations that, in normal animals, regardless of the respiratory rate, sufficient inspiratory pressure and inflation are necessary to prevent the extensive collapse of lung units (18). This phenomenon



**Figure 3.** (A and B) Time courses of total  $\dot{V}O_2$  (A) and total  $\dot{V}CO_2$  (B) in hydrochloric acid (HCl)-treated and oleic acid (OA)-treated animals according to support method (ECMO in red, ECCO<sub>2</sub>R in blue, no treatment in gray). Values are represented as mean  $\pm$  SE. “Baseline” refers to values measured before lung injury (light blue background), “After Injury” refers to values after HCl or OA administration before extracorporeal treatment (light blue background), “1h” to “23h” refer to values recorded during treatment (light pink background), and “End” refers to values measured 1 hour after extracorporeal treatment withdrawal while ventilating the pig with the same setting applied after injury (light blue background). ECCO<sub>2</sub>R=extracorporeal CO<sub>2</sub> removal; ECMO=extracorporeal membrane oxygenation.

cannot be prevented by a small PEEP increase, as PEEP keeps open only the alveolar units already opened by tidal inflation. Actually, our experimental model was characterized by a great tendency for the lung to collapse because of extensive lung edema. To avoid or attenuate collapse under such conditions, sufficient plateau pressure must be provided at an adequate respiratory rate. The cost to maintain lung gas volume

and preserve elastance is increased mechanical power, which was greater in the ECCO<sub>2</sub>R group (19).

#### Limitations

The major limitation of this study is that the injury stimuli we used, despite leading to severe and hyperacute impairment in gas exchange that mimics clinical ARDS, reflect cardiopulmonary rather than

inflammatory edema, even though the two often coexist. Consequently, our results may not translate directly to all etiologies and stages of ARDS encountered in the clinical setting.

In addition, the sample size used in this study is a limitation to the clinical application of our results, and a sufficiently powered clinical study will be necessary to validate these data.

**Table 4.** Anatomical Variables according to Extracorporeal Support and Lung Injury

	Hydrochloric Acid				Oleic Acid			
	ECMO (n=5)	ECCO <sub>2</sub> R (n=5)	Control (n=2)	P Value	ECMO (n=5)	ECCO <sub>2</sub> R (n=5)	Control (n=2)	P Value
Lung wet-to-dry ratio	8.4 ± 1.5	7.3 ± 0.4	7.2 ± 1.0	0.313	7.0 ± 1.4	7.7 ± 0.8	9.3 ± 1.3	0.180
Liver wet-to-dry ratio	4.0 ± 0.5	4.0 ± 0.2	4.2 ± 0.3	0.846	3.7 ± 0.4	4.0 ± 0.4	4.0 ± 0.2	0.417
Muscle wet-to-dry ratio	4.0 ± 0.3	4.1 ± 0.3	3.9 ± 0.5	0.581	4.2 ± 0.3	4.3 ± 0.2	3.8 ± 0.2	0.104
Kidney wet-to-dry ratio	4.8 ± 1.4	5.8 ± 0.3	4.5 ± 0.4	0.107	5.8 ± 0.2	6.0 ± 0.7	4.6 ± 0.8	0.054
Bowel wet-to-dry ratio	5.0 ± 0.4	4.9 ± 0.3	6.1 ± 0.5* <sup>†</sup>	0.015	5.2 ± 0.5	5.0 ± 0.7	6.3 ± 1.3	0.105
Lung weight, g	1,394 ± 298	960 ± 162	898 ± 225*	0.030	868 ± 271	932 ± 149	995 ± 84	0.755
Lung weight per kilogram, g/kg	20.5 ± 4.0	15.0 ± 2.0	13.8 ± 2.5*	<b>0.028</b>	13.3 ± 3.9	14.2 ± 3.3	13.9 ± 2.1	0.917

Definition of abbreviations: ECCO<sub>2</sub>R = extracorporeal CO<sub>2</sub> removal; ECMO = extracorporeal membrane oxygenation. P values in boldface type denote statistical significance.

\*Significant comparison with respect to ECMO treatment group.

<sup>†</sup>Significant comparison with respect to ECCO<sub>2</sub>R treatment group.

**Clinical Consequences**

This study shows that the more effective approach to correct severe hypoxemia is high-flow ECMO. Indeed, in contrast to

ECMO, the only way to improve oxygenation during ECCO<sub>2</sub>R is to decrease shunt through better ventilation or increased airway pressure. The overall results of our

study, however, clearly show that the different behavior between models and treatment groups is related to three main factors: 1) the model we used, 2) the effects of

Putative Causes for Variation	Changes in Physiological variables	
	HCl acid	Oleic acid
Model	Less Severe hypoxemia Lower EVLW High hypoxic vasoconstriction	More Severe hypoxemia Greater EVLW High hypoxic vasoconstriction
Technique	ECMO Increase in SvO <sub>2</sub> Abolition of hypoxic vasoconstriction Preserved hemodynamics Lower total VO <sub>2</sub> - VCO <sub>2</sub>	ECCO <sub>2</sub> R Lower SvO <sub>2</sub> Maintenance of pulmonary vasoconstriction Compromised hemodynamics Higher VO <sub>2</sub> - VCO <sub>2</sub>
Operator	Protective MV Maintained respiratory mechanics	Ultra-protective MV Worsening in Respiratory Mechanics: Reabsorption atelectasis Lung collapse Increased elastance

**Figure 4.** Trends of physiological variable alterations according to model, technique, and operator. “Model” refers to HCl or oleic acid injury, “Technique” refers to ECMO or ECCO<sub>2</sub>R application, and “Operator” refers to mechanical ventilator settings chosen by the physicians. ECCO<sub>2</sub>R = extracorporeal CO<sub>2</sub> removal; ECMO = extracorporeal membrane oxygenation; EVLW = extravascular lung water; HCl = hydrochloric acid; MV = mechanical ventilation; SvO<sub>2</sub> = mixed venous oxygen saturation.

ECMO or ECCO<sub>2</sub>R *per se*, and 3) the ventilatory setting imposed by the operator.

For the sake of clarity, we have summarized the interaction pattern among these three factors in Figure 4. As shown, OA compared with HCl led to greater lung edema, as evidenced by a threefold increase in extravascular lung water, and its associated hypoxemia. We may hypothesize that, before the beginning of extracorporeal support, hypoxic vasoconstriction had a lesser effect on gas exchange in the OA model, as all the lung parenchyma was injured. In contrast, the slightly better oxygenation after patchy HCl injury may be due to hypoxic vasoconstriction, which affected oxygenation by diverting blood flow to uninjured lung parenchyma.

ECMO and ECCO<sub>2</sub>R produced profoundly different results in these lung injury models, both of which are characterized by severe pulmonary hypertension and vasoconstriction, supposedly more immediate and severe than early-stage human ARDS. Indeed, beyond the more rapid and greater recovery of systemic oxygenation, the greatly increased mixed venous oxygen saturation during ECMO likely reversed hypoxic

vasoconstriction, with immediate effects on pulmonary and systemic hemodynamics and total  $\dot{V}O_2$ . In contrast, mixed venous oxygen saturation was unmodified during ECCO<sub>2</sub>R, so that hypoxic vasoconstriction and its effects on systemic hemodynamics were unaffected.

Finally, the greater impairment of respiratory mechanics during ECMO treatment does not appear dependent on the injury model or ECMO versus ECCO<sub>2</sub>R treatment *per se* but rather on the clinical choice of ventilatory settings. How to best ventilate these patients, however, remains a major issue, likely requiring a compromise. Indeed, the hyperprotective lung strategy, as in our ECMO group, tends to progressively reduce lung volumes and deteriorate lung mechanics, whereas higher ventilation, as in our ECCO<sub>2</sub>R group, may be associated with harmful mechanical power. We may hypothesize that reconsidering a low-frequency sigh could represent an acceptable compromise.

### Conclusions

Compared with low-flow ECCO<sub>2</sub>R (0.4 L/min), high-flow ECMO (3–5 L/min)

provides more rapid and better oxygenation. In addition, the possible effects of ECMO on  $\dot{V}O_2$  and hemodynamics should be considered in clinical settings. Our data suggest caution when considering ECCO<sub>2</sub>R for severe hypoxemia given the effects of ECCO<sub>2</sub>R on pulmonary hypertension and hemodynamics, for which ECMO has shown to be clinically beneficial. Although the results from the experimental data comparing these two extracorporeal techniques cannot be translated directly into clinical practice, some of the experimental results may generate clinically relevant hypotheses to inform future studies to establish the role of extracorporeal support at lower invasiveness in the management of moderate to severe ARDS. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

**Acknowledgment:** The authors thank General Electric for the generous supply of the CARESCAPE R860 ventilator. The authors thank Estor for providing study material without additional costs.

### References

- Hill JD, O'Brien TG, Murray JJ, Dontigny L, Bramson ML, Osborn JJ, *et al*. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome): use of the Bramson membrane lung. *N Engl J Med* 1972;286:629–634.
- Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, *et al*. Extracorporeal membrane oxygenation in severe acute respiratory failure: a randomized prospective study. *JAMA* 1979;242:2193–2196.
- Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, *et al*.; CESAR Trial Collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;374:1351–1363.
- Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, *et al*.; Australia, New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A(H<sub>1</sub>N<sub>1</sub>) acute respiratory distress syndrome. *JAMA* 2009;302:1888–1895.
- Combes A, Hajage D, Capellier G, Demoué A, Lavoué S, Guervilly C, *et al*.; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018;378:1965–1975.
- Gattinoni L, Agostoni A, Pesenti A, Pelizzola A, Rossi GP, Langer M, *et al*. Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO<sub>2</sub>. *Lancet* 1980;2:292–294.
- Gattinoni L, Kolobow T, Tomlinson T, White D, Pierce J. Control of intermittent positive pressure breathing (IPPB) by extracorporeal removal of carbon dioxide. *Br J Anaesth* 1978;50:753–758.
- Gattinoni L, Marini JJ, Pesenti A, Quintel M, Mancebo J, Brochard L. The "baby lung" became an adult. *Intensive Care Med* 2016;42:663–673.
- McNamee JJ, Gillies MA, Barrett NA, Perkins GD, Tunnicliffe W, Young D, *et al*.; REST Investigators. Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: the REST randomized clinical trial. *JAMA* 2021;326:1013–1023.
- Duscio E, Cipulli F, Vasques F, Collino F, Rapetti F, Romitti F, *et al*. Extracorporeal CO<sub>2</sub> removal: the minimally invasive approach, theory, and practice. *Crit Care Med* 2019;47:33–40.
- Wang YM, Sun XM, Zhou YM, Chen JR, Cheng KM, Li HL, *et al*. Effect of positive end-expiratory pressure on functional residual capacity in two experimental models of acute respiratory distress syndrome. *J Int Med Res* 2020;48:300060520920426.
- Cressoni M, Chiurazzi C, Gotti M, Amini M, Brioni M, Algieri I, *et al*. Lung inhomogeneities and time course of ventilator-induced mechanical injuries. *Anesthesiology* 2015;123:618–627.
- Riley RL, Courmand A. Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J Appl Physiol* 1949;1:825–847.
- Butterfield GE, Gates J, Fleming S, Brooks GA, Sutton JR, Reeves JT. Increased energy intake minimizes weight loss in men at high altitude. *J Appl Physiol* (1985) 1992;72:1741–1748.
- Gu C, Jun JC. Does hypoxia decrease the metabolic rate? *Front Endocrinol (Lausanne)* 2018;9:668.
- Kolobow T, Gattinoni L, Tomlinson T, White D, Pierce J, Iapichino G. The carbon dioxide membrane lung (CDML): a new concept. *Trans Am Soc Artif Intern Organs* 1977;23:17–21.
- Ensinger H, Weichel T, Lindner KH, Grünert A, Ahnefeld FW. Effects of norepinephrine, epinephrine, and dopamine infusions on oxygen consumption in volunteers. *Crit Care Med* 1993;21:1502–1508.
- Gattinoni L, Kolobow T, Tomlinson T, Iapichino G, Samaja M, White D, *et al*. Low-frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-ECCO<sub>2</sub>R): an experimental study. *Anesth Analg* 1978;57:470–477.
- Quintel M, Busana M, Gattinoni L. Breathing and ventilation during extracorporeal membrane oxygenation: how to find the balance between rest and load. *Am J Respir Crit Care Med* 2019;200:954–956.