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

ORIGINAL ARTICLE

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

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

[1]Department of Anesthesiology, University Medical Center Göttingen, Göttingen, Germany; [2]IRCCS San Raffaele Scientific Institute, Milan, Italy; [3]Department of Anesthesiology, Intensive Care and Emergency Medicine, Donau Isar Hospital Deggendorf, Deggendorf, Germany; [4]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 [5]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_2 removal ($ECCO_2R$), provided oxygenation remains acceptable.

Objectives: To compare the effects of $ECCO_2R$ 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 (Pa_{O_2}:$F_{I_{O_2}} \leq 150$ mm Hg) were randomized to ECMO (blood flow 50–60 ml/kg/min), $ECCO_2R$ (0.4 L/min), or mechanical ventilation alone.

Measurements and Main Results: $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, 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 ± 419 vs. 574 ± 195 ml; $P < 0.001$), worse oxygenation (Pa_{O_2}:$F_{I_{O_2}}$ = 125 ± 14 vs. 151 ± 11 mm Hg; $P < 0.001$), but better respiratory mechanics (plateau pressure 27 ± 4 vs. 30 ± 3 cm H_2O; $P = 0.017$). Both models led to acute severe pulmonary hypertension. In both models, ECMO (3.7 ± 0.5 L/min), compared with $ECCO_2R$ (0.4 L/min), increased mixed venous oxygen saturation and oxygenation, and improved hemodynamics (cardiac output = 6.0 ± 1.4 vs. 5.2 ± 1.4 L/min; $P = 0.003$). $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, irrespective of lung injury model, were lower during ECMO, resulting in lower Pa_{CO_2} and $\dot{V}_E$ but worse respiratory elastance compared with $ECCO_2R$ (64 ± 27 vs. 40 ± 8 cm H_2O/L; $P < 0.001$).

Conclusions: ECMO was associated with better oxygenation, lower $\dot{V}_{O_2}$, and better hemodynamics. $ECCO_2R$ 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_2 removal; acute respiratory distress syndrome; $\dot{V}O_2$; $\dot{V}CO_2$

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*These authors contributed equally to this work.

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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.

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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_2 removal. Low-flow extracorporeal CO_2 removal ($ECCO_2R$) has been used to reduce the intensity of mechanical ventilation by decreasing the CO_2 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_2 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 $ECCO_2R$ 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 $ECCO_2R$ 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_1N_1 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_2 removal ($ECCO_2R$) in laboratory animal models, and we hypothesized that this technique could be used to allow lung rest and avoid the high V_T and pressure traditionally used to ventilate patients with acute respiratory distress syndrome (ARDS) (6, 7). Unlike ECMO, the primary indication for $ECCO_2R$ 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 $ECCO_2R$ showed that Pa_{O_2} was similar between the intervention group (i.e., ECMO or $ECCO_2R$) 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_2. 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_2 can be removed by the less invasive (and lower blood flow requiring) $ECCO_2R$ 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 $ECCO_2R$. Mechanical ventilation was adjusted to maintain the arterial Pa_{CO_2} 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 $ECCO_2R$ 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 $ECCO_2R$ 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_T of 8 ml/kg, positive end-expiratory pressure (PEEP) of 4 cm H_2O, $F_{I_{O_2}}$ 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 $ECCO_2R$, respectively.

Lung Damage Induction

With extracorporeal support already initiated but with zero sweep gas flow, pigs were ventilated protectively with V_T of 6 ml/kg, PEEP of 10 cm H_2O, $F_{I_{O_2}}$ of 40%, inspiratory:expiratory ratio of 1:2, and respiratory rate set to achieve Pa_{CO_2} 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.

a direct pulmonary injury) until Pa_{O_2}:FI_{O_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 $ECCO_2R$ 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_2O, V_T was reduced accordingly. The four control animals were connected to ECMO or $ECCO_2R$ 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 ± 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 Pa_{O_2}:FI_{O_2} ratio of <150 mm Hg in approximately 4 hours. The physiological characteristics at the target Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_2} ratio in the HCl model (151 ± 11 vs. 125 ± 14 mm Hg; $P < 0.001$). Extravascular lung water was almost threefold greater in the OA group compared with the HCl group (1,424 ± 419 vs. 574 ± 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 Sa_{O_2} and Pa_{O_2}:FI_{O_2} ratio were significantly lower during $ECCO_2R$ compared with ECMO treatment (*see* Table 1). Venous admixture was significantly higher in the ECMO group. The time courses for Sa_{O_2}, Pa_{O_2}, pulmonary venous admixture, and Pa_{O_2}:FI_{O_2} are presented in Figures 1 and E4A. As shown, in the HCl lung injury model, both Sa_{O_2} and Pa_{O_2} rapidly improved and became similar between $ECCO_2R$ 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 $ECCO_2R$ group. In the OA lung injury model, Sa_{O_2} and Pa_{O_2} rose rapidly and were similar between the ECMO and $ECCO_2R$ groups after 4 (Pa_{O_2}) and 8 (Sa_{O_2}) hours. In the corresponding control animals without extracorporeal support, oxygenation remained severely impaired throughout the experiment.

CO_2 clearance. The average 24-hour values of Pa_{CO_2} in both HCl and OA models were significantly higher during $ECCO_2R$ compared with ECMO, because of lower CO_2 fraction eliminated by the membrane lung. This occurred despite significantly higher $\dot{V}_E$, V_T, and respiratory rates required in the $ECCO_2R$ group to maintain Pa_{CO_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 $\dot{V}_{O_2}$ and 65% of total CO_2 clearance in both groups. The time courses of membrane lung $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are shown in Figure E6.

$ECCO_2R$. The details of $ECCO_2R$ treatment are reported in Table 2. As shown, $ECCO_2R$ blood flow represented about 10% of cardiac output in both the HCl and OA groups. The oxygen transfer provided by $ECCO_2R$ was negligible, and the mixed venous oxygen content was unaffected by $ECCO_2R$ treatment. Consequently, oxygen transfer occurred almost totally through the natural lung, while the CO_2 cleared by $ECCO_2R$ was about 40% of the total $\dot{V}_{CO_2}$ in both groups. The time courses of membrane lung $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are shown in Figure E6.

Respiratory mechanics. The average 24-hour respiratory mechanics variables are detailed in Table 3. Compared with $ECCO_2R$, 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 $ECCO_2R$ 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 ($n=5$)	$ECCO_2R$ ($n=5$)	Control ($n=2$)	*P* Value	ECMO ($n=5$)	$ECCO_2R$ ($n=5$)	Control ($n=2$)	*P* Value
Metabolism								
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**
Gas exchange								
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_{O_2}:$F_{I_{O_2}}$, mm Hg	321 ± 68	262 ± 52	270 ± 70*†	**<0.001**	334 ± 88	251 ± 117*	123 ± 19*†	**<0.001**
Pa_{O_2}, mm Hg	118 ± 24	109 ± 21	108 ± 28	0.221	147 ± 52	124 ± 61	55 ± 4*†	**<0.001**
Pa_{CO_2}, mm Hg	47 ± 5	53 ± 6*	50 ± 8	**<0.001**	44 ± 4	49 ± 5*	55 ± 5*†	**<0.001**
Pet_{CO_2}, 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**
V_T per IBW, kg/m^2	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: $ECCO_2R$ = extracorporeal CO_2 removal; ECMO = extracorporeal membrane oxygenation; IBW = ideal body weight; Pet_{CO_2} = end-tidal Pa_{CO_2}.
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 $ECCO_2R$ treatment group.

resistance, cardiac output, stroke volume, and heart rate were significantly higher when applying $ECCO_2R$ compared with ECMO. The time course of pulmonary artery resistance is reported in Figure 2A. Significantly higher doses of epinephrine were required in the $ECCO_2R$ 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 $ECCO_2R$ 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 $ECCO_2R$. 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 $ECCO_2R$ 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 $ECCO_2R$.

The lower $\dot{V}O_2$ during ECMO compared with $ECCO_2R$ appeared significantly related, in various degrees, to lower pulmonary vascular resistance, higher mixed venous oxygen saturation, lower mixed venous P_{CO_2}, 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 $ECCO_2R$ 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 $ECCO_2R$ support; and *3*) ECMO achieved better oxygenation, CO_2 removal, and hemodynamics in both injury models but resulted in worse respiratory mechanics compared with $ECCO_2R$.

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.

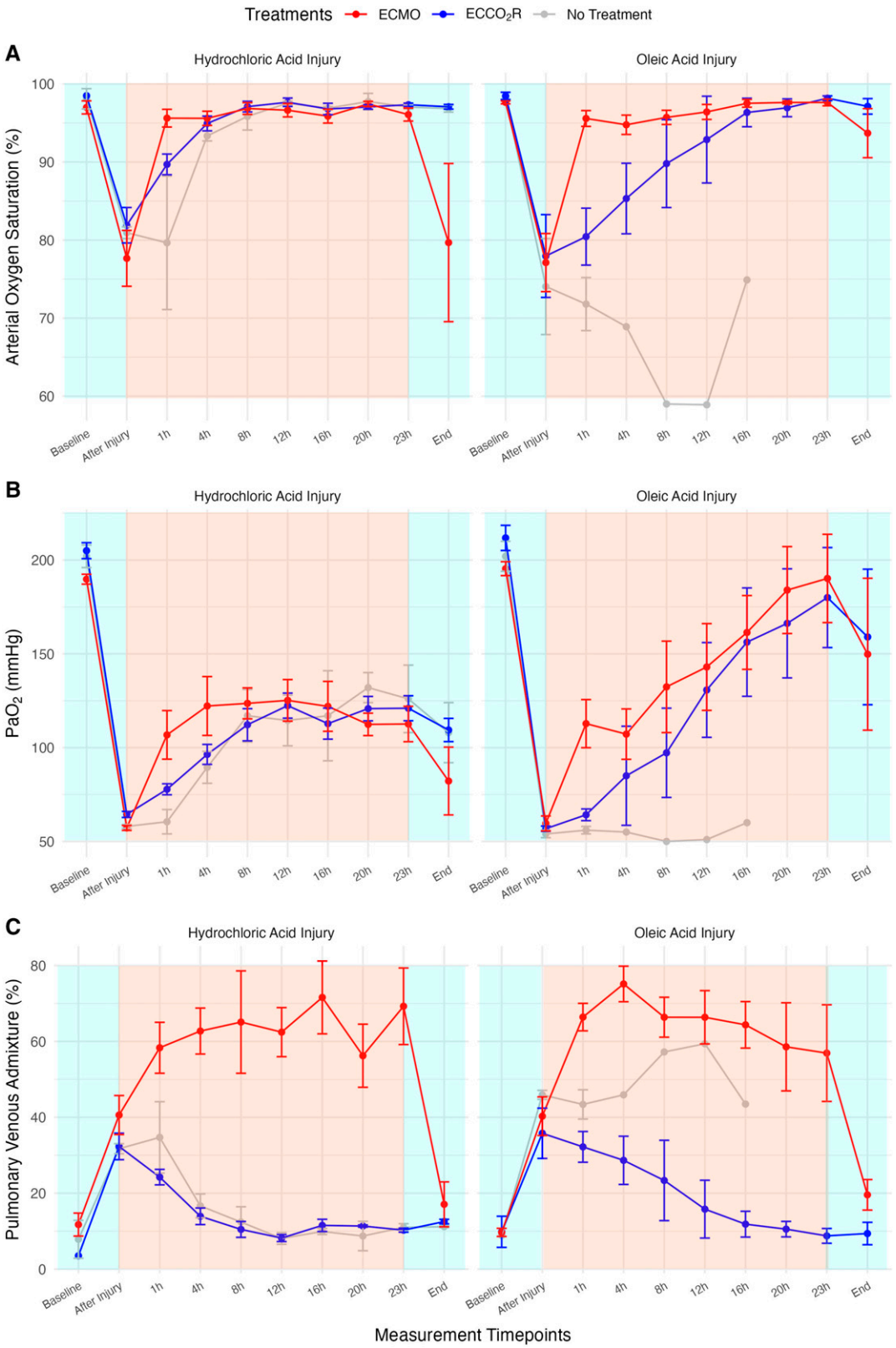

Figure 1. (*A–C*) Time courses of Sa_{O_2} (*A*), Pa_{O_2} (*B*), and pulmonary venous admixture fraction (*C*) in hydrochloric acid (HCl)–treated and oleic acid (OA)-treated animals according to support method (ECMO in red, $ECCO_2R$ in blue, no treatment in gray). Values are represented as mean ± SE. "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 ($n = 5$)	$ECCO_2R$ ($n = 5$)	Control ($n = 2$)	*P* Value	ECMO ($n = 5$)	$ECCO_2R$ ($n = 5$)	Control ($n = 2$)	*P* Value
Blood flow, L/min	3.6 ± 0.5	0.4 ± 0.0*	2.0 ± 1.7*†	**<0.001**	3.7 ± 0.4	0.4 ± 0.0*	3.2 ± 1.5*†	**<0.001**
Blood flow as % of cardiac output	59 ± 11	8 ± 2*	42 ± 38*†	**<0.001**	67 ± 13	9 ± 3*	69 ± 8*†	**<0.001**
Sweep gas flow, L/min	4.0 ± 0.7	15.0 ± 0.0	—	**<0.001**	3.6 ± 0.8	13.6 ± 1.5	—	**<0.001**
Pin_{O_2}, mm Hg	41 ± 3	51 ± 4*	36 ± 10*†	**<0.001**	45 ± 5	47 ± 7	34 ± 5*†	**<0.001**
$Pout_{O_2}$, mm Hg	388 ± 35	114 ± 38*	36 ± 4*†	**<0.001**	363 ± 43	129 ± 15*	37 ± 10*†	**<0.001**
$\dot{V}o_{2NL}$, ml/min	30 ± 23	293 ± 51*	340 ± 3*	**<0.001**	28 ± 13	330 ± 65*	401 ± 15*†	**<0.001**
$\dot{V}o_{2ML}$, ml/min	235 ± 43	24 ± 3	—	**<0.001**	242 ± 49	31 ± 7	—	**<0.001**
$\dot{V}o_{2ML}$:total $\dot{V}o_2$, %	84 ± 6	6 ± 1	—	**<0.001**	83 ± 6	7 ± 3	—	**<0.001**
Pin_{CO_2}, mm Hg	53 ± 5	53 ± 7	59 ± 8*†	**0.004**	51 ± 6	48 ± 8	69 ± 6*†	**<0.001**
$Pout_{CO_2}$, mm Hg	44 ± 5	11 ± 4*	60 ± 9*†	**<0.001**	42 ± 4	16 ± 16	70 ± 5	**<0.001**
$\dot{V}co_{2NL}$, ml/min	63 ± 26	167 ± 31*	230 ± 65†	**<0.001**	67 ± 22	190 ± 44*	344 ± 14*†	**<0.001**
$\dot{V}co_{2ML}$, ml/min	147 ± 47	113 ± 26	—	**<0.001**	119 ± 37	112 ± 61	—	0.547
$\dot{V}co_{2ML}$:total $\dot{V}co_2$, %	68 ± 13	41 ± 7	—	**<0.001**	64 ± 10	36 ± 15	—	**<0.001**

Definition of abbreviations: $ECCO_2R$ = extracorporeal CO_2 removal; ECMO = extracorporeal membrane oxygenation; $Pin_{CO_2} = Pa_{CO_2}$ to the membrane lung; $Pin_{O_2} = Pa_{O_2}$ to the membrane lung; $Pout_{CO_2} = Pa_{CO_2}$ out of the membrane lung; $Pout_{O_2} = Pa_{O_2}$ out of the membrane lung; $\dot{V}co_{2NL}$ = natural lung carbon dioxide removal; $\dot{V}co_{2ML}$ = membrane lung carbon dioxide removal; $\dot{V}o_{2ML}$ = 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.
†Significant comparison with respect to $ECCO_2R$ 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_{O_2} 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 $\dot{V}o_2$, which is inversely related to Pa_{O_2}:Fi_{O_2} 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 $\dot{V}o_2$) (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 $\dot{V}o_2$ and shunt. In HCl injury, the expected increase of Pa_{O_2}:Fi_{O_2} due to the progressive decrease in $\dot{V}o_2$ was likely offset by worsening of the shunt fraction. In contrast, the decline in $\dot{V}o_2$ 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 $ECCO_2R$, the increase of oxygenation is best explained by a decrease in shunt, as the extracorporeal addition of oxygen was almost negligible (about 7% of $\dot{V}o_2$), and $\dot{V}o_2$ 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 $ECCO_2R$ 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 $ECCO_2R$ 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_2 Removal

Pa_{CO_2} was a function of the amount of total $\dot{V}co_2$, the amount of CO_2 removed by the membrane lung, the physiological dead space, and $\dot{V}_E$. In our study, the amount of CO_2 removed by ECMO and by $ECCO_2R$ was similar in both the HCl and OA groups. This would have allowed a similar decrease in $\dot{V}_E$, if the total $\dot{V}co_2$ had been similar between ECMO- and $ECCO_2R$-treated animals (16); however, total $\dot{V}co_2$ was markedly higher in animals undergoing $ECCO_2R$. The higher $\dot{V}co_2$ was associated, however, with higher $\dot{V}o_2$ (Figure 3), indicating that the overall metabolic rate was about 20–30% higher with $ECCO_2R$ compared with ECMO. A possible explanation is the metabolic effects of the higher dose of epinephrine required to maintain hemodynamic status in the $ECCO_2R$ group (*see* the next section). Consequently, Pa_{CO_2} increased significantly during $ECCO_2R$ compared with ECMO. To maintain Pa_{CO_2} 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). $ECCO_2R$ = extracorporeal CO_2 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 ($n=5$)	$ECCO_2R$ ($n=5$)	Control ($n=2$)	*P* Value	ECMO ($n=5$)	$ECCO_2R$ ($n=5$)	Control ($n=2$)	*P* Value
Respiratory mechanics								
Plateau pressure, cm H_2O	31 ± 3	26 ± 2*	28 ± 4*	**<0.001**	30 ± 4	25 ± 4*	28 ± 3	**<0.001**
Mean airway pressure, cm H_2O	18 ± 2	17 ± 2	16 ± 2	0.090	18 ± 2	16 ± 3*	18 ± 1	**<0.001**
PEEP, cm H_2O	13 ± 2	12 ± 1*	10 ± 0*†	**<0.001**	13 ± 1	11 ± 1*	10 ± 0*†	**<0.001**
Respiratory system elastance, cm H_2O/L	68 ± 34	41 ± 6*	52 ± 10	**<0.001**	59 ± 16	39 ± 9*	41 ± 4*	**<0.001**
Lung elastance, cm H_2O/L	57 ± 36	30 ± 7*	40 ± 7	**<0.001**	47 ± 15	29 ± 11*	30 ± 5*	**<0.001**
Stress, cm H_2O	25 ± 5	19 ± 4*	22 ± 3*†	**<0.001**	24 ± 4	18 ± 6*	21 ± 3	**<0.001**
Driving pressure, cm H_2O	18 ± 3	14 ± 2	19 ± 4*†	**<0.001**	17 ± 4	14 ± 3	17 ± 2†	**0.008**
Mechanical power, J/min	9.3 ± 3.0	18.7 ± 3.7*	28.4 ± 7.1*†	**<0.001**	10.1 ± 2.6	19.6 ± 8.4*	41.0 ± 3.7*†	**<0.001**
Extravascular lung water, ml	1,167 ± 359	501 ± 123*	431 ± 88*	**<0.001**	1,320 ± 550	1,093 ± 223	2,018 ± 514*†	**<0.001**
Hemodynamics								
Mean arterial pressure, mm Hg	73 ± 11	64 ± 8*	67 ± 10	**<0.001**	70 ± 12	63 ± 15	51 ± 8*	**0.004**
Central venous pressure, mm Hg	8 ± 2	9 ± 3*	8 ± 2	**0.034**	7 ± 3	8 ± 3	5 ± 1*†	0.059
Systemic vascular resistance, dynes/s/cm^5	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^5	242 ± 60	304 ± 102*	280 ± 130	**0.024**	239 ± 96	361 ± 216*	467 ± 134*	**0.001**
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*	**0.002**	5.7 ± 1.3	4.8 ± 1.5*	5.5 ± 0.6	**0.042**
Stroke volume, ml	69 ± 19	56 ± 20*	53 ± 22*	**0.008**	67 ± 14	52 ± 20*	37 ± 13*	**<0.001**
Heart rate, beats/min	114 ± 31	136 ± 45*	147 ± 39*	**0.013**	107 ± 40	146 ± 47*	181 ± 18*	**<0.001**
Fluid administered, L	6.9 ± 2.1	9.7 ± 2.2*	9.4 ± 2.1*	**<0.001**	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†	**<0.001**	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*†	**<0.001**	0.09 ± 0.09	0.10 ± 0.08	0.80 ± 0.30*†	**<0.001**

Definition of abbreviations: $ECCO_2R$ = extracorporeal CO_2 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 $ECCO_2R$ 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 $ECCO_2R$, 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

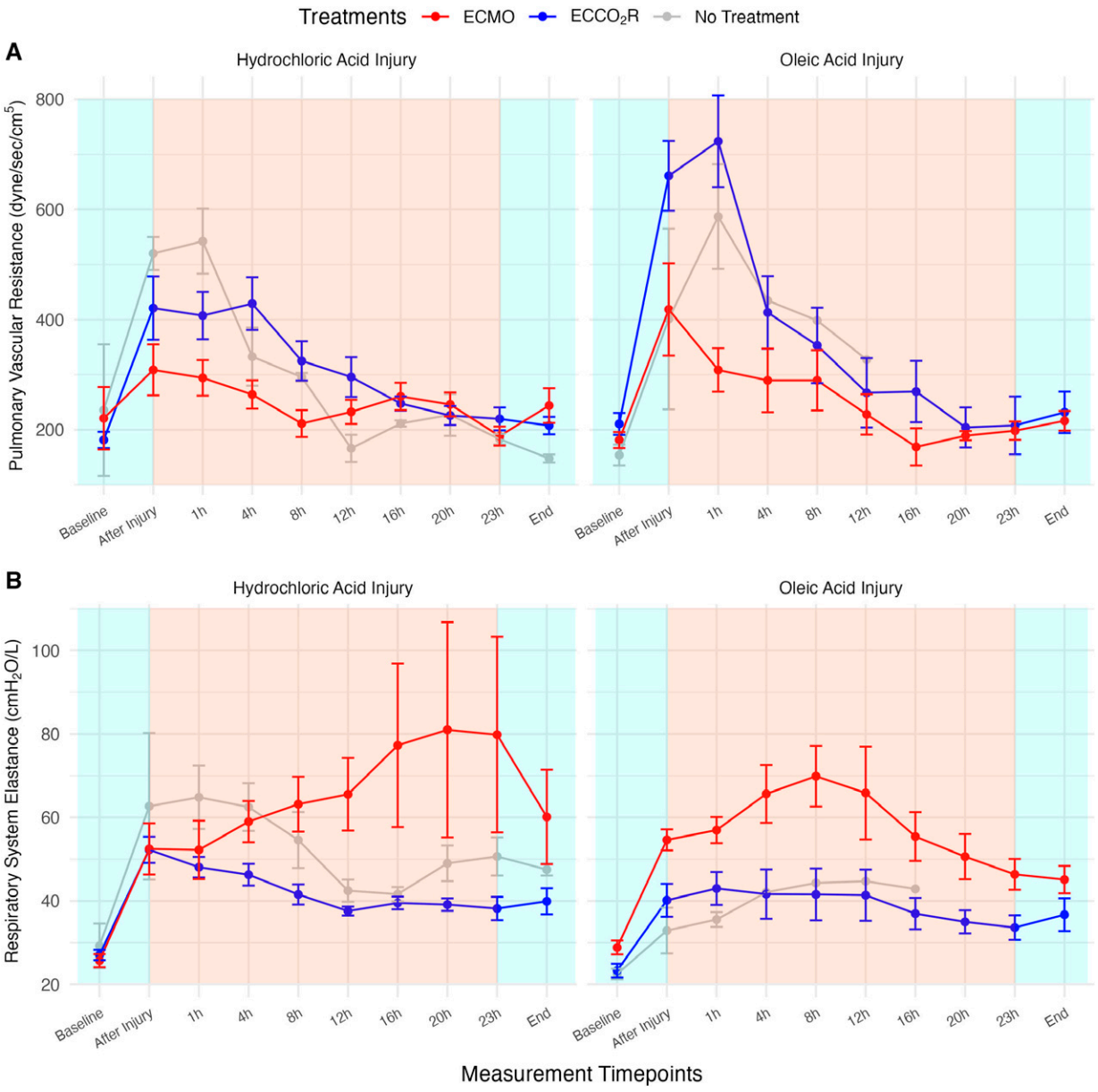

Figure 2. (*A* and *B*) Time courses of total pulmonary vascular resistance (*A*) and respiratory system elastance (*B*) in hydrochloric acid (HCl)–treated and oleic acid (OA)-treated animals according to method of support (ECMO in red, $ECCO_2R$ in blue, no treatment in gray). Values are represented as mean ± SE. "Baseline" refers to values measured before lung injury (light blue background), "After Injury" refers to values after HCl or OA administration 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). $ECCO_2R$ = extracorporeal CO_2 removal; ECMO = extracorporeal membrane oxygenation.

pressures and pulmonary vascular resistance in $ECCO_2R$, such as lower mixed venous pH and higher mixed venous P_{CO_2} (*see* Figures E17–E19).

The different hemodynamic patterns during ECMO and $ECCO_2R$ 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 $ECCO_2R$ (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 $ECCO_2R$ counterparts. Indeed, the *hyperprotective* mechanical ventilation applied in ECMO-treated animals was associated with increased elastance, and a remarkable association was found between the 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

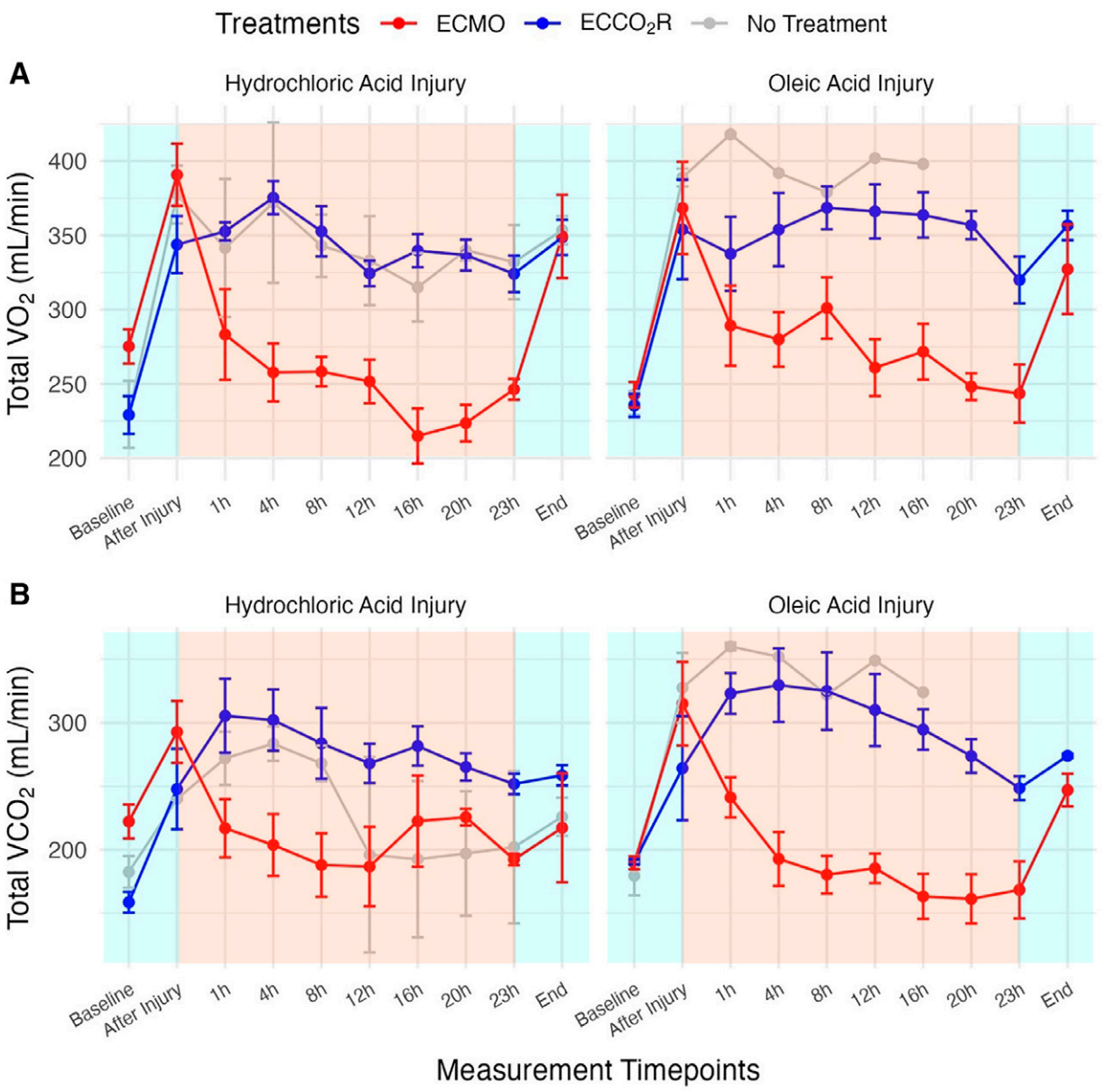

Figure 3. (*A* and *B*) Time courses of total $\dot{V}_{O_2}$ (*A*) and total $\dot{V}_{CO_2}$ (*B*) in hydrochloric acid (HCl)–treated and oleic acid (OA)-treated animals according to support method (ECMO in red, $ECCO_2R$ in blue, no treatment in gray). Values are represented as mean ± SE. "Baseline" refers to values measured before lung injury (light blue background), "After Injury" refers to values after HCl or OA administration 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). $ECCO_2R$ = extracorporeal CO_2 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 $ECCO_2R$ 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 ($n=5$)	$ECCO_2R$ ($n=5$)	Control ($n=2$)	*P* Value	ECMO ($n=5$)	$ECCO_2R$ ($n=5$)	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*†	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*	**0.028**	13.3 ± 3.9	14.2 ± 3.3	13.9 ± 2.1	0.917

Definition of abbreviations: $ECCO_2R$ = extracorporeal CO_2 removal; ECMO = extracorporeal membrane oxygenation.
P values in boldface type denote statistical significance.
*Significant comparison with respect to ECMO treatment group.
†Significant comparison with respect to $ECCO_2R$ 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 $ECCO_2R$ 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

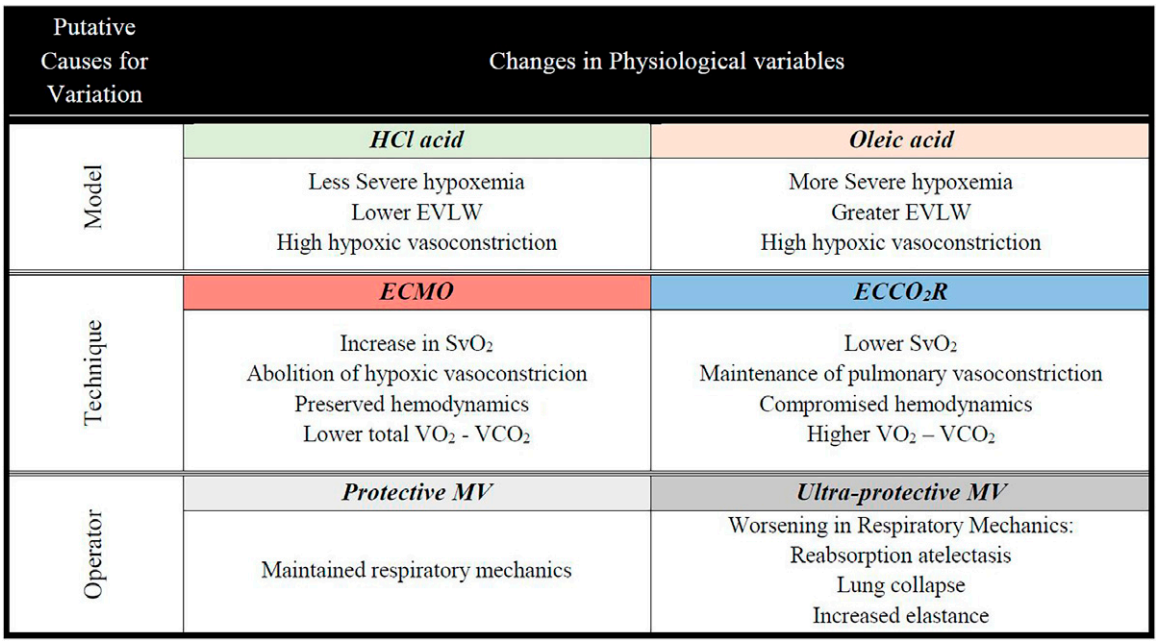

Figure 4. Trends of physiological variable alterations according to model, technique, and operator. "Model" refers to HCl or oleic acid injury, "Technique" refers to ECMO or $ECCO_2R$ application, and "Operator" refers to mechanical ventilator settings chosen by the physicians. $ECCO_2R$ = extracorporeal CO_2 removal; ECMO = extracorporeal membrane oxygenation; EVLW = extravascular lung water; HCl = hydrochloric acid; MV = mechanical ventilation; Sv_{O_2} = mixed venous oxygen saturation.

ECMO or $ECCO_2R$ *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 $ECCO_2R$ 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 $ECCO_2R$, 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 $ECCO_2R$ 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 $ECCO_2R$ 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 $ECCO_2R$ (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 $ECCO_2R$ for severe hypoxemia given the effects of $ECCO_2R$ 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.

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