Physiologic Effects of ECMO in Patients with Severe Acute Respiratory Distress Syndrome

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At a Glance Commentary

Current Scientific Knowledge on the Subject: Physiological effects of ECMO blood flow rates have not been studied: change in mixed venous saturation could impact pulmonary hemodynamics and ventilation/perfusion matching.

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What This Study Adds to the Field: Increasing ECMO blood flow rate and patient's SvO2 decreases cardiac output and pulmonary artery pressure. Pulmonary artery compliance and right heart workload improve, too. Complex physiological interactions drive such changes, with the aim of minimising cardiac output while maintaining adequate systemic oxygen delivery. Ventilation perfusion mismatch is not affected by higher SvO2 in the range explored by this study (70-90%).

This article has an online data supplement, which is accessible at the Supplements tab.

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Abstract

Rationale: Blood flow rate affects mixed venous oxygenation (SvO_2) during venovenous extracorporeal membrane oxygenation (ECMO), with possible effects on the pulmonary circulation and the right heart function.

Objectives: We aimed at describing the physiologic effects of different levels of SvO_2 obtained by changing ECMO blood flow, in patients with severe ARDS receiving ECMO and controlled mechanical ventilation.

Methods: Low (SvO_2 target 70-75%), intermediate (SvO_2 target 75-80%) and high (SvO_2 target > 80%) ECMO blood flows were applied for 30 minutes in random order in 20 patients. Mechanical ventilation settings were left unchanged. The hemodynamic and pulmonary effects were assessed with pulmonary artery catheter and electrical impedance tomography (EIT).

Measurements and Main Results: Cardiac output decreased from low to intermediate and to high blood flow/SvO_2 (9.2 [6.2-10.9] vs 8.3 [5.9-9.8] vs 7.9 [6.5-9.1] L/min, $p = 0.014$), as well as mean pulmonary artery pressure (34 ± 6 vs 31 ± 6 vs 30 ± 5 mmHg, $p < 0.001$), and right ventricle stroke work index (14.2 ± 4.4 vs 12.2 ± 3.6 vs 11.4 ± 3.2 g*m/beat/m^2, $p = 0.002$). Cardiac output was inversely correlated with mixed venous and arterial PO_2 values ($R^2 = 0.257$, $p = 0.031$ and $R^2 = 0.324$, $p = 0.05$). Pulmonary artery pressure was correlated with decreasing mixed venous PO_2 ($R^2 = 0.29$, $p <0.001$) and with increasing cardiac output ($R^2 = 0.378$ $p < 0.007$). Measures of ventilation/perfusion mismatch did not differ between the three steps.

Conclusions: In severe ARDS patients, increased ECMO blood flow rate resulting in higher SvO_2 decreases pulmonary artery pressure, cardiac output, and right heart workload.

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Keywords: extracorporeal membrane oxygenation, blood flow, pulmonary artery pressure, right heart workload

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Introduction

Life-threatening impairment of gas exchange, risk of ventilation-induced lung injury (VILI) (1) and pulmonary arterial hypertension leading to right ventricular failure (2) represent major clinical challenges for the treatment of patients with severe ARDS. Venovenous extracorporeal membrane oxygenation (ECMO) is currently applied in patients with severe ARDS and refractory hypoxemia, despite optimization of protective ventilation (3). Venovenous ECMO is highly effective in obtaining adequate gas exchange and decreasing ventilatory pressures (3), whereas it does not provide direct cardiovascular support for the heart.

Lately, clinical evidence suggested that start of venovenous ECMO could unload the right ventricle by attenuating pulmonary hypertension (4–6). Normalization of blood gases and reduced ventilation likely play a major role upon ECMO initiation (7), but higher saturation of mixed venous blood produced by ECMO blood flow returning to the right heart could also impact the pulmonary circulation (8). Early experimental studies applied ECMO to manipulate mixed venous oxygen saturation (SvO_2) and showed reversal of hypoxic pulmonary vasoconstriction (HPV), albeit with variable effects on pulmonary arterial pressures and intrapulmonary shunt (9–11). Theoretically, reversal of HPV due to increased SvO_2 could decrease pulmonary arterial pressure, possibly at the expenses of higher intrapulmonary shunt (12). Among clinical ECMO settings, blood flow rate is the main determinant of SvO_2 (13) but there is a large variation in values reported by observational studies and clinical trials (3, 13). No previous study has formally tested the relationships between ECMO blood flow, the resulting SvO_2 and cardiopulmonary physiology. If the modulation of SvO_2 could induce physiologically relevant protective effects on the right heart and the pulmonary circulation, then titration of ECMO blood flow in severe ARDS patients

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might aim at optimization of the right heart workload, providing an additional benefit beyond the reduction of tidal volume and the achievement of viable gas exchange (although changes in arterial O_2 content could have indirect cardiac effects).

We designed the current physiologic study to investigate, in severe ARDS patients, the effects of ECMO blood flow targeted to three levels of SvO_2. The aim was to assess the impact of ECMO blood flow and SvO_2 on the pulmonary circulation, right ventricular workload and intrapulmonary ventilation/perfusion matching.

Methods

This was a prospective physiologic randomized cross-over study of patients with severe ARDS who were undergoing venovenous ECMO for clinical reasons between June 2021 and June 2022. The study was conducted in the General ICUs of Maggiore Policlinico (Milan, Italy) and San Gerardo (Monza, Italy) Hospitals. The study protocol was approved by the ethical committees of the two participating centers (reference number 968_2020 and 3896, respectively) and informed consent requirements were met according to local regulations.

We enrolled intubated, deeply sedated, paralyzed patients undergoing ECMO for severe ARDS. All patients were receiving controlled mechanical ventilation and had a pulmonary artery catheter in place. Exclusion criteria included: age <18 years, pregnancy, contraindication to the use of electrical impedance tomography (EIT; e.g. pacemaker or implantable cardioverter defibrillator), hemodynamic instability, peripheral oxygen saturation (SpO_2) <80% despite ECMO FdO_2 and FiO_2 set at 100%, moribund status, refusal by the attending physician. Severe ARDS patients on

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ECMO were screened daily and enrolled when they fulfilled all the inclusion criteria, and no exclusion criteria were present.

At enrollment, we collected the patients' main demographics and clinical data.

Clinical ventilation and ECMO settings and gas exchanges were recorded.

After enrollment, ventilation and ECMO were adjusted to the following standardized settings:

- Ventilation: pressure control mode with clinical PEEP, inspiratory pressure 12 cmH_2O above PEEP, respiratory rate (RR) 10-12 breaths per minute, I:E ratio 1:2, clinical FiO_2
- ECMO: sweep gas flow set to obtain arterial pH between 7.35 and 7.45 at clinical blood flow, fraction of delivered oxygen in the sweep gas flow (FdO_2) equal to clinical FiO_2

All the standardized ventilation and ECMO settings were left unchanged throughout all the study steps. EIT monitoring (Pulmovista Drager, Lubeck, Germany) was applied before starting the protocol.

The study protocol consisted of three randomized cross-over steps (each step lasted 30 minutes), corresponding to three levels of ECMO blood flow rate manually adjusted to target 3 ranges of mixed venous SvO_2:

- Low ECMO blood flow, set to obtain SvO_2 of 70-75%
- Intermediate ECMO blood flow, set to obtain SvO_2 of 75-80%
- High ECMO blood flow, set to obtain SvO_2 > 80%

Invasive systemic and pulmonary arterial pressure, heart rate and SpO_2 were continuously monitored. Additional details about the study protocol are reported in the Online data Supplement.

During the last minutes of each study steps, we collected:

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- ECMO blood flow rate
- Hemodynamics, including heart rate (HR), cardiac output (CO, thermodilution technique), cardiac index (CI = CO/body surface area) and central pressures (central venous pressure: CVP; pulmonary arterial occlusion pressure: PAOP; systolic, diastolic and mean pulmonary arterial pressure: PAPs, PAPd and PAPm) measured with the pulmonary artery catheter
- Arterial and mixed venous blood gases
- Recordings of EIT waveforms with ventilation and perfusion data. Perfusion was assessed during an inspiratory breath hold plus bolus injection of 5% saline (10 ml) in the central line, as previously described (14)

Data from arterial and mixed venous blood gases were used to calculate intrapulmonary shunt. Oxygen exchange through the natural lung (VO_2 NL) was calculated as previously reported (15).

Impact of ECMO blood flow rate on pulmonary circulation was evaluated also by calculation of pulmonary vascular resistance [PVR = (PAPm - PAOP)/CO].

Pulmonary arterial compliance (PA compliance) was calculated as stroke volume (SV) divided by PA pulse pressure [PA compliance = (CO/HR)/(PAPs-PAPd)] (16).

Right heart workload was quantified through the calculation of the right ventricular stroke work index [RVSWI = (CI/HR) × (PAPm − CVP) × 0.0136] (17).

EIT-based distribution of ventilation (V) and perfusion (Q) and V/Q mismatch were assessed offline, as in previous studies (14). The following parameters were quantified:

- regional lung ventilation and perfusion in three horizontal gravitational regions of interest (ROIs) of the same size (ventral, middle, dorsal)
- % of unmatched units (only ventilated units + only perfused units)

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Additional details about the study measurements can be found in the Online Data Supplement.

Statistics. Normal distribution of the study variables was assessed with Shapiro–Wilk test. Data are expressed as mean ± standard deviation or median [interquartile range] and graphed as bars or boxplot, as appropriate. Comparison between physiologic variables (means or medians) measured at the end of the three steps was performed by one-way repeated measures analysis of variance (ANOVA) or Friedman repeated measures ANOVA on ranks, as appropriated. Post-hoc pairwise multiple comparisons were performed using Holm-Sidak's or Tukey's multiple comparison tests, respectively.

Then, the data from the three study steps were pooled together to explore physiological interactions with a more continuous approach. Linear correlations between variables were assessed using linear mixed-effect models for repeated measures with patient as random effect or Spearman's test for non-repeated measures, as appropriate. For non-linear correlations, Akaike's information criteria (AIC) was applied to identify the best-fit curve to describe correlations between physiological variables (e.g., between PAP and CO). Correlations prone to mathematical coupling (e.g., between CO and PAC or RVSWI) were not tested. Statistical analysis was conducted with JMP® Pro software, Version 15 (SAS Institute Inc., Cary, NC).

Results

Study population. Twenty patients were enrolled. Patients' characteristics are reported in Table 1. Etiology of ARDS was infectious for all patients: 70% had

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COVID-19 and 30% bacterial pneumonia. Right before ECMO initiation, patients' PaO_2/FiO_2 was 76 ± 18 mmHg, $PaCO_2$ 63 ± 11 mmHg, arterial pH 7.32 ± 0.07. Patients were started on ECMO after 3 [0.5-5] days of intubation and the study was performed on ECMO day 4 [2-6].

Total number of days on ECMO was 17 ± 10, with in-hospital mortality of 35%.

Study protocol. During the 3 study steps, all ventilation and ECMO settings remained unchanged, apart from ECMO blood flow rate. PEEP was 15 [12-16] cmH_2O, tidal volume 4.1 ± 1.0 ml/kg PBW, respiratory rate 12 ± 0.5 bpm, plateau pressure 27 [25-29] cmH_2O, FiO_2 and FdO_2 66 ± 16%, sweep ECMO gas flow 4.5 [3.8-6.5] L/min. The blood flow rates at the low, intermediate, and high steps were 1.51 [1.16—1.94] vs. 2.44 [2.03-2.93] vs. 3.43 [3.01-3.74] L/min (p <0.001), corresponding to progressively more negative but acceptable ECMO drainage pressures and well separated levels of SvO_2 (Table 2 and Figure E1).

All patients tolerated the 3 randomized study steps, without any safety issue.

Blood gases. Mixed venous oxygen tension (PvO_2) increased at higher ECMO blood flow rates (42 ± 3 vs. 47 ± 3 vs. 53 ± 4 mmHg, for low, intermediate and high blood flow, respectively, p< 0.001), while the amount of oxygen added by the patient's native lung (VO_2 NL) progressively decreased from low to intermediate to high blood flow step (199 [148-253] vs 140 [124-195] vs 107 [94-141] ml/min, respectively; p <0.001). As expected, $PvCO_2$ and $PaCO_2$ also decreased at higher ECMO blood flow rates, albeit slightly, and pH values remained within the normal range (Table 3).

Pulmonary circulation and right heart hemodynamics. Systolic (50 ± 11 vs. 46 ± 12 vs. 41 ± 8 mmHg, p <0.001), diastolic (23 ± 5 vs. 22 ± 5 vs. 21 ± 6 mmHg, p =0.01) and mean (34 ± 6 vs 31 ± 6 vs 30 ± 5 mmHg, p <0.001) pulmonary arterial pressures decreased from low to intermediate to high blood flow step (Figure 1 A-C). The

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decrease in pulmonary pressures was associated with a progressive parallel improvement of pulmonary arterial compliance (3.8 ± 1.5 vs. 4.0 ± 1.5 vs. 4.6 ± 1.9 ml/mmHg for low, intermediate and high step, respectively; p <0.001) (Figure 2A). The decrease in pulmonary vascular resistance also showed a trend between study steps (180 [154-232] vs 170 [152-240] vs 159 [138-232] dyn·s·cm^{-5} for low, intermediate, and high step, respectively; p =0.064).

In terms of right heart workload, cardiac output decreased from low to intermediate to high blood flow step (9.2 [6.2-10.9] vs 8.3 [5.9-9.8] vs 7.9 [6.5-9.1] L/min, p =0.01) (Figure 2B), as did central venous pressure, albeit slightly (11 [8-1] vs. 10 [9-13] vs. 10 [8-12] mmHg, p = 0.044). The RVSWI also progressively decreased with higher blood flows (14.2 ± 4.4 vs 12.2 ± 3.6 vs 11.4 ± 3.2 g*m/beat/m^2 for low, intermediate and high step, respectively; p = 0.002) (Figure 2C).

Hemodynamic variables during the 3 study steps are reported in Table 2.

V/Q mismatch. Changes in pulmonary hemodynamics and right heart workload were not associated with worsening V/Q mismatch. Calculated intrapulmonary shunt did not differ for the three study steps (51.5 [41.9-64.6] % vs. 50.9 [40.2-60.2] % vs. 52.6 [45.3-64.9] % for low, intermediate and high step, respectively; p = 0.638) and more advanced regional EIT data showed similar stable values for the distribution of ventilation and perfusion and for the % of unmatched units (Table 3).

Physiological interactions underlying main cardiopulmonary effects. When data from the three study steps were pooled together, pulmonary artery pressure was inversely correlated with PvO_2 (R^2 =0.29 p <0.001 for PAPs, R^2 =0.16, p = 0.012 for PAPm) and directly with CO (non-linear quadratic R^2 = 0.378 p < 0.007 for PAPs, R^2 = 0.287, p = 0.011 for PAPm) (Figure 3 A and B). Cardiac output was inversely correlated with PvO_2 and PaO_2 (R^2 = 0.257 p = 0.031 and R^2 = 0.324 p = 0.05,

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respectively) (Figure 4 A and B) and VO_2 NL showed an inverse correlation with PvO_2, too (R^2 =0.33, p <0.0001) (Figure 4 C). Right ventricle workload (RVSWI) decreased at higher PvO_2 values (R^2 =0.21 p = 0.004) (Figure 4 D). Pulmonary artery compliance was directly correlated with PvO_2 (R^2 = 0.198 p = 0.029) (Figure E1).

The correlations between cardiopulmonary hemodynamic variables and SvO_2, $PvCO_2$ and ECMO blood flow rates were much weaker or inexistent (Table E1-4 in the Supplementary Results).

Variables associated with decrease of the right heart work. The decrease in RVSWI from low to high blood flow step was directly correlated with PAPs (Figure 5A) and PAPm (R^2 =0.39, p = 0.003 and R^2 =0.33, p = 0.009, respectively), cardiac output (R^2 = 0.66, p <0.0001) (Figure 5B) and heart rate (R^2 = 0.33, p = 0.009)(Figure 5C) measured at the low blood flow step, likely meaning that patients with more severe pulmonary hypertension and higher sympathetic stimulation at the lowest ECMO blood flow may obtain greater unloading of the right heart at higher flow rates.

Discussion

This study describes the physiologic effects induced by different ECMO blood flows and SvO_2 across a spectrum of clinically acceptable values in severe ARDS patients. The study main findings can be summarized as follows: higher mixed venous saturation achieved by increasing ECMO blood flow resulted in a reduction of cardiac output and pulmonary artery pressure. Main hemodynamic changes were also associated with improved pulmonary artery compliance and reduced work of the right heart at higher SvO_2 and ECMO blood flow. The changes in pulmonary

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circulation were not associated with evident and measurable changes in the distribution of ventilation and lung perfusion, nor with worsening of V/Q mismatch. Finally, the protective effect of higher blood flow and SvO_2 on the right heart was more pronounced in patients with higher PA pressure, cardiac output and heart rate at lowest blood flow.

Early experimental studies investigated the cardiopulmonary effects of isolated changes of SvO_2 at constant cardiac output, with variable results depending on the target oxygenation values (PvO_2 and/or SvO_2) and on the lung condition. In healthy dogs, high PvO_2 (> 100 mmHg) abolished the HPV in atelectatic lung regions and this effect was associated with a dramatic decrease in pulmonary vascular resistance and an increase of intrapulmonary shunt (roughly from 20 into 50%), in comparison with lower PvO_2 (around 30 mmHg) (9). However, smaller changes in PvO_2 (from around 30 to around 50 mmHg) did not induce any of these effects. Changes in SvO_2 from around 30 to around 60% caused minimal variations in intrapulmonary shunt (3-4%) with no changes in pulmonary vascular resistance in dogs with oleic-acid induced pulmonary edema (11).

While providing a physiological basis for hypothesizing the effects of higher mixed venous oxygenation on the pulmonary circulation, these experimental data did not allow us to precisely predict the cardiopulmonary effects of different levels of ECMO blood flow in severe ARDS patients for three main reasons. First, modulation of ECMO blood flow could target values of mixed venous oxygenation within a more limited range, both for technical limits and patient safety (18). Second, in patients with severe ARDS, even if ECMO allows control of SvO_2, modifying the amount of oxygen delivered by ECMO triggers complex hemodynamic responses which possibly include variations in cardiac output (19). Third, the heterogeneity of ARDS

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pathophysiology (e.g., % of non-ventilated lung, degree of activation of HPV, presence of pulmonary vascular occlusions, etc.) could lead to variable response between patients.

Few clinical observations reported the cardiopulmonary effects of ECMO initiation in ARDS patients (5, 6, 20). A decrease in PAP was observed within few hours after ECMO initiation (5). However, the contribution of increased SvO_2 could not be separated from the concomitant correction of hypercapnic acidosis (21) and severe hypoxemia, and from the reduction of ventilation. It is reasonable to speculate that all these factors could contribute to the unloading of the right ventricle which has been documented by echocardiographic examination in severe ARDS patients during the first days of ECMO (6).

Our study investigated the physiological effects of different ECMO blood flow targeting varying SvO_2 levels, without changing ventilation. We explored the range of SvO_2 which can be “safely” applied in the acute phase of severe ARDS on ECMO (i.e., 70-90%): lower values could induce severe arterial desaturation, while higher values could be difficult to achieve for reasons which limit the increase of blood flow rate (smaller cannula size and relative or absolute hypovolemia) and/or of SvO_2 (high cardiac output, recirculation)(18).

The most physiologically and clinically relevant result of our study is probably the decrease in PA pressure and in cardiac output at higher ECMO blood flow (Figure E2). Correlations between physiological variables were investigated to explore the interactions between all the physiological effects induced by higher ECMO blood flow. The correlation between higher PvO_2/PaO_2 and lower cardiac output confirms that the goal of hemodynamic regulation is lowest cardiac workload to maintain

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adequate VO_2/DO_2 relationship (22). Increasing mixed venous oxygen by increasing the ECMO flow rate decreased the need for native cardiac output to maintain DO_2. Moreover, the decrease in cardiac output likely contributed to the decrease in PA pressure. However, direct effect of PvO_2 on pulmonary circulation cannot be excluded and it is strongly suggested by the relationship between PvO_2 and pulmonary artery pressure and compliance. Relatively small changes in PvO_2 (e.g., 40 to 55 mmHg, see Figure 5) have a significant impact on pulmonary vascular function, even during protective ventilation. However, if the improvement in pulmonary vascular mechanics were the only effect of higher ECMO blood flow, we might have rather found stable PAP with increased CO or lower PAP with stable CO (15). Of note, decreased cardiac output in our patients was not associated with higher central venous pressure, suggesting changes in systemic venous resistance or in systemic vascular capacitance dampening excessive venous return.

Interestingly, in our study, the decrease in PAP at higher ECMO blood flow was associated with slight decrease of pulmonary vascular resistance and more pronounced improvement of PA compliance. The pulmonary vasomotor tone consists not only of a resistive but also of a capacitive component, which is measured by the PA compliance (23). It is known that PA compliance is a sensitive index of pulmonary vascular dysfunction, especially when pulmonary vascular resistances are not markedly increased (16), as it was in our patients. However, given the dynamic nature of this measure (PA compliance is measured while blood flows into the arterial vasculature), and the short observation period (30 minutes), we cannot exclude that the increase in PA compliance could have been subtended by reduced vascular resistance or just reflect the decrease of cardiac output.

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Not only do the hemodynamic effects of higher ECMO blood flow all contribute to the reduction in right heart workload, but each one could also have a lung protective effect *per se*. In fact, higher pulmonary vascular pressures and/or flows have been shown to contribute to VILI in experimental models (24–26). Our study shows that ECMO could potentially impact the “vascular side” of VILI, through the decrease in arterial pressures, the reduction in pulmonary blood flow (CO) and the improved distensibility of the pulmonary circulation (PA compliance).

The current study also shows that, within the explored range of PvO_2/SvO_2, changes in ECMO blood flow do not have an impact on ventilation/perfusion mismatch, as assessed both by calculation of intrapulmonary shunt and by the % of unmatched units measured by EIT. These data confirm earlier experiments which showed that the changes in intrapulmonary shunt are minimal for comparable small variations of PvO_2/SvO_2. Similarly to a recent study (12), we also confirmed that these variations do not affect the EIT-based distribution of perfusion. Finally, in line with previous finding that the pulmonary vasculature directly reacts to pulmonary artery oxygen tension level (which could vary between patients even for similar SvO_2 values) (27), the cardiopulmonary physiological changes induced by different ECMO blood flow correlated better with PvO_2 than with SvO_2 levels and were more relevant between the low and the intermediate steps.

There are currently no recommended indications for setting ECMO blood flow rate in severe ARDS patients. Both low and high ECMO blood flow rates could provide acceptable arterial oxygenation while significantly decreasing the ventilatory load (15)(28). In clinical practice, the risks of high blood flow rate include complications due to the use of large cannulas, increased fluid balance to facilitate venous

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drainage, hemolysis, hemorrhage and possibly prolonged ECMO duration (29). On the other hand, lower blood flow could be associated with less effective lung rest and metabolic activation decreasing ECMO efficiency (15). A recent analysis of data from the ELSO registry shows that higher ratio of blood flow rate to square cannula size is associated with improved survival in patients with severe ARDS on ECMO (30). Our results indicate that the degree of unloading of the right ventricle correlates with the degree of pulmonary arterial hypertension and with higher cardiac output at lower blood flow, in line with the data of early physiologic studies (9). Alternatively, a less invasive bedside measure (tachycardia at low ECMO blood flow) could identify more "activated" patients likely benefiting from increased blood flow rate.

Our study has several limitations. The duration of each study steps was relatively short, allowing for the assessment of the acute physiological changes, but not of the long-term effects of different levels of ECMO support. Hemodynamic instability was an exclusion criterion for safety reason and repeating the study in patients with shock and severe right heart dysfunction could be even more interesting. We chose to target SvO_2 to titrate ECMO blood flow at each study steps; while this allows for a meaningful analysis of the physiological effects, mixed venous oxygenation is not available in many patients on ECMO and surrogate targets for clinical blood flow titration remain to be assessed. Moreover, the achievement of high SvO_2 could be more challenging in more severe patients. Measures of cardiac output by PA catheter during ECMO might be influenced by recirculation of the saline bolus but have already been reported in previous studies (31). Moreover, in presence of partial suctioning of the bolus by the ECMO system, cardiac output could be over-estimated. Given higher risk for bolus recirculation at higher ECMO blood flow, this limitation could have led to an underestimation of the results from this study (i.e.,

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lower cardiac output at higher ECMO blood flow). The study population mostly included patients with COVID-19 ARDS (32) and our data are limited to “classic” venovenous ECMO configuration with double site cannulation (no double lumen single cannula). Finally, even if performed after a few days on ECMO, patient’s hypoxemia was already improving, as indicated by the ECMO blood flow/CO ratios (Table 2), and this could limit generalizability of the study results.

Conclusions

The present study explored the hemodynamic and pulmonary vascular modifications induced by three different levels of ECMO blood flow rate, titrated to 3 “clinical” ranges of SvO_2 values. Higher ECMO blood flow rate with a resultant higher SvO_2 decreased the need for cardiac output to maintain the same O_2 delivery. The decrease in cardiac output consequently decreased pulmonary arterial pressure, improving the pulmonary arterial compliance and the unloading of the right heart, without worsening ventilation/perfusion mismatch. Our results suggest that personalized titration of ECMO blood flow may decrease the risk of right heart failure associated with severe ARDS and mechanical ventilation.

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Figure Legends

Figure 1 A-C. Pulmonary arterial pressures at the three study steps. Systolic (1A), mean (1B) and diastolic (1C) pulmonary arterial pressures decrease from low to high ECMO blood flow and SvO_2.

Data are expressed as scatter plot with bars and error bars (mean and standard deviation). Comparisons were performed by ANOVA test for repeated measures for normally distributed values (P-value reported in the graph) followed by Holm-Sidak's multiple comparisons test (* p < 0.05, ** p < 0.01, *** p<0.001 LOW vs HIGH; § p < 0.05, §§ p < 0.01, §§§ p < 0.001 LOW vs INTERMEDIATE; ^ p < 0.05, ^^ p < 0.01, ^^^ p < 0.001 INTERMEDIATE vs HIGH).

PAPs/m/d: pulmonary arterial pressure systolic/mean/diastolic

Figure 2 A-C. Pulmonary arterial compliance, cardiac output and right ventricular stroke work index at the three study steps.

Pulmonary arterial compliance (PA compliance) increases, cardiac output and right ventricular stroke work index (RVSWI)decreases from low to high ECMO blood flow.

Data are expressed as scatter plot with bars and error bars (mean and standard deviation). Comparisons were performed by ANOVA test for repeated measures for normally distributed values (P-value reported in the graph) followed by Holm-Sidak's multiple comparisons test (* p < 0.05, ** p < 0.01, *** p<0.001 LOW vs HIGH; § p < 0.05, §§ p < 0.01, §§§ p < 0.001 LOW vs INTERMEDIATE; ^ p < 0.05, ^^ p < 0.01, ^^^ p < 0.001 INTERMEDIATE vs HIGH).

Figure 3 A-B. Relationships between PAPs and PvO_2 and between PAPs and CO.

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PAPs in relation to PvO_2 (5A). Values of PvO_2 are grouped into quintiles, and the PAPs is presented as mean ± standard error. Regression line is computed on individual data points using linear mixed-effect models for repeated measures with patient as random effect (R^2 and p-values reported in the graph)

PAPs in relation to CO (5 B). Values of CO are grouped into quintiles, and the PAPs is presented as mean ± standard error. The best-fit curve demonstrated a non-linear (quadratic) relationship between PAPs and CO (AIC weight 0.92, R^2 and p-values reported in the graph).

PAPs: pulmonary arterial pressure systolic; CO: cardiac output

Figure 4 A-D. Correlations between CO and oxygenation (A-B). Correlations between PvO_2 and VO_2 NL (C) and between PvO_2 and RVSWI (D)

CO is presented in relation to PvO_2 (6 A) and PaO_2 (6 B). Values of x variable (PvO_2 and PaO_2) are grouped into quintiles, and the CO is presented as mean ± standard error. Regression lines are computed on individual data points using linear mixed-effect models for repeated measures with patient as random effect (R^2 and p-values reported in the graph).

VO_2 NL and RVSWI are presented in relation to PvO_2 (6C and 6D, respectively). Values of PvO_2 are grouped into quintiles, and the Y variable is presented as mean ± standard error. Regression line is computed on individual data points using linear mixed-effect models for repeated measures with patient as random effect (R^2 and p-values reported in the graph)

CO: cardiac output; VO_2 NL: oxygen exchange through the natural lung; RVSWI: right ventricular stroke work index

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Figure 5 A-C. Correlations between the improvement in RVSWI between low and high blood flow and PAPs, CO and heart rate measured at low blood flow and SvO_2 step

The decrease in RVSWI from low to high ECMO blood flow is presented in relation to PAPs (A), CO (B) and heart rate (C) at low ECMO blood flow step.

Regression lines with intervals of confidence (R^2 and p-values for Spearman correlation reported in the graphs)

PAPs: systolic pulmonary arterial pressure; CO: cardiac output

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Figure 1.

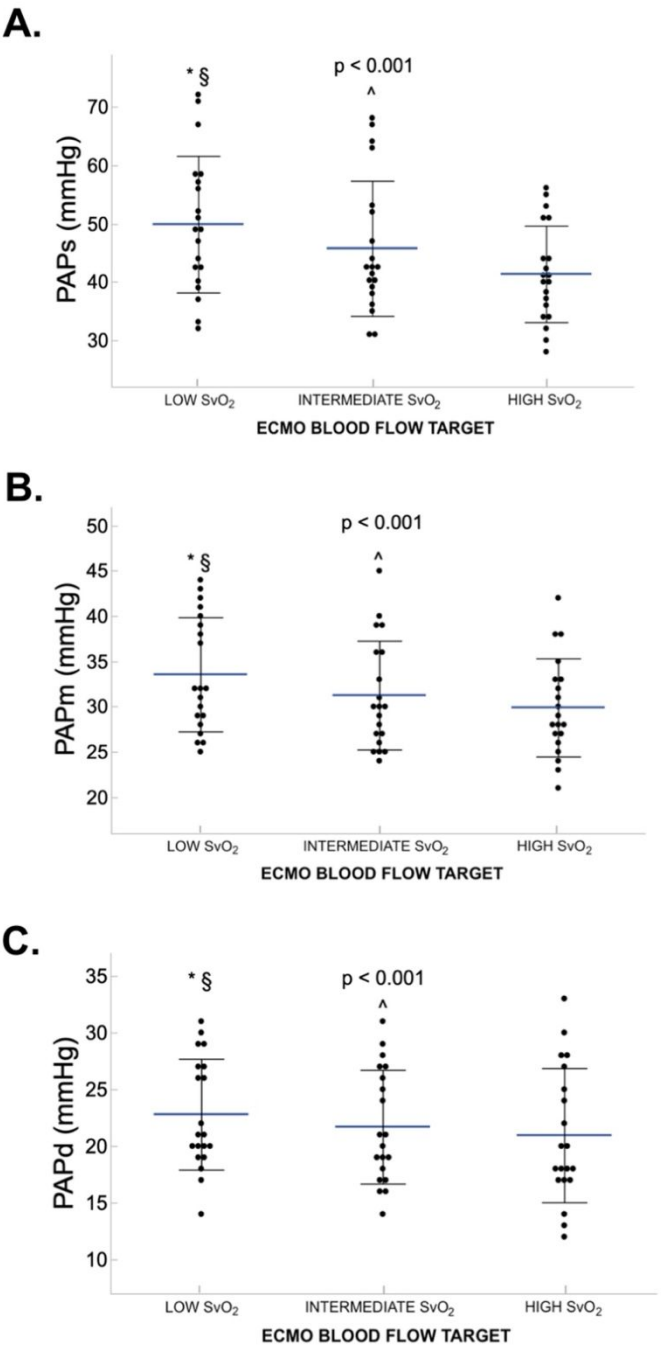

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Figure 2.

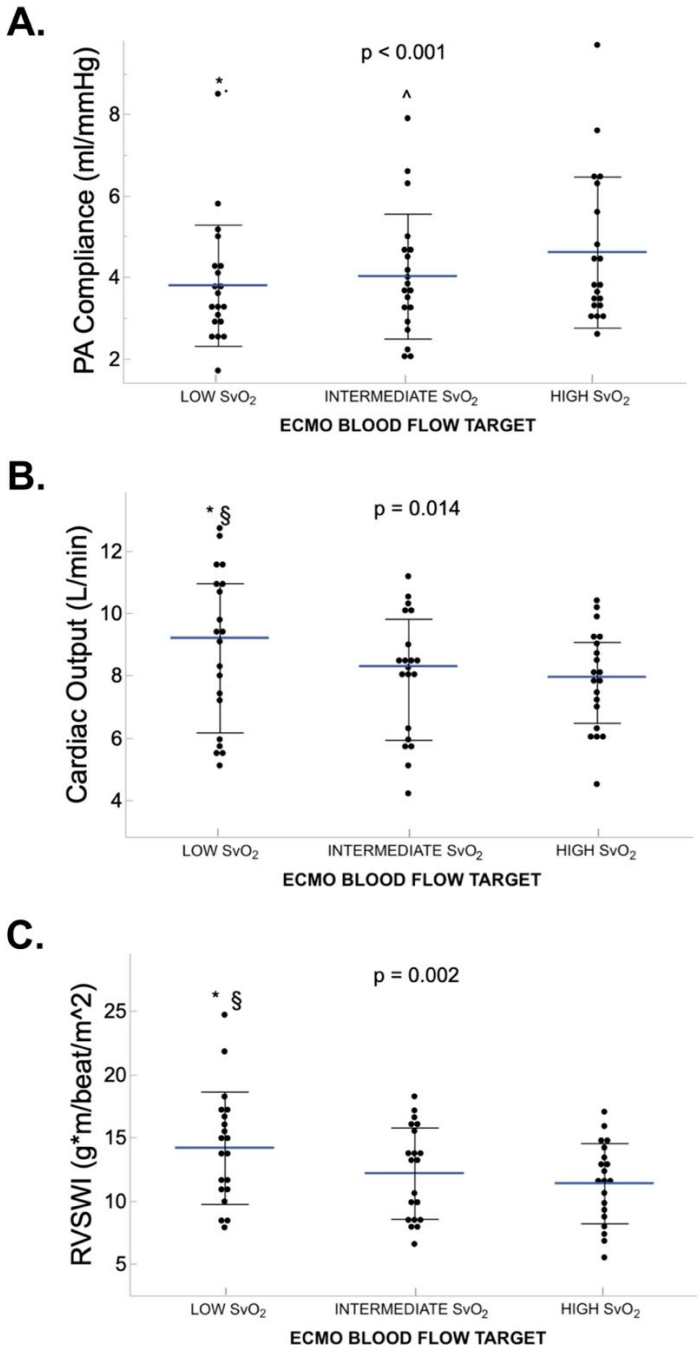

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Figure 3.

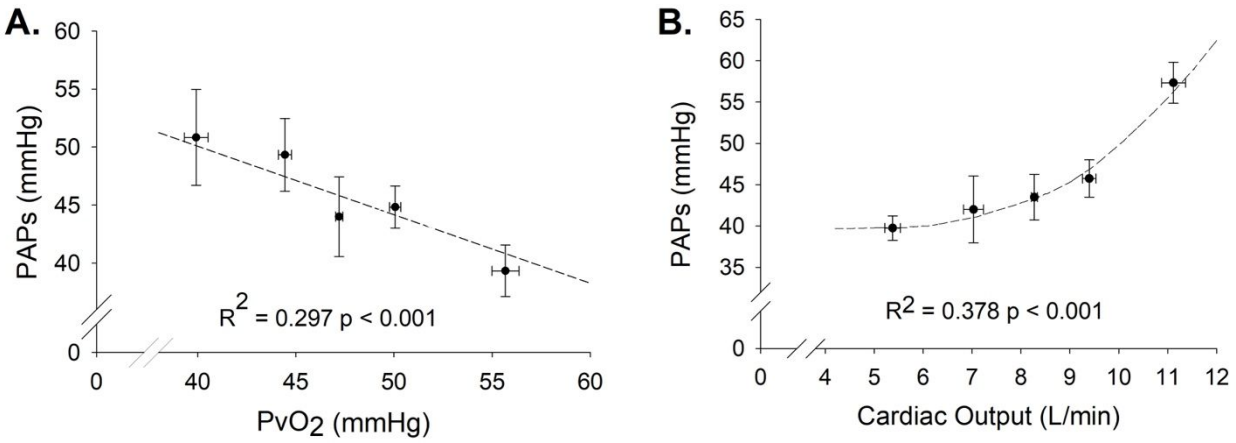

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Figure 4.

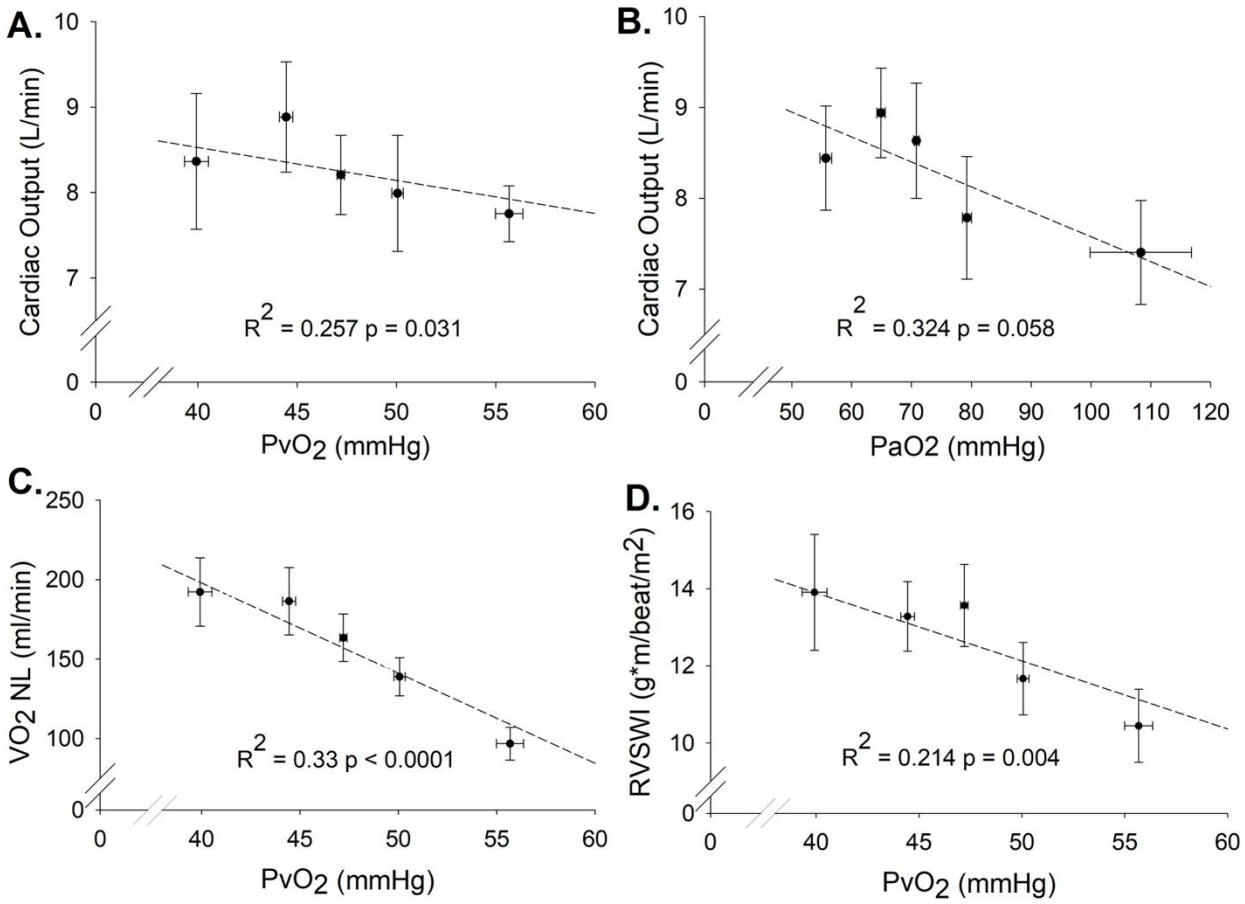

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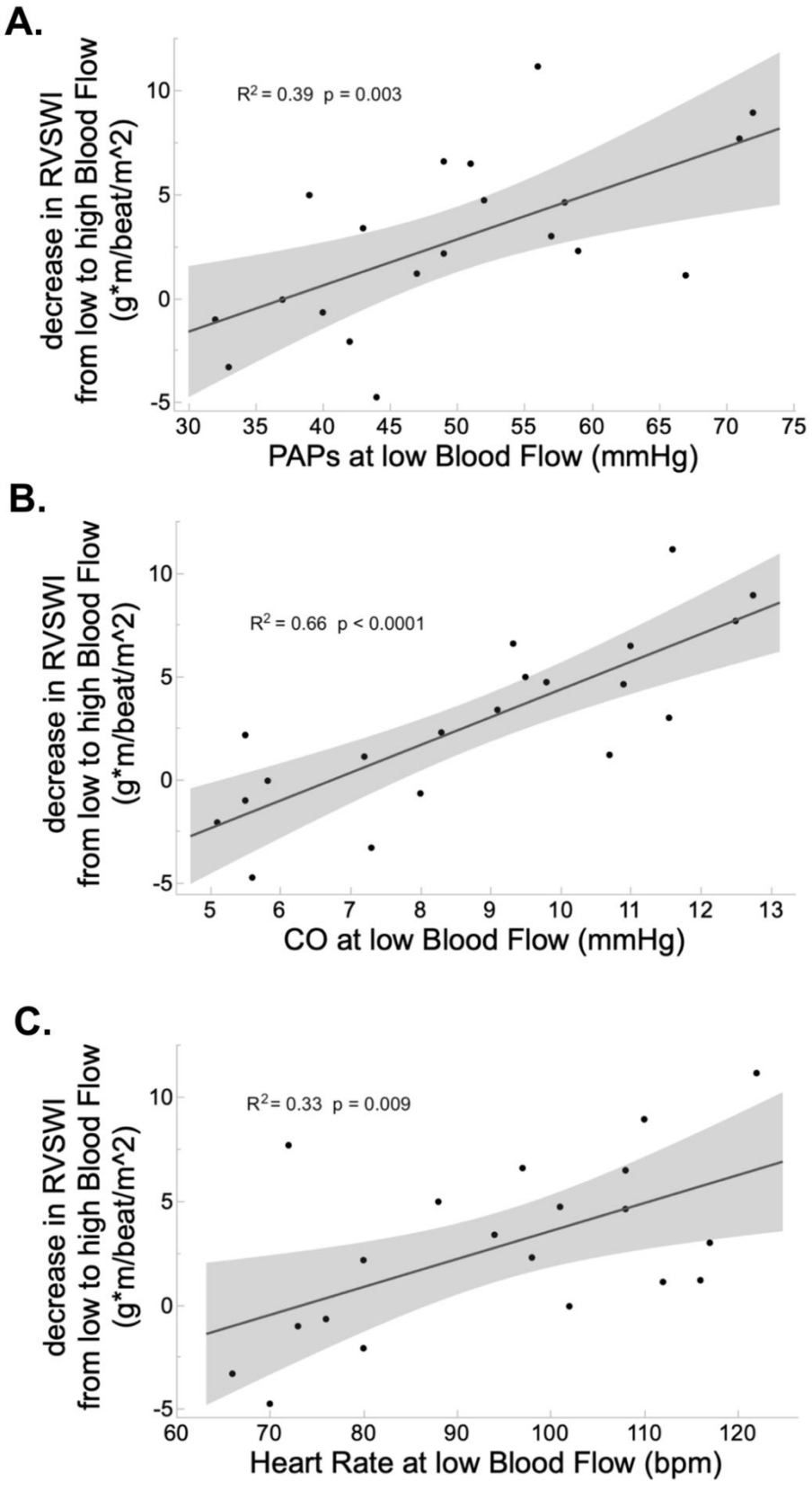
Figure 5.



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Tables.

Table 1. Main characteristics of the study population

Characteristics*	
Age (years)	51 ± 9
Male (no., %)	11, 55%
ARDS etiology COVID-19 (no., %) Bacterial Pneumonia (no., %)	 14, 70% 6, 30%
SOFA score	6 ± 3
Days of intubation before ECMO start	3 [0.5-5]
ECMO configuration Femoro-jugular (no., %) Femoro-femoral (no., %)	 12, 60% 8, 40%
Femoral drainage cannula size (Fr)	25 ± 1
Days of ECMO at enrollment	4 [2-6]
Gas exchange before ECMO start PaO_2/FiO_2 (mmHg) PaO_2 (mmHg) $PaCO_2$ (mmHg) Arterial pH	 75 ± 18 63 ± 11 62 ± 11 7.31 ± 0.07
Total days on ECMO	17 ± 10
ICU length of stay (days)	30 ± 14
Hospital mortality (%)	35

Abbreviations: ARDS: acute respiratory distress syndrome; SOFA: Sequential Organ Failure Assessment; PaO_2: arterial O_2 tension; FiO_2: inspired O_2 fraction; $PaCO_2$: arterial CO_2 tension

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Table 2. ECMO settings and hemodynamics for the three study steps

Variables	ECMO Blood Flow Target			p-value
	Low SvO_2	Intermediate SvO_2	High SvO_2	
ECMO settings				
Blood Flow rate (L/min)	1.51 [1.16-1.94] *** §§§	2.44 [2.03-2.93] ^^^	3.43 [3.01-3.75]	< 0.001
BF/CO (%)	20 ± 8 *** §§§	32 ± 9 ^^^	44 ± 9	<0.001
ECMO drainage pressure (mmHg)	15 [4-25]	-5]-12-12]	-27 [-36—9]	< 0.001
BF/C^2 (ml/min/Fr^2)	2.56 [1.93-3.11] * §	3.90 [3.47-4.77] ^	5.49 [4.82-6.35]	<0.001
Hemodynamics				
CO (L/min)	9.2 [6.2-10.9] * §	8.3 [5.9-9.8]	7.9 [6.5-9.1]	0.014
CI (L/min/m^2)	4.7 [3.4-5.3] * §	4.1 [3.2-4.6]^	3.9 [3.5-4.4]	0.014
Heart Rate (bpm)	95 ± 18	87 ± 19	87 ± 20	0.186
Stroke Volume (ml)	94 ± 25	87 ± 4^	87 ± 8^	<0.01
PAPs (mmHg)	50 ± 12* §	46 ± 12^	41 ± 8	< 0.001
PAPm (mmHg)	34 ± 6* §	31 ± 6	30 ± 5	< 0.001
PAPd (mmHg)	23 ± 5*	22 ± 5	21 ± 6	0.014
CVP (mmHg)	11 [8-14]	10 [9-13]	10 [8-12]	0.044
PAOP (mmHg)	13 [10-16]	13 [10-14]	12 10-14]	0.062
PAPm – PAOP (mmHg)	21 ± 2	19 ± 2	18 ± 2	<0.001
Diastolic pulmonary gradient (mmHg)	10 [7-12]	8.5 [6-10]	8 [6-11]	0.132
Pulmonary artery RC time constant (ms)	659 [582-815]	665 [575-858]	747 [564-955]	0.705
PVR (dyn·s·cm^{-5})	180 [154-232]	170 [152-240]	159 [138-232]	0.064
PAC (ml/mmHg)	3.8 ± 1.5	4.0 ± 1.5	4.6 ± 1.9	<0.001
DO_2 (ml/min)	1110 ± 335	1027 ± 266	1041 ± 217	0.044

Data are expressed ad mean ± standard deviation or as median [IQR], as appropriate. Comparisons were performed by ANOVA test for repeated measures followed by Holm-Sidak's multiple comparisons test for normally distributed values (P-value reported in the graph) and with Friedman ANOVA on ranks test for repeated measures followed by Tukey's multiple comparison test for non-normally distributed values
* $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ LOW vs HIGH; § $p < 0.05$, §§ $p < 0.01$, §§§ $p < 0.001$ LOW vs INTERMEDIATE; ^ $p < 0.05$, ^^ $p < 0.01$, ^^^ $p < 0.001$ INTERMEDIATE vs HIGH.

Abbreviations: BF/CO: ratio between blood flow and cardiac output; BF/C^2: ratio between blood flow and the square of drainage cannula size; CI: Cardiac Index; DO_2: Oxygen Delivery; PAOP: Pulmonary Artery Occlusion Pressure; PAPm: Mean Pulmonary Artery Pressure; Diastolic pulmonary gradient = PAPd-PAOP; Pulmonary artery RC time constant = PA Compliance * PVR; PAC: PA compliance; PVR: pulmonary vascular resistance.

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Table 3. Blood gases and EIT data on ventilation, perfusion and V/Q mismatch for the three study steps

Variables	ECMO Blood Flow Target			p-value
	Low SvO_2	Intermediate SvO_2	High SvO_2	
Blood gases				
SvO_2 (%)	73.9 ± 2.8 * §	79.4 ± 2.7 ^	86.7 ± 3.5	< 0.001
PvO_2 (mmHg)	42 ± 3 *** §§§	47 ± 3 ^^^	53 ± 4	< 0.001
$PvCO_2$ (mmHg)	53 ± 5	50 ± 5	48 ± 5	<0.001
PaO_2	63 [57-70] * §	70 [62-81] ^	83 [72-99`	< 0.001
$PaCO_2$ (mmHg)	52 ± 6 *** §§§	49 ± 5 ^^	47 ± 6	<0.001
Intrapulmonary shunt (%)	51.5 [41.9-64.6]	50.9 [40.2-60.2]^	52.6 [45.3-64.9]	0.638
Arterial pH	7.39 ± 0.05	7.41 ± 0.05	7.42 ± 0.05	< 0.001
EIT ventilation and perfusion				
Ventral Ventilation (%)	28 [21-34]	29 [24-36]	29 [24-35]	0.511
Middle Ventilation (%)	60 [43-69]	56 [43-69]	58 [44-68]	0.443
Dorsal Ventilation (%)	11 [7-25]	16 [6-25]	15 [5-24]	0.511
Ventral Perfusion (%)	21 [15-29]	21 [15-28]	21 [15-27]	0.520
Middle Perfusion (%)	67 [53-69]	65 [56-67]	64 [54-70]	0.336
Dorsal Perfusion (%)	15 [10-20]	16 [13-22]	15 [13-19]	0.115
EIT V/Q mismatch				
Only ventilated units (%)	10.7 [4.7-14.5] *	6.7 [3.8-10.9]	10.9 [5.5-19.6]	0.016
Only perfused units (%)	16.7 [7.9-22.5]	17.3 [12.2-22.5]	16.6 [12.8-21.2]	0.212
Unmatched units (%)	25.2 [10.3-27.7]	23.1 [19.6-31.8]	27.8 [24.7-31.3]	0.086

Data are expressed ad mean ± standard deviation or as median [IQR], as appropriate. Comparisons were performed by ANOVA test for repeated measures followed by Holm-Sidak's multiple comparisons test for normally distributed values (P-value reported in the graph) and with Friedman ANOVA on ranks test for repeated measures followed by Tukey's multiple comparison test for non-normally distributed values
* $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ LOW vs HIGH; § $p < 0.05$, §§ $p < 0.01$, §§§ $p < 0.001$ LOW vs INTERMEDIATE; ^ $p < 0.05$, ^^ $p < 0.01$, ^^^ $p < 0.001$ INTERMEDIATE vs HIGH.

Abbreviations: SvO_2: of mixed venous blood oxygen saturation; PvO2: mixed venous oxygen tension; PvCO2: mixed venous carbon dioxide tension; PaO_2: arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension

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Physiologic Effects of ECMO in Patients with Severe Acute Respiratory Distress Syndrome

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ONLINE DATA SUPPLEMENT

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Appendix 1. Supplementary methods

ECMO. Criteria for ECMO initiation follow the disease-severity criteria of the EOLIA trial, including persisting severe hypoxia and/or respiratory acidosis despite ventilator optimization.

The ECMO systems available at the two participating centers were the Maquet CardioHelp device with MAQUET HLS Set Advanced 7.0 ECMO circuits or the Rotaflow® pump and console with MAQUET PLS® membrane oxygenator. The adopted ECMO configuration was either femoro-femoral or femoro-jugular. A large venous drainage cannula (21-25 Fr) was placed into the femoral vein and advanced to the lower part of the inferior vena cava. The return cannula (21-23 Fr) was inserted in the opposite femoral vein up to the right atrium or into the jugular vein to the superior vena cava. Cannulas were inserted percutaneously.

Monitoring and study measurements. All patients had a radial or femoral arterial catheter and a Swan-Ganz pulmonary arterial catheter in place. Invasive systemic and pulmonary arterial pressures, central venous pressure (CVP) and mixed-venous oxygen saturation (SvO_2, Vigilance, Edwards Lifesciences) were continuously monitored. Pulmonary artery occlusion pressure (PAOP) and cardiac output (CO, thermodilution technique, Vigilance, Edwards Lifesciences) were measured towards the end of each study step. The pressure in the drainage cannula (ECMO drainage pressure) was also monitored and recorded.

For electrical impedance tomography (EIT) monitoring, a 16-electrodes belt was placed around the patient's thorax at the fifth or sixth intercostal space and connected to a dedicated monitor (PulmoVista® 500, Dräger, Lübeck, Germany), before initiating the study protocol. Recordings of EIT data (5 minutes) were performed towards the end of each study step. EIT data were acquired at a frame

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rate of 50 Hz and stored for offline analysis to generate the ventilation and perfusion maps (1,2). Regional distribution of ventilation and perfusion was computed by horizontally splitting the EIT images into three contiguous regions of interests of the same size: ventral, middle, and dorsal. The pulmonary perfusion map was obtained from the slope of the impedance deflection following a 10 ml bolus of a NaCl 5% solution injected via the central venous catheter during an end-inspiratory occlusion (1). A filter of 20% of the maximal impedance variation was then applied for recognition of ventilated and/or perfused pixels. Ventilation/perfusion matching was assessed through the overlapping of the two maps, which allowed the detection of "only ventilated" units (i.e. ventilated but non-perfused), "only perfused" units (perfused and non-ventilated) and unmatched units (the sum of only ventilated and only perfused units) (2).

Safety criteria. Hemodynamic instability, defined as mean arterial pressure lower than 60 mmHg combined with lactates >2 mmol/l and high doses of vasoactive drugs (> 0.1 mcg/kg/min norepinephrine equivalent) was an exclusion criterion.
For patient safety, the study protocol had to be interrupted promptly in case of: desaturation with SpO2 <80%; systolic blood pressure <90 mmHg; significant tachyarrhythmia with heart rate >150 bpm or bradycardia with heart rate <40 bpm.

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Appendix II. Supplementary results

Supplementary Figures.

Figure E1. ECMO Blood Flow Rate and SvO_2 at the three study steps.

The study protocol consisted of three steps applied in random order: three ranges of SvO_2 (low 70-75%, intermediate 75-80%, high >80%) were targeted through the adjustment of ECMO blood flow rate. The figure shows the blood flow rates at the low, intermediate and high step and the corresponding well-separate levels of SvO_2. Data are expressed as scatter plot and bars (mean and standard deviation or median with IQR, as appropriate). Comparisons were performed by ANOVA for repeated measures or Friedman test (ANOVA on ranks for repeated measures) for normally and non-normally distributed values (p-values reported in the graph), followed by Holm-Sidak and Tukey's multiple comparisons test, respectively (* $p<0.05$, ** $p < 0.01$, *** $p < 0.001$ low vs high;

§ $p > 0.05$, §§ $p < 0.01$, §§§ $p < 0.001$ low vs intermediate; ^ $p < 0.05$, ^^ $p < 0.01$, ^^^ $p < 0.001$ intermediate vs high).

Figure E2. Diagram representing the physiologic interactions induced by increasing ECMO blood flow rate and SvO_2.

VO_2 NL: oxygen exchange through the natural lung; DO_2: systemic oxygen delivery; PAP: pulmonary arterial pressure; CO: cardiac output; RVSWI: right ventricular stroke work index

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Figure E1.

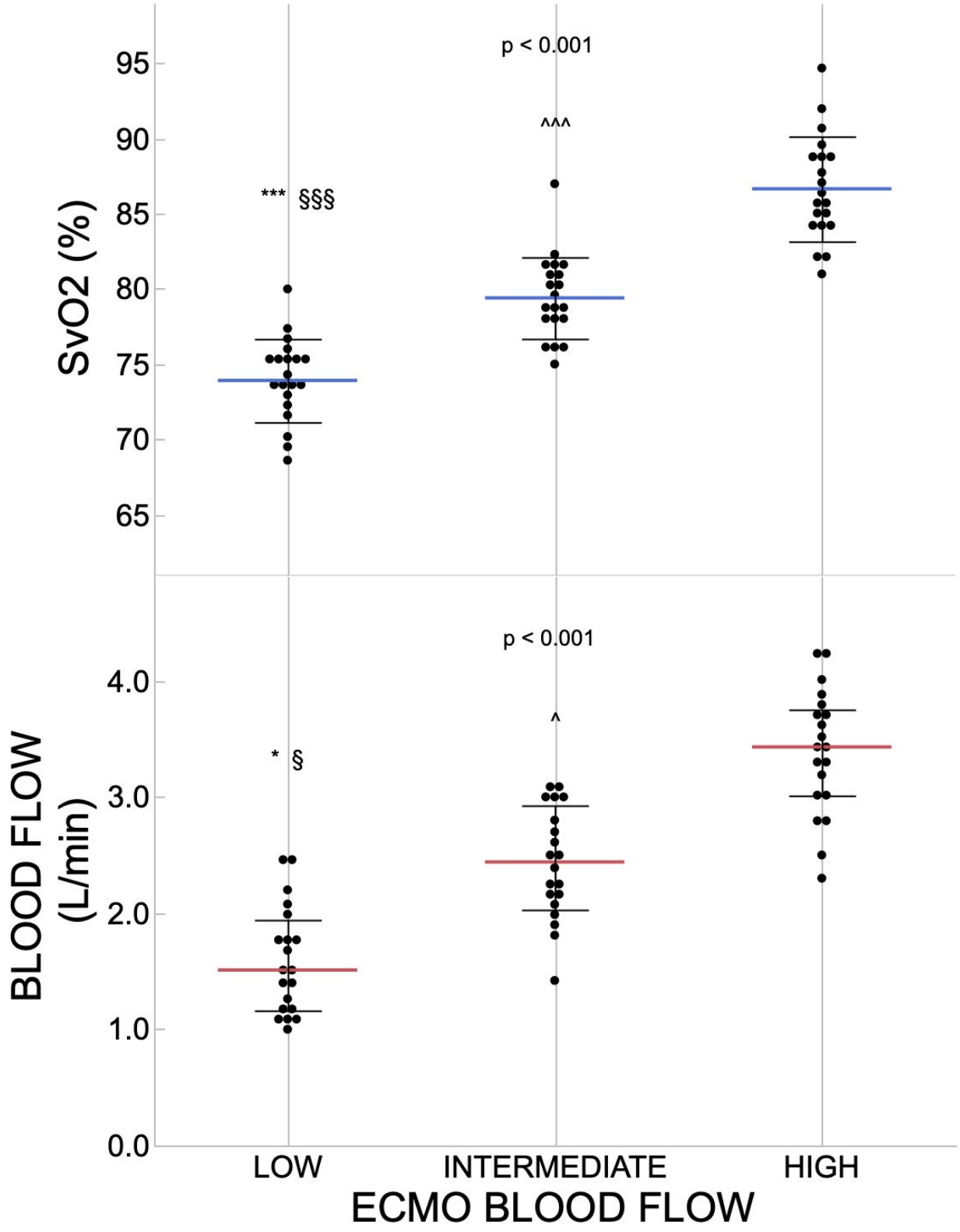

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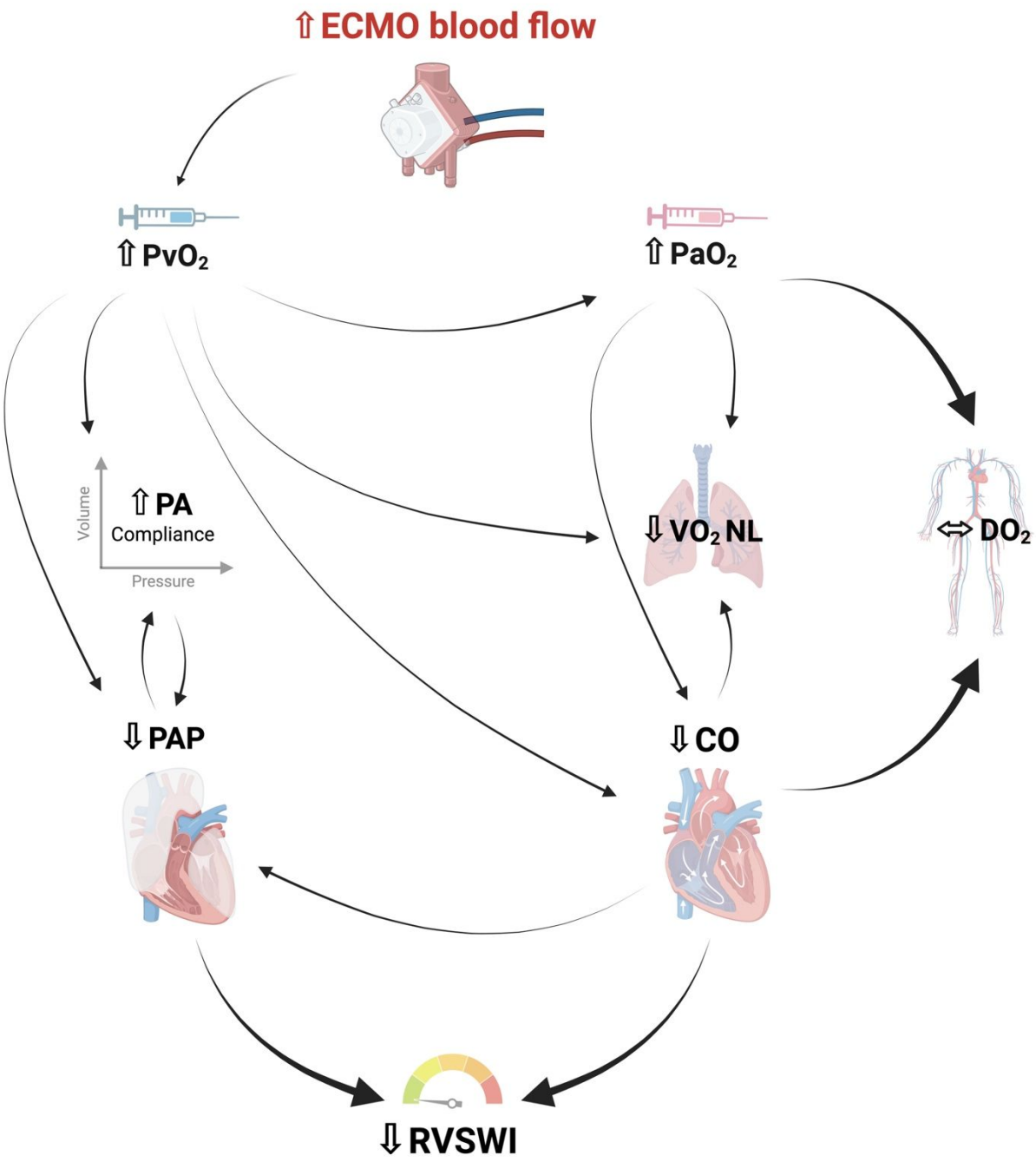
Figure E2.



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Supplementary Tables.

Table E1. Correlations between PvO_2 and cardiopulmonary effects of different ECMO blood flow rates

Variable	p	R^2
VO_2 NL (ml/min)	< 0.001	0.33
CO (L/min)	0.031	0.26
PAPs (mmHg)	< 0.001	0.29
PAPm (mmHg)	0.012	0.16
Pulmonary Arterial Compliance (ml/mmHg)	0.029	0.2
RVSWI (gm/beat/m^2)	0.004	0.21

Table E2. Correlations between SvO_2 and cardiopulmonary effects of different ECMO blood flow rates

Variable	p	R^2
VO_2 NL (ml/min)	< 0.001	0.35
CO (L/min)	0.256	-
PAPs (mmHg)	0.151	-
PAPm (mmHg)	0.485	-
Pulmonary Arterial Compliance (ml/mmHg)	0.209	-
RVSWI (gm/beat/m^2)	0.05	-

Table E3. Correlations between blood flow rate and cardiopulmonary effects of different ECMO blood flow rates

Variable	p	R^2
VO_2 NL (ml/min)	< 0.001	0.33
CO (L/min)	0.34	-
PAPs (mmHg)	0.003	0.23
PAPm (mmHg)	0.015	0.14
Pulmonary Arterial Compliance (ml/mmHg)	0.006	0.23
RVSWI (gm/beat/m^2)	0.06	-

Table E4. Correlations between $PvCO_2$ and cardiopulmonary effects of different ECMO blood flow rates

Variable	p	R^2
VO_2 NL (ml/min)	0.135	-
CO (L/min)	0.178	-
PAPs (mmHg)	0.262	-
PAPm (mmHg)	0.198	-

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Pulmonary Arterial Compliance (ml/mmHg)	0.997	-
RVSWI (gm/beat/m^2)	0.637	-

Statistical analysis was performed using linear mixed-effect models for repeated measures with patient as random effect. R^2 was not reported for non-significant correlations.
Abbreviations: VO_2 NL: oxygen exchange through the natural lung; CO: cardiac output; PAPs/m: pulmonary arterial pressure systolic/mean; RVSWI: right ventricular stroke work index

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