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ORIGINAL

Determinants of the effect of extracorporeal carbon dioxide removal in the SUPERNOVA trial: implications for trial design

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Abstract

Purpose: To describe the variability and determinants of the effect of extracorporeal CO_2 removal ($ECCO_2R$) on tidal volume (V_t), driving pressure (ΔP), and mechanical power ($Power_{RS}$) and to determine whether highly responsive patients can be identified for the purpose of predictive enrichment in $ECCO_2R$ trial design.

Methods: Using data from the SUPERNOVA trial (95 patients with early moderate acute respiratory distress syndrome), the independent effects of alveolar dead space fraction (ADF), respiratory system compliance (Crs), hypoxemia (PaO_2/FiO_2), and device performance (higher vs lower CO_2 extraction) on the magnitude of reduction in V_t, ΔP, and $Power_{RS}$ permitted by $ECCO_2R$ were assessed by linear regression. Predicted and observed changes in ΔP were compared by Bland–Altman analysis. Hypothetical trials of $ECCO_2R$, incorporating predictive enrichment and different target CO_2 removal rates, were simulated in the SUPERNOVA study population.

Results: Changes in V_t permitted by $ECCO_2R$ were independently associated with ADF and device performance but not PaO_2/FiO_2. Changes in ΔP and $Power_{RS}$ were independently associated with ADF, Crs, and device performance but not PaO_2/FiO_2. The change in ΔP predicted from ADF and Crs was moderately correlated with observed change in ΔP (R^2 0.32, $p < 0.001$); limits of agreement between observed and predicted changes in ΔP were ± 3.9 cmH_2O. In simulated trials, restricting enrollment to patients with a larger predicted decrease in ΔP enhanced the average reduction in ΔP, increased predicted mortality benefit, and reduced sample size and screening size requirements. The increase in statistical power obtained by restricting enrollment based on predicted ΔP response varied according to device performance as specified by the target CO_2 removal rate.

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Conclusions: The lung-protective benefits of $ECCO_2R$ increase with higher alveolar dead space fraction, lower respiratory system compliance, and higher device performance. ADF and Crs, rather than severity of hypoxemia, should be the primary factors determining whether to enroll patients in clinical trials of $ECCO_2R$.

Keywords: Acute respiratory distress syndrome, Extracorporeal carbon dioxide removal, Artificial ventilation, Ventilator-induced lung injury, Predictive enrichment

Introduction

In patients with acute respiratory distress syndrome (ARDS), lowering tidal volume (V_t) and driving pressure (i.e. end-inspiratory plateau pressure minus positive end-expiratory pressure: ΔP) to reduce pulmonary stress and strain can decrease ventilator-induced lung injury and improve survival [1–3]. However, lowering V_t is often associated with respiratory acidosis, even if respiratory rate (RR) is increased, and there is evidence that hypercapnia along with the use of high RR may worsen clinical outcomes [1, 2].

Removing carbon dioxide via an external membrane lung (extracorporeal CO_2 removal, $ECCO_2R$) can attenuate respiratory acidosis, permitting greater reductions in V_t, ΔP, and RR [3, 4], and thereby may improve outcomes in ARDS. $ECCO_2R$, however, is invasive, costly, and carries significant risks including hemorrhage, hemolysis, and thrombosis [5]. Applying $ECCO_2R$ to reduce V_t to very low levels may also worsen lung mechanics by increasing atelectasis. To optimize the balance of benefit and risk, $ECCO_2R$ should ideally be applied specifically to patients who stand to accrue the greatest clinical benefit [6].

Based on a theoretical analysis of physiological equations defining alveolar ventilation [6], we hypothesize that for a given $PaCO_2$ the reduction in V_t, ΔP, and mechanical power ($Power_{RS}$) enabled by $ECCO_2R$ depends on specific patient physiological characteristics [i.e., alveolar dead space fraction (ADF) and respiratory system compliance (Crs)], and on the CO_2 clearance rate achieved by the $ECCO_2R$ device. In the current study, we aimed to test this hypothesis using data from the SUPERNOVA trial [7] to inform the design of a future trial of $ECCO_2R$.

Take-home messages

The lung-protective benefits of $ECCO_2R$ increase with higher alveolar dead space fraction, lower respiratory system compliance, and higher device performance. Alveolar dead space fraction and respiratory system compliance, rather than severity of hypoxemia, should be the primary factors determining whether to enroll patients in clinical trials of $ECCO_2R$. Restricting enrollment based on the predicted treatment effect may enhance statistical power in a future trial of $ECCO_2R$.

Methods

The SUPERNOVA trial

SUPERNOVA was a pilot trial evaluating the efficacy and safety of $ECCO_2R$ to achieve ultra-protective ventilation (V_t of 4 ml/kg predicted body weight [PBW]) in 95 patients with moderate ARDS ($100 < PaO_2/FiO_2 \leq 200$ mmHg) from 23 centers [7]. At different centers $ECCO_2R$ was applied using either the Hemolung Respiratory Assist System (ALung Technologies, Pittsburgh, USA), the iLA Activve (Xenios, Heilbronn, Germany), or the Cardiohelp® HLS 5.0 (GETINGE Cardiopulmonary Care, Rastatt, Germany). The first device (lower CO_2 extraction device) employs a membrane lung with a cross-sectional area of 0.59 m^2 and is run at an extracorporeal blood flow between 300 and 500 ml/min. The other two devices (higher CO_2 extraction devices) employ membrane lungs of 1.30 m^2; in the trial they were operated with blood flows of 800–1000 ml/min. The primary endpoint in the trial was the number of patients who successfully achieved a V_T of 4 ml/kg PBW with arterial $pH > 7.30$ and $PaCO_2$ not increasing more than 20% relative to baseline condition (where V_T was set at 6 ml/kg PBW, positive end-expiratory pressure (PEEP) was adjusted to obtain an end-inspiratory plateau airway pressure (P_{PLAT}) between 28 and 30 cmH_2O, and sweep gas flow was set to 0 l/min).

Physiological computations

Crs, anatomical dead space volume, ADF [6], ventilatory ratio (VR) [8], and $Power_{RS}$ [9] were calculated as previously described using relevant physiological variables collected at baseline. Computations are detailed in the Online Supplement.

Quantifying the effect of $ECCO_2R$

There were two discrete interventions in SUPERNOVA: first, reductions in V_t permitted by $ECCO_2R$, and second, reductions in V_t enabled by more permissive ventilation targets for $PaCO_2$ (allowed to increase by up to 20% to achieve the V_t 4 ml/kg). To isolate the effect of $ECCO_2R$ on V_t independent of the change in $PaCO_2$ target and to enable comparisons of treatment effect between patients, V_t before $ECCO_2R$ (at the moment before sweep gas flow commenced) and after $ECCO_2R$ (once the 4 ml/kg step

was reached) were normalized to the V_t that would have been required to obtain a $PaCO_2$ of 45 mmHg at RR of 30 breaths/min. $Power_{RS}$ was standardized for a $PaCO_2$ of 45 mmHg. Computations are described in detail in the Online Supplement.

The effect of $ECCO_2R$ was also quantified in terms of the probability of reaching the SUPERNOVA trial primary end-point at 8 h after initiating $ECCO_2R$.

Determinants of the effect of $ECCO_2R$

Baseline characteristics were compared between patients with smaller (< median) or larger (> median) changes in standardized ΔP after applying $ECCO_2R$. Device performance was classified according to expected CO_2 extraction capability (lower—Hemolung; higher—Cardiohelp and iLA activve) based on previously reported CO_2 removal rates [10]. The independent effects of patient physiological characteristics (PaO_2/FiO_2, ADF, VR, Crs) and device performance (lower vs. higher CO_2 extraction) on the change in standardized values of V_t, ΔP, and $Power_{RS}$ obtained by applying $ECCO_2R$ were evaluated using pre-specified bivariate and multiple linear regression models (see Table E1 for description of multivariable models). The effects of these characteristics on the probability of achieving the primary endpoint was evaluated using multivariable logistic regression (see Table E1 for description of model).

Predicting the effect of $ECCO_2R$ on driving pressure

We previously showed that the reduction in ΔP that would be obtained by applying $ECCO_2R$ can theoretically be predicted according to the following relation, derived from the physiological equations defining alveolar ventilation [6]:

$$\Delta P_{aw,2} - \Delta P_{aw,1} = \frac{-k}{C_{RS} \cdot \left(1 - {V_{d,alv}}/{V_t}\right) \cdot RR \times P_{aCO_2}} \cdot \dot{V}_{CO_2,ECML}, \quad (1)$$

where Crs is the compliance of the respiratory system, $V_{d,alv}/V_t$ = ADF; RR = respiratory rate (breaths/min); $\dot{V}_{CO_2,ECML}$ = CO_2 removal rate by the $ECCO_2R$ device (ml/min); and $k = 0.863$. The predicted change in ΔP was computed for each patient using Eq. 1. Because the actual CO_2 clearance rate achieved in each patient was not measured in SUPERNOVA, we assessed the impact of three different possible values for average CO_2 removal (80 ml/min, 120 ml/min, and 150 ml/min).

The predicted and observed changes in ΔP obtained after applying $ECCO_2R$ were compared using linear regression, Bland–Altman analysis, and receiver operating characteristic curve (ROC) analysis. For the purpose of this analysis, we estimated that a sample size of 85 patients would yield 90% power to detect a correlation between predicted and observed changes in ΔP with $r \geq 0.4$ at a Type 1 error risk of 1%. This sample size was also sufficient to estimate the Bland–Altman limits of agreement with confidence intervals of ± 0.1 cmH_2O assuming the standard deviation of the difference between predicted and observed changes in ΔP was ≤ 2 cmH_2O.

Because lowering V_t may alter Crs by relieving hyperinflation (increasing Crs) or exacerbating atelectasis (worsening Crs), the resulting change in ΔP may reflect both reductions in V_t and changes in Crs. Worsening compliance after lowering V_t would attenuate the effect of lowering V_t on ΔP and such changes in Crs might be prevented by increasing PEEP. To estimate the accuracy of predicting changes in ΔP with such a PEEP titration strategy, we compared the observed and predicted changes in ΔP using the baseline Crs value to compute ΔP before and after the application of $ECCO_2R$.

Simulating potential clinical trials designed based on predicted treatment effect

Sample size and screening size requirements were estimated for possible future $ECCO_2R$ trial designs with mortality as the primary endpoint. Trial designs employing different CO_2 removal rates and varying degrees of predictive enrichment (restricting enrollment based on predicted ΔP response) were compared. For each trial design, the predicted change in ΔP that would be obtained by $ECCO_2R$ at the planned CO_2 removal rate was calculated for all patients in the SUPERNOVA study population based on Eq. 1. To account for possible error in the predicted change in ΔP, random error (95% CI ± 4 cmH_2O) was added to the predicted change in ΔP (4 cmH_2O was chosen based on the limits of agreement for predicted and observed changes in ΔP). Each trial design was simulated 500 times, and the median, 5th percentile, and 95th percentile values for the predicted change in ΔP were used to predict the absolute risk reduction in mortality (ARR). To compute ARR, we assumed that a 7 cmH_2O reduction in ΔP was associated with a hazard ratio for mortality (HR) of 0.68 as previously reported [11] and that $ECCO_2R$ carries a 1% increase in absolute risk of death due to treatment-related complications [5]. We further assumed a control group

Table 1 Baseline clinical and physiological characteristics of the study population

Characteristic	Study population ($n=95$)	Decrease in standardized ΔP with $ECCO_2R$ ($n=87$)		
		≤ 4 cmH_2O ($n=41$, 47%)	>4 cm H_2O ($n=46$, 53%)	*p*-value
Age (years)	60.2 (14)	61.1 (16)	59.3 (12.7)	0.55
Sex (*n*, % female)	30 (32%)	12 (29%)	16 (35%)	0.75
SAPS II	44 (34–58)	43 (31–50)	45 (34–60)	0.23
SOFA	7 (5–10)	6 (4–9)	8 (6–10)	0.055
Cause of respiratory failure				
Bacterial pneumonia	65 (68%)	26 (63%)	31 (67%)	0.90
Viral pneumonia	13 (14%)	7 (17%)	6 (13%)	0.90
Non-pulmonary sepsis	3 (3%)	1 (2%)	2 (4%)	0.90
Other	14 (15%)	7 (17%)	7 (15%)	0.90
PaO_2/FiO_2 (mmHg)	153 (121–178)	160 (136–174)	143 (119–182)	0.42
Compliance (ml/cm H_2O)	31 (24–38)	32 (26–39)	28 (20–35)	0.008
Estimated alveolar dead space fraction	0.32 (0.22–0.37)	0.28 (0.21–0.35)	0.33 (0.26–0.41)	0.016
Ventilatory ratio	2.00 (1.63–2.48)	1.74 (1.57–2.14)	2.18 (1.88–2.59)	0.002
Minute ventilation (l/min)	10.4 (8.5–11.9)	10.2 (8.5–11.2)	10.7 (8.6–12.6)	0.28
Tidal volume at baseline (ml/kg PBW)				
Observed	6.0 (5.9–6.1)	6.0 (5.9–6.1)	6.0 (5.9–6.1)	0.93
Standardized	5.9 (5.3–6.5)	5.5 (5.1–6.3)	6.2 (5.6–6.6)	0.009
Tidal volume after applying $ECCO_2R$ (ml/kg PBW)				
Observed	4.0 (3.9–4.1)	4.0 (4.0–4.1)	4.0 (3.9–4.1)	0.65
Standardized	3.9 (3.7–4.1)	3.9 (3.7–4.1)	4.0 (3.8–4.1)	0.55
Respiratory rate (min^{-1})	28 (24–30)	27 (22–30)	28 (25–31)	0.25
Plateau pressure (cm H_2O)	27 (25–28)	26 (25–27)	28 (27–29)	<0.001
Driving pressure at baseline (cm H_2O)				
Observed	13 (10–15)	12 (10–13)	14 (11–18)	<0.001
Standardized	12 (10–15)	10 (9–13)	13 (12–18)	<0.001
Driving pressure after applying $ECCO_2R$ (cmH_2O)				
Observed	9 (6–11)	9 (7–11)	9 (6–12)	0.95
Standardized	8 (6–11)	8 (7–11)	8 (6–11)	0.99
$ECCO_2R$ device type				
Lower CO_2 extraction	33 (35%)	19 (46%)	12 (26%)	0.08
Higher CO_2 extraction	62 (65%)	22 (54%)	34 (74%)	0.08
PEEP (cmH_2O)	14 (10–16)	15 (12–16)	12 (10–16)	0.12
FiO_2	60 (50–70)	60 (50–70)	60 (50–70)	0.62
pH	7.34 (7.3–7.4)	7.34 (7.29–7.40)	7.34 (7.30–7.39)	0.84
$PaCO_2$ (mm Hg)	45 (41–55)	43 (39–48)	50 (43–56)	0.011
Bicarbonate (mmol L^{-1})	25 (22–28)	23 (22–25)	26 (23–30)	0.019
Base excess (mmol L^{-1})	0 (− 3–2)	− 2 (− 5 –1)	1 (− 2 –4)	0.026

ΔP, airway driving pressure; $ECCO_2R$, extracorporeal CO_2 removal; SAPS II, severe acute physiology score; SOFA, sequential organ failure assessment; PBW, predicted body weight; PEEP, positive end-expiratory pressure

mortality rate based on the mortality rates observed for each subgroup of predicted responders in SUPERNOVA. Sample size estimates were computed from predicted ARR values assuming a 5% risk of Type I error and a 20% risk of Type II error. In a sensitivity analysis, ARR and sample size were re-estimated using an HR of 0.75 (based on the treatment effect observed in a previous trial of lung-protective ventilation) [6] instead of 0.68. The number of serious adverse events in patients randomized to $ECCO_2R$ was predicted based on the rate observed in SUPERNOVA (6/95, 6%).

All analyses were conducted using R version 3.5.1 (http://www.r-project.org).

Results

Patient physiological characteristics and responses to $ECCO_2R$

Patient clinical and physiological characteristics are shown in Table 1. Due to missing data in plateau pressure measurements ($n=4$), $PaCO_2$ ($n=1$), and computed alveolar dead space fraction ($n=2$), and because sweep gas flow was not applied in 1 patient, the changes in standardized V_t and ΔP could be computed in 87 patients. The median time between baseline and post-$ECCO_2R$ measurements was 150 min (IQR 80–300 min). $ECCO_2R$ was applied using a higher CO_2 extraction device in 62 patients (65%) and a lower CO_2 extraction device in 33 patients (35%).

The change in standardized V_t after applying $ECCO_2R$ varied widely among patients (Figure E1, median −2.0 ml/kg, range −1.1 to −4.0 ml/kg). The change in standardized ΔP after applying $ECCO_2R$ also varied widely (Figure E1, median −4.1 cmH_2O, range −11.1 to 1.7 cmH_2O), partly because of large changes in Crs in some patients (Figure E1, Crs increased or decreased by more than 5 ml/cmH_2O in 35% of patients). The change in standardized $Power_{RS}$ also varied widely (Figure E1, median −3.8 J/min, range −8.7 to 0.3 J/min).

At 8 h from $ECCO_2R$ initiation, 74 patients (78%) achieved the primary end-point: 18 of 33 patients (55%) on the lower CO_2 extraction device and 56 of 62 patients (90%) on the higher CO_2 extraction devices ($p<0.001$).

Demographics, cause of ARDS, baseline PaO_2/FiO_2, and severity of illness were similar among patients with smaller (>median of −4 cmH_2O) vs. larger (≤median of −4 cmH_2O) changes in standardized ΔP after applying $ECCO_2R$ (Table 1). Baseline ΔP, plateau pressure, VR, and $PaCO_2$ were significantly higher in patients with a larger reduction in standardized ΔP with $ECCO_2R$, reflecting lower Crs and higher ADF (Table 1).

Determinants of effect of $ECCO_2R$ on tidal volume, driving pressure, and mechanical power

In bivariate linear regression, the change in standardized V_t after applying $ECCO_2R$ was associated with ADF, VR, and device performance, but not with Crs or PaO_2/FiO_2 (Fig. 1); similar findings were obtained in multivariable regression incorporating all these variables (Table E1).

The change in standardized ΔP after the application of $ECCO_2R$ was associated with ADF, VR, Crs, and PaO_2/FiO_2 (Fig. 2); in multivariable analysis incorporating all these variables, the effect of PaO_2/FiO_2 was no longer significant (Table E1).

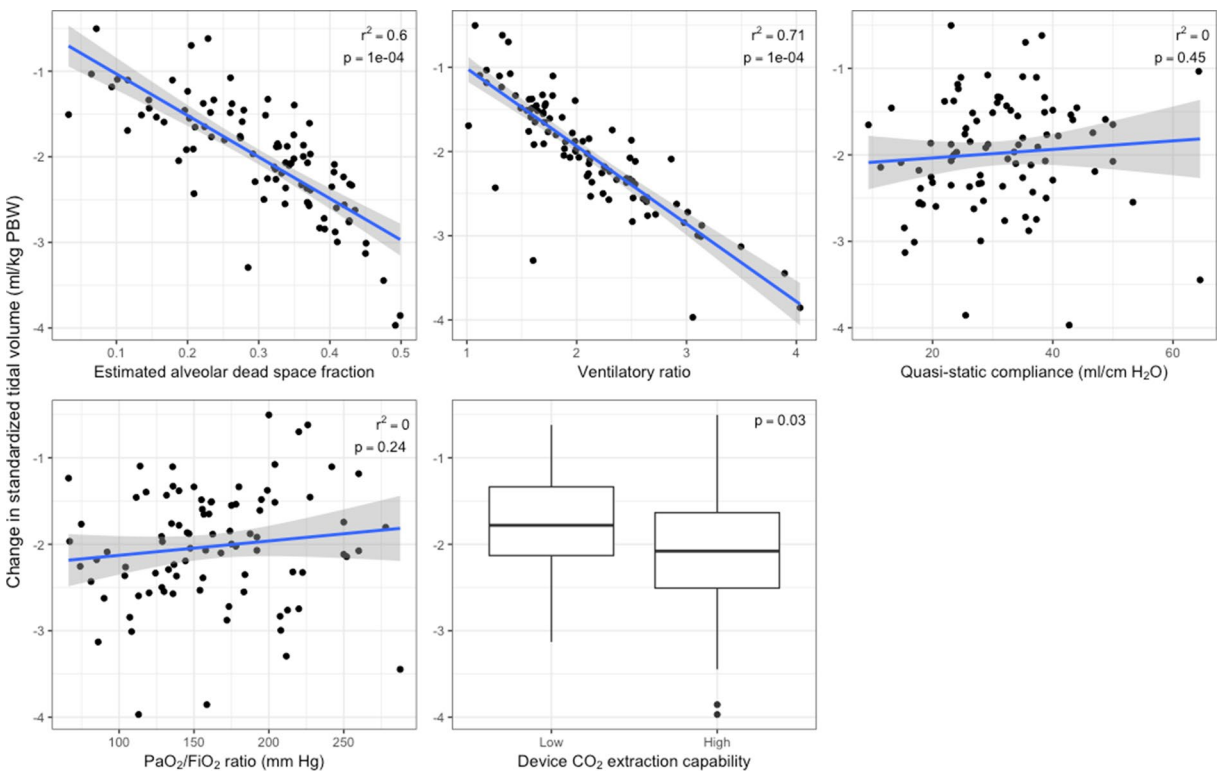

Fig. 1 Determinants of the change in tidal volume (standardized to $PaCO_2$ 45 mmHg and respiratory rate of 30/min) after applying $ECCO_2R$

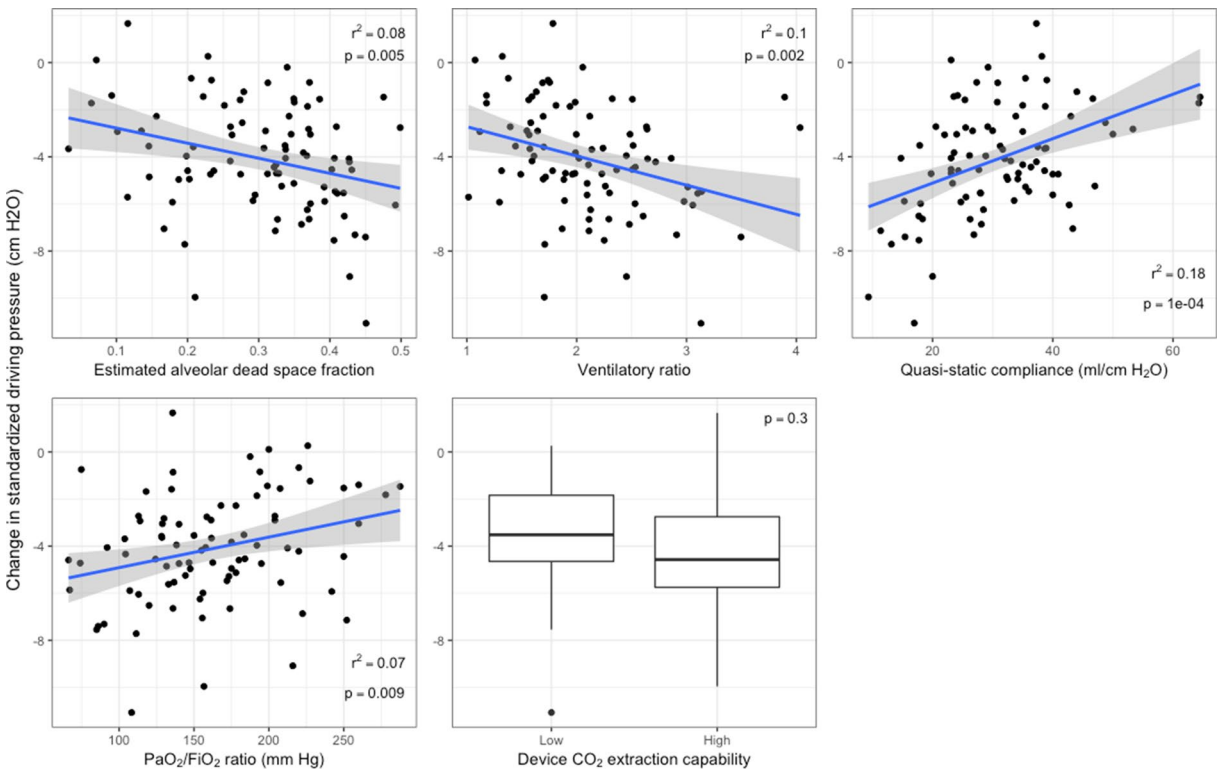

Fig. 2 Determinants of the change in driving pressure (standardized to $PaCO_2$ 45 mmHg and respiratory rate of 30/min) after applying $ECCO_2R$. After adjusting for alveolar dead space fraction and compliance, the effect of PaO_2/FiO_2 was no longer significant

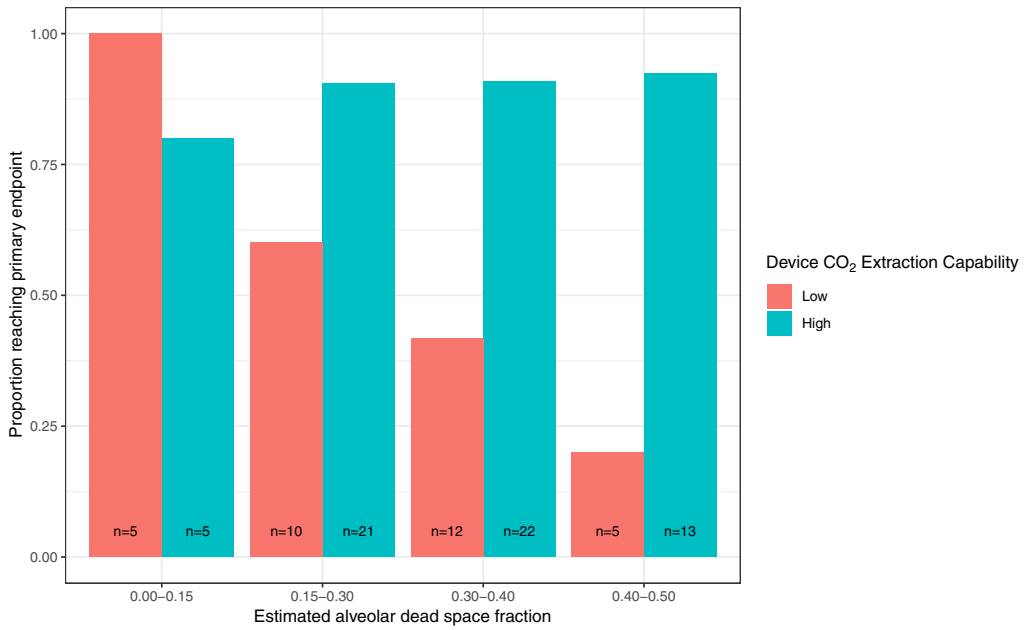

Fig. 3 Alveolar dead space fraction determines the degree of CO_2 removal required to achieve the primary endpoint in the SUPERNOVA trial (tidal volume $\leq$ 4 ml/kg PBW and pH $\geq$ 7.3 and $PaCO_2$ within 20% of baseline) at 8 h after initiation of $ECCO_2R$ ($p = 0.03$ for interaction). At lower alveolar dead space fraction, reductions in V_t from 6 to 4 ml/kg can be achieved with relatively less extracorporeal CO_2 removal whereas patients with higher alveolar dead space fraction require higher CO_2 removal to reduce V_t. The number of patients in each group is shown within the bar

The change in standardized $Power_{RS}$ after the application of $ECCO_2R$ was associated with ADF, VR, Crs, PaO_2/FiO_2, and device performance (Figure E2); in multivariable analysis incorporating all these variables, the effect of PaO_2/FiO_2 was no longer significant (Table E1).

The combined effects of Crs and ADF on the change in standardized ΔP and standardized $Power_{RS}$ are represented in Figure E3.

The probability of reaching the SUPERNOVA trial primary end-point was higher when $ECCO_2R$ was applied using a higher CO_2 extraction device (Figure E4), particularly in patients with higher ADF (Fig. 3, $p=0.03$ for interaction). This interaction with ADF persisted in multivariable analysis (Table E1). All patients on lower CO_2 extraction devices required maximum sweep gas flow to achieve the study endpoint, whereas in patients on higher CO_2 extraction devices, the sweep gas flow required to achieve the study endpoint progressively increased with increasing ADF (Figure E5).

Predicting the effect of $ECCO_2R$ on driving pressure

The observed change in standardized ΔP was correlated with the predicted change in driving pressure ($R^2=0.32$, $p<0.001$, Figure E6). In Bland–Altman analysis, predicted and observed changes in ΔP differed by up to ± 3.9 cmH_2O (Figure E6, Table E2); the bias varied with

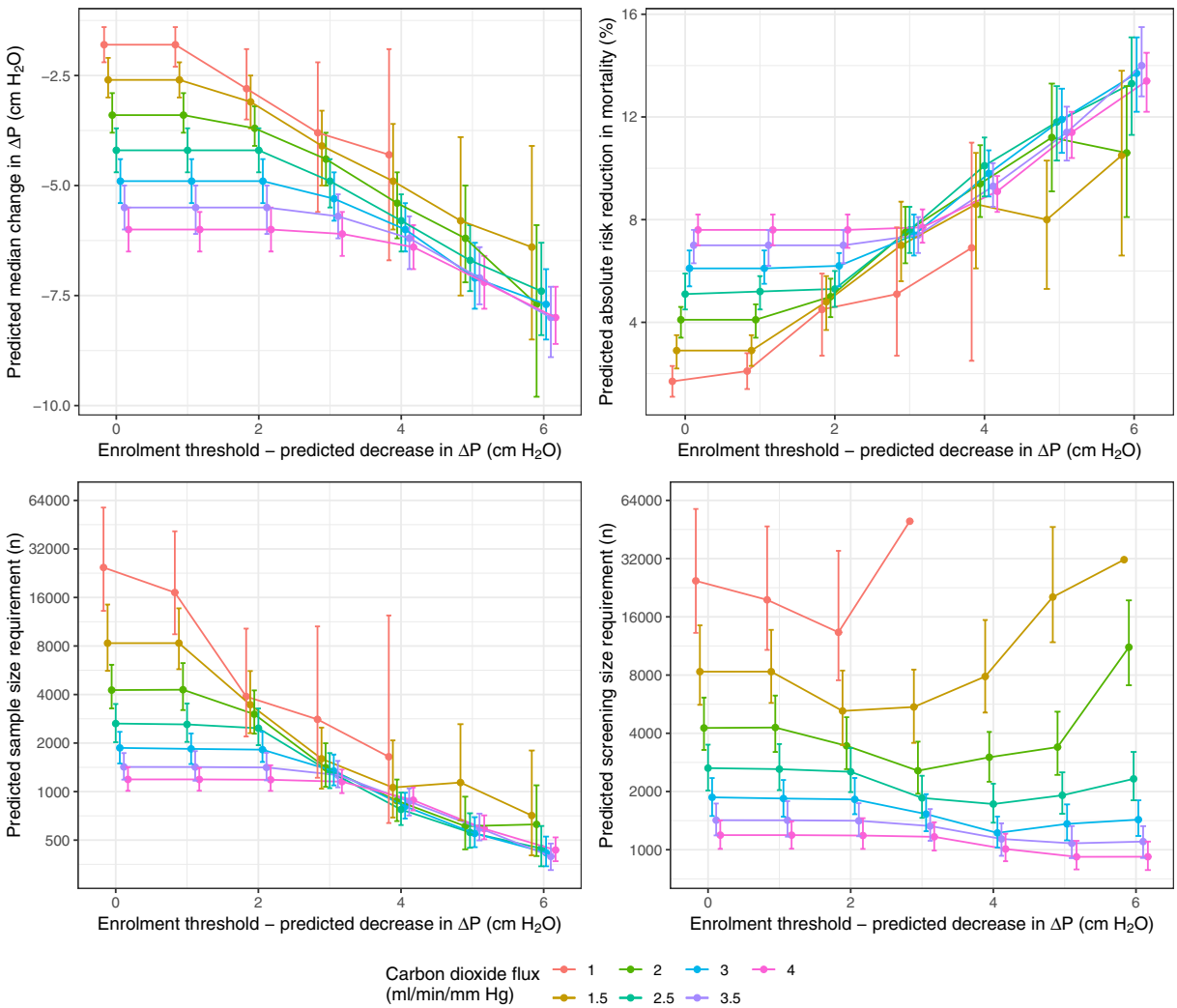

Fig. 4 Predicted effect of $ECCO_2R$ on ΔP (top left panel) and mortality risk (top right panel) in trial designs using different enrollment criteria and different degrees of device performance (CO_2 removal). The error bars represent the 5th and 95th percentile values for the median change in ΔP predicted after incorporating random prediction error of ± 4 cmH_2O. The predicted effect on mortality was used to compute sample size requirement (bottom left panel). Because only a subset of patients meet the threshold for inclusion, the number of otherwise eligible ARDS patients who need to be identified by screening (bottom right panel) is higher than the sample size for randomization

the assumed rate of CO_2 removal used to predict the change in ΔP (Table E2). Discrimination between higher and lower responders was moderately acceptable (area under receiver operating characteristic curve 0.72, Figure E6).

After recomputing the predicted change in ΔP using the same value for Crs at both baseline and at 4 ml/kg to evaluate predictive performance under conditions of stable Crs (e.g. to simulate the effect of titrating PEEP to prevent decreases in Crs resulting from $ECCO_2R$-facilitated reductions in V_t), the correlation between predicted and observed values was considerably higher ($R^2 = 0.74$), limits of agreement were narrower (± 2.1 cmH_2O), and predictive discrimination improved substantially (area under receiver operating characteristic curve 0.92) (Table E2).

Trial design simulations

Figure 4 provides predicted sample size requirements computed in $ECCO_2R$ trial simulations using different values of predicted change in ΔP to define eligibility for enrolment. Results at predicted change in $\Delta P = 0$ represent the sample sizes required in the absence of predictive enrichment. Greater CO_2 removal and restricting enrollment to patients with a higher predicted ΔP response reduced predicted sample size requirements (Fig. 4). The effect of restricting enrollment to patients with a greater predicted reduction in ΔP on sample size requirements (Fig. 4) and hence on serious adverse event rates (Figure E7) was greatest at lower CO_2 removal rates.

Based on these calculations, a trial designed applying $ECCO_2R$ of at least 3 ml/min/mmHg (approximately 135 ml/min assuming an average $PaCO_2$ of 45 mmHg) to patients like those in SUPERNOVA and using a predicted reduction in $\Delta P \geq 5$ cmH_2O to determine eligibility for randomization would need to identify 1340 otherwise eligible patients with ARDS, of whom 548 (41%) would meet enrollment criteria and be randomized to refute a predicted 12% absolute risk reduction in mortality. In a sensitivity analysis employing a less optimistic mortality effect (HR 0.75), the same trial design would need to identify 2460 eligible patients, of whom 1006 would meet enrollment criteria and be randomized (see Supplemental Tables and Online Supplement for details).

An online calculator to predict treatment response in individual patients has been made available at https://bit.ly/2RRHevj.

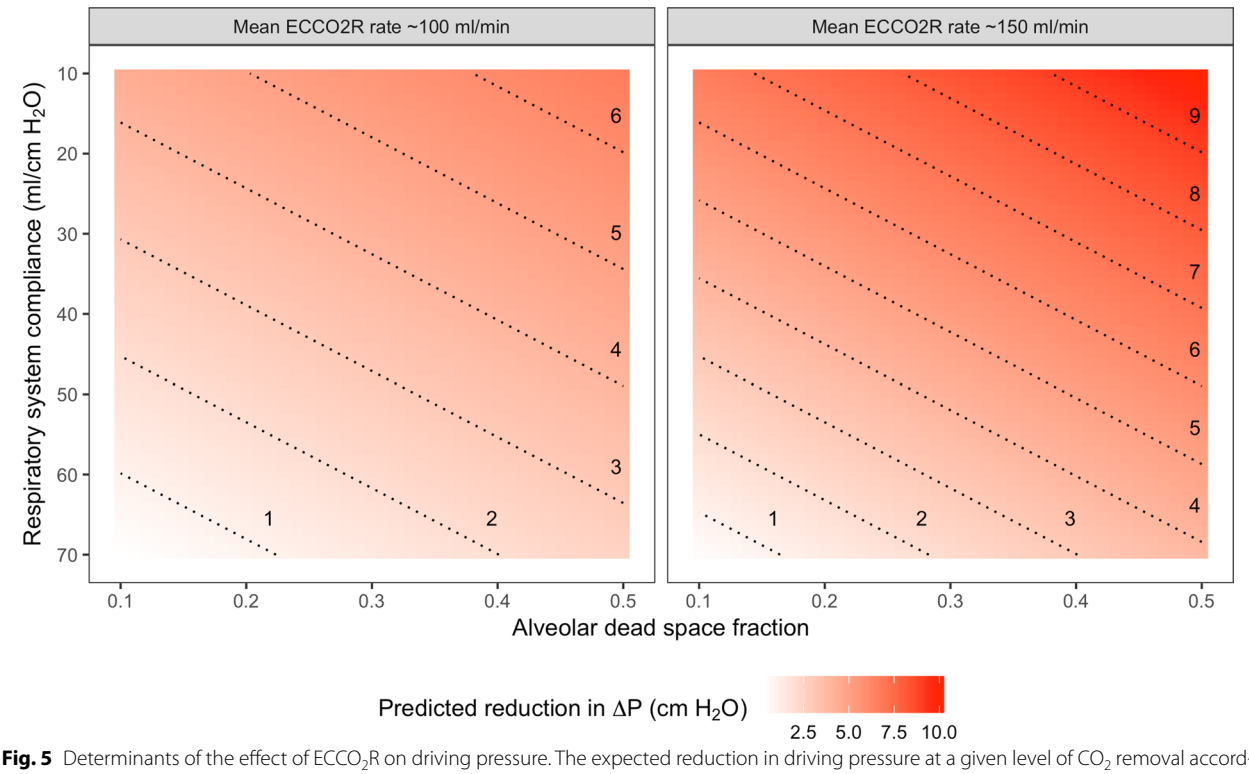

Fig. 5 Determinants of the effect of $ECCO_2R$ on driving pressure. The expected reduction in driving pressure at a given level of CO_2 removal according to compliance and alveolar dead space fraction computed from the effects observed in SUPERNOVA is represented as a heat map; isopleths of driving pressure reduction are represented by the dashed lines. Heats maps are shown for two different levels of CO_2 removal: the approximate rate in the SUPERNOVA trial (~ 100 ml/min), and the distribution predicted for a 50% increase in extracorporeal CO_2 clearance

Discussion

This study demonstrates that the effect of $ECCO_2R$ on V_t, ΔP, and $Power_{RS}$ varies widely in patients with moderate ARDS as substantially determined by ADF, Crs, and the CO_2 extraction capability of the $ECCO_2R$ device. These findings suggest that patients with higher ADF or lower Crs and patients treated with higher CO_2 extraction are most likely to benefit from $ECCO_2R$ (Fig. 5 and Figure E8). We also found that the a priori model for predicting the change in ΔP obtained by $ECCO_2R$ was only moderately accurate, possibly because a number of key variables (e.g. actual CO_2 removal rate) were not measured in the SUPERNOVA trial and because of changes in Crs after applying $ECCO_2R$ and reducing V_t. Finally, simulations of treatment effect in different trial designs contingent upon a range of assumptions (discussed below) suggest that a future trial of $ECCO_2R$-facilitated ultra-protective ventilation powered to detect impact on clinical outcomes, incorporating both predictive enrichment and enhanced CO_2 clearance, is feasible.

Even in an age of 'big data', the randomized clinical trial remains the most powerful and reliable tool to test new therapies in clinical practice. However, the many 'negative' trials in critical care have spurred important innovations in trial design [12, 13]. Predictive enrichment is one approach to enhance the probability of demonstrating benefit (if any) by selecting patients most likely to respond. The importance of enrichment in the case of $ECCO_2R$ is highlighted by the widely varying effect of $ECCO_2R$ on ΔP observed in this study and the known risk of treatment-related complications.

A theoretical analysis of the physiological equations defining alveolar ventilation suggested that the effect of $ECCO_2R$ on ΔP would be positively correlated to ADF and inversely related to Crs [6]. ADF determines the magnitude and frequency of tidal inflation required for pulmonary ventilation, while Crs determines the pressure required to achieve this tidal inflation. Accordingly, reducing the requirement for pulmonary ventilation by $ECCO_2R$ will reduce the requirement for tidal volume and pressure in proportion to ADF and Crs. This study confirms this hypothesis. Although we did not directly measure ADF, empirical estimates of ADF were strongly correlated with changes in V_t, ΔP, and $Power_{RS}$, and this finding was corroborated by observing similar effects with VR (a surrogate marker for physiological dead space) [8]. The effect of $ECCO_2R$ on ΔP and $Power_{RS}$ was correlated with baseline respiratory compliance as expected, given the mathematical and physiological coupling between these variables. Importantly, although baseline PaO_2/FiO_2 ranged between 92 and 242 mmHg in SUPERNOVA, the effect of $ECCO_2R$ on ΔP was unrelated to the severity of hypoxemia (the usual measure of ARDS severity) after adjusting for ADF and Crs. This suggests that ADF and Crs, rather than severity of hypoxemia, should be the primary factors in determining whether to enroll patients in clinical trials of $ECCO_2R$.

The success of predictive enrichment is contingent upon two conditions: (a) the availability of a predictive 'biomarker' that reliably reflects the causal mechanism conditioning outcome [14]; and (b) reliable and feasible detection or prediction of the biomarker response. The predictive validity ('credentials') of various biomarkers of ventilator-induced lung injury remains the subject of considerable debate: options include V_t, ΔP, and $Power_{RS}$. There is evidence that both the magnitude and frequency of tidal ventilation contribute to lung injury as reflected by $Power_{RS}$ [15]—$ECCO_2R$ could permit both tidal volume and respiratory frequency to be lowered, leading to substantial reductions in $Power_{RS}$. Our trial design simulation analysis focused on driving pressure given the body of evidence in its favor and data linking ΔP with mortality [2, 11].

Even if a biomarker with acceptable credentials is available, the effect of treatment on that biomarker must be reliably determined before randomization. While a 'test dose' of some therapies could be used to assess biomarker response (e.g. the gas exchange response to higher PEEP in mechanical ventilation) [16], a 'test dose' of $ECCO_2R$ cannot be applied because it is invasive, costly, and associated with potentially serious adverse events. Predicting the response to $ECCO_2R$ is therefore crucial to incorporating predictive enrichment in the design of trials evaluating $ECCO_2R$-facilitated ultra-protective ventilation.

Despite a sound theoretical basis and confirmatory associations between treatment effect and both ADF and Crs, a previously derived model based on these parameters was only moderately successful in predicting the $ECCO_2R$ response in this study. Limits of agreement between predicted and observed changes in ΔP were wide and the ability to discriminate between patients with or without a significant treatment response (arbitrarily defined based on the median change in ΔP) was limited. Several factors likely account for this. First, ADF was not measured, but was estimated empirically—a future trial could easily incorporate direct estimates of ADF based on end-tidal CO_2 measurements. Second, Crs changed before and after $ECCO_2R$ application in many patients, possibly because lowering tidal volume relieved hyperdistention (compliance increased by 5 ml/cmH_2O or more in 16% of patients) or caused alveolar derecruitment (compliance decreased by 5 ml/cmH_2O or more in 19% of patients). Using a constant value for Crs substantially improved predictive discrimination. A future trial could incorporate a physiological strategy that aims to maintain [17] or even improve [18] Crs to maximize

predictive accuracy and also to minimize ΔP as part of its interventional approach.

Third, accurate prediction of device performance (CO_2 removal) is crucial for accurate predictions of patient response. CO_2 removal rates were not directly measured in SUPERNOVA, but predicted device CO_2 extraction strongly modified the ability to achieve ultra-protective ventilation targets, particularly in patients with higher ADF. In patients with lower ADF, considerable reductions in V_t can be achieved while applying little or no CO_2 removal (as indicated by the relatively low sweep gas flow requirements in these patients, Figure E4), whereas patients with higher ADF can attain only small decreases in V_t apart from CO_2 removal (illustrated in Figure E6). Given the importance of device performance, particularly in patients with high ADF, device performance (i.e. CO_2 removal) must be accurately predicted when deciding whether to apply $ECCO_2R$. CO_2 elimination rates by membrane lungs are a complex function of several factors including sweep gas flow rate, membrane area, extracorporeal blood flow rate, venous CO_2 tension, and membrane materials and design. The respective contributions of each of these variables are well understood from a biophysical perspective [10] and CO_2 removal should in theory be highly predictable. Future studies should focus on developing and validating reliable models to predict CO_2 removal under specified device settings for each of the devices on the market.

Despite the imperfect reliability of predicted treatment response, we show that predicting treatment effect would nevertheless substantially reduce sample size requirements, as suggested by the trial simulation results. Even when incorporating a random error in the predicted change in ΔP consistent with the limits of agreement between predicted and observed effects obtained in this study, simulated median changes in ΔP were substantially higher in predicted responders.

The estimated decrease in mortality using $ECCO_2R$ was computed from the predicted decrease in ΔP based on two crucial assumptions. First, the computation assumes that the association between ΔP and mortality reported in a previous mediation analysis is entirely causal [11]. In a sensitivity analysis, the use of a less optimistic hazard ratio for treatment effect on mortality increased sample size requirements. Second, this analysis assumes that the effect of reducing ΔP on mortality is independent of the baseline ΔP (i.e. there is no threshold effect). The benefit of reducing driving pressure even when plateau pressure is not elevated has been suggested in secondary analyses of clinical trials [11, 19] but remains unconfirmed. These assumptions are considered and discussed in detail elsewhere [6]. A future clinical trial is required to address these uncertainties. Assumptions about treatment effect are unavoidable in trial design, particularly in sample size computations. Adaptive designs can help to mitigate such assumptions by permitting ongoing enrollment if the treatment effect is weaker than expected [20]. An adaptive design might also initially employ broad inclusion criteria and adopt increasingly restrictive criteria if evidence accumulates that predicted responders experience greater benefit than predicted non-responders.

The main limitation of this analysis, aside from those reviewed above, is that the SUPERNOVA study was planned and carried out before the theoretical analysis linking changes in ΔP obtained with $ECCO_2R$ to individual patient physiological characteristics was published. For this reason, the measurements and procedures required to optimize predictive accuracy were not performed and adjustments were required to address confounding factors (i.e. concomitant changes in respiratory rate and $PaCO_2$ target). A future $ECCO_2R$ trial designed to maximize the reduction in ΔP obtained from $ECCO_2R$ could address these limitations by directly measuring all relevant baseline variables prospectively (ADF, Crs, CO_2 elimination) and computing the predicted change in ΔP prior to initiation of $ECCO_2R$.

Conclusions

The effect of $ECCO_2R$ on V_t, ΔP, and $Power_{RS}$ varies widely in patients with moderate ARDS as substantially determined by ADF and Crs. These findings suggest that patients with higher ADF or lower Crs and patients treated with higher CO_2 extraction devices are most likely to benefit from $ECCO_2R$ (Fig. 5). Incorporating predicted treatment response and higher CO_2 removal rates as factors in trial design might substantially reduce screening and sample size requirements in a future trial of $ECCO_2R$-facilitated ultra-protective ventilation.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05708-9) contains supplementary material, which is available to authorized users.

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Author contributions
EG and AS conceived the study. EG, AC, DB, VMR, and AS designed the study. AC, DB, NDF, VMR, and AS acquired the study measurements. EG conducted the analysis. All authors contributed to the interpretation of the findings. EG and AS drafted the manuscript and all authors critically revised the manuscript for intellectually important content. All authors gave final approval for the publication of the work and all accepted responsibility for the integrity of the work.

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Compliance with ethical standards

Conflicts of interest
Dr. Goligher reports receiving personal fees and research support in the form of equipment from Getinge. Dr. Brodie is on the medical advisory boards for Baxter, BREETHE, and Hemovent, and past medical advisory board member for ALung Technologies. He currently serves on the Trial Steering Committee for the VENT-AVOID trial sponsored by ALung Technologies. Dr. Ferguson reports receiving personal fees from Getinge, Baxter, and Sedana Medical. Dr. Slutsky reports receiving personal fees from Getinge, Baxter, and Novalung/Xenios.

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