Applying Precision Medicine to Trial Design Using Physiology
Extracorporeal CO_2 Removal for Acute Respiratory Distress Syndrome

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Abstract

In clinical trials of therapies for acute respiratory distress syndrome (ARDS), the average treatment effect in the study population may be attenuated because individual patient responses vary widely. This inflates sample size requirements and increases the cost and difficulty of conducting successful clinical trials. One solution is to enrich the study population with patients most likely to benefit, based on predicted patient response to treatment (predictive enrichment). In this perspective, we apply the precision medicine paradigm to the emerging use of extracorporeal CO_2 removal ($ECCO_2R$) for ultraprotective ventilation in ARDS. $ECCO_2R$ enables reductions in tidal volume and driving pressure, key determinants of ventilator-induced lung injury. Using basic physiological concepts, we demonstrate that dead space and static compliance determine the effect of $ECCO_2R$ on driving pressure and mechanical power. This framework might enable prediction of individual treatment responses to $ECCO_2R$. Enriching clinical trials by selectively enrolling patients with a significant predicted treatment response can increase treatment effect size and statistical power more efficiently than conventional enrichment strategies that restrict enrollment according to the baseline risk of death. To support this claim, we simulated the predicted effect of $ECCO_2R$ on driving pressure and mortality in a preexisting cohort of patients with ARDS. Our computations suggest that restricting enrollment to patients in whom $ECCO_2R$ allows driving pressure to be decreased by 5 cm H_2O or more can reduce sample size requirement by more than 50% without increasing the total number of patients to be screened. We discuss potential implications for trial design based on this framework.

Keywords: ARDS; driving pressure; precision medicine; predictive enrichment; trial design

Trial Design in Critical Care Medicine: Challenges and Solutions

The randomized clinical trial has been the "gold standard" of empirical evidence in medicine since its introduction in the mid-twentieth century with the publication of a trial of streptomycin in pulmonary tuberculosis (1). A number of seminal trials published over the last several decades have heavily influenced the practice of intensive care medicine (2–4), but many trials have proved disappointing in that interventions with strong biological plausibility were found to be ineffective (5–7).

Failure to demonstrate benefit may be attributable to "true" absence of any treatment effect, chance, or inadequate trial design. Because of feasibility concerns, trials in critical care are frequently underpowered to detect realistic treatment effects (8). Challenges in trial design and execution are compounded by phenotypic heterogeneity in populations of critically ill patients, so that it may be difficult to discern the treatment "signal" among the "noise" of competing effects on outcome (9). Heterogeneity of treatment effect (due to variation in baseline risk and/or treatment response) may obscure potentially important benefits of therapy (10). The challenge is to deliver the right treatment in the right dose to the right patient at the right time—this is the fundamental premise of the precision medicine paradigm (11).

(Received in original form January 30, 2017; accepted in final form June 21, 2017)

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 196, Iss 5, pp 558–568, Sep 1, 2017

Originally Published in Press as DOI: 10.1164/rccm.201701-0248CP on June 21, 2017
Internet address: www.atsjournals.org

Definitions of Physiological Abbreviations

ΔPaw: airway driving pressure
Cstat,rs: static compliance of the respiratory system
$ECCO_2R$: extracorporeal CO_2 removal
fR: respiratory frequency (respiratory rate) per minute
$Power_{rs}$: mechanical power of the respiratory system
$\dot{V}A$: alveolar ventilation per minute
$\dot{V}CO_2$,ECML: rate of CO_2 clearance through the extracorporeal membrane lung
$\dot{V}CO_2$,pulm: rate of CO_2 clearance from the lung per minute
$\dot{V}CO_2$,syst: rate of systemic CO_2 production per minute
VD,alv: alveolar dead space volume
VD,alv/VT: alveolar dead space fraction
VD,anat: anatomical dead space volume
VD/VT: physiological dead space fraction
VILI: ventilator-induced lung injury

To render trials more efficient and effective, several innovations have been proposed (12). One approach to enhance the signal-to-noise ratio in a clinical trial is to enrich the trial population to magnify treatment effect (13). Prognostic enrichment is accomplished by enrolling subjects at higher risk of the event of interest. This increases absolute risk reduction without any increase in relative risk reduction. Trials of interventions such as prone positioning and neuromuscular blockade employed prognostic enrichment by restricting enrollment to patients with more severe baseline hypoxemia (14, 15).

Predictive enrichment, by contrast, aims to increase relative risk reduction by enrolling patients with the greatest probability of responding favorably. This magnifies absolute risk reduction apart from any change in baseline risk. The precision medicine paradigm is an important example of predictive enrichment: by understanding the pathobiology of disease in individual patients based on molecular signatures, biomarker data, or clinical characteristics, we can theoretically predict those most likely to benefit from a given intervention (11).

Although precision medicine is largely considered in the context of molecular biology and genetics, insights from physiology—a mainstay of practice in critical care—may also be used for predictive enrichment. Physiological characteristics and responses are relevant to patient selection for treatment insofar as they reflect the effect of treatment on the mechanistic pathways leading to injury and subsequent outcome. For example, one proposal suggested that the oxygenation response to positive end-expiratory pressure (PEEP) (which largely reflects lung recruitability) might guide patient selection for future trials of higher versus lower PEEP ventilation strategies (16).

The Need for Predictive Enrichment in Trials of Extracorporeal CO_2 Clearance for Ultraprotective Ventilation in Acute Respiratory Distress Syndrome

Patients with acute respiratory distress syndrome (ARDS) are at risk of ventilator-induced lung injury (VILI) (17). The established lung-protective approach is to limit tidal volumes to 6 ml/kg predicted body weight, but several lines of evidence suggest that clinical outcomes might be further improved by additional reductions in tidal stress and strain. A secondary analysis of the ARDSNet (NHLBI ARDS Clinical Trials Network) low-VT ventilation trial found lower mortality in patients with lower plateau pressures, with no threshold effect (18). In patients subjected to low-VT ventilation, lower driving pressures (ΔPaw)—which better reflect tidal strain—are associated with improved survival (19). And a *post hoc* analysis of a trial comparing tidal volumes of 3 versus 6 ml/kg in patients with a P/F ratio (i.e., the ratio of Pa_{O_2} to fraction of inspired oxygen [FI_{O_2}]) less than 150 mm Hg suggested that the lower VT group had greater ventilator-free days (20). Consequently, ultraprotective ventilation with very low VT has been proposed to further reduce VILI and mortality in ARDS (21).

The major limiting factor in reducing VT is the development of respiratory acidosis. As VT is reduced, the anatomical dead space fraction (VD,anat/VT) increases and alveolar ventilation ($\dot{V}A$) falls, worsening hypercapnia and leading to potentially life-threatening acidosis. Eliminating CO_2 via an external membrane lung (extracorporeal CO_2 removal [$ECCO_2R$]) can avert this problem (22, 23). $ECCO_2R$, sometimes referred to as *respiratory dialysis*, employs an artificial membrane lung to remove CO_2 from the blood. The potential clinical benefits of $ECCO_2R$ for VILI in ARDS are now under evaluation in clinical studies (SUPERNOVA [Strategy of Ultraprotective Lung Ventilation with Extracorporeal CO_2 Removal for New-Onset Moderate to Severe ARDS], NCT02282657; and REST [Protective Ventilation with Veno-venous Lung Assist in Respiratory Failure], NCT02654327).

Despite a strong physiological and therapeutic rationale for $ECCO_2R$ in ARDS, caution is warranted. First, the mortality reduction obtained by further relatively small reductions in VT may be limited, and large sample sizes may be required to demonstrate significant effects. Second, $ECCO_2R$ is associated with a reasonably high rate of complications (24). Third, $ECCO_2R$ is costly and could impose a significant economic burden on patients and health systems (25). $ECCO_2R$ therefore requires careful evaluation before widespread adoption as an adjunct treatment for ARDS.

In this study we set out to determine how physiology might enable predictive enrichment in trials of $ECCO_2R$ in ARDS. We contend that the effect of $ECCO_2R$ on the determinants of VILI can be predicted from two physiological measurements: alveolar dead space fraction and static respiratory compliance. Selecting patients with favorable response characteristics for trials of $ECCO_2R$ will enhance treatment effect and statistical power, resulting in more efficient trial design. We now set out to develop this case.

Physiological Basis for Predicting Benefit from $ECCO_2R$

Selecting Target Variables to Quantify Treatment Response

The primary driver of VILI in patients with ARDS is thought to be the tidal mechanical stress applied to the lung during ventilation. The magnitude of this stress is related to V_T, and thus V_T reduction is the primary means employed to prevent VILI. The goal of $ECCO_2R$ in patients with ARDS is to reduce alveolar ventilation requirements so that V_T (and hence lung stress) can be reduced. Mechanical stress may be more accurately quantified using ΔPaw and possibly mechanical power ($Power_{rs}$; *see* the online supplement for rationale) (26). We will therefore examine how variations in dead space and respiratory compliance modify the effect of $ECCO_2R$ on both ΔPaw and $Power_{rs}$, and hence on mortality.

Step 1: Effect of $ECCO_2R$ on Tidal Volume and Respiratory Frequency

The relationship between $\dot{V}_A$ and the rate of CO_2 clearance from the lung ($\dot{V}_{CO_2,pulm}$) is given by:

$$Pa_{CO_2} = k\frac{\dot{V}_{CO_2,pulm}}{\dot{V}_A}$$
$$\Rightarrow \dot{V}_A = \frac{k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,pulm}. \quad (1)$$

$\dot{V}_A$ is, in turn, related to V_T, respiratory frequency (f_R), and V_D/V_T (27). V_D/V_T is composed of anatomic dead space ($V_{D,anat}$) and alveolar dead space ($V_{D,alv}$). Whereas $V_{D,anat}$ is relatively constant and minimally affected by changes in V_T, $V_{D,alv}$ generally varies as a constant fraction of V_T (27). Therefore, we will treat $V_{D,anat}$ as a fixed volume and $V_{D,alv}$ as a fixed fraction of tidal volume ($V_{D,alv}/V_T$). Substituting these quantities into Equation 1 and rearranging gives:

$$V_T \cdot f_R\left(1-\frac{V_{D,alv}}{V_T}-\frac{V_{D,anat}}{V_T}\right)$$
$$= \dot{V}_A = \frac{k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,pulm}$$
$$\Rightarrow f_R\left[\left(1-\frac{V_{D,alv}}{V}\right)V_T - V_{D,anat}\right]$$
$$= \dot{V}_A = \frac{k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,pulm}. \quad (2)$$

Under usual steady-state conditions, the volume of CO_2 eliminated via the lungs ($\dot{V}_{CO_2,pulm}$) is equal to the systemic CO_2 production ($\dot{V}_{CO_2,syst}$):

$$\dot{V}_{CO_2,pulm} = \dot{V}_{CO_2,syst}. \quad (3)$$

Applying $ECCO_2R$ removes a portion of $\dot{V}_{CO_2,syst}$, reducing $\dot{V}_{CO_2,pulm}$ by an amount equal to CO_2 flux through the extracorporeal membrane lung ($\dot{V}_{CO_2,ECML}$) (28), as given by:

$$\Delta\dot{V}_{CO_2,pulm} = -\dot{V}_{CO_2,ECML}. \quad (4)$$

Therefore, by Equation 1, the change in alveolar ventilation ($\Delta\dot{V}_A$) required to maintain the same Pa_{CO_2} after applying $ECCO_2R$ is given by:

$$\Delta\dot{V}_A = \frac{k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,pulm}$$
$$= \frac{-k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML}. \quad (5)$$

$\Delta\dot{V}_A$ results from the changes in V_T and f_R from their baseline values (V_{T_1} and f_{R_1}) to their values after application of $ECCO_2R$ (V_{T_2} and f_{R_2}). By Equation 2:

$$f_{R_1}\left[\left(1-\frac{V_{D,alv}}{V_T}\right)V_{T_1} - V_{D,anat}\right] = \dot{V}_{A_1}$$
$$f_{R_2}\left[\left(1-\frac{V_{D,alv}}{V_T}\right)V_{T_2} - V_{D,anat}\right] = \dot{V}_{A_2}$$
$$\Rightarrow \Delta\dot{V}_A = \Delta\dot{V}_{A_2} - \Delta\dot{V}_{A_1}$$
$$= f_{R_2}\left[\left(1-\frac{V_{D,alv}}{V_T}\right)V_{T_2} - V_{D,anat}\right]$$
$$-f_{R_1}\left[\left(1-\frac{V_{D,alv}}{V_T}\right)V_{T_1} - V_{D,anat}\right]. \quad (6)$$

It is important to note that the alveolar dead space *fraction* (represented by $V_{D,alv}/V_T$) and the anatomical dead space *volume* (represented by $V_{D,anat}$) are assumed to remain unchanged for varying V_T. Assuming that V_T and f_R are adjusted after initiation of $ECCO_2R$ to maintain the same Pa_{CO_2}, one can substitute Equation 6 into Equation 5 to obtain:

$$f_{R_2}\left[\left(1-\frac{V_{D,alv}}{V_T}\right)V_{T_2} - V_{D,anat}\right]$$
$$- f_{R_1}\left[\left(1-\frac{V_{D,alv}}{V_T}\right)V_{T_1} - V_{D,anat}\right]$$
$$= \frac{-k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML} \quad (7)$$

$$\Rightarrow \left(1-\frac{V_{D,alv}}{V_T}\right)(V_{T_2} \cdot f_{R_2} - V_{T_1} \cdot f_{R_1})$$
$$- V_{D,anat}(f_{R_2} - f_{R_1})$$
$$= \frac{-k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML} \quad (8)$$

Equations 7 and 8 may be considered as a general description of the relationship among the ventilator settings (f_R, V_T) applied pre- and post-$ECCO_2R$ while maintaining a constant Pa_{CO_2}. Consistent with physiological intuition, Equation 8 indicates that part of $\dot{V}_E$ is expended to overcome $V_{D,anat}$, and this component can be reduced only by reducing f_R (i.e., reducing V_T has no effect on this component of $\dot{V}_E$).

Step 2: Applying $ECCO_2R$ to Maximally Reduce Driving Pressure

The reduced $\dot{V}_E$ requirement resulting from $ECCO_2R$ permits reductions in either V_T or f_R. Suppose that our primary goal is to reduce V_T while holding f_R unchanged (i.e., $f_{R_2} = f_{R_1} = f_R$). Then Equation 8 simplifies to:

$$\left(1-\frac{V_{D,alv}}{V_T}\right)(V_{T_2} \cdot f_R - V_{T_1} \cdot f_R)$$
$$= \frac{-k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML}$$
$$\Rightarrow \left(1-\frac{V_{D,alv}}{V_T}\right) \cdot f_R \cdot (V_{T_2} - V_{T_1})$$
$$= \frac{-k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML}$$
$$\Rightarrow V_{T_2} - V_{T_1} = \frac{-k}{[1-(V_{D,alv}/V_T)] \cdot f_R \cdot Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML}. \quad (9)$$

Because tidal volume is the product of ΔPaw and static respiratory compliance (Cstat,rs):

$$V_T = \Delta Paw \cdot C_{stat,rs}$$
$$\Rightarrow V_{T_2} - V_{T_1}$$
$$= (\Delta Paw_2 - \Delta Paw_1) \cdot C_{stat,rs} \quad (10)$$

Substituting Equation 10 into Equation 9 and rearranging yields:

$$\Delta Paw_2 - \Delta Paw_1$$
$$= \frac{-k}{C_{stat,rs} \cdot [1-(V_{D,alv}/V_T)] \cdot f_R \cdot Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML} \quad (11)$$

Equation 11 gives the relationship between the patient's physiological characteristics and the predicted change in ΔPaw resulting from the application of $ECCO_2R$. This relationship indicates that patients with lower Cstat,rs and higher $V_{D,alv}/V_T$ will obtain greater reductions in ΔPaw at a given $\dot{V}_{CO_2,ECML}$ (visualized in Figures 1A and 1B).

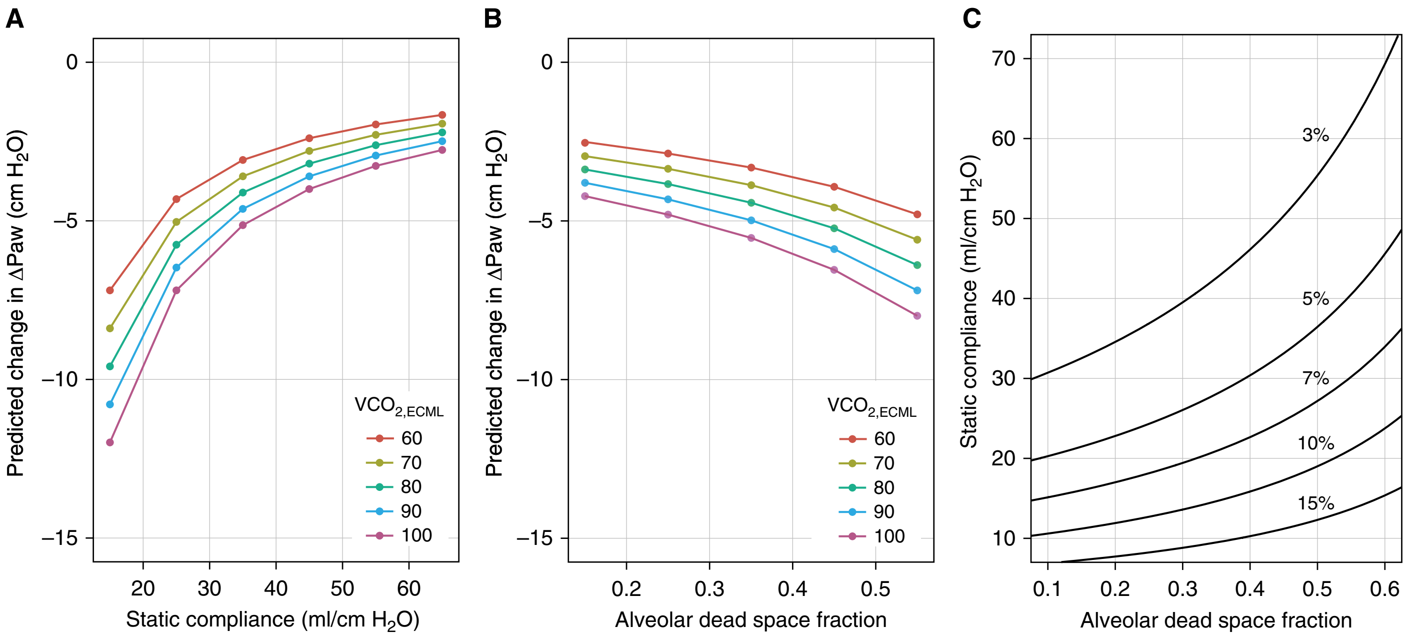

Figure 1. The predicted effect of extracorporeal CO_2 removal ($ECCO_2R$) on airway driving pressure (ΔPaw) varies with patient physiological characteristics. For a given CO_2 clearance rate ($\dot{V}CO_{2,ECML}$), greater reductions in ΔPaw are obtained with lower static compliance (*A*, assumed $V_{D,alv}/V_T$ = 0.4) and with higher alveolar dead space fraction (*B*, assumed Cstat,rs = 30 ml/cm H_2O). (*C*) Values of static respiratory compliance and alveolar dead space fraction required to obtain a given predicted reduction in mortality risk from the application of $ECCO_2R$. Values are plotted according to isopleths of hypothesized absolute risk reduction in mortality (labeled on each *curve*). *See* text for computational details. Cstat,rs = static compliance of the respiratory system; $\dot{V}CO_{2,ECML}$ = rate of CO_2 clearance through the extracorporeal membrane lung; $V_{D,alv}/V_T$ = alveolar dead space fraction.

Other components of Equation 11 merit scrutiny. First, the equation suggests that the reduction in ΔPaw is attenuated at a higher f_R set before $ECCO_2R$. This is simply due to the fact that, at higher respiratory rates, a smaller change in $\dot{V}CO_2$,pulm/breath (considering it in absolute numbers) is required to obtain the same reduction in the total pulmonary CO_2 clearance ($\dot{V}CO_2$,pulm/min). The potential changes in ΔPaw are related to changes in V_T (also in absolute numbers) and, consequently, to $\dot{V}CO_2$,pulm/breath, not $\dot{V}CO_2$,pulm/min.

Second, the change in ΔPaw is inversely related to baseline Pa_{CO_2}: at higher baseline Pa_{CO_2}, smaller reductions in ΔPaw are required to maintain a stable Pa_{CO_2} after $ECCO_2R$ implementation. The efficiency of each breath in removing CO_2 is increased at higher Pa_{CO_2} levels, with more CO_2 being extracted per breath for the same V_T. Consequently, a smaller change in V_T and ΔPaw will be required to match the $\dot{V}CO_{2,ECML}$. This might be taken to suggest that the effect of $ECCO_2R$ on ΔPaw can be enhanced by lowering baseline Pa_{CO_2}. However, because $\dot{V}CO_{2,ECML}$ varies directly with venous PCO_2 (29) and venous PCO_2 is linearly related to Pa_{CO_2}, higher values of Pa_{CO_2} will drive higher $\dot{V}CO_{2,ECML}$, effectively rendering the impact of $ECCO_2R$ on ΔPaw relatively independent of Pa_{CO_2}.

In summary, patients with lower Cstat,rs and higher $V_{D,alv}/V_T$ will accrue greater reductions in ΔPaw from the application of $ECCO_2R$. Both these variables are readily measurable at the bedside (30).

Step 3: Applying $ECCO_2R$ to Maximally Reduce Mechanical Power

$ECCO_2R$ may also be applied with a goal of reducing $Power_{rs}$. On the basis of Equation 7, V_D/V_T and Cstat,rs would be expected to significantly modify both the effect of $ECCO_2R$ on $Power_{rs}$ and also the values of V_T and f_R at which $Power_{rs}$ is minimized for any given $\dot{V}CO_{2,ECML}$. On this basis, one might apply the precision medicine paradigm to mechanical ventilation itself by selecting V_T and f_R in individual patients based on their physiological characteristics (precision ventilation). Because the clinical relevance of $Power_{rs}$ remains uncertain, these considerations are presented in the online supplement.

Impact on Treatment Efficacy and Trial Design

A number of clinical trials of $ECCO_2R$ are currently being planned, and our analysis has potentially important implications for the design of these trials. Predicting the physiological response to an intervention is clinically relevant when that response is mechanistically linked to patient outcomes. ΔPaw or $Power_{rs}$—insofar as they reflect the injurious mechanical stress applied to the lung during ventilation—are mechanistically relevant physiological targets for the application of $ECCO_2R$. The ability to predict the effect of applying $ECCO_2R$ on these parameters could guide the selection of patients who are most likely to benefit from $ECCO_2R$. Enriching the study population with these "responders" can significantly enhance statistical power and reduce sample size requirements.

To illustrate the potential impact of this approach on treatment effect and trial design, we estimated the reduction in ΔPaw that would be obtained by applying $ECCO_2R$ in a cohort of patients with ARDS enrolled in a previous randomized trial of higher versus lower PEEP—the LOVS (Lung Open Ventilation Study) randomized trial (6). We chose to focus on ΔPaw over $Power_{rs}$ because observational data are available to estimate the magnitude of the potential causal effect of changes in ΔPaw on mortality (19), whereas no such data

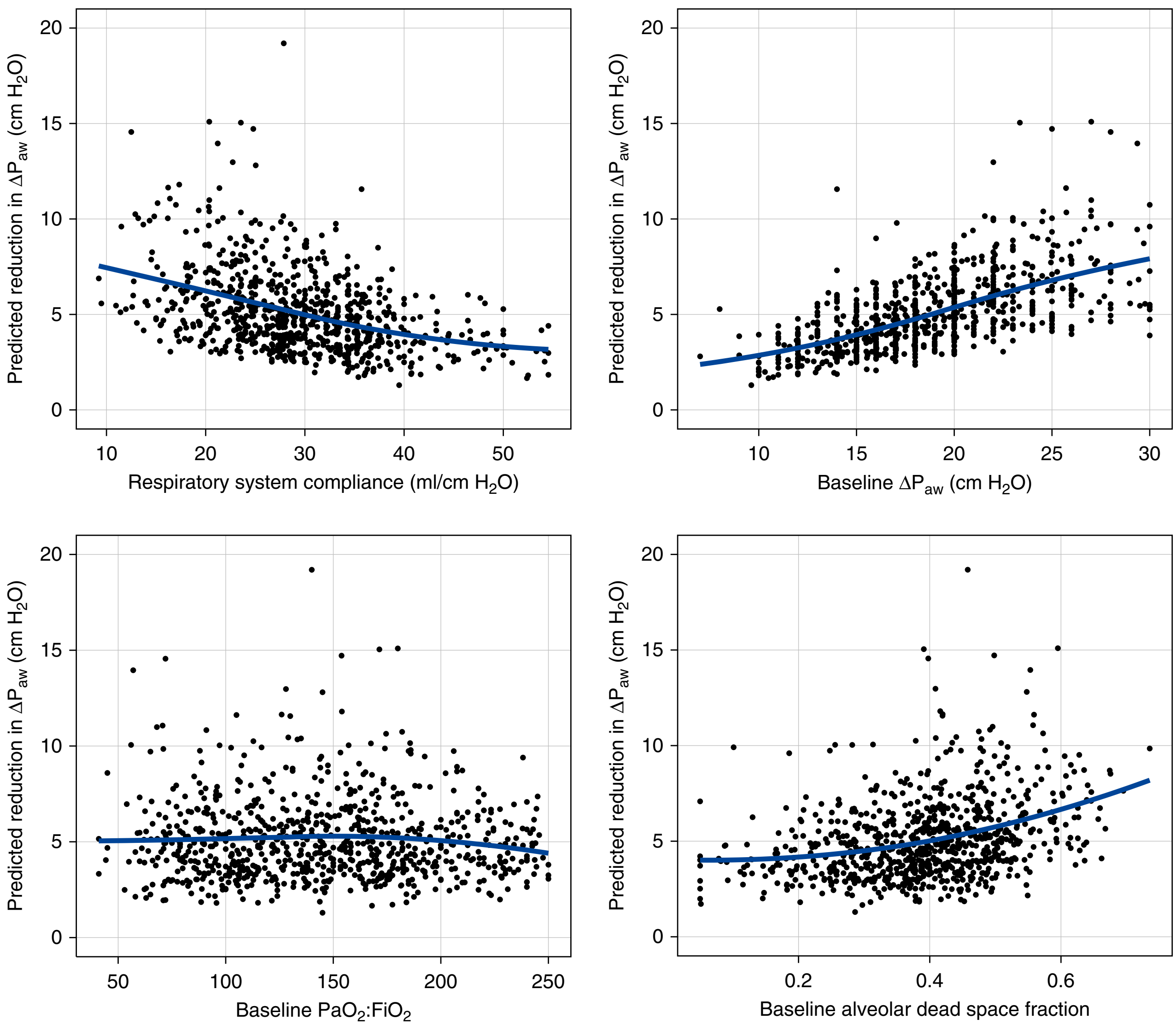

Figure 2. Exploratory analysis of the predicted effect of extracorporeal CO_2 removal (80 ml/min) on driving pressure (ΔPaw) according to the baseline physiological characteristics of patients with acute respiratory distress syndrome enrolled in LOVS (Lung Open Ventilation Study) (6). The *blue line* indicates the LOESS smoothed fit. The predicted reduction in ΔPaw varies widely among patients in relation to respiratory system compliance (R^2 = 0.08, P < 0.001), baseline ΔPaw (R^2 = 0.21, P < 0.001), and the baseline alveolar dead space fraction (R^2 = 0.27, P < 0.001), but not with the baseline severity of hypoxemia (R^2 = 0.001, P = 0.09). LOESS = local regression.

exist as yet for $Power_{rs}$. VD/VT was not measured in the LOVS trial, so we used previously validated formulas to estimate VD,anat (31) and VD,alv/VT (32) for each patient (*see* the online supplement for computational details).

We estimated the effect of reducing ΔPaw on mortality, using the reported hazard ratio for mortality associated with ΔPaw (19). To account for potential treatment-related deaths (estimated to be in the range of 1%) (24), we subtracted 1% from the predicted absolute effect on mortality. We estimated treatment effect size, required sample size, number of patients to be screened, and the predicted complication rate for varying threshold values of predicted changes in ΔPaw. Computational methods are detailed in the online supplement.

The predicted reduction in ΔPaw obtained by $ECCO_2R$ (assuming 80 ml/min of CO_2 removal) varied widely in the LOVS cohort (median, 4.7 cm H_2O; interquartile range, 3.6–6.1 cm H_2O) (Figure 2). In a sensitivity analysis employing the distribution of VD/VT reported by Nuckton and colleagues (33), the predicted reduction was somewhat lower (median, 3.2 cm H_2O; interquartile range, 2.4–4.0 cm H_2O).

Predicted changes in ΔPaw were related to baseline ΔPaw but were unrelated to baseline severity of hypoxemia (Figure 2). On the other hand, the hypothesized predicted absolute risk reduction in mortality varied considerably in relation to factors that reflect either the baseline risk of death or the anticipated physiological response (Figure 3). $ECCO_2R$ device performance ($\dot{V}CO_{2,ECML}$) modifies the predicted treatment effect, but our analysis suggests that clinically important reductions in mortality risk might be obtained even at low $\dot{V}CO_{2,ECML}$ when response characteristics are favorable (Figure 3).

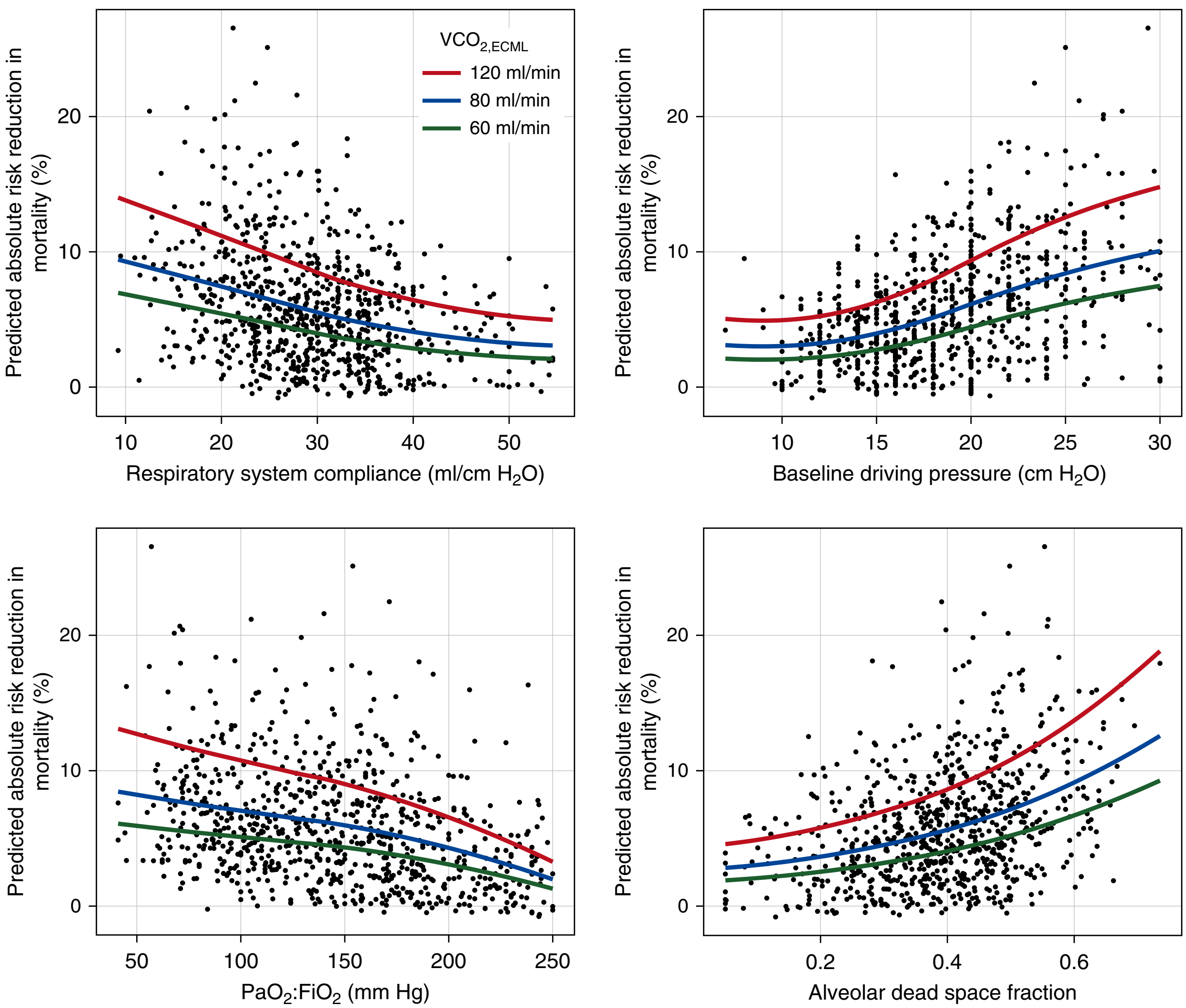

Figure 3. Influence of baseline characteristics on the effect of extracorporeal CO_2 removal ($ECCO_2R$) on the risk of death. The baseline risk of death and effect of $ECCO_2R$ on driving pressure were estimated for patients with acute respiratory distress syndrome enrolled in LOVS (Lung Open Ventilation Study) (6), assuming a CO_2 clearance rate ($\dot{V}_{CO_2,ECML}$) of 80 ml/min. From these data we estimated the absolute risk reduction in mortality (treatment effect) of $ECCO_2R$ for each patient. Each *point* represents an individual patient's estimated treatment effect size; exploratory effects are fitted by LOESS smoothing (*blue line*). The hypothesized predicted effect on mortality was correlated with respiratory system compliance ($R^2 = 0.09$, $P < 0.001$), baseline airway driving pressure ($R^2 = 0.21$, $P < 0.001$), baseline Pa_{O_2}/Fi_{O_2} ratio ($R^2 = 0.11$, $P < 0.001$), and baseline alveolar dead space fraction ($R^2 = 0.13$, $P < 0.001$). The *red fitted line* indicates how the relation would be shifted by a 50% increase in $\dot{V}_{CO_2,ECML}$ to 120 ml/min. The *green fitted line* indicates how the relation would be shifted by a 25% decrease in $\dot{V}_{CO_2,ECML}$ to 60 ml/min. LOESS = local regression.

Different thresholds and parameters for selecting patients for inclusion in clinical trials yield very different results in terms of treatment effect and sample size requirement (Table 1). Our computations suggest that selecting patients on the basis of the predicted physiological response to $ECCO_2R$ can significantly reduce sample size requirements, although more patients may need to be screened to find the requisite number of patients with the predicted response required for inclusion. This substantially lowers the number of patients exposed to $ECCO_2R$, lowering the costs of conducting the trial and reducing the number of serious complications (Table 1).

Importantly, using the predicted response criterion as an inclusion criterion (predictive enrichment strategy) is substantially more effective at reducing sample size than selecting patients on the basis of severity of hypoxemia (prognostic enrichment strategy). For example, our computations suggest that restricting enrollment to patients with severe ARDS lowers sample size requirement by approximately 40% at the cost of increasing screening requirements by nearly 300%, whereas restricting enrollment to patients with a predicted driving pressure reduction of at least 5 cm H_2O lowers sample size requirements by more than 50% without any increase in screening requirements (Table 1). It should be noted that this proposed enrollment criterion combines the advantages of both predictive and prognostic enrichment, because $C_{stat,rs}$ and $V_{D,alv}/V_T$ also predict higher baseline risk of death.

Similar effects were observed in sensitivity analyses. We recomputed sample size requirements on the basis of the mortality effect size associated with the driving pressure reduction in the original ARDSNet low tidal volume ventilation

Table 1. Clinical Trial Design Considerations Based on Patient Selection and Predicted Response to Extracorporeal CO_2 Removal

Threshold for Inclusion	Patient Group (% of Sample)	Baseline P/F (*Mean* ± *SD*) (*mm Hg*)	Baseline Mortality Rate (%)	Median Predicted Decrease in ΔPaw* (*cm H_2O*)	Predicted Absolute Risk Reduction† (%)	Predicted Number Needed to Treat	Sample Size Requirement (80% Power)	Number of Patients to Screen	Predicted Serious Complications from $ECCO_2R$ (*n*)‡
All patients with ARDS	100%	145 ± 49	38	4.7	6.1	17	1,888	1,888	119
Baseline P/F ⩽ 150 mm Hg	⩽150 mm Hg (56%)	109 ± 26	46	4.8	7.3	14	1,432	2,558	91
	>150 mm Hg (44%)	191 ± 27	29	4.7	4.8	21	—	—	—
Baseline P/F ⩽ 100 mm Hg	⩽100 mm Hg (21%)	81 ± 14	56	4.9	8.4	12	1,100	5,239	70
	>100 mm Hg (79%)	162 ± 39	34	4.7	5.6	18	—	—	—
Baseline ΔPaw ⩾ 15 cm H_2O	⩾15 cm H_2O (78%)	143 ± 48	39	5.1	6.9	15	1,530	1,962	97
	<15 cm H_2O (22%)	153 ± 48	36	3.2	3.8	27	—	—	—
Predicted decrease in ΔPaw ⩾ 4 cm H_2O	Responders (66%)	144 ± 49	41	5.6	7.9	13	1,180	1,788	75
	Nonresponders (34%)	146 ± 50	32	3.3	3.5	29	—	—	—
Predicted decrease in ΔPaw ⩾ 5 cm H_2O	Responders (44%)	142 ± 47	44	6.4	9.5	11	822	1,869	52
	Nonresponders (56%)	147 ± 50	34	3.7	4.3	24	—	—	—
Predicted decrease in ΔPaw ⩾ 6 cm H_2O	Responders (27%)	143 ± 46	45	7.3	11.2	9	598	2,215	38
	Nonresponders (73%)	145 ± 50	36	4.1	5.3	19	—	—	—

Definition of abbreviations: ARDS = acute respiratory distress syndrome; $ECCO_2R$ = extracorporeal CO_2 removal; P/F = Pa_{O_2}/fraction of inspired oxygen; ΔPaw = change in airway driving pressure.

*Computed assuming a CO_2 clearance rate of 80 ml/min through the extracorporeal membrane lung.

†Computed assuming a hazard ratio for mortality of 0.68 per 7–cm H_2O reduction in ΔPaw and a 1% risk of $ECCO_2R$-related death (*see* text and the online supplement for details).

‡Based on an assumed 12.6% rate of serious complications in patients randomized to undergo $ECCO_2R$.

trial. Sample size requirements increased significantly, but the predictive enrichment strategy remained more effective at enhancing statistical power (*see* Table E1 in the online supplement). Similarly, employing the distribution of V_D/V_T reported by Nuckton and colleagues (33) attenuated the predicted ΔPaw reduction and increased sample size requirements, but the advantages of the predictive enrichment strategy—reduced sample size requirement (and hence some trial costs) and total adverse events—persisted (Table E2).

The estimated effect of $ECCO_2R$ on mortality in individual patients is visualized by plotting the relationship between V_D/V_T,alv and Cstat,rs along isopleths of predicted absolute risk reduction in mortality (Figure 1C). An interactive tool to predict the estimated effect of $ECCO_2R$ on ΔPaw and mortality, based on the foregoing considerations, is available in the online supplement (not intended for clinical decision-making).

Validating the Theoretical Model

How can this framework be validated? Demonstrating a significant mortality reduction in a randomized trial of patients with a high predicted physiological response (design D, Figure 4) would not be sufficient to validate our paradigm because it would leave open the question of whether the patients excluded from the study (i.e., nonresponders) might have benefited from $ECCO_2R$.

There are essentially two major steps required to validate our paradigm. The first step is the prediction of ΔPaw based on Cstat,rs, V_D,alv/V_T, and CO_2 eliminated by the $ECCO_2R$ circuit ($\dot{V}CO_{2,ECML}$). Testing this is theoretically quite straightforward: patients are placed on $ECCO_2R$, and the

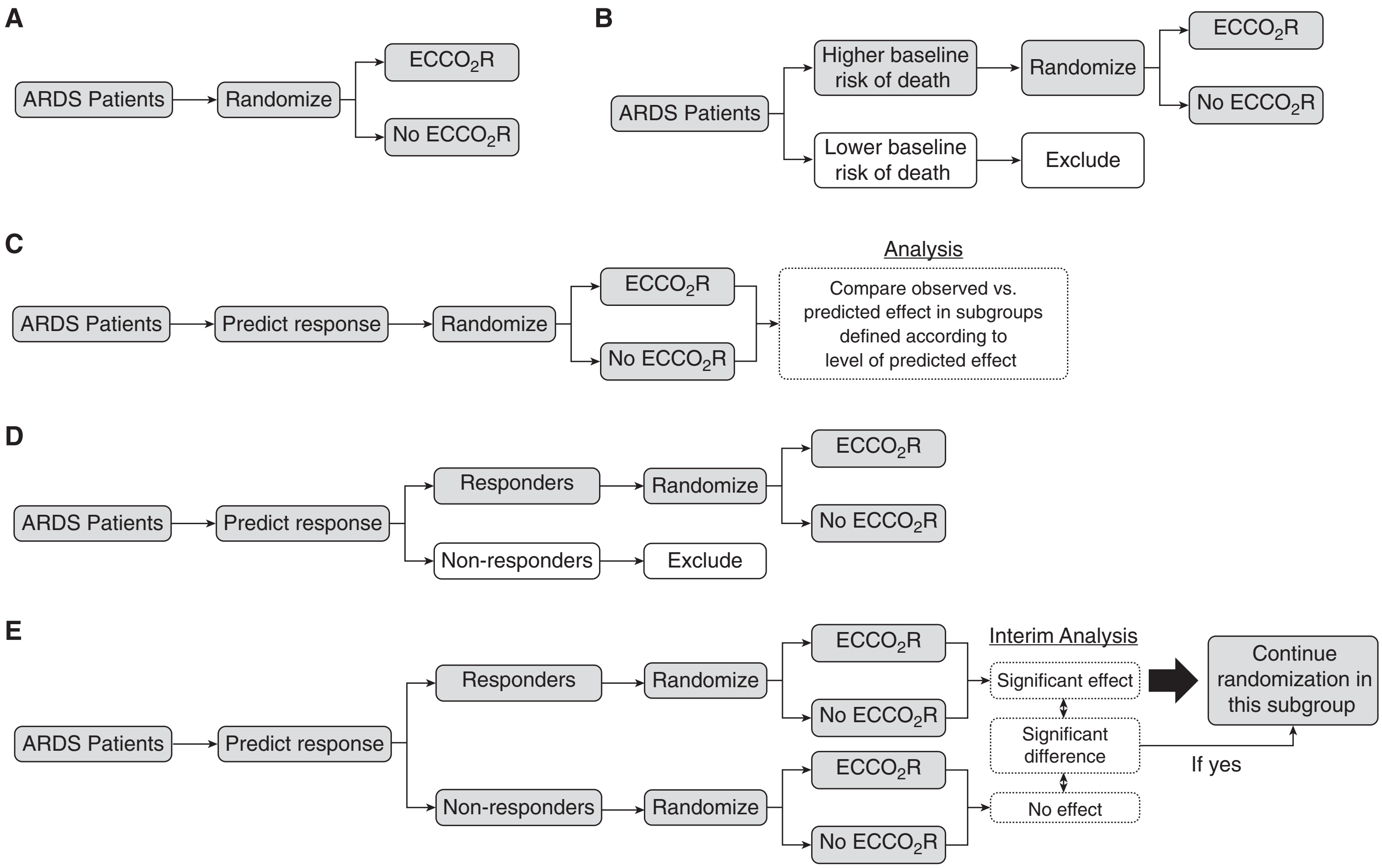

Figure 4. Possible approaches to trial design incorporating the predictive enrichment paradigm. Here we are employing the predicted physiological response as the biomarker for predictive enrichment. In the traditional approaches to trial design, trials randomize all patients (design A) or patients at higher baseline risk of the event of interest (design B) to intervention or placebo. Alternatively, treatment response could be predicted at baseline based on physiological characteristics or other biomarkers. To validate the predictive enrichment paradigm, the observed and predicted differences in mortality between patients randomized to extracorporeal CO_2 removal ($ECCO_2R$) versus control (absolute risk reduction) could be compared within subgroups of patients according to the level of predicted response (design C; *see* also Figure E4). The paradigm is valid if the absolute risk reduction between $ECCO_2R$ and control is higher in patients with a larger predicted treatment response. This would require sufficient statistical power to detect differences in treatment effect between patient subgroups, potentially increasing sample size requirements above that of even design A. Alternatively, the predicted treatment response could be used as a basis for selecting patients for enrollment (design D). Design D would have the highest statistical power and require the lowest sample size, but it would not permit prospective confirmation that the treatment is more efficacious in predicted responders than predicted nonresponders. Design D is appropriate only if biomarker credentials are very strong (*see* text for rationale). An adaptive design (design E) might permit prospective confirmation of this hypothesis at an interim analysis, after which enrollment could be limited to predicted responders (if the hypothesis is supported). ARDS = acute respiratory distress syndrome.

actual change in ΔPaw obtained by $\dot{V}CO_2$,ECML is compared with the expected change in ΔPaw according to Equation 11. Indeed, the data to address this question could be obtained from various studies, using various levels of $\dot{V}CO_2$,ECML, as long as the key variables were collected among studies in an identical manner.

The second validation step is to confirm that the observed change in ΔPaw, using $ECCO_2R$, results in the expected decrease in mortality. This is much more difficult and can be accomplished only by a large clinical trial. One approach would be to perform a randomized controlled trial in which patients provided baseline physiological measurements and then were randomized to $ECCO_2R$ or control (e.g., design C in Figure 4). On the basis of the baseline measurements, the expected decrease in mortality from being placed on $ECCO_2R$ could be calculated. At the end of the study, control and $ECCO_2R$ patients with similar predicted responses would be matched to ascertain whether treatment effect varied according to predicted treatment response. In the online supplement, we provide an example of the potential results obtained by this approach (Figure E4).

Practical Aspects of Trial Design

The physiological responsiveness paradigm can be applied to trial design in a variety of ways. One could stratify randomization according to baseline predicted responsiveness, or restrict enrollment to patients with a desired predicted response, or employ an intermediate adaptive design (Figure 4). Selecting among these options depends on one's confidence in the physiological response to predict treatment effect ("biomarker credentials"; see FREQUENTLY ASKED QUESTIONS in the online supplement). For example, if *a priori* confidence in the predicted ΔPaw response as a biomarker predicting treatment effect is very high, based on existing data (i.e., one deems the second stage of the validation procedure described above as unnecessary), then one might adopt a more restrictive design (i.e., design D in Figure 4). We draw attention to a number of important considerations in the FREQUENTLY ASKED QUESTIONS section of the online supplement.

Assumptions and Limitations

The foregoing analysis relies on first principles and well-established physiological relationships between CO_2 production, CO_2 elimination, and arterial CO_2 gas tensions to yield insights on the relationship between CO_2 elimination by $ECCO_2R$ and predicted decreases in ΔPaw. However, we do not present empirical data to confirm the validity of these predicted effects of $ECCO_2R$, and our analysis relies on a number of critical assumptions.

First, we assume that VD,alv/VT varies minimally with changes in VT. Given that VD,alv/VT is largely a function of derangements in pulmonary perfusion and that reductions in VT in the clinically relevant range under consideration are unlikely to cause significant changes in the distribution of pulmonary perfusion, this assumption seems reasonable (27). Large decreases in VT may reduce mean airway pressure somewhat, leading to small improvements in pulmonary perfusion, thereby reducing VD,alv/VT and increasing pulmonary CO_2 elimination, which would permit even greater reductions in driving pressure (34–36). In this case, our analysis would in fact underestimate the effect of $ECCO_2R$ on ΔPaw or $Power_{rs}$. Available studies suggest that changes in VD,alv/VT with varying VT are generally minimal (37, 38). In practice, higher PEEP levels will likely be required to maintain oxygenation with the lower VT, which would abrogate this effect (39).

Second, we assume that VD,anat and VD,alv can be measured reliably in mechanically ventilated patients. The advent of volumetric capnography has greatly facilitated the bedside measurement of these parameters, but technical and clinical expertise is required to ensure that valid measurements are obtained (40, 41).

Third, our sample size calculations are based on a $\dot{V}CO_2$,ECML of 80 ml/min in all subjects. The literature suggests the actual $\dot{V}CO_2$,ECML achieved varies among patients dependent on baseline venous PCO_2 (42), blood flow through the gas exchanger, differing $ECCO_2R$ systems, and over time as membrane performance may deteriorate as fibrin clot builds up on the membrane. Predicting the physiological response accurately requires an ability to reliably predict device performance. A sensitivity analysis suggested that $ECCO_2R$ might nevertheless provide significant benefit even at lower $\dot{V}CO_2$,ECML in patients with the most favorable values for predictors of response.

Fourth, our sample size calculations rest on the assumption that the association between ΔPaw and mortality obtained from mediation analysis conducted as part of an individual patient meta-analysis is entirely causal; that assumption remains unproven, despite a strong biological rationale in its support. To address this concern, we performed a sensitivity analysis using "real world" data from the original ARDSNet low tidal volume ventilation trial (Table E1). We also assume that the effect of reducing ΔPaw on mortality is independent of the baseline value of ΔPaw. This assumption is tentatively supported (but not definitively confirmed) by the fact that the logarithm of the hazard for mortality is linearly related to driving pressure in the previously referenced study of driving pressure (Figure E5) (19). Finally, both $ECCO_2R$ and reduced VT may cause hypoxemia requiring increases in PEEP, with variable effects on lung stress. We sought to be conservative in our estimates by reducing the predicted absolute risk reduction by 1% to account for potential treatment-related deaths.

Fifth, our analysis may not apply in spontaneously breathing mechanically ventilated patients, in whom respiratory control may be determined by factors other than gas exchange (43).

Conclusions

$ECCO_2R$ holds great promise to minimize ventilator-induced lung injury in patients with ARDS. Because basic physiological parameters of pulmonary function and mechanics significantly affect the physiological response to $ECCO_2R$, its efficacy is likely to vary widely among patients. We suggest that measuring VD,alv/VT and Cstat,rs can guide patient selection for clinical trials of $ECCO_2R$ more efficiently than other indices of severity (e.g., oxygenation). If future studies suggest that $Power_{rs}$ is the prime determinant of ventilator-induced lung injury, then measurement of $V_{D,anat}$ and $V_{D,alv}$ takes on even greater importance to predict both the effect of $ECCO_2R$ on $Power_{rs}$ and to identify the optimal values of f_R and V_T to minimize $Power_{rs}$. Applying the physiological response prediction framework to trial design may significantly enhance the feasibility and impact of clinical trials. Physiological assessment enabling predictive enrichment may greatly facilitate the implementation of the precision medicine paradigm in ARDS management. ■

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

Acknowledgment: The LOVS (Lung Open Ventilation Study) trial was conducted with funding support from the Canadian Institutes of Health Research. The authors thank Dr. Maureen Meade and Dr. Tom Stewart for granting permission to use these data. The authors also thank Dr. George Tomlinson for helpful comments on statistical issues. Dr. Eduardo L. V. Costa provided some of the statistical analyses presented in this article; the authors are deeply grateful for his important contribution.

References

1. Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948;2:769–782.
2. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
3. Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006;354:2213–2224.
4. Girard TD, Kress JP, Fuchs BD, Thomason JWW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, *et al*. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–134.
5. Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S; SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007;357:874–884.
6. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, *et al*.; Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:637–645.
7. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, *et al*.; TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369:2197–2206.
8. Harhay MO, Wagner J, Ratcliffe SJ, Bronheim RS, Gopal A, Green S, Cooney E, Mikkelsen ME, Kerlin MP, Small DS, *et al*. Outcomes and statistical power in adult critical care randomized trials. *Am J Respir Crit Care Med* 2014;189:1469–1478.
9. Sackett DL. Why randomized controlled trials fail but needn't. 1. Failure to gain "coal-face" commitment and to use the uncertainty principle. *CMAJ* 2000;162:1311–1314.
10. Iwashyna TJ, Burke JF, Sussman JB, Prescott HC, Hayward RA, Angus DC. Implications of heterogeneity of treatment effect for reporting and analysis of randomized trials in critical care. *Am J Respir Crit Care Med* 2015;192: 1045–1051.
11. Jameson JL, Longo DL. Precision medicine: personalized, problematic, and promising. *N Engl J Med* 2015;372:2229–2234.
12. Bhatt DL, Mehta C. Adaptive designs for clinical trials. *N Engl J Med* 2016;375:65–74.
13. U.S. Department of Health and Human Services, Food and Drug Administration. Enrichment strategies for clinical trials to support approval of human drugs and biological products. 2012 Dec [accessed 2017 Jul 10]. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf
14. Papazian L, Forel J-M, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal J-M, Perez D, Seghboyan J-M, *et al*.; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363:1107–1116.
15. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, *et al*.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–2168.
16. Goligher EC, Kavanagh BP, Rubenfeld GD, Ferguson ND. Physiologic responsiveness should guide entry into randomized controlled trials. *Am J Respir Crit Care Med* 2015;192:1416–1419.
17. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013;369:2126–2136.
18. Hager DN, Krishnan JA, Hayden DL, Brower RG; ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005;172:1241–1245.
19. Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, *et al*. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747–755.
20. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, Muellenbach R, Dembinski R, Graf BM, Wewalka M, *et al*. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO_2 removal versus "conventional" protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med* 2013;39:847–856.
21. Gattinoni L, Carlesso E, Langer T. Towards ultraprotective mechanical ventilation. *Curr Opin Anaesthesiol* 2012;25:141–147.
22. Del Sorbo L, Pisani L, Filippini C, Fanelli V, Fasano L, Terragni P, Dell'Amore A, Urbino R, Mascia L, Evangelista A, *et al*. Extracorporeal CO2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med* 2015;43:120–127.
23. Del Sorbo L, Cypel M, Fan E. Extracorporeal life support for adults with severe acute respiratory failure. *Lancet Respir Med* 2014;2: 154–164.
24. Sklar MC, Beloncle F, Katsios CM, Brochard L, Friedrich JO. Extracorporeal carbon dioxide removal in patients with chronic obstructive pulmonary disease: a systematic review. *Intensive Care Med* 2015;41:1752–1762.
25. Braune S, Burchardi H, Engel M, Nierhaus A, Ebelt H, Metschke M, \Rosseau S, Kluge S. The use of extracorporeal carbon dioxide removal to avoid intubation in patients failing non-invasive ventilation: a cost analysis. *BMC Anesthesiol* 2015;15:160.
26. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, Protti A, Gotti M, Chiurazzi C, Carlesso E, *et al*. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016;42:1567–1575.
27. Lucangelo U, Blanch L. Dead space. *Intensive Care Med* 2004;30: 576–579.
28. Mauri T, Grasselli G, Suriano G, Eronia N, Spadaro S, Turrini C, Patroniti N, Bellani G, Pesenti A. Control of respiratory drive and effort in extracorporeal membrane oxygenation patients recovering from severe acute respiratory distress syndrome. *Anesthesiology* 2016;125:159–167.
29. Schmidt GA, editor. Extracorporeal life support for adults. New York: Springer New York; 2016.

30. Henderson WR, Chen L, Amato MBP, Brochard LJ. Fifty years of research in ARDS: respiratory mechanics in acute respiratory distress syndrome. *Am J Respir Crit Care Med* [online ahead of print] 17 Mar 2017; DOI: 10.1164/rccm.201612-2495CI.
31. Brewer LM, Orr JA, Pace NL. Anatomic dead space cannot be predicted by body weight. *Respir Care* 2008;53: 885–891.
32. Siddiki H, Kojicic M, Li G, Yilmaz M, Thompson TB, Hubmayr RD, Gajic O. Bedside quantification of dead-space fraction using routine clinical data in patients with acute lung injury: secondary analysis of two prospective trials. *Crit Care* 2010;14:R141.
33. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet J-F, Eisner MD, Matthay MA. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002; 346:1281–1286.
34. Bikker IG, Blankman P, Specht P, Bakker J, Gommers D. Global and regional parameters to visualize the “best” PEEP during a PEEP trial in a porcine model with and without acute lung injury. *Minerva Anestesiol* 2013;79:983–992.
35. Fengmei G, Jin C, Songqiao L, Congshan Y, Yi Y. Dead space fraction changes during PEEP titration following lung recruitment in patients with ARDS. *Respir Care* 2012;57:1578–1585.
36. Ferrando C, Suárez-Sipmann F, Gutierrez A, Tusman G, Carbonell J, García M, Piqueras L, Compañ D, Flores S, Soro M, *et al*. Adjusting tidal volume to stress index in an open lung condition optimizes ventilation and prevents overdistension in an experimental model of lung injury and reduced chest wall compliance. *Crit Care* 2015;19:9.
37. Kiiski R, Takala J, Kari A, Milic-Emili J. Effect of tidal volume on gas exchange and oxygen transport in the adult respiratory distress syndrome. *Am Rev Respir Dis* 1992;146:1131–1135.
38. Kiiski R, Kaitainen S, Karppi R, Takala J. Physiological effects of reduced tidal volume at constant minute ventilation and inspiratory flow rate in acute respiratory distress syndrome. *Intensive Care Med* 1996;22:192–198.
39. Gattinoni L. Ultra-protective ventilation and hypoxemia. *Crit Care* 2016; 20:130.
40. Tusman G, Sipmann FS, Böhm SH. Rationale of dead space measurement by volumetric capnography. *Anesth Analg* 2012; 114:866–874.
41. Doorduin J, Nollet JL, Vugts MPAJ, Roesthuis LH, Akankan F, van der Hoeven JG, van Hees HW, Heunks LM. Assessment of dead-space ventilation in patients with acute respiratory distress syndrome: a prospective observational study. *Crit Care* 2016;20:121.
42. Fanelli V, Ranieri MV, Mancebo J, Moerer O, Quintel M, Morley S, Moran I, Parrilla F, Costamagna A, Gaudiosi M, *et al*. Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. *Crit Care* 2016;20:36.
43. Jacono FJ. Control of ventilation in COPD and lung injury. *Respir Physiol Neurobiol* 2013;189:371–376.