

## Applying Precision Medicine to Trial Design Using Physiology Extracorporeal CO<sub>2</sub> Removal for Acute Respiratory Distress Syndrome

Ewan C. Goligher<sup>1,2</sup>, Marcelo B. P. Amato<sup>3</sup>, and Arthur S. Slutsky<sup>1,4</sup>

<sup>1</sup>Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada; <sup>2</sup>Division of Respiriology, Department of Medicine, University Health Network and Mount Sinai Hospital, Toronto, Ontario, Canada; <sup>3</sup>Laboratório de Pneumologia LIM-09, Disciplina de Pneumologia, Heart Institute (Incor), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; and <sup>4</sup>Keenan Centre for Biomedical Research, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

ORCID IDs: 0000-0002-0990-6701 (E.C.G.); 0000-0002-6063-3876 (A.S.S.).

### 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<sub>2</sub> removal (ECCO<sub>2</sub>R) for ultraprotective ventilation in ARDS. ECCO<sub>2</sub>R 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<sub>2</sub>R on driving pressure and mechanical power. This

framework might enable prediction of individual treatment responses to ECCO<sub>2</sub>R. 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<sub>2</sub>R on driving pressure and mortality in a preexisting cohort of patients with ARDS. Our computations suggest that restricting enrollment to patients in whom ECCO<sub>2</sub>R allows driving pressure to be decreased by 5 cm H<sub>2</sub>O 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).

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Correspondence and requests for reprints should be addressed to Ewan C. Goligher, M.D., Ph.D., Mount Sinai Hospital, 600 University Avenue, 18-206, Toronto, ON, Canada M5G 1X5. E-mail: ewan.goligher@mail.utoronto.ca

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## Definitions of Physiological Abbreviations

$\Delta P_{aw}$ : airway driving pressure  
 $C_{stat,rs}$ : 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  
 $V_{D,alv}$ : alveolar dead space volume  
 $V_{D,alv}/V_T$ : alveolar dead space fraction  
 $V_{D,anat}$ : anatomical dead space volume  
 $V_D/V_T$ : 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- $V_T$  ventilation trial found lower mortality in patients with lower plateau pressures, with no threshold effect (18). In patients subjected to low- $V_T$  ventilation, lower driving pressures ( $\Delta P_{aw}$ )—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  $V_T$  group had greater ventilator-free days (20). Consequently, ultraprotective ventilation with very low  $V_T$  has been proposed to further reduce VILI and mortality in ARDS (21).

The major limiting factor in reducing  $V_T$  is the development of respiratory acidosis. As  $V_T$  is reduced, the anatomical dead space fraction ( $V_{D,anat}/V_T$ ) 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 Venovenous 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  $V_T$  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<sub>2</sub>R

### 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<sub>2</sub>R 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  $\Delta P_{aw}$  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<sub>2</sub>R on both  $\Delta P_{aw}$  and  $Power_{rs}$ , and hence on mortality.

### Step 1: Effect of ECCO<sub>2</sub>R on Tidal Volume and Respiratory Frequency

The relationship between  $V_A$  and the rate of CO<sub>2</sub> 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:

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

Under usual steady-state conditions, the volume of CO<sub>2</sub> eliminated via the lungs ( $\dot{V}_{CO_2,pulm}$ ) is equal to the systemic CO<sub>2</sub> production ( $\dot{V}_{CO_2,syst}$ ):

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

Applying ECCO<sub>2</sub>R removes a portion of  $\dot{V}_{CO_2,syst}$ , reducing  $\dot{V}_{CO_2,pulm}$  by an amount equal to CO<sub>2</sub> 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<sub>2</sub>R 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 ( $V_{T1}$  and  $f_{R1}$ ) to their values after application of ECCO<sub>2</sub>R ( $V_{T2}$  and  $f_{R2}$ ). By Equation 2:

$$f_{R1} \left[ \left( 1 - \frac{V_{D,alv}}{V_T} \right) V_{T1} - V_{D,anat} \right] = \dot{V}_{A1} \\ f_{R2} \left[ \left( 1 - \frac{V_{D,alv}}{V_T} \right) V_{T2} - V_{D,anat} \right] = \dot{V}_{A2} \\ \Rightarrow \Delta \dot{V}_A = \Delta \dot{V}_{A2} - \Delta \dot{V}_{A1} \\ = f_{R2} \left[ \left( 1 - \frac{V_{D,alv}}{V_T} \right) V_{T2} - V_{D,anat} \right] \\ - f_{R1} \left[ \left( 1 - \frac{V_{D,alv}}{V_T} \right) V_{T1} - V_{D,anat} \right]. \quad (6)$$

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<sub>2</sub>R to maintain the same  $Pa_{CO_2}$ , one can substitute Equation 6 into Equation 5 to obtain:

$$f_{R2} \left[ \left( 1 - \frac{V_{D,alv}}{V_T} \right) V_{T2} - V_{D,anat} \right] \\ - f_{R1} \left[ \left( 1 - \frac{V_{D,alv}}{V_T} \right) V_{T1} - V_{D,anat} \right] \\ = \frac{-k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML} \quad (7) \\ \Rightarrow \left( 1 - \frac{V_{D,alv}}{V_T} \right) (V_{T2} \cdot f_{R2} - V_{T1} \cdot f_{R1}) \\ - V_{D,anat}(f_{R2} - f_{R1}) \\ = \frac{-k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML} \quad (8)$$

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<sub>2</sub>R 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<sub>2</sub>R to Maximally Reduce Driving Pressure

The reduced  $\dot{V}_E$  requirement resulting from ECCO<sub>2</sub>R 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.,  $f_{R2} = f_{R1} = f_R$ ). Then Equation 8 simplifies to:

$$\left( 1 - \frac{V_{D,alv}}{V_T} \right) (V_{T2} \cdot f_R - V_{T1} \cdot f_R) \\ = \frac{-k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML} \\ \Rightarrow \left( 1 - \frac{V_{D,alv}}{V_T} \right) \cdot f_R \cdot (V_{T2} - V_{T1}) \\ = \frac{-k}{Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML} \\ \Rightarrow V_{T2} - V_{T1} = \frac{-k}{[1 - (V_{D,alv}/V_T)] \cdot f_R \cdot Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML}. \quad (9)$$

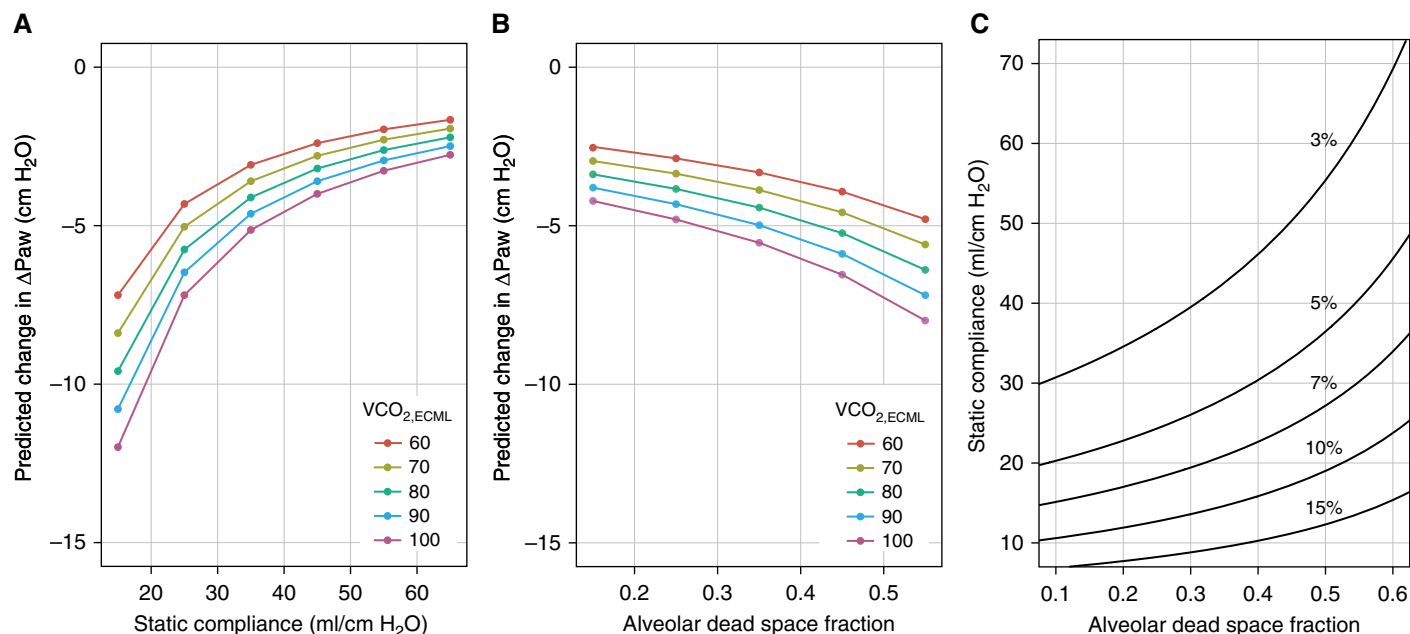
Because tidal volume is the product of  $\Delta P_{aw}$  and static respiratory compliance ( $C_{stat,rs}$ ):

$$V_T = \Delta P_{aw} \cdot C_{stat,rs} \\ \Rightarrow V_{T2} - V_{T1} \\ = (\Delta P_{aw2} - \Delta P_{aw1}) \cdot C_{stat,rs} \quad (10)$$

Substituting Equation 10 into Equation 9 and rearranging yields:

$$\Delta P_{aw2} - \Delta P_{aw1} \\ = \frac{-k}{C_{stat,rs} \cdot [1 - (V_{D,alv}/V_T)] \cdot f_R \cdot Pa_{CO_2}} \cdot \dot{V}_{CO_2,ECML} \quad (11)$$

Equation 11 gives the relationship between the patient's physiological characteristics and the predicted change in  $\Delta P_{aw}$  resulting from the application of ECCO<sub>2</sub>R. This relationship indicates that patients with lower  $C_{stat,rs}$  and higher  $V_{D,alv}/V_T$  will obtain greater reductions in  $\Delta P_{aw}$  at a given  $\dot{V}_{CO_2,ECML}$  (visualized in Figures 1A and 1B).



**Figure 1.** The predicted effect of extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) on airway driving pressure (ΔPaw) varies with patient physiological characteristics. For a given CO<sub>2</sub> 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  $C_{stat,rs} = 30$  ml/cm H<sub>2</sub>O). (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<sub>2</sub>R. Values are plotted according to isopleths of hypothesized absolute risk reduction in mortality (labeled on each curve). See text for computational details.  $C_{stat,rs}$  = static compliance of the respiratory system;  $\dot{V}_{CO_2,ECML}$  = rate of CO<sub>2</sub> 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<sub>2</sub>R. 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<sub>2</sub> 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<sub>2</sub>R implementation. The efficiency of each breath in removing CO<sub>2</sub> is increased at higher  $Pa_{CO_2}$  levels, with more CO<sub>2</sub> 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<sub>2</sub>R on ΔPaw can be enhanced by lowering baseline  $Pa_{CO_2}$ . However, because  $\dot{V}_{CO_2,ECML}$  varies directly with venous  $P_{CO_2}$  (29) and venous  $P_{CO_2}$  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<sub>2</sub>R on ΔPaw relatively independent of  $Pa_{CO_2}$ .

In summary, patients with lower  $C_{stat,rs}$  and higher  $V_{D,alv}/V_T$  will accrue greater reductions in ΔPaw from the application of ECCO<sub>2</sub>R. Both these variables are readily measurable at the bedside (30).

### Step 3: Applying ECCO<sub>2</sub>R to Maximally Reduce Mechanical Power

ECCO<sub>2</sub>R may also be applied with a goal of reducing  $Power_{rs}$ . On the basis of Equation 7,  $V_D/V_T$  and  $C_{stat,rs}$  would be expected to significantly modify both the effect of ECCO<sub>2</sub>R 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.

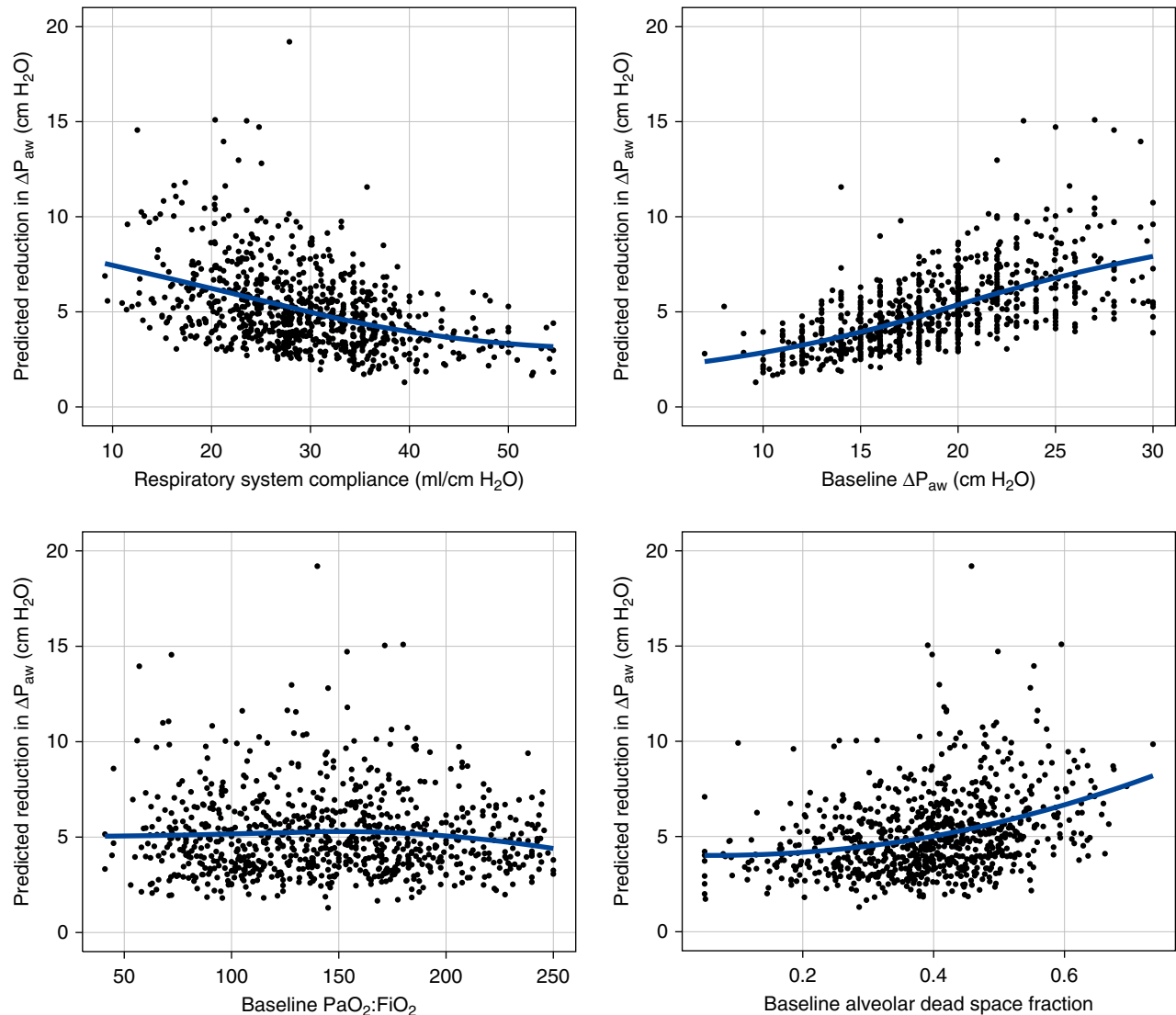
### Impact on Treatment Efficacy and Trial Design

A number of clinical trials of ECCO<sub>2</sub>R 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<sub>2</sub>R. The ability to predict the effect of applying ECCO<sub>2</sub>R on these parameters could guide the selection of patients who are most likely to benefit from ECCO<sub>2</sub>R. 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<sub>2</sub>R 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<sub>2</sub> removal (80 ml/min) on driving pressure ( $\Delta P_{aw}$ ) 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  $\Delta P_{aw}$  varies widely among patients in relation to respiratory system compliance ( $R^2 = 0.08$ ,  $P < 0.001$ ), baseline  $\Delta P_{aw}$  ( $R^2 = 0.21$ ,  $P < 0.001$ ), 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.

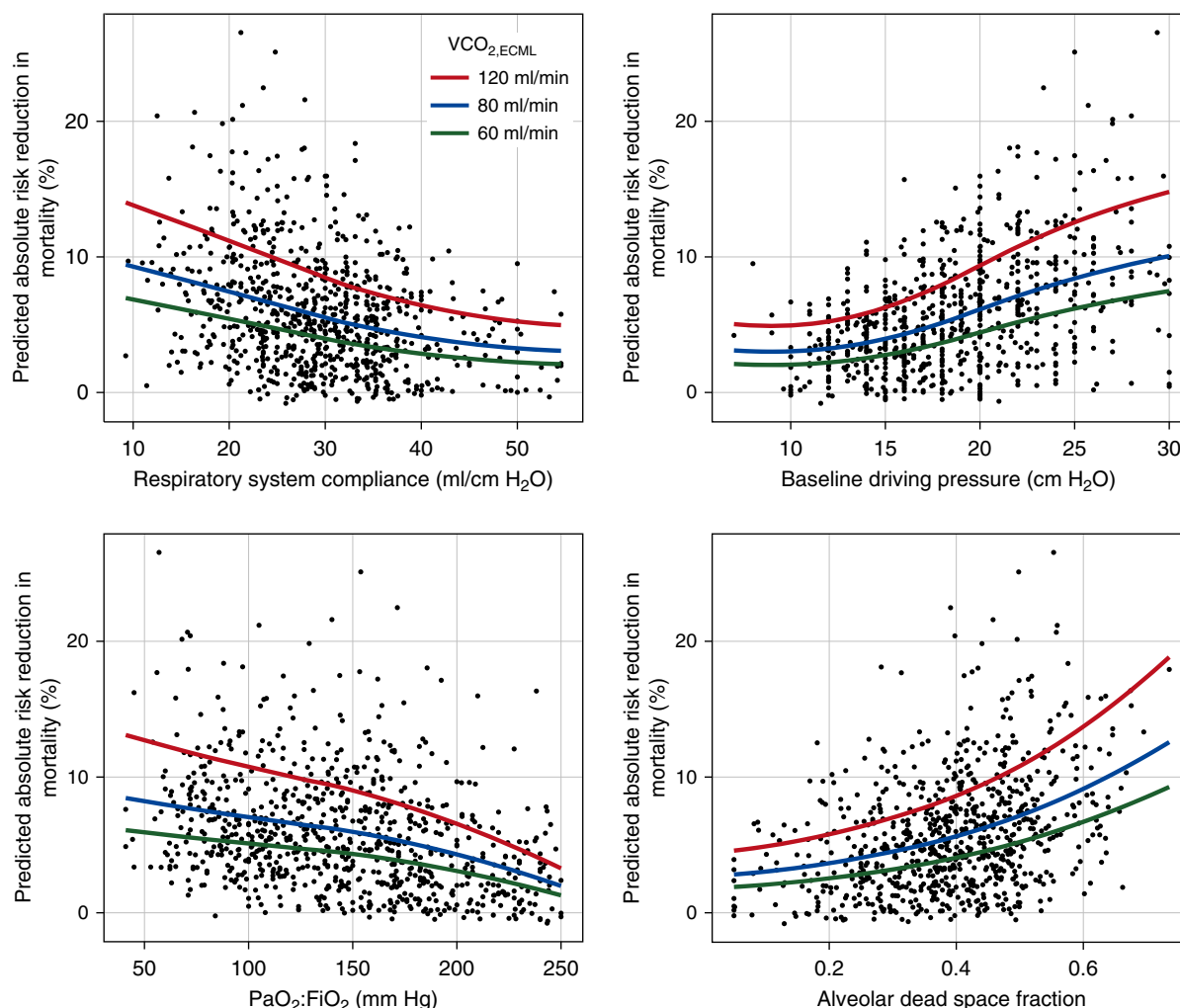
exist as yet for  $Power_{rs}$ .  $V_D/V_T$  was not measured in the LOVS trial, so we used previously validated formulas to estimate  $V_{D,anat}$  (31) and  $V_{D,alv}/V_T$  (32) for each patient (see the online supplement for computational details).

We estimated the effect of reducing  $\Delta P_{aw}$  on mortality, using the reported hazard ratio for mortality associated with  $\Delta P_{aw}$  (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  $\Delta P_{aw}$ . Computational methods are detailed in the online supplement.

The predicted reduction in  $\Delta P_{aw}$  obtained by ECCO<sub>2</sub>R (assuming 80 ml/min of CO<sub>2</sub> removal) varied widely in the LOVS cohort (median, 4.7 cm H<sub>2</sub>O; interquartile range, 3.6–6.1 cm H<sub>2</sub>O) (Figure 2). In a sensitivity analysis employing the distribution of  $V_D/V_T$  reported by Nuckton and colleagues (33), the predicted reduction was somewhat lower (median, 3.2 cm H<sub>2</sub>O; interquartile range, 2.4–4.0 cm H<sub>2</sub>O).

Predicted changes in  $\Delta P_{aw}$  were related to baseline  $\Delta P_{aw}$  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<sub>2</sub>R 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<sub>2</sub> removal (ECCO<sub>2</sub>R) on the risk of death. The baseline risk of death and effect of ECCO<sub>2</sub>R on driving pressure were estimated for patients with acute respiratory distress syndrome enrolled in LOVS (Lung Open Ventilation Study) (6), assuming a CO<sub>2</sub> 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<sub>2</sub>R 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 PaO<sub>2</sub>/FiO<sub>2</sub> 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<sub>2</sub>R 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<sub>2</sub>R, 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<sub>2</sub>O 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 Cstat<sub>rs</sub> and V<sub>D,alv</sub>/V<sub>T</sub> 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<sub>2</sub> Removal

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

*Definition of abbreviations:* ARDS = acute respiratory distress syndrome; ECCO<sub>2</sub>R = extracorporeal CO<sub>2</sub> removal; P/F = PaO<sub>2</sub>/fraction of inspired oxygen;  $\Delta$ Paw = change in airway driving pressure.

\*Computed assuming a CO<sub>2</sub> 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<sub>2</sub>O reduction in  $\Delta$ Paw and a 1% risk of ECCO<sub>2</sub>R-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<sub>2</sub>R.

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  $\Delta P_{aw}$  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<sub>2</sub>R on mortality in individual patients is visualized

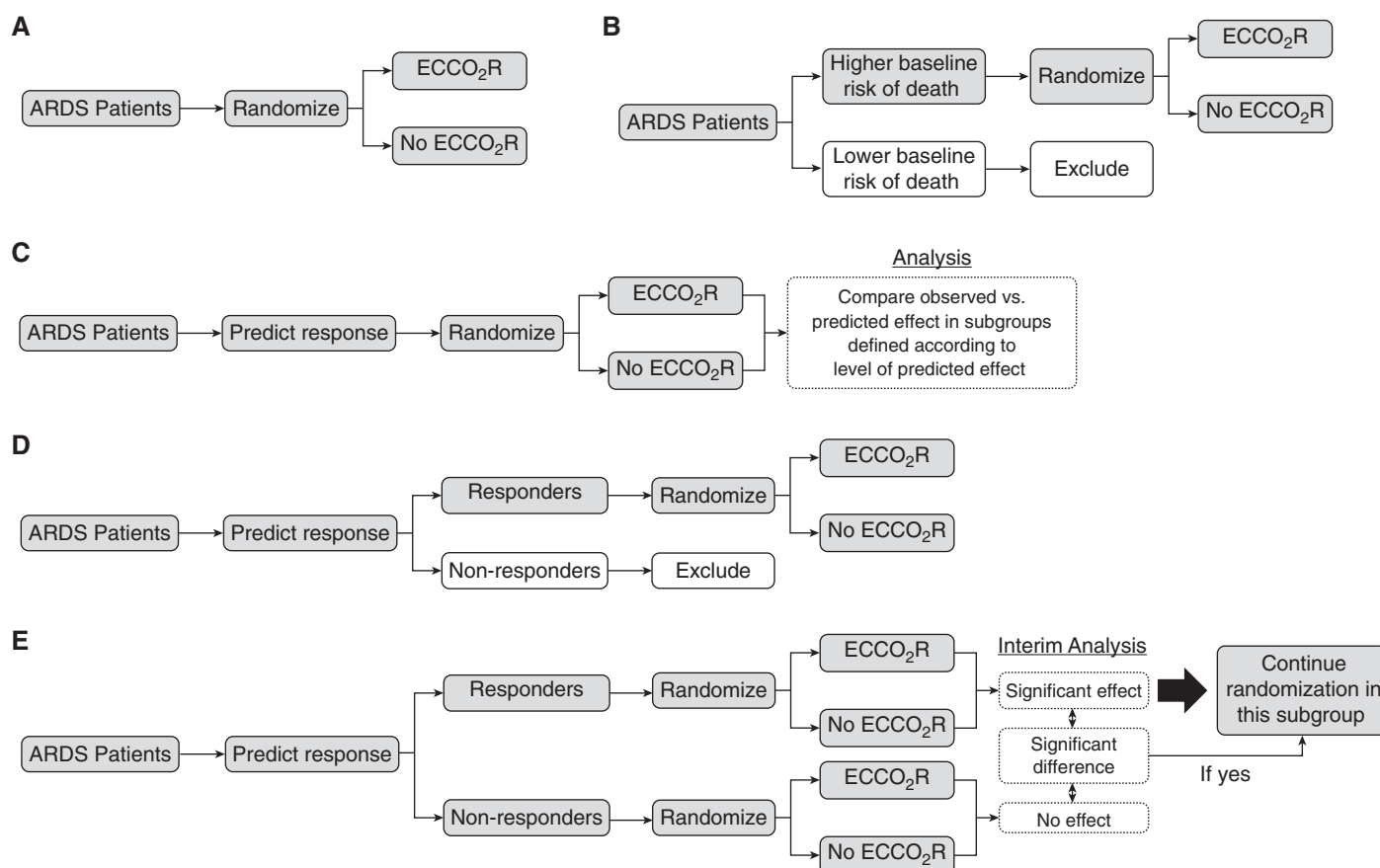
by plotting the relationship between  $V_D/V_T$ ,  $alv$  and  $C_{stat,rs}$  along isopleths of predicted absolute risk reduction in mortality (Figure 1C). An interactive tool to predict the estimated effect of ECCO<sub>2</sub>R on  $\Delta P_{aw}$  and mortality, based on the foregoing considerations, 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<sub>2</sub>R.

There are essentially two major steps required to validate our paradigm. The first step is the prediction of  $\Delta P_{aw}$  based on  $C_{stat,rs}$ ,  $V_D, alv/V_T$ , and  $CO_2$  eliminated by the ECCO<sub>2</sub>R circuit ( $\dot{V}_{CO_2,ECML}$ ). Testing this is theoretically quite straightforward: patients are placed on ECCO<sub>2</sub>R, 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<sub>2</sub>R) 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<sub>2</sub>R 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  $\Delta P_{aw}$  obtained by  $\dot{V}_{CO_2,ECML}$  is compared with the expected change in  $\Delta P_{aw}$  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  $\Delta P_{aw}$ , using ECCO<sub>2</sub>R, 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<sub>2</sub>R 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<sub>2</sub>R could be calculated. At the end of the study, control and ECCO<sub>2</sub>R 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  $\Delta P_{aw}$  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<sub>2</sub> production, CO<sub>2</sub> elimination, and arterial CO<sub>2</sub> gas tensions to yield insights on the relationship between CO<sub>2</sub> elimination by ECCO<sub>2</sub>R and predicted decreases in  $\Delta P_{aw}$ . However, we do not present empirical data to confirm the validity of these predicted effects of ECCO<sub>2</sub>R, and our analysis relies on a number of critical assumptions.

First, we assume that  $V_{D,alv}/V_T$  varies minimally with changes in  $V_T$ . Given that  $V_{D,alv}/V_T$  is largely a function of derangements in pulmonary perfusion and that reductions in  $V_T$  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  $V_T$  may reduce mean airway pressure somewhat, leading to small improvements in pulmonary perfusion, thereby reducing  $V_{D,alv}/V_T$  and increasing pulmonary CO<sub>2</sub> 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<sub>2</sub>R on  $\Delta P_{aw}$  or  $Power_{rs}$ . Available studies suggest that changes in  $V_{D,alv}/V_T$  with varying  $V_T$  are generally minimal (37, 38). In practice, higher PEEP levels will likely be required to maintain oxygenation with the lower  $V_T$ , which would abrogate this effect (39).

Second, we assume that  $V_{D,anat}$  and  $V_{D,alv}$  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  $P_{CO_2}$  (42), blood flow through the gas exchanger, differing ECCO<sub>2</sub>R 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<sub>2</sub>R 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  $\Delta P_{aw}$  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  $\Delta P_{aw}$  on mortality is independent of the baseline value of  $\Delta P_{aw}$ . 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<sub>2</sub>R and reduced  $V_T$  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<sub>2</sub>R 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<sub>2</sub>R, its efficacy is likely to vary widely among patients. We suggest that measuring  $V_{D,alv}/V_T$  and  $C_{stat,rs}$  can guide patient selection for clinical trials of ECCO<sub>2</sub>R 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<sub>2</sub>R 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. ■

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