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Extracorporeal carbon dioxide removal requirements for ultraprotective mechanical ventilation: Mathematical model predictions

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Abstract

Extracorporeal carbon dioxide (CO_2) removal ($ECCO_2R$) facilitates the use of low tidal volumes during protective or ultraprotective mechanical ventilation when managing patients with acute respiratory distress syndrome (ARDS); however, the rate of $ECCO_2R$ required to avoid hypercapnia remains unclear. We calculated $ECCO_2R$ rate requirements to maintain arterial partial pressure of CO_2 ($PaCO_2$) at clinically desirable levels in mechanically ventilated ARDS patients using a six-compartment mathematical model of CO_2 and oxygen (O_2) biochemistry and whole-body transport with the inclusion of an $ECCO_2R$ device for extracorporeal veno-venous removal of CO_2. The model assumes steady state conditions. Model compartments were lung capillary blood, arterial blood, venous blood, post-$ECCO_2R$ venous blood, interstitial fluid and tissue cells, with CO_2 and O_2 distribution within each compartment; biochemistry included equilibrium among bicarbonate and non-bicarbonate buffers and CO_2 and O_2 binding to hemoglobin to elucidate Bohr and Haldane effects. O_2 consumption and CO_2 production rates were assumed proportional to predicted body weight (PBW) and adjusted to achieve reported arterial partial pressure of O_2 and a $PaCO_2$ level of 46 mmHg at a tidal volume of 7.6 mL/kg PBW in the absence of an $ECCO_2R$ device based on average data from LUNG SAFE. Model calculations showed that $ECCO_2R$ rates required to achieve mild permissive hypercapnia ($PaCO_2$ of 46 mmHg) at a ventilation frequency or respiratory rate of 20.8/min during mechanical ventilation increased when tidal volumes decreased from 7.6 to 3 mL/kg PBW. Higher ECCO2R rates were required to achieve normocapnia (PaCO2 of 40 mmHg). Model calculations also showed that required ECCO2R rates were lower when ventilation frequencies were increased from 20.8/min to 26/min. The current mathematical model predicts that ECCO2R rates resulting in clinically desirable PaCO2 levels at tidal volumes of 5-6 mL/kg PBW can likely be achieved in mechanically ventilated ARDS patients with current technologies; use of ultraprotective tidal volumes (3-4 mL/kg PBW) may be challenging unless high mechanical ventilation frequencies are used.

1 | INTRODUCTION

When managing patients with acute respiratory distress syndrome (ARDS), it is strongly recommended to target tidal volumes of 6 mL/kg predicted body weight (PBW)[1] to limit overdistention of lung tissues and ventilator-induced lung injury (VILI).[2] Such low tidal volumes may however result in hypercapnia and respiratory acidosis, potentially limiting their routine use. Several clinical strategies for minimizing hypercapnia and VILI include higher levels of positive end-expiratory pressure, higher ventilation frequencies or respiratory rates, and the use of prone positioning or extracorporeal carbon dioxide (CO_2) removal (ECCO₂R).[3,4] The degree to which hypercapnia can be mitigated with such strategies, thereby improving patient outcomes, remains to be demonstrated in robust clinical trials.

LUNG SAFE[5] was an international observational cohort study to evaluate the incidence and outcomes of ARDS and to assess practice patterns when treating ARDS patients. The results from that study suggest that clinicians favor a balance of mild permissive hypercapnia (as defined in[6]) and moderate tidal volumes; the mean tidal volume in LUNG SAFE was 7.6 mL/kg PBW. However, several small clinical studies[7–12] have suggested that the use of tidal volumes lower than 6 mL/kg PBW, so-called ultraprotective ventilation strategies, may provide additional clinical benefits. Because the achievement of such ultralow tidal volumes will exacerbate hypercapnia, ARDS patients so treated will likely require the use of a combination of clinical strategies that include ECCO₂R.

There are several ECCO₂R devices currently available[13] with varying abilities to remove CO_2 depending on the rate of blood flow through the device and the surface area available for transmembrane diffusion. These devices have generally been categorized as lower or higher CO_2 extraction devices[14,15] with the former containing relatively small membrane surface area using blood flow rates ≤500 mL/min and the latter containing relatively large membrane surface area using blood flow rates >500 mL/min. Improvement in ECCO₂R technologies has great potential as such devices can be integrated into a continuous renal replacement extracorporeal circuit[13] and their efficacy for CO_2 removal may be increased by using physical principles other than diffusion such as electrodialysis[13] or novel membrane fabrication techniques.[16,17] However, the ECCO₂R requirements for achieving adequate blood gas chemistry or normocapnia in lung-protective strategies have not been quantitatively evaluated except in preclinical studies.[18]

In this report, we explore the effects of low tidal volumes and ECCO₂R on total body CO_2 content and blood gas chemistry using a mathematical model of CO_2 biochemistry and transport. In so doing, this study defines the ECCO₂R requirements for extracorporeal devices to achieve adequate blood gas chemistry when using protective and ultraprotective strategies during mechanical ventilation in ARDS patients.

2 | METHODS

The six-compartment model of CO_2 and oxygen (O_2) whole-body storage and transport employed in this study was that developed by others,[19] only modified structurally by the inclusion of an ECCO₂R device for extracorporeal venovenous removal of CO_2. Only steady state conditions were considered. The compartments included were: lung capillary blood, arterial blood, venous blood, post-ECCO₂R venous blood, interstitial fluid, and tissue cells; the model separately calculated the acid-base and O_2 contents of each compartment. As proposed previously,[19] it was assumed that interstitial fluid and tissue cell acid-base and O_2 contents could be calculated from those in venous blood only; thus, those compartments were not directly involved in formulating mass transport relationships. The volumes of each fluid compartment were assumed as 0.75% (arterial blood), 6.75% (venous blood), 0% (lung capillary blood and post-ECCO₂R venous blood), 12.6% (interstitial fluid), and 20% (tissue cells) of the predicted body weight. The latter volume was based on assuming muscle is the only store of CO_2 from a well-perfused tissue. Muscle tissue volume is an underestimate of total tissue volume containing CO_2 and neglects the largest store in bone; it has been previously proposed to be an approximation for estimating changes in CO_2 tissue content that occur over short periods of time.[19]

Figure 1 shows a schematic of the mathematical model for total CO_2 whole-body transport. The model for O_2 whole-body transport is identical to that proposed previously[19] as O_2 transport across the ECCO₂R device was neglected. The lung was simply characterized by three separate elements: alveoli that are involved in gas exchange describing ventilation and perfusion of the lung, alveoli dead space (ventilation but no perfusion), and a pulmonary shunt (perfusion but no ventilation). The lung was considered to be mechanically ventilated with a given frequency or respiratory rate, a tidal volume per PBW and a ratio of dead space to tidal volume fixed at 0.60; the latter is the average value reported for patients with ARDS.[20] This lung model allows the volume of gases flowing
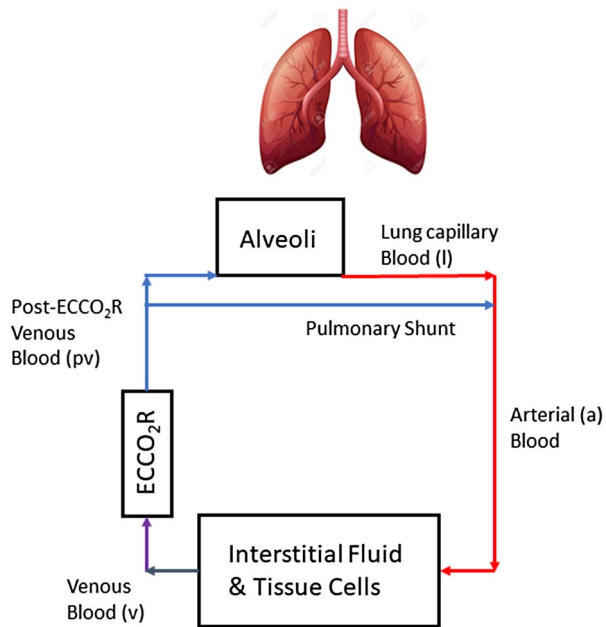
FIGURE 1 A schematic of the compartmental model for whole-body CO_2 transport used in this study. Blood from four compartments are involved in the CO_2 whole-body transport model as detailed in the Appendix. The ECCO$_2$R device was added to the model previously described by others[19] [Color figure can be viewed at wileyonlinelibrary.com]

into the alveoli per minute to be calculated from the fractional concentration of these gases in inspired and expired air. The partial pressures of CO_2 and O_2 in the alveoli and lung capillary blood were assumed in equilibrium, that is, no resistance to gas exchange across the alveoli/lung capillary membrane. Total concentrations of CO_2 and O_2 in arterial blood were the weighted average of their concentrations in lung capillary and pulmonary shunt blood flows. The ECCO$_2$R device was characterized by a CO_2 removal rate, expressed as mL of CO_2 removed per min. The equations describing CO_2 whole-body transport are outlined in the Appendix; the complete model equations describing O_2 whole-body transport and other elements of the model were previously described.[19]

Acid-base and O_2 chemistry of blood, including separate chemical reactions in plasma and erythrocytes, were formulated as described previously.[21,22] The acid-base reactions included equilibrium for bicarbonate and nonbicarbonate buffers in both plasma and erythrocytes and the binding of CO_2 to hemoglobin in the erythrocytes. The model included competitive binding of O_2, CO_2, and hydrogen ions to hemoglobin to elucidate Bohr and Haldane effects as described by others.[21] This model of acid-base and O_2 chemistry in blood is comprehensive; it requires solving, in general, 28 equations and 12 parameters for each compartment containing blood (lung capillary blood, arterial blood, venous blood, and post-ECCO$_2$R venous blood). This model has been previously shown to accurately describe changes in acid-base chemistry

after addition to or removal of CO_2 and strong acid from blood,[21] the mixing of blood samples with differing contents of CO_2 and O_2,[23] and the distribution of bicarbonate to interstitial fluids.[19] The chemical mass action equations are not described here as they can be found in detail elsewhere.[21] The gas solubility parameters and equilibrium constants for the various acid-base reactions in blood were those reported previously.[21] The governing equations describing whole-body biochemistry and transport as outlined above and in the Appendix were solved using Matlab R2018a (Mathworks, Natick, MA, USA).

The total CO_2 concentrations of arterial blood, venous blood, and post-ECCO$_2$R venous blood were calculated as the volume-weighted average of the CO_2 contents in plasma and erythrocytes based on the calculated partial pressure of CO_2 (PaCO$_2$), bicarbonate concentration, and carbaminohemoglobin concentrations, the latter in erythrocytes only. The total amount of CO_2 in each compartment was calculated by multiplying the total concentration by their volume.

In the current study, several parameters were assumed for average patients with ARDS. PBW was assumed as 85% of actual body weight, as approximated previously for critically ill patients.[24] Blood hematocrit was fixed at 30%, and arterial blood base excess was assumed to be −3 mEq/L, a value intermediate between those reported in the literature for ARDS patients.[25,26] Cardiac output was assumed to be proportional to body surface area and was calculated in units of L/min using the relationship developed from The Strong Heart Study of $0.251 \times$ (kg PBW)$^{0.67}$.[27] Certain parameters of the model were adjusted to agree with the current standard of care as defined by the average mechanical ventilation practices for treating ARDS patients from LUNG SAFE.[5] Based on that report, the current standard of care prescription for treating average ARDS patients was a ventilation frequency of 20.8/min, a tidal volume of 7.6 mL/kg PBW, and a median fraction of inspired O_2 of 0.6. Using the reported average partial pressure of O_2 to fraction of inspired O_2 ratio of 161 and average PaCO$_2$ in arterial blood of 46.0 mm Hg,[5] the pulmonary shunt fraction was estimated as 0.176, the O_2 tissue uptake rate as 4.0 mL of O_2 per kg PBW and a respiratory quotient as 0.966. Therefore, for patients with an actual body weight of 78 kg, as in LUNG SAFE,[5] this work assumed the O_2 tissue uptake rate was 265 mL of O_2/min and the CO_2 production rate was 256 mL of CO_2/min. The pulmonary shunt fraction, O_2 tissue uptake rate and respiratory quotient as reported above were fixed for all simulations in this study.

3 | RESULTS

All calculated results assumed an actual patient body weight of 78 kg.

The effect of reductions in tidal volume during mechanical ventilation in ARDS patients on acid-base chemistry was

first evaluated in the absence of the $ECCO_2R$ device; Table 1 summarizes results from these initial model simulations. As calibrated by the initial assumed parameters, the partial pressure of arterial blood ($PaCO_2$) at a tidal volume of 7.6 mL/kg PBW was identical to that reported in LUNG SAFE[5] and the arterial blood (plasma) pH (pHa) was 7.32. At a tidal volume of 7.6 mL/kg PBW, total CO_2 concentrations varied in the model compartments containing blood—the simulated total CO_2 concentrations were 21.8 mM in arterial blood, 24.5 mM in venous blood, 27.3 mM in interstitial fluids, and 10.5 mM in tissue cells. When tidal volume decreased from 7.6 to 3 mL/kg PBW, $PaCO_2$ increased and pHa decreased progressively as expected, and there was a maximal increase in total body mass of CO_2 of approximately 50% when decreasing tidal volume from 7.6 to 3 mL/kg PBW. Note that the $PaCO_2$ in venous blood ($PvCO_2$) was calculated to be approximately 10 mm Hg higher than in arterial blood when the tidal volume was 7.6 mL/kg PBW, and this difference between $PvCO_2$ and $PaCO_2$ increased at lower tidal volumes. Figure 2 shows the effect of tidal volume on the total amount of CO_2 in the various model compartments in the absence of the $ECCO_2R$ device. As expected, the total amount of CO_2 in arterial blood was negligibly small and that in interstitial fluids was approximately one-half of the total body CO_2. There was a progressive increase in total mass of CO_2 in each compartment as tidal volume was reduced.

Figure 3 compares changes in $PaCO_2$ when altering tidal volume and respiratory rate during mechanical ventilation in the absence of the $ECCO_2R$ device. Higher ventilation frequencies significantly reduced $PaCO_2$ when tidal volume was reduced. The increase in respiratory rate from 20.8/min to 26/min also resulted in higher arterial pH by 0.07 units at each tidal volume (results not shown).

The $ECCO_2R$ rate from the extracorporeal device to achieve a $PaCO_2$ of 46 mm Hg (mild permissive hypercapnia), considered as standard of care based on LUNG SAFE,[5] and 40 mm Hg (normocapnia) is shown in Figure 4 at ventilation frequencies of 20.8 and 26/min and various tidal volumes. As tidal volume was reduced, the required $ECCO_2R$ rate increased. Increasing ventilation frequency from 20.8 to 26/min substantially decreased the required $ECCO_2R$ rate. $ECCO_2R$ rates required to achieve normocapnia were correspondingly higher and were achieved at a $PvCO_2$ of 48.7 mm Hg.

TABLE 1 Effect of tidal volume on acid-base blood chemistry and total body CO_2 mass in the absence of the $ECCO_2R$ device (patient body weight of 78 kg with a mechanical ventilation frequency of 20.8/min)

Tidal Volume (mL/kg PBW)	PaCO₂ (mm Hg)	pHa	PvCO₂ (mm Hg)	pHv	Total Body CO₂ (mmol)
7.6	46.0	7.32	55.5	7.28	544
6	58.0	7.25	69.1	7.21	600
5	69.3	7.20	82.0	7.16	647
4	86.3	7.13	101.0	7.09	710
3	114.5	7.04	132.5	7.00	801

$PaCO_2$ denotes partial pressure of CO_2 in arterial blood; pHa denotes the pH of arterial plasma; $PvCO_2$ denotes partial pressure of CO_2 in venous blood; pHv denotes the pH of venous plasma.
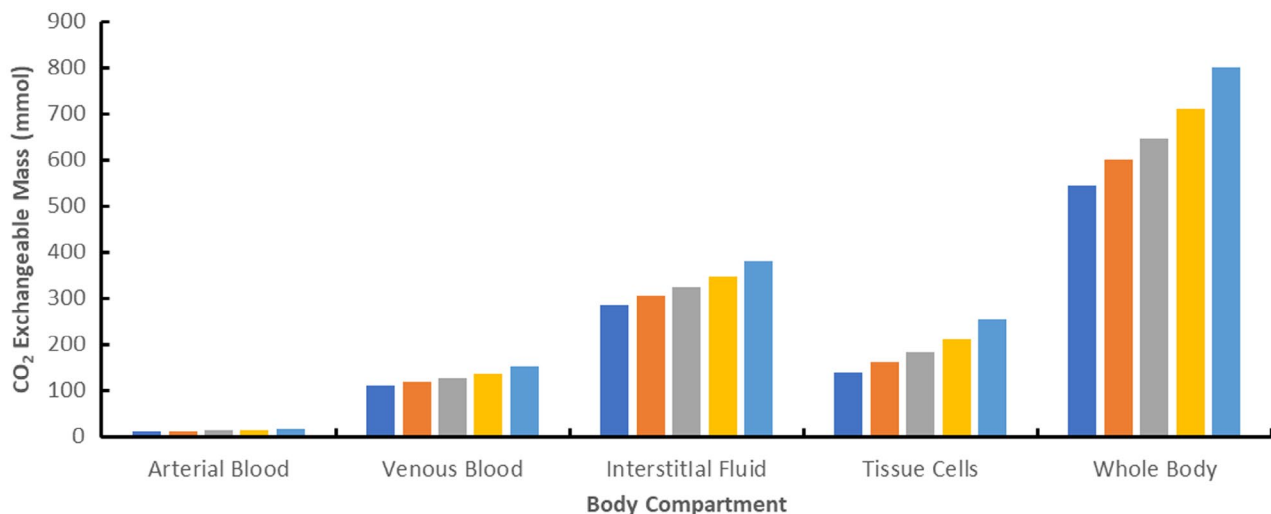

FIGURE 2 Effect of tidal volume on total body CO_2 in the model compartments in the absence of the $ECCO_2R$ device. Results are shown at tidal volumes of 7.6 (dark blue bars), 6 (orange bars), 5 (gray bars), 4 (yellow bars), and 3 (light blue bars) mL/kg PBW [Color figure can be viewed at wileyonlinelibrary.com]
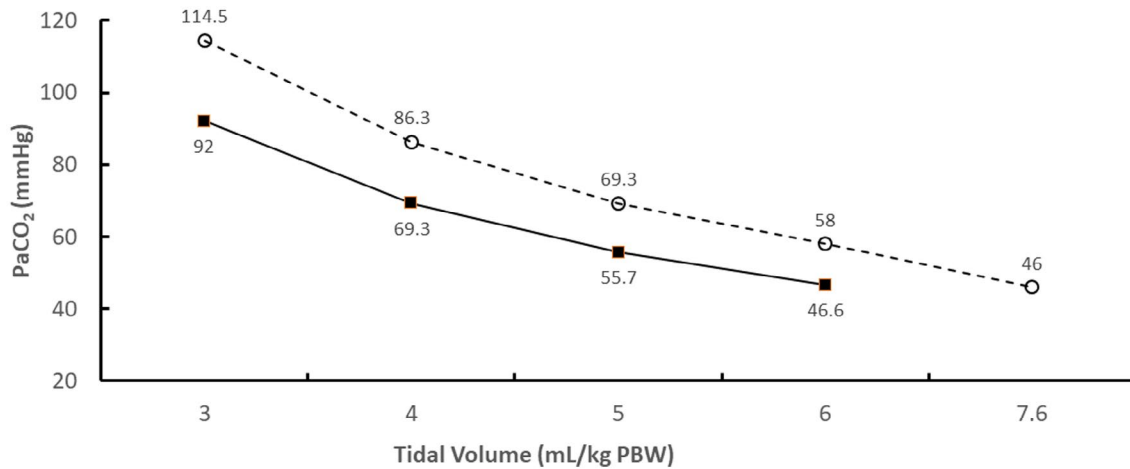
FIGURE 3 The effect of tidal volume and mechanical ventilation frequency on arterial partial pressure of CO_2 ($PaCO_2$) in the absence of the $ECCO_2R$ device. Results are shown for ventilation frequencies of 20.8/min (circles, dashed line) and 26/min (squares, solid line). Note that the results at a tidal volume of 7.6 mL/kg PBW were for a ventilation frequency of 20.8/min only
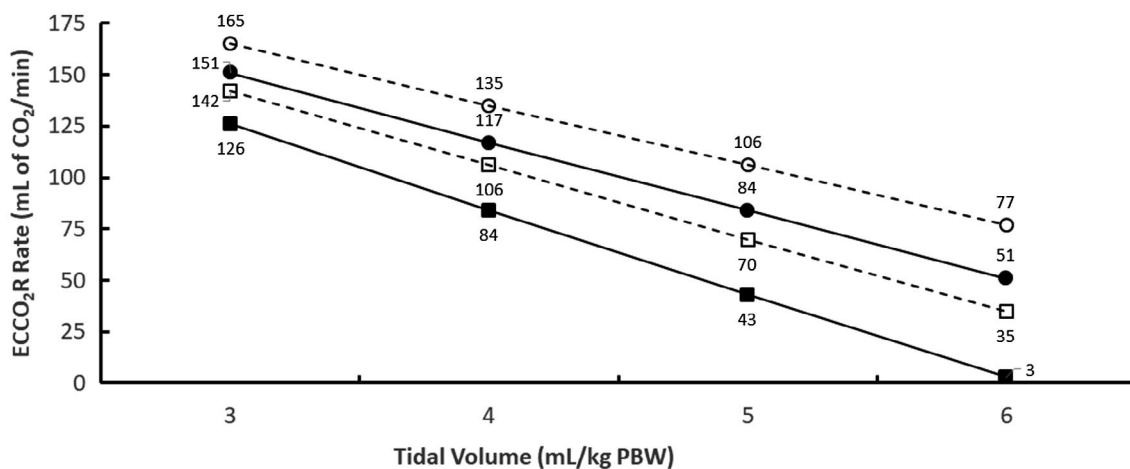

FIGURE 4 Calculated $ECCO_2R$ rate required to achieve a $PaCO_2$ of 46 mm Hg (filled symbols, solid lines) and 40 mm Hg (open symbols, dashed lines) at various tidal volumes and mechanical ventilation frequencies. Results are shown for ventilation frequencies of 20.8/min (circles) and 26/min (squares)

4 | DISCUSSION

The current standard of care for mechanical ventilation in ARDS patients was identified in LUNG SAFE as mild permissive hypercapnia, a $PaCO_2$ of 46 mm Hg, pHa of 7.33, and moderately low tidal volumes. Further reductions in tidal volume would be accompanied by elevated levels of $PaCO_2$ and reductions in arterial pH, but permissive hypercapnia with $PaCO_2$ ≥50 mm Hg during the first 48 hours after initiating mechanical ventilation is associated with an increased risk of intensive care unit mortality in ARDS patients.[28] To ameliorate the unphysiological effects of hypercapnia, it has been established clinically that the use of $ECCO_2R$ results in variable reductions in $PaCO_2$ within a few hours[29]; this is expected depending on the characteristics of the $ECCO_2R$ device used, as well as other clinical variables. As noted

however by others,[29] previous clinical studies have found it difficult to quantify the specific contribution of the $ECCO_2R$ device to the reduction in $PaCO_2$. The approach taken in the current study was to quantify the relationship between the $ECCO_2R$ rate and changes in $PaCO_2$ and other components of acid-base chemistry in ARDS patients undergoing mechanical ventilation using a comprehensive biochemical and physiological simulation model.

This theoretical effort extends a previously published mathematical model of CO_2 and O_2 chemistry and whole-body storage and transport[19,21] to provide estimates of the $ECCO_2R$ rate requirements for mechanically ventilated ARDS patients treated with low tidal volumes. Others[30] have recently developed an alternative mathematical model to predict changes in $PaCO_2$ as a function of treatment time and the blood flow rate for one specific $ECCO_2R$ device and

compared their model predictions with empirical data from preclinical studies in a porcine model. The current mathematical model is comparable to this latter model in overall design but differs in three major ways. First, the current model only predicts the relationship between acid-base chemistry and the ECCO$_2$R rate; thus, the current approach is general and not dependent on the performance characteristics of a specific device. In practical clinical applications, the predictions from the current model may require supplementary data relating the ECCO$_2$R rate to the blood flow rate for a specific device.[13] Second, the current model is limited by the assumption of steady state conditions. The previous model[30] was developed to explain time-dependent changes in PaCO$_2$ after abrupt, transient changes in the ECCO$_2$R rate as well as time-dependent changes in temperature and metabolic rate during the preclinical experiments. Those time-dependent model elements were necessary to explain the data from their porcine experiments[30] but are not relevant to the approximate steady state conditions when treating mechanically ventilated ARDS patients over the period of hours or days in the intensive care unit. Third, the current model provides a comprehensive description of CO$_2$, O$_2$, and acid-base chemistry; thus, it is more general and applicable to a greater variety of clinical conditions. We believe our model and the previous model[30] are complementary and applicable to different study objectives.

The structure of the mathematical model used in current study is however relatively simple from a physiological perspective. For example, we used a simple model of CO$_2$ and O$_2$ exchange in the lung that is unlikely to accurately represent the pathophysiological conditions in ARDS patients such as ventilation/perfusion inequalities.[31] More extensive pulmonary gas exchange models[32] can readily be incorporated into the current model if these predictions are empirically demonstrated to be quantitatively inaccurate. In addition, we have only considered a single tissue store of CO$_2$ in muscle cells; thus, the estimate of tissue cell volume and mass of CO$_2$ stored in tissues is likely an underestimate (see Figure 2). It should however be noted that the magnitude of tissue volume does not significantly influence the calculated ECCO$_2$R rate in the current model as steady state conditions have been assumed. Moreover, specific phenomenon that might reduce device efficiency in vivo such as recirculation[13] have also not been included in the current model. Our model is comparable in overall complexity to that recently described for extracorporeal membrane oxygenation.[33]

The current model demonstrates the strong dependence of PaCO$_2$ and other components of acid-base chemistry on respiratory rate during mechanical ventilation, both with and without ECCO$_2$R. The use of high-frequency ventilation was not evaluated in this study as it has been shown to not reduce, and may even increase, in-hospital mortality,[34] and such high-frequency settings are not recommended for routine use

in ARDS patients.[1,3] Although there is both theoretical[35] and empirical[36–38] evidence that low respiratory rates during mechanical ventilation may reduce VILI, it should be emphasized that the low tidal volume patient group in the ARDS Network trial[39] was ventilated at respiratory rates of approximately 30/min and achieved low mortality rates. The higher ventilation frequencies considered in the current study were below these limits.

A major limitation of this work is the lack of empirical confirmation of the accuracy of the model predictions, partially because there are few clinical studies to date that have measured both ECCO$_2$R rates and changes in acid-base chemistry in ARDS patients. Nevertheless, other data in the literature do not contradict the results from the current work. For example, Winiszewski et al.[12] reported that mechanically ventilated ARDS patients treated using a tidal volume of 5.3 mL/kg PBW and a respiratory rate of 26/min achieved a baseline PaCO$_2$ of 50 mm Hg and a pH of 7.31; the former level in arterial blood is similar to that in Figure 3 at the same respiratory rate with a tidal volume of 6 mL/kg PBW (PaCO$_2$ of 46.6 mm Hg). ECCO$_2$R rates were not however reported from that study. In addition, Schmidt et al.[10] reported that ARDS patients treated using a tidal volume of 6.1 mL/kg PBW and a ventilation frequency of 26/min achieved a baseline PaCO$_2$ of 43 mm Hg and a pH of 7.39; again, the former level in arterial blood is similar to that in Figure 3 at the same ventilation frequency. In that study, patients who had tidal volumes reduced to 3.98 mL/kg PBW and received ECCO$_2$R at a rate of 51 mL of CO$_2$/min achieved a PaCO$_2$ of 53 mm Hg. The calculated predictions in Figure 4 suggest that those patients could have achieved a lower PaCO$_2$ of 46 mm Hg if the ECCO$_2$R was increased to 84 mL of CO$_2$/min.

As this study was being finalized to first submit for publication, the results from the SUPERNOVA trial were published.[14] That prospective, multicenter, international phase 2 study of 95 mechanically ventilated ARDS patients demonstrated that it is feasible to use veno-venous ECCO$_2$R to allow reductions in tidal volume from 6 to 4 mL/kg PBW without a 20% increase in PaCO$_2$ in approximately 80% of patients. Overall, reductions in tidal volume to 4 mL/kg PBW with simultaneous use of ECCO$_2$R maintained PaCO$_2$ at 46.7-48.0 mm Hg with ventilation frequencies of 23.5-27.4/min during the first 24 hours of treatment. A shortcoming of this trial was the inability to measure clearance and total amount of CO$_2$ removal by ECCO$_2$R as originally planned as a secondary endpoint of that trial.[14] We can however use the mathematical predictions in Figure 4 to estimate the ECCO$_2$R rate required to achieve approximately these same conditions (4 mL/kg PBW and ventilation frequency of 26/min) as 84 mL of CO$_2$/min at a PvCO$_2$ of 55.6 mm Hg (neglecting the calculated ECCO$_2$R rate of 3 mL of CO$_2$/min at a tidal volume of 6 mL/kg PBW). Obviously, higher ECCO$_2$R rates

would be required to achieve reductions in tidal volumes to 4 mL/kg PBW in closer to 100% of patients.

Additional limitations to this work include the following. First, the PBW could only be estimated from the actual body weight because the data necessary for calculating PBW in the LUNG SAFE publication were not reported. Second, model predictions were only reported for patients with an actual body weight of 78 kg. Because larger patients have higher rates of CO_2 production, higher $ECCO_2R$ rates will likely be required. Most relevant parameters in the current model have been scaled to patient body weight; thus, a simple approach to extrapolate the reported required $ECCO_2R$ rates to other patients would be by body weight. Preliminary calculations from the current model have theoretically confirmed this hypothesis. Third, several other biochemical data were not reported in the LUNG SAFE publication, such as arterial bicarbonate concentration or base excess; those values could only be estimated based on values previously reported in the literature.

5 | CONCLUSIONS

The current mathematical model predicts that $ECCO_2R$ rates resulting in clinically desirable $PaCO_2$ levels at tidal volumes of 5-6 mL/kg PBW can likely be achieved in mechanically ventilated ARDS patients with current technologies; use of ultraprotective tidal volumes (3-4 mL/kg PBW) may be challenging unless higher mechanical ventilation frequencies are used. The recently reported secondary analysis from the SUPERNOVA trial that lower CO_2 extraction devices required high mechanical ventilation frequencies to achieve clinically acceptable $PaCO_2$ levels at ultraprotective tidal volumes[15] supports the theoretical predictions in this work.

CONFLICT OF INTEREST
JKL is a consultant to Baxter International and NxStage Medical Inc. (now Fresenius Medical Care). JG, DP, and KH are full-time employees of Baxter International with ownership interests.

AUTHOR CONTRIBUTIONS
JKL designed the study, developed the mathematical model, wrote the computer program, and wrote the first draft of the manuscript. DP provide advice on the development of the mathematical model. JG and KH provided clinical input into the study design. DP, JG, and KH also reviewed the manuscript and provided valuable input to the revisions of the manuscript. All authors read and approved the final manuscript.

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APPENDIX

Figure 1 shows a schematic of the whole-body CO_2 transport model used in this study. The model structure is identical to that proposed previously by others[19] except to include an extracorporeal CO_2 removal device into the venous circulation with a rate equal to JCO2. Only the four blood-containing compartments (lung capillary blood exchanging gas with alveoli, arterial blood, venous blood, and post-ECCO$_2$R venous blood) from the six-compartment model were used to formulate CO_2 mass balance relationships. The transport of CO_2 between the lung and the environment can be described by the following equations at steady state (following along the lines described by others[19])

$$\dot{V}_A = f \times [V_T - V_D] \quad (A1)$$

$$\dot{V}CO2 - JCO2 = \dot{V}_A \times \frac{P_A CO_2}{P_B - P_{H2O}} \quad (A2)$$

where $\dot{V}_A$ denotes the volume of gas flowing into the alveoli per unit time, f denotes the respiratory frequency, V_T denotes the tidal volume, and V_D denotes the dead space volume. The net rate of CO_2 exchange in the lung at steady state is equal to the tissue CO_2 production rate ($\dot{V}CO2$) minus the extracorporeal CO_2 removal rate by the ECCO$_2$R device (JCO2) and can be related to the partial pressure of CO_2 in the alveoli ($P_A CO_2$), the barometric pressure (P_B) assumed equal to 760 mm Hg (101.3 kPa), and the pressure of saturated water (P_{H2O}) assumed equal to 47 mm Hg (6.3 kPa) as shown in equation (A2). It should be noted that the fractional concentration of CO_2 in inspired air is assumed to be zero in equation (A2). If it is also assumed that the $PaCO_2$ in alveoli and lung capillary blood equilibrate, then equation (A2) can be rearranged to calculate the $PaCO_2$ in lung capillary blood which can be used to calculate the total CO_2 concentration in lung capillary blood ($tCO_{2,l}$) from the acid-base chemistry model described previously by others.[21]

The total CO_2 concentration in arterial blood ($tCO_{2,a}$) is a flow-weighted average of that in lung capillary CO_2 and in post-ECCO$_2$R venous blood ($tCO_{2,pv}$) as given by

$$tCO_{2,a} = (1-s) \times tCO_{2,l} + s \times tCO_{2,pv} \quad (A3)$$

where s denotes the pulmonary shunt fraction. CO_2 mass balance at steady state in the alveoli of the lung also requires

$$\dot{V}CO2 - JCO2 = Q(1-s)\left[tCO_{2,pv} - tCO_{2,l}\right] \quad (A4)$$

where Q denotes cardiac output. Equations (A3) and (A4) can be combined to solve for $tCO_{2,a}$ as

$$tCO_{2,a} = tCO_{2,l} + \frac{s \times [\dot{V}CO2 - JCO2]}{Q \times (1-s)} \quad (A5)$$

and then the total CO_2 concentration in venous blood ($tCO_{2,v}$) and $tCO_{2,pv}$ can be sequentially calculated as

$$tCO_{2,v} = tCO_{2,a} + \frac{\dot{V}CO2}{Q} \quad (A6)$$

$$tCO_{2,pv} = tCO_{2,v} - \frac{JCO2}{Q} \quad (A7)$$

Note that equations (A5), (A6), and (A7) can be solved using the acid-base chemistry model, as described by others,[21] sequentially once the total CO_2 concentration in lung capillary blood is known. Note also that solving the acid-base chemistry model requires simultaneously solving O_2 whole body transport relationships described by others[21] (not shown here). All model equations were solved using Matlab (R2018a, The Mathworks Inc., Natick, MA, USA).