Extracorporeal Membrane Oxygenation for End-Stage Interstitial Lung Disease With Secondary Pulmonary Hypertension at Rest and Exercise: Insights From Simulation Modeling

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Interstitial lung disease (ILD) represents a collection of lung disorders with a lethal trajectory with few therapeutic options with the exception of lung transplantation. Various extracorporeal membrane oxygenation (ECMO) configurations have been used for bridge to transplant (BTT), yet no optimal configuration has been clearly demonstrated. Using a cardiopulmonary simulation, we assessed different ECMO configurations for patients with end-stage ILD to assess the physiologic deficits and help guide the development of new long-term pulmonary support devices. A cardiopulmonary ECMO simulation was created, and changes in hemodynamics and blood gases were compared for different inflow and outflow anatomic locations and for different sweep gas and blood pump flow rates. The system simulated the physiologic response of patients with severe ILD at rest and during exercise with central ECMO, peripheral ECMO, and with no ECMO. The output parameters were total cardiac output (CO), mixed venous oxygen (O_2) saturation, arterial pH, and O_2 delivery (DO_2)/O_2 utilization (VO_2) at different levels of exercise. The model described the physiologic state of progressive ILD and showed the relative effects of using various ECMO configurations to support them. It elucidated the optimal device configurations and required physiologic pump performance and provided insight into the physiologic demands of exercise in ILD patients. The simulation program was able to model the pathophysiologic state of progressive ILD with PH and demonstrate how mechanical support devices can be implemented to improve cardiopulmonary function at rest and during exercise. The information generated from simulation can be used to optimize ECMO configuration selection for BTT patients and provide design guidance for new devices to better meet the physiologic demands of exercise associated with normal activities of daily living. *ASAIO Journal* 2017; XX:00–00.

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Interstitial lung disease (ILD) represents a diverse set of lung diseases that impair gas exchange and are associated with the development of secondary pulmonary hypertension (PH) and right heart failure.[1] The combination of ILD and PH (ILD-PH) is associated with marked decreases in exercise tolerance.[2,3] Such patients have significantly lower 6-minute walk distances (6MWDs) and lung cardiac output (CO) diffusion capacities (DLCO) and significantly higher FiO_2 requirements compared with ILD patients without PH.[2,4,5] Many mechanisms contribute to decreased exercise tolerance in ILD with PH, including a high degree of intrapulmonary shunt, exercise-induced increased V/Q mismatch, and impaired CO reserve; combined, these result in rapid induction of hypoxemia, decreased oxygen delivery (DO_2) to the periphery, and lactic acid accumulation.[4,6,7]

Another characteristic of patients with ILD-PH is episodic, rapid deterioration of exercise tolerance with progression to fulminant cardiac and pulmonary failure associated with mortality rates approaching 60–100%.[8,9] In select pretransplant cases, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has been used to provide cardiopulmonary support as a bridge to transplant (BTT).[10,11] In some cases, ILD-PH patients supported by VA-ECMO with cannulation from the subclavian vessels, can be transferred to a chair, ambulate with assistance and even participate in mild physical therapy while awaiting transplant.[10]

Currently there is no information available on how much DO_2, carbon dioxide (CO_2) removal, and blood flow need be provided by a VA-ECMO device to allow an ILD-PH patient to achieve a reasonable level of exercise. Cardiovascular simulations based on validated models have yielded significant insights into the hemodynamics, clinical role and limitations of various forms of mechanical circulatory support in cardiogenic shock, and other types of devices for heart failure.[13,14] In the current study, we extended that model to include the physiology of gas exchange in the lungs, periphery, and in an extracorporeal membrane gas exchange unit (GEU). We simulated severe ILD-PH and then determined the extent of arterial and venous oxygen (O_2) desaturation and the development of lactic acidosis at varying degrees of exertion. We then simulated various configurations of extracorporeal membrane oxygenation (ECMO) with variable rates of blood flow and sweep gas flow. The purpose of this study was to estimate the optimal

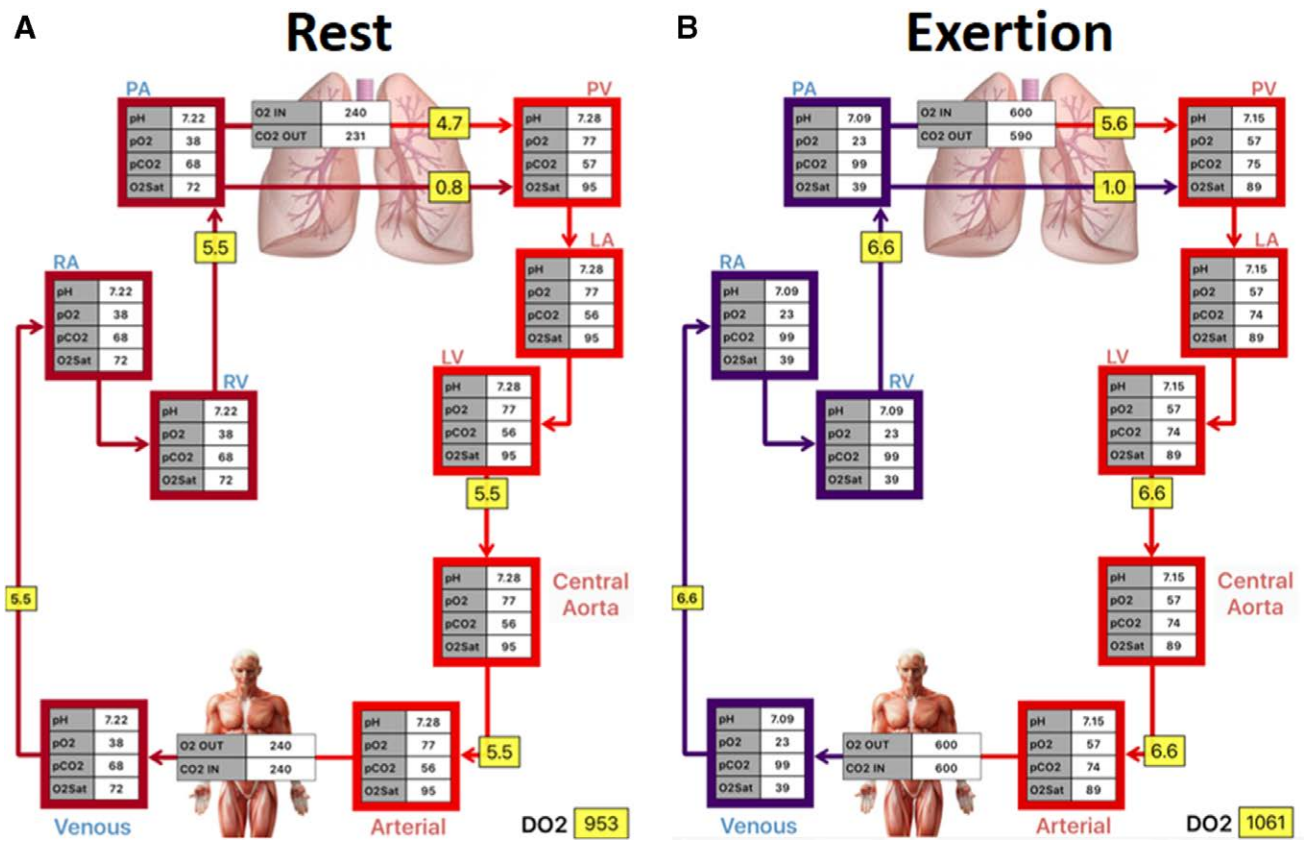

Figure 1. Blood gas values in each of 10 vascular compartments at rest (**A**) and at exercise to a level that results in a blood lactate levels of 4 mEq/L. pO_2 and pCO_2 in units of mm Hg and O_2 saturation in units of %. Boxes over the illustrations of the lung and body show the rate of oxygen (ml/min) and carbon dioxide (ml/min) intake or output. Values in yellow boxes show blood flows in L/min. O_2, oxygen.

configuration, blood flow, and gas exchange requirements of an ECMO device that would allow these patients to achieve levels of exertion required for performance of activities consistent with at least NYHA functional class III symptoms.

Methods

Overview

We employed a previously developed and validated model of the cardiovascular system that was modified to include the basic physiology of O_2 and CO_2 exchange in the lungs, periphery, and in an extracorporeal membrane oxygenator. We established reasonable hemodynamic and blood gas profiles for a patient with severe ILD-PH. Because we were unable to identify the necessary data in the literature, these conditions were based on experience with such patients at our center. Changes in cardiovascular and pulmonary parameters that would be appropriate for such a patient during mild exercise, with and without the assistance of ECMO, were then imposed. To define performance criteria for such an ECMO system, we simulated cases where blood flow and sweep gas flows were constant and then allowed to vary together to account for increased metabolic demands of exercise.

Cardiopulmonary Model

The model used to simulate hemodynamics has been described previously in detail[13,14] and is summarized in the Appendix (see Appendix, Supplemental Digital Content, http://links.lww.com/ASAIO/A177). The model consists of 10 vascular compartments illustrated by the boxes in **Figure 1A**. Details of the model are provided in the Appendix.

For simulation of blood gas fluxes across a GEU, it was assumed that pO_2 and pCO_2 of blood leaving the oxygenator equilibrated with those of the sweep gas. Accordingly, the amount of O_2 and CO_2 exchange was determined by blood flow, the sweep gas flow, the fractional pressure of O_2 in the sweep gas (F_DO_2), and the pO_2 and pCO_2 of blood entering the membrane oxygenator.

Simulation of Exercise

To establish the baseline "resting" conditions, we relied on our own (unpublished) data available from patients with mild-to-moderate ILD-PH and on expert opinion to arrive at reasonable starting values to guide this simulation as shown in **Table 1**. The resulting physiologic output values for these "resting" conditions are summarized in **Table 2**.

Exercise was simulated by estimating relevant parameters that would be achieved whether the patient could exercise to an extent where total body O_2 utilization (VO_2) would equal ~14 ml O_2/kg/min, which roughly corresponds with exercise tolerance of a patient with functional class NYHA III symptoms; for a 70 kg person, this equates with a VO_2 of ~960 ml/min. Exercise induces changes in several parameters characterized by changing cardiovascular and pulmonary properties.

Table 1. Model Parameter Values for Simulating Severe ILD at Rest

Parameters	Values		Units
Heart rate	60		Beats/min
Stressed blood volume	2,960		ml
Vascular system	Pulmonic	Systemic	
Rc,Prox	0.024	0.025	mHg.s/ml
Ca,Prox	1.00	0.10	ml/mm Hg
Rc	0.25	0.03	mHg.s/ml
Ca	30.00	1.43	ml/mm Hg
Ra	0.28	0.70	mHg.s/ml
Cv	7.0	70.0	ml/mm Hg
Rv	0.015	0.025	mHg.s/ml
Mirtal resistance	0.025		mHg.s/ml
Tricuspid resistance	0.025		mHg.s/ml
Ventricles	Right	Left	
Ees	0.5	2.18	mm Hg/ml
Vo	15	0	ml
Alpha	0.019	0.036	1/ml
Beta	0.24	0.34	mm Hg
Tmax	195		msec
Tau	40		msec
AV delay	160		msec
Atria	Right	Left	
Ees	0.23	0.30	mm Hg/ml
Vo	10	5	ml
Alpha	0.028	0.037	1/ml
Beta	0.44	0.44	mm Hg
Tmax	125		msec
Tau	20		msec
Pulmonary and metabolic physiology			
Hemoglobin	13.5		g/dL
Shunt fraction	15		%
FiO_2	50		%
DLCO	20		%
Alveolar ventilation	3.25		L/min
MVO_2	240		ml/min
VCO_2	204		ml/min
RQ	0.85		Unitless

DLCO, lung cardiac output diffusion capacities; ILD, interstitial lung disease.

Table 3 shows the parameters that were changed in linear proportion along with imposed changes in VO_2 from initial resting values of 260 ml/min (0% exercise) to the peak of 960 ml/min (100% exercise).

Table 2. Simulation-Derived Hemodynamic and Metabolic Parameters at Rest

Parameters	Value	Units
AoP (s/d [m])	114/68 (86)	mm Hg
PAP (s/d [m])	85/43 (60)	mm Hg
CVP	17	mm Hg
PCWP	10	mm Hg
CO	5.5	L/min
LV EF	55	%
RV EF	24	%
pH	7.31	
pO_2	77	mm Hg
O_2 saturation	95	%
pCO_2	50	mm Hg
MVO_2 saturation	72	%
DO_2	520	ml/min
Lactate	1.0	mEq/L

CO, cardiac output; DO_2, oxygen delivery; PAP, pulmonary arterial pressure.

Table 3. Variables Changed With Increasing Exercise in Simulation

		Value		
Variable Name	Parameters	Rest	Peak Exercise	Units
O_2 consumption	VO_2	260	960	ml/min
Heart rate	HR	60	145	beats/min
Systemic vascular resistance	SVR	13	11.8	mm Hg.min/L
Stressed blood volume	SBV	2,960	3,360*	L
Respiratory exchange ratio	RER	1	1	none
Ventilation	Ventilation	3.25	9.75	L/min
Right ventricular contractility	RV Ees	0.5	0.75	mm Hg/ml
Left ventricular contractility	LV Ees	2.18	2.72	mm Hg/ml
Sweep gas flow	Sweep gas flow	2.5	8.5	L/min
Fractional pressure of O_2 in sweep gas	FdO_2	100	100	%
ECMO flow	ECMO flow	2.5	8.5	L/min

*Nonuniform change in SBV throughout different configurations: RA→ LA and PA→ LA required decreases in SBV to maintain physiologic pulmonary capillary wedge pressure.

ECMO, extracorporeal membrane oxygenation; LA, left atrial; O_2, oxygen; PA, pulmonary artery; RA, right atrial.

Extracorporeal Membrane Oxygenation Configurations

Five different ECMO configurations were explored. Standard VA-ECMO was simulated as shown in **Figure 2** by sourcing blood from the systemic venous system and pumping to the proximal arterial system. Other configurations included VV-ECMO (sourcing blood from the systemic vein and returning it to the right atrium), right atrial-to-left atrial ECMO (RA→LA ECMO), RA-to-pulmonary artery ECMO (RA→PA ECMO), and PA-to-LA ECMO (PA→LA). For each ECMO configuration, the initial exercise simulation was performed with a fixed blood flow of 2.5 L/min and a fixed sweep gas flow of 2.5 L/min, which are typical initial values we employ in bed-bound ILD-PH patients on ECMO. Next, for each ECMO configuration, the exercise simulation was run with ECMO pump flow and sweep gas flow increased in a matched 1:1 ratio to maintain mixed venous O_2 saturation greater than 50% within the defined limits of device performance. The main restrictions imposed on the simulated ECMO device were a maximum blood flow of 9 L/min (which is achievable by currently available continuous flow ventricular assist devices) and an imposed F_DO_2 limit of 50% (as opposed to 100% which is typically used for in hospital bed-bound patients). This restricted F_DO_2 could lessen the O_2 tank/reservoir burden for an out-of-hospital ambulatory system. The 1:1 increases of blood and sweep gas flows was chosen to simplify the number of simulations and for ease of explanation of results. Obviously, there is no practical limitation (neither in the simulation nor in reality) that such a restriction be imposed.

DO_2 Two key parameters determined during the simulation were DO_2 and the ratio between DO_2 and VO_2. DO_2 is the product of total blood flow reaching the body and its O_2 content. Under normal conditions, the DO_2/VO_2 ratio is greater than two and is an important parameter in that it provides an

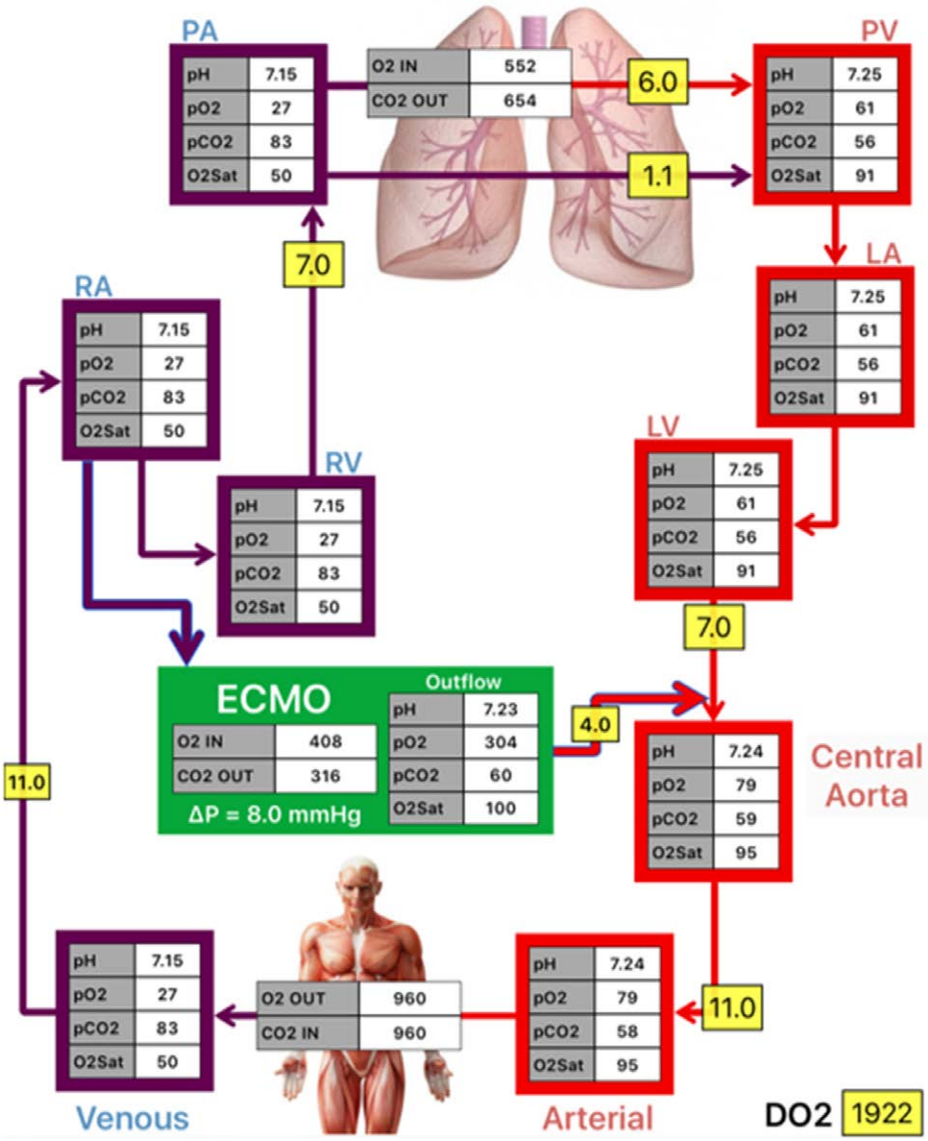

Figure 2. Blood gas values in each of 10 vascular compartments with VA-ECMO at peak exercise. There is notable increase in total cardiac output, DO_2, and with preservation of venous oxygen saturation as compared with **Figure 1B**. DO_2, oxygen delivery; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

index of the adequacy of DO_2. When DO_2/VO_2 falls below two, O_2 supply generally fails to meet needs, and lactic acid accumulation can begin.[16,17]

Results

Typical simulation-derived blood gas values at different sites in the circulation at rest and during mild exercise in a patient with severe ILD are shown in **Figure 1**, A and B, respectively, without any ECMO. The degree of exercise in this example was limited to an increase of VO_2 from the resting value of 240 ml/min (as shown in **Figure 1A)** to 609 ml/min, which was the exercise level at which DO_2/VO_2 fell below two. The profound degree of exercise-induced venous O_2 desaturation and acidosis are evident in the values displayed in **Figure 1B**.

Simulations with VA-ECMO in which blood flow and sweep gas flow were fixed (2.5 L/min and 2.5 L/min, respectively) are shown in red in **Figure 2**. This shows simulation results for this specific configuration and the blood gas values at various points in the circulatory system. Compared with no ECMO support in **Figure 1B**, the additional CO provided by the ECMO pump increased mixed venous saturation and helped maintain arterial pH throughout exercise. Total flow reaching the periphery was 12.9 L/min, with 6.4 L/min contributed by the ECMO pump. Of the total 960 ml O_2 consumed per minute, the membrane oxygenator contributed ~540 ml/min (56%) compared with the lungs which contributed ~420 ml/min (44%). Of the total 1,077 ml CO_2 produced per minute, the membrane oxygenator removed 565 ml/min (52%) compared with the lung which removed 520 ml/min (48%), which obviously could be altered by adjusting F_DO_2 and sweep gas flow levels.

The simulation results of each of the five described configurations at peak exercise with fixed and variable ECMO and sweep flow are summarized in **Table 4**. Output parameter

Table 4. Output Variables at Peak Exercise

		pH	pCO_2 (mm Hg)	Mixed Venous O_2 Saturation (%)	DO_2 (ml/min)	DO_2/VO_2
VA	Fixed	7.18	93	39	1,635	1.70
	Variable	7.25	80	50	1,994	2.08
RA-->LA	Fixed	7.15	101	36	1,323	1.38
	Variable	7.26	27	50	1,810	1.89
RA-->PA	Fixed	7.16	96	27	1,355	1.41
	Variable	7.39	65	47	1,757	1.83
VV	Fixed	7.15	98	21	1,253	1.31
	Variable	7.34	73	36	1,425	1.48
PA-->LA	Fixed	7.17	97	33	1,463	1.52
	Variable	7.24	87	50	1,801	1.88

DO_2, oxygen delivery; LA, left atrial; PA, pulmonary artery; RA, right atrial; VA, veno-arterial; VO_2, oxygen consumption.

results in this table indicate that for every configuration, simultaneous variation of blood flow and sweep flow was able to better maintain normal physiologic response to exercise and increased maximum exercise threshold. The VA-ECMO configuration with variable ECMO flow and sweep was the only configuration able to maintain $DO_2/VO_2 > 2$ at peak exercise. The VV-ECMO configuration provided the least support at peak exercise with regard to DO_2, DO_2/VO_2, and mixed venous saturation.

Figures 3 and 4 summarize device performance specifics and physiologic responses, respectively, over the range of exercise intensities investigated. Device performance curves in **Figure 3** show that increased ECMO blood and sweep flow are required to maintain $DO_2/VO_2 > 2$ for each configuration between VO_2 of 500–700 ml/min. Veno-arterial extracorporeal membrane oxygenation required the least amount of total flow to allow continued exercise, whereas all other configurations required maximum simulated flow (8 L/m) to exercise beyond VO_2 of 700 ml/min. The physiologic response to exercise achieved by the five different ECMO configurations (**Figure 4**) shows the largest increase in CO was provided by VA-ECMO. All configurations with variable sweep and ECMO blood flow were able to maintain the mixed venous saturation above 50% with the exception of VV-ECMO (see discussion below). VA-ECMO was the only configuration to achieve normal physiologic support

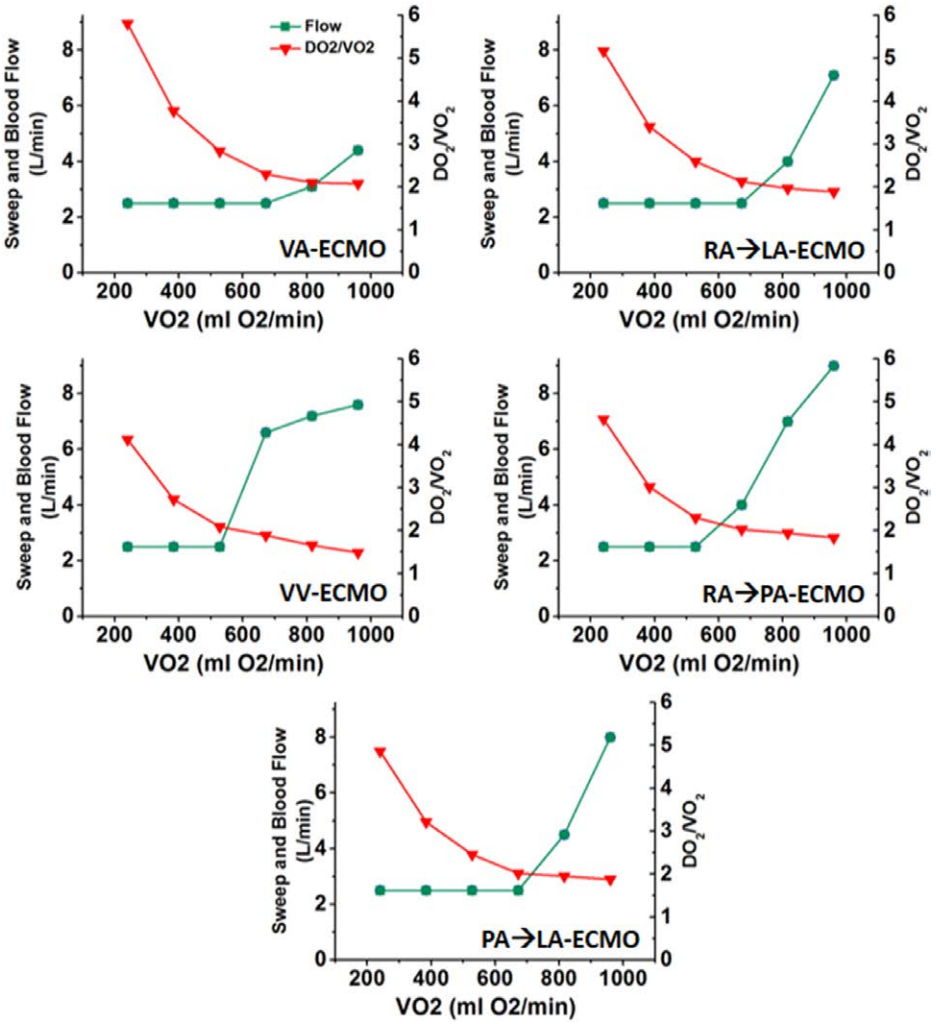

Figure 3. Effects of increasing degrees of exercise as indexed by total body VO_2 on CO, mixed venous saturation, arterial pH, and blood lactate concentration. Effects are shown with right atrial-to-arterial (VA) ECMO with different means of handling of pump flow and gas sweep speed. Blood gasses are maintained best when pump flow and gas sweep speed are increased with increased exercise intensity. CO, cardiac output; ECMO, extracorporeal membrane oxygenation; VA, veno-arterial; VO_2, oxygen consumption.

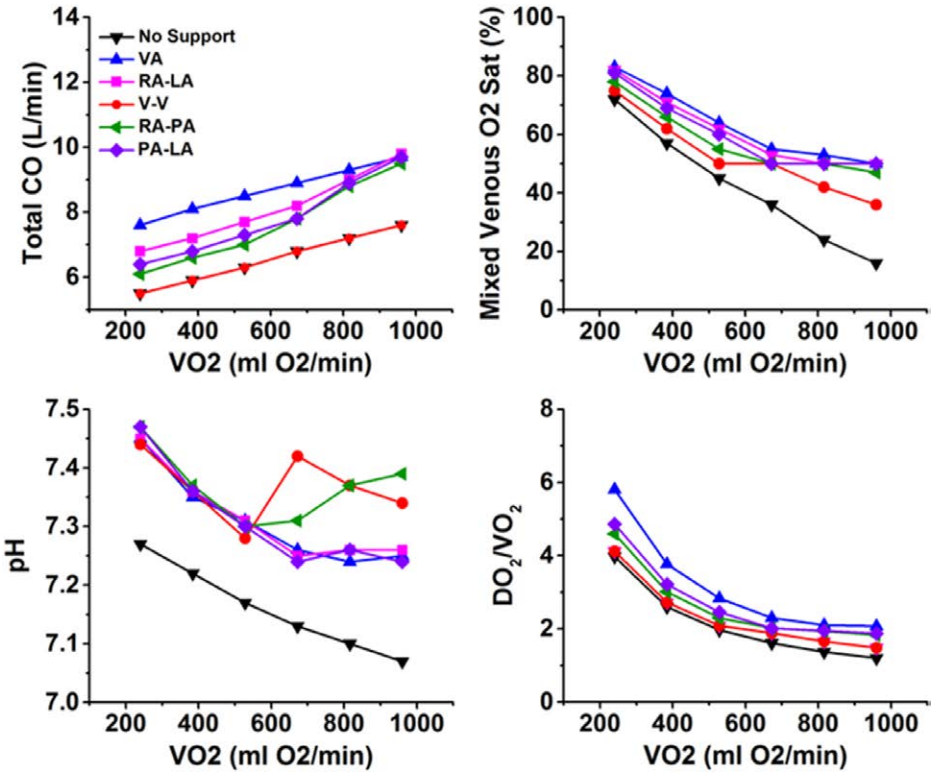

Figure 4. Overall performance of each of four configurations of cardiopulmonary support, each with 1:1 sweep and pump blood flow rates. Total cardiac output is net flow to the arterial system which is the sum of native left ventricular flow plus pump flow.

throughout exercise to a VO_2 of 960 ml/min. The increase in pH noted in the VV-ECMO and RA-to-PA ECMO configuration is likely because of high pump flow and sweep gas flow required to support the patient exercise and could be eliminated by reducing gas sweep flow.

Predicted hemodynamic responses to ECMO flow and pressure in the various configurations are also summarized in **Table 5**. Findings from the simulation demonstrate a significant increase in mean pulmonary arterial pressure (mPAP) with RA-PA ECMO compared with other configurations, whereas RA-LA and PA-LA configurations decreased mPAP during exercise. Mean arterial pressure (MAP) was slightly elevated at peak exercise in VA configuration only because of increased afterload of higher ECMO flow.

Table 5. Hemodynamic Response to Exercise

		Variable Speed and Sweep with 1:1 Ratio				
Configuration	No Support	VA-ECMO	RA-->LA	RA-->PA	VV-ECMO	PA-->LA
LV perspective		Parallel	Series	Series	Series	Series
CO at rest (L/min)	5.5	7.6	6.8	6.1	5.5	6.4
CO at peak (L/min)	7.6	11.4	9.8	9.5	7.6	9.7
MAP at rest (mm Hg)	86	108	96	91	86	96
MAP at peak (mm Hg)	104	142	118	117	104	119
PAPmean at rest (mm Hg)	60	60	59	69	60	52
PAPmean at peak (mm Hg)	80	78	46	104	80	39
DO_2 at rest (ml/min)	956	1,394	1,240	1,103	989	1,167
DO_2 at peak (ml/min)	1,153	1,994	1,810	1,757	1,425	1,801
pH at peak	7.07	7.25	7.26	7.39	7.34	7.24
Gas exchange at peak exercise						
% VO_2 by ECMO	0	45%	76%	99%	100%	85%
% VO_2 by lung	100	55%	24%	1%	0%	15%
% VCO_2 by ECMO	0	36%	58%	59%	56%	68%
% VCO_2 by lung	100	64%	43%	41%	44%	32%
MVO2 at $DO_2/VO_2 < 2.0$ (ml/min)	521	960	816	672	614	672
Fluid management	None	None	Diuresis	none	none	Diuresis
Lung as filter	N/A	No	No	Yes	Yes	No

CO, cardiac output; DO2, oxygen delivery; LA, left atrial; MAP, mean arterial pressure; PA, pulmonary artery; RA, right atrial; PAP, pulmonary arterial pressure; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VO2, oxygen consumption.

Discussion

Overall Perspective

Despite recent advances in ECMO, pulmonary assist devices (PADs) remain cumbersome and require intensive care unit (ICU) level care throughout the duration of support. Smaller more ergonomic devices could facilitate patient ambulation and improve quality of life while awaiting transplant, and they would serve as the foundation for destination therapy (DT). In our experience,[10,11] improvements in exercise capacity vary among patients placed on ECMO support and have even less peak exercise capacities than heart failure patients put on ventricular assist devices.[18–20] The goal of our study was to estimate performance criteria for a PAD that could support reasonable levels of exertion in ILD-PH patients. With our current approaches, our ECMO patients are able to achieve minimal degrees of ambulation. Understanding the reasons for these limitations will enable clinicians and engineers to select optimal PAD configurations and device performance characteristics to improve exercise capacity in these patients.

In our model, we identified estimates of blood flow and gas exchange requirements for an ECMO device that would permit exertion to levels equivalent to total O_2 consumption of ~14 ml O_2/kg/min. A "critical finding" was that even with maximal pump and sweep gas flows, the specific ECMO configuration has a profound effect on the amount of hemodynamic-metabolic support delivered.

Clinical Correlations

The model of the cardiovascular system employed in the current study was validated previously in investigations of left heart failure. Using baseline hemodynamic and metabolic data acquired from clinical studies in the ILD-PH patient population, we adapted the earlier model to incorporate gas exchange in the pulmonary system and a membrane oxygenator.

The initial model parameter values at baseline were selected to mimic clinically observed hemodynamic and metabolic responses to exercise.[10,11] This was successfully implemented in that observed clinical response of these patients mimics our simulated responses to exertion without support (**Figure 4**, black lines), which are characterized by minimal increases in CO, rapid reductions in mixed venous O_2 saturation and arterial pH, and rapid lactate accumulation (indexed by reductions in DO_2/VO_2). Clinically, we have observed that patients supported with flow-limited VA-ECMO often take a longer time to ambulate and experience greater degrees of desaturation and hemodynamic deterioration with little exertion. This observation has led us to temporally increase pump and sweep gas flows when mobilizing patients being bridged to transplant for physical rehabilitation. The benefit of this clinical practice is predicted by the model when we compare physiologic responses to exercise with fixed sweep and ECMO blood flows to variable sweep and flow. Not surprisingly, our model predicts significantly greater physiologic and metabolic benefits with variable flow, resulting in increases in total CO, mixed venous O_2 saturations, pH, and DO_2/VO_2. Based on these simulations, it is evident that a device with the capability to respond to exercise by varying both ECMO blood flow and sweep gas flow according to an appropriate metabolic feedback signal (e.g., blood pH or mixed venous O_2 saturation) has the greatest potential to meaningfully enhance exercise tolerance in ILD-PH patients. As noted above, we artificially (for simplicity) restricted changes in blood and gas sweep flow with a 1:1 ratio. Additional optimization of metabolic responses might be achieved by relaxing this restriction. However, in additional simulations (results not presented here), we observed that allowing sweep gas and blood flows to vary independently with exercise did not significantly alter the ability of any of the ECMO configuration to support hemodynamic or metabolic demands during exercise. Notably, it was required that both blood and gas flows be increased during exercise to achieve the metabolic goals of DO_2 and CO_2 removal.

Use of different ECMO configurations yielded marked variations in simulated hemodynamic responses to exercise (**Table 3**). Regarding an RA→LA ECMO and PA→LA ECMO configurations, the simulation predicts a potentially deleterious marked increase in LA and pulmonary venous pressures. This observation correlates with our clinical experience where initiation of RA→LA ECMO can induce rapid and substantial volume shifts from the systemic to pulmonary venous systems, potentially unmasking left ventricular diastolic dysfunction. Clinically, as accurately predicted by the simulation, we alleviate this effect through aggressive diuresis before initiating flow and use a gradual ramp-up protocol of pump flow.

The major limitations of the RA→PA ECMO configuration are its dependence upon native CO with restricted O_2 delivery and predicted increases in mPAP (mPAP > 100) which could be injurious to the pulmonary vascular bed. Although the lungs would filter potential emboli from the ECMO system with this configuration, our simulation predicts a significantly increased mPAP with suboptimal DO_2/VO_2 at maximum ECMO flow. Clinically, this could result in elevated risks of pulmonary hemorrhage while achieving lower values of DO_2 compared with the other configurations investigated.

The VV-ECMO configuration supported only oxygenation without increasing forward flow, and our simulation shows that this results in poor peak exercise tolerance. In our experience, end-stage ILD/PH patients on VV-ECMO were unable to ambulate because of rapid desaturation and hypotension regardless of changing sweep or flow with exertion likely attributable to the cardiogenic milieu of severe ILD-PH and RV-PA decoupling.

Limitations

Validation of the current model would ideally involve prospective data collection at rest and during exertion in ILD-PH patients. However, it is our policy to limit the risks of exercise and instrumentation of these patients given their vulnerability to abrupt cardiovascular collapse. To our knowledge, no such studies exist in this patient cohort and would be difficult to obtain. In view of these limitations, we used previous exercise studies obtained in our own population of pre- and posttransplant patients to guide establishment of reasonable baseline parameters to characterize their responses to low levels of exercise. In addition, we compared model predictions with our own clinical experience in ILD-PH patients before initiation of and during ECMO support. Such qualitative comparisons should not be considered as validation of the model predictions. Rather, the current simulation results may be considered

as a guide for designing clinical physiology studies to obtain validation data. The significance of such studies is not aimed at model validation for its own sake. Rather, it is evident that validation and heuristic refinement of such a model would be an invaluable tool for establishing the hemodynamic-metabolic design requirements for an ambulatory ECMO device, not only for ILD-PH patients but for the full range of end-stage lung disease patients.

In addition to the general limitation to which all models are subject,[13] there are some disease-specific phenomena that have not been included in the model that require further study. First, the model did not account for RV-LV interactions. With severe PH and RV dysfunction and dilation, septal bowing may have a detrimental impact on LV systolic and diastolic function. With ECMO-mediated RV unloading, septal bowing may be diminished, and LV filling and function may be improved. Second, the development of hypoxia can induce pulmonary vasoconstriction, and improvement in pulmonary venous O_2 tension can reduce pulmonary vascular resistance, although not very consistently or substantially in ILD-PH; nevertheless, it should be noted that the impact of hypoxic vasoconstriction has not been included in the present simulation.

As noted above, we artificially imposed 1:1 changes in blood and sweep gas flows to reduce the number of simulations and for simplicity of explanation of findings. However, in data not included in this report, we found that independent variations of these flows did not substantially alter the conclusions.

Summary and Conclusions

The simulation presented herein reveals important insights regarding design features of an ideal cardiopulmonary support device for ILD-PH patients. For use in the ICU setting, higher levels of exercise (e.g., for the purpose of physical therapy) may be achieved by more aggressive adjustments of blood pump flow and sweep gas flow. Novel system designs will need to have the capability to autoregulate both sweep gas and pump flow to support exercise demands related to performance of ADLs and low levels of exercise of these patients in non-ICU settings (i.e., for BTT or DT). Our findings suggest that a veno-arterial configuration provides optimal hemometabolic support in the most efficient use of available blood flow and sweep gas flow.

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