

# Supplementary Material

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# **1 DERIVATIONS AND FINITE DIFFERENCE FORMS OF EQUATIONS**

Variable	Definition	Equation	Units in	Initial
			Model	Condition
				(Source)
$C_{A,O_2}$	Dissolved oxygen	Eq. 4c	mol/mL	Eq. 4c
, 2	concentration in alveolar			
	membrane			
$C_{c,O_2}$	Spatially averaged	Eq. 5c	mol/mL	Eq. 5c
, -	dissolved oxygen			
	concentration in pulmonary			
	capillary compartment			
$C_{cv,d}$	Dissolved oxygen	Eq. 4	mol/mL	N/A
,	concentration in control			
	volume			
$C_{cv,T}$	Total oxygen concentration	Eq. S2 (Systemic	mol/mL	N/A
	in control volume	capillary		
		compartment) or S7		
		(Pulmonary capillary		
		compartment)		
$C_{pa,O_2d}$	Dissolved oxygen	Eq. 2 solved for	mol/mL	Eq. 2 solved for
	concentration in pulmonary	$C_{pa,O_2d}$		$C_{pa,O_2d}$
	arteries			
$C_{pa,O_2T}$	Total oxygen concentration	Eq. S4	mol/mL	Eq. S4
	in pulmonary arteries			
$C_{pc,O_2d}$	Dissolved oxygen	Eq. 2 solved for	mol/mL	Eq. 2 solved for
	concentration in pulmonary	$C_{pc,O_2d}$		$C_{pc,O_2d}$
	capillary compartment			
$C_{pc,O_2T}$	Total oxygen concentration	Eq. 88	mol/mL	Eq. S14
	in pulmonary capillary			
	compartment			
$C_{pv,O_2d}$	Dissolved oxygen	Eq. 2 solved for	mol/mL	Eq. 3a solved
	concentration in pulmonary	$C_{pv,O_2d}$		for $C_{pv,O_2d}$
	veins			
$C_{pv,O_2T}$	Total oxygen concentration	Eq. S11	mol/mL	Eq. 2
	in pulmonary veins			
$C_{sa,O_2d}$	Dissolved oxygen	Eq. 2 solved for	mol/mL	Eq. 3a solved
	concentration in systemic	$C_{sa,O_2d}$		for $C_{sa,O_2d}$
	arteries	_		
$C_{sa,O_2T}$	Total oxygen concentration	Eq. S5	mol/mL	Eq. 2
	in systemic arteries			

Table S1: Model Variables and Terms (in Main Paper)

Variable	Definition	Equation	Units in	Initial
			Model	Condition
				(Source)
$C_{sv,O_2d}$	Dissolved oxygen	Eq. 2 solved for	mol/mL	Eq. 2 solved for
, -	concentration in systemic	$C_{sv,O_2d}$		$C_{sv,O_2d}$
	veins	,		, ,
$C_{sv,O_2T}$	Total oxygen concentration	Eq. S3	mol/mL	Eq. S3
	in systemic veins			
$P_{A,O_2}$	Alveolar oxygen partial	Eqs. S12	mmHg	104 mmHg
	pressure	(Inspiration) and S13		(Guyton and
		(Expiration)		Hall (2000))
$P_{pa,O_2}$	Oxygen partial pressure in	Eq. 3a	mmHg	Eq. 3a
	pulmonary arteries			
$P_{pc,O_2}$	Oxygen partial pressure in	Eq. 3a	mmHg	Eq. 3a
	pulmonary capillary			
	compartment			
$P_{pv,O_2}$	Oxygen partial pressure in	Eq. 3a	mmHg	104 mmHg
	pulmonary veins			(Guyton and
				Hall (2000))
$P_{sa,O_2}$	Oxygen partial pressure in	Eq. 3a	mmHg	104 mmHg
	systemic arteries			(Guyton and
				Hall (2000))
$P_{sv,O_2}$	Oxygen partial pressure in	Eq. 3a	mmHg	Eq. 3a
	systemic veins			
$S_{pa,O_2}$	Fraction of hemoglobin	Eq. 3	Unitless	Eq. 3
	saturation in pulmonary			
	arteries			
$S_{pc,O_2}$	Fraction of hemoglobin	Eq. 3	Unitless	Eq. 3
	oxygen saturation in			
	pulmonary capillary			
~	compartment			
$S_{pv,O_2}$	Fraction of hemoglobin	Eq. 3	Unitless	Eq. 3
	oxygen saturation in			
	pulmonary veins		TT 1.1	
$S_{sa,O_2}$	Fraction of hemoglobin	Eq. 3	Unitless	Eq. 3
	oxygen saturation in			
	systemic arteries		TT 1/1	E 2
$S_{sv,O_2}$	Fraction of hemoglobin	Eq. 3	Unitless	Eq. 3
	oxygen saturation in			
	systemic veins	Tadaganda ( 11		0
	lime	independent variable	S	US

Variable	Definition	Equation	Units in	Initial
			Model	Condition
				(Source)
$\Delta V$	Differential volume	Eq. S1a (Systemic capillary	mL	N/A
		compartment) or S6a		
		(Pulmonary capillary compartment)		
VA	Simulated alveolar volume	Normal, Severe	mL	Normal, Severe
		OSA, Sim. 1-9:		OSA, Sim. 1-9:
		Variation of Eq. 7,		2,300 mL
		Patient Cases: Eq.		(Reynolds et al.
		S17		(2010)), Patient
				Case 1: 3,700
				mL and Patient
				Case 2: 3,400
				mL (Abdeyrim
				et al. (2015))
z	Spatial coordinate	Independent variable	cm	N/A

# Table S1: continued

# Table S2: Physiological Parameters (in Main Paper)

Parameter	Definition	Value (Source)/Equation	Units in Model
$A_{eff}$	Effective	3,000 cm <sup>2</sup> (Aird (2005);	$cm^2$
	cross-sectional area	Boron and Boulpaep (2009);	
	of all pulmonary	Guyton and Hall (2000))	
	capillaries		
$\beta_p$	Oxygen solubility in	$1.4 \times 10^{-9}$	$\operatorname{mol} O_2 \cdot \mathrm{mL}^{-1} \cdot \mathrm{mmHg}^{-1}$
	alveolar-capillary	$mol O_2 \cdot mL^{-1} \cdot mmHg^{-1}$	
	membrane and blood	(Frank et al. (1997))	
	plasma		
$b_r$	Breathing rate	Normal, Severe OSA, Sim.	breaths/s
		1-9, and Sim. Patient Case	
		2: 12 breaths/min, Sim.	
		Patient Case 1: 20	
		breaths/min, Severe OSA:	
		24 breaths/min	
		(hyperventilation), Sim. 2:	
		24 breaths/min	
		(hyperventilation)	

Parameter	Definition	Value (Source)/Equation	Units in Model
$C_{Hb}$	Hemoglobin	$2.3  imes 10^{-6}$ mol/mL (Dash	mol/mL
	concentration in	and Bassingthwaighte	
	blood	(2010))	
$D_{L,O_2}$	Normal oxygen lung	21	$\operatorname{mol} O_2 \cdot \mathrm{s}^{-1} \cdot \mathrm{mmHg}^{-1}$
	diffusing capacity	$mL O_2 \cdot min^{-1} \cdot mmHg^{-1}$	
		(Guyton and Hall (2000))	
$k_l$	Lung mass transfer	Eq. 5b	cm <sup>3</sup> /s
	coefficient		
$k_{pc}$	Pulmonary capillary	Eq. 4a	cm <sup>3</sup> /s
	control volume mass		
	transfer coefficient		
$L_c$	Pulmonary capillary	Eq. 4b	cm
	compartment length		
$MR_{O_2}$	Total basal	240 mL $O_2$ /min	$mol O_2/s$
	metabolic rate for	(MacIntyre (2014))	
	oxygen consumption		
$P_B$	Barometric pressure	760 mmHg (Guyton and	mmHg
		Hall (2000))	
$P_{H_2O}$	Water vapor pressure	47 mmHg (Guyton and Hall	mmHg
	at normal body	(2000))	
	temperature		
$P_{I,O_2}$	Inspired oxygen	Eq. 5a	mmHg
	partial pressure	<i>(</i> <b>) )</b> ( <b>)</b>	· · · · · · · · · · · · · · · · · · ·
R	Ideal gas constant	62,360	$mL \cdot mmHg \cdot mol^{-1} \cdot K^{-1}$
	NT 11 1	$mL \cdot mmHg \cdot mol^{-1} \cdot K^{-1}$	
T'	Normal body	37°C	K
	temperature		
$V_D$	Dead space volume	150 mL (Reynolds et al.	mL
		(2010))	Ŧ
$V_{End}$	End-expiration	Normal, Severe OSA, Sim.	mL
	alveolar volume	1-9: 2,300 mL (Reynolds	
		et al. (2010)), Patient Case	
		1: $3,700 \text{ mL}$ and Patient	
		Case 2: $3,400$ IIIL	
	Total nulmanamy	(AUUUUUIIIII et al. $(2013)$ ) 120 mL (Dan Tal (2006))	mI
$V_{pc}$	iotal pullionary	150  IIIL (Defi-1al (2000); Equation at al. (2012))	IIIL
	valuma	roucquier et al. (2015))	
V	Total avatamia	220 mL (Paran and	mI
V <sub>sys,cap</sub>	conjillaries blood	Boulpaen (2000))	111L
	volume	Douipaep (2009))	
	volume		

# Table S2: continued

Parameter	Definition	Value (Source)/Equation	Units in Model
$V_T$	Tidal volume	Normal and Sim. 1-9: 500	mL
		mL (Reynolds et al. (2010)),	
		Severe OSA: 1,000 mL	
		(Cheng and Khoo (2012)),	
		Sim. Patient Case 1: 510	
		mL and Sim. Patient Case 2:	
		560 mL (ARD (2014))	
Vvent	Alveolar ventilation	Eq. 7a	mL
	volume		
$y_{O_2}$	Inspired oxygen	0.21 (Guyton and Hall	Unitless
	mole fraction	(2000))	

# Table S3: Additional Model Variables and Terms

Variable/Term	Description	Equation	Units in Model	Initial Condition (Source)
$C_{d,O_2}$	Dissolved oxygen concentration	Eq. S15	mol/mL	N/A
$J_{O_2,x}$	Molar flux of oxygen across alveolar-capillary membrane	Eq. 89	mol/cm <sup>2</sup>	Eq. 89
HR	Heart rate	Normal, Severe OSA, Sim. 1-9: Constant, Patient Cases: Clinical data	beats/s	73 beats/min (Cheng and Khoo (2012))
P <sub>c,O2</sub>	Average oxygen partial pressure in pulmonary capillary compartment	Eq. S12a	mmHg	Eq. S12a
$P_N$	Normalized OSA patient nasal pressure	Eq. S31	$\operatorname{cm} H_2O$	Input
$P_{N,m}$	Measured OSA patient nasal pressure	Clinical data	$\operatorname{cm} H_2O$	Input
$Q_N$	OSA patient nasal flow	Eq. S20	mL/s	Input

0	Pulmonary flow	Normal Severe	mI /s	Ea S6b
$\triangleleft \qquad \bigtriangledown p$	rate	OSA, Sim, 1-9	1111/3	Lq. 500
	1400	Constant. Patient		
		Cases: Eq. S6b		
$Q_s$	Systemic flow rate	Normal, Severe	mL/s	Eq. S1b
		OSA, Sim. 1-9:		1
		Constant, Patient		
		Cases: Eq. S1b		
$\Delta t$	Differential time	Normal, Severe	s	Normal, Severe
	step	OSA, Sim. 1-9:		OSA, Sim. 1-9:
		Constant, Patient		0.01 s, Patient
		Cases: Eq. S1c		Case 1: 0.008 s,
				Patient Case 2:
				0.007 s
V <sub>A,OSA</sub>	OSA patient	Eq. S21	mL	Case 1: 3,700
	alveolar volume			mL and Case 2:
				3,400 mL
				(Abdeyrim et al.
				(2015))
$v_{pc}$	Pulmonary	Normal, Severe	cm/s	Eq. S8b
	capillary blood	OSA, Sim. 1-9:		
	velocity	Constant, Patient		
		Cases: Eq. S8b		

# Table S4: Additional Physiological and Fitting Parameters

Parameter	Definition	Value (Source)/Equation	Units in Model
A	Total surface area for	84 m <sup>2</sup> (Hsia et al. (2016))	$\mathrm{cm}^2$
	gas exchange in lungs,		
	at rest		
$D_{eff}$	Effective oxygen	Eq. S9a	cm <sup>2</sup> /s
	diffusion coefficient		
$\gamma$	Fitting parameter for	Eq. S19	$mL \cdot s^{-1} \cdot cm H_2 O^{-1}$
	conversion of patient		
	nasal pressure to nasal		
	flow		
$l_{mem}$	Harmonic mean	0.6 µm (Hsia et al. (2016))	cm
	thickness of		
	alveolar-capillary		
	membrane		
$n_V$	Molar volume at STP	$1/22,400 \text{ mol } O_2/\text{mL } O_2$	$mol O_2/mL O_2$
SV	Stroke volume	70 mL/beat (Bruss and	mL/beat
		Raja (2022))	

Parameter	Definition	Value (Source)/Equation	Units in Model
$t_{cycle}$	Total time for control	Eq. S1d	8
-	volume of blood to		
	pass through systemic		
	circulation		
$t_d$	Diffusion time across	Eq. S16	S
	alveolar-capillary		
	membrane		
$t_{sa}$	Total time for control	Eq. S5a	S
	volume of blood to		
	pass through systemic		
	arteries/arterioles		
$t_{sys,cap}$	Total time for control	Eq. S3a	S
	volume of blood to		
	pass through systemic		
	capillaries		
Vsys	Systemic circulation	4,600 mL (Boron and	mL
	blood volume	Boulpaep (2009))	
V <sub>sys,a</sub>	Systemic	770 mL (Boron and	mL
	arteries/arterioles	Boulpaep (2009))	
	blood volume		
$\Delta z$	Differential distance	Eq. S8a	cm

# Table S4: continued



**Figure S1.** A flow diagram depicting the model physiology. The alveoli, pulmonary capillaries, and systemic capillaries were modeled as single compartments. Parameters related to the ambient air (external environment), anatomical dead space, heart, and body tissues were included in the model, but no mass balances were performed over these regions. All oxygen transfer in the systemic circulation was assumed to occur in the capillary region. Therefore, the pulmonary venous and arterial total oxygen concentrations were assumed to be equivalent to the systemic arterial and venous total oxygen concentrations, respectively.

### 1.1 Pulmonary Arterial Oxygenation

Equation 1, as restated below in its expanded form, was obtained by performing an unsteady-state mass balance over a moving control volume in the systemic capillary compartment, with an overall metabolic rate used for modeling oxygen transfer to the body tissues. To determine the mass transfer only occurring out of the control volume, the overall oxygen metabolic rate was multiplied by a ratio quantifying the fraction of the systemic capillary compartment occupied by the control volume:

$$\Delta V \frac{dC_{cv,T}}{dt} = -MR_{O_2} \left(\frac{\Delta V}{V_{sys,cap}}\right)$$

$$\Delta V = Q_s(t) \cdot \Delta t(t) \qquad (S1a) \qquad Q_s(t) = HR(t) \cdot SV \qquad (S1b)$$

$$\Delta t(t) = \frac{t_{cycle}(t) \cdot \Delta t(t=0)}{t_{cucle}(t=0)}$$
(S1c) 
$$t_{cycle}(t) = \frac{V_{sys}}{Q_s(t)}$$
(S1d)

For the OSA patient cases, the systemic blood flow is a function of time as it varies with the input heart rate (Equation S1b). In addition, since  $\Delta t$  was made to vary proportionally with the heart rate, for data storage purposes (Appendix S5.1),  $\Delta V$  remains constant. The finite difference form of Equation 1 is:

$$C_{cv,T}(t + \Delta t) = C_{cv,T}(t) - MR_{O_2}\left(\frac{\Delta t}{V_{sys,cap}}\right)$$
(S2)

Solving Equation S2 over time resulted in the following relation between the total oxygen concentration exiting and entering the systemic capillary compartment:

$$C_{sv,O_2T}(t + t_{sys,cap}(t)) = C_{sa,O_2T}(t) - \frac{MR_{O_2}}{Q_s(t)}$$
(S3)

$$t_{sys,cap}(t) = \frac{V_{sys,cap}}{Q_s(t)}$$
(S3a)

Assuming that all oxygen transfer in the systemic circulation occurs in the capillary region, the total oxygen concentration in the pulmonary arteries and veins was related as:

$$C_{pa,O_2T}(t + t_{cycle}(t)) = C_{pv,O_2T}(t) - \frac{MR_{O_2}}{Q_s(t)}$$
(S4)

In addition, the total oxygen concentration in the pulmonary veins and that entering the systemic capillary compartment were related in time as:

$$C_{sa,O_2T}(t + t_{sa}(t)) = C_{pv,O_2T}(t)$$
(S5)

$$t_{sa}(t) = \frac{V_{sys,a}}{Q_s(t)} \tag{S5a}$$

This assumes no oxygen leakage in the arteriole system. If there is possible arteriolar oxygen transfer to the tissues, the model will be adjusted accordingly. Due to their dependence on the systemic flow rate,  $t_{sys,cap}$ ,  $t_{cycle}$ , and  $t_{sa}$  were all functions of time for the patient cases. However, for the simulations,  $Q_s$ ,  $\Delta t$ ,  $t_{sys,cap}$ ,  $t_{cycle}$ , and  $t_{sa}$  were all constant due to an assumed constant heart rate (Table S3).

## 1.2 Pulmonary Capillary Mass Transfer



**Figure S2.** A schematic of the pulmonary capillary compartment. Deoxygenated blood enters from the pulmonary arteries and is oxygenated as a result of diffusion across the alveolar-capillary membrane.  $\Delta z$  is the length of the differential control volume. Since the overall pulmonary flow passes through the compartment, an effective cross-sectional area is used (sum of all pulmonary capillaries),  $A_{eff}$ , to determine the compartment length,  $L_c$ . Oxygenated blood exits the compartment in the pulmonary veins.

Equation 4, as restated below, was obtained by performing an unsteady-state mass balance over a moving control volume in the pulmonary capillary compartment:

$$\Delta V \frac{dC_{cv,T}}{dt} = k_{pc} \left( C_{A,O_2}(t) - C_{cv,d}(t) \right)$$
$$\Delta V = Q_p(t) \cdot \Delta t(t) \qquad (S6a) \qquad Q_p(t) = HR(t) \cdot SV \qquad (S6b)$$

For the OSA patient cases, the pulmonary blood flow is a function of time as it varies with the input heart rate (Equation S6b). Considering that the total pulmonary and systemic flow rates are equal to the cardiac output,  $\Delta V$  for the pulmonary capillary compartment is constant due to the varying  $\Delta t$ .

The finite difference form of Equation 4 is:

$$C_{cv,T}(t) = C_{cv,T}(t - \Delta t) + \frac{k_{pc}}{Q_p(t - \Delta t)} \left( C_{A,O_2}(t - \Delta t) - C_{cv,d}(t - \Delta t) \right)$$
(S7)



**Figure S3.** Effect of perfusion on model results. As the heart rate is increased, equilibration between the alveolar (dashed lines) and pulmonary capillary (solid lines) oxygen partial pressures occurs further along the capillary due to reduced residence time, indicating the limiting effect of perfusion in mass transfer.

To obtain an oxygen profile along the pulmonary capillaries, the starting boundary of the control volume was used to define its location. The pulmonary blood velocity was then used to track the movement of this volume along the pulmonary capillary compartment, introducing spatial dimensionality into the model and ensuring the significant influence of perfusion, which controls the equilibration between alveolar and end-capillary oxygen partial pressure (demonstrated with Figure S3).As a result, Equation S7 was transformed into:

$$C_{pc,O_2T}(z,t) = C_{pc,O_2T}(z-\Delta z,t-\Delta t) + \frac{k_{pc}}{Q_p(t-\Delta t)} \left( C_{A,O_2}(t-\Delta t) - C_{pc,O_2d}(z-\Delta z,t-\Delta t) \right)$$
(S8)  
$$\Delta z = v_{pc}(t) \cdot \Delta t(t)$$
(S8a) 
$$v_{pc}(t) = \frac{Q_p(t)}{A_{eff}}$$
(S8b)

Due to its dependence on the pulmonary flow rate,  $v_{pc}$  is also function of time for the patient cases. However, since  $\Delta t$  varies proportionally with the heart rate,  $\Delta z$  remains constant.  $Q_p$ ,  $\Delta t$ , and  $v_{pc}$  were kept constant for all the simulated cases due to an assumed constant heart rate (Table S3). Oxygen transfer into the control volume was modeled assuming a pseudo-steady state diffusion process across the alveolar-capillary membrane:

$$J_{O_2,x}(z,t) = \frac{D_{eff}}{l_{mem}} \left( C_{A,O_2}(t) - C_{pc,O_2d}(z,t) \right)$$
(S9)

$$D_{eff} = \frac{D_{L,O_2} \cdot l_{mem}}{\beta_p \cdot A} \tag{S9a}$$

In addition, the total oxygen concentration at the entrance of the pulmonary capillary compartment was set as pulmonary arterial value, while the total oxygen concentration in the pulmonary veins was set as the end-capillary value.

$$C_{pc,O_2T}(0,t) = C_{pa,O_2T}(t)$$
(S10)

$$C_{pv,O_2T}(t) = C_{pc,O_2T}(L_c,t)$$
 (S11)

#### 1.3 Alveolar Oxygenation

Converting Equation 5 to a finite difference form enabled efficient calculation of the alveolar oxygen partial pressure at any time point during inspiration. This equation was used under the condition that  $\frac{V_A(t) - V_A(t - \Delta t)}{\Delta t} > 0.$ 

$$P_{A,O_{2}}(t) = \frac{\left(V_{A}(t) - V_{A}(t - \Delta t)\right)\left(P_{I,O_{2}} - P_{A,O_{2}}(t - \Delta t)\right)}{V_{A}(t - \Delta t)}$$

$$- \frac{k_{l} \cdot \beta_{p} \cdot \Delta t \left(P_{A,O_{2}}(t - \Delta t) - P_{c,O_{2}}(t - \Delta t)\right)R \cdot T}{V_{A}(t - \Delta t)} + P_{A,O_{2}}(t - \Delta t)$$

$$P_{c,O_{2}}(t) = \frac{C_{c,O_{2}}(t)}{\beta_{p}}$$
(S12)
(S12)

Converting Equation 6 to a finite difference form enabled efficient calculation of the alveolar oxygen partial pressure at any time point during expiration. This equation was used under the condition that  $\frac{V_A(t) - V_A(t - \Delta t)}{\Delta t} < 0.$ 

$$P_{A,O_2}(t) = -\frac{k_l \cdot \beta_p \cdot \Delta t \left( P_{A,O_2}(t - \Delta t) - P_{c,O_2}(t - \Delta t) \right) R \cdot T}{V_A(t - \Delta t)} + P_{A,O_2}(t - \Delta t)$$
(S13)

 $\Delta t$  was kept constant for all the simulations but varied for the OSA patient cases according to Equation S1c.

# 2 INITIAL CONDITION FOR PULMONARY CAPILLARY PROFILE

As an approximation, the initial oxygen profile (t=0) along the pulmonary capillary compartment was determined by solving a steady state mass balance over a fixed control volume.

$$C_{pc,O_2T}(z) = C_{pc,O_2T}(z - \Delta z) + \frac{k_{pc}}{Q_p(t=0)} (C_{A,O_2}(t=0) - C_{pc,O_2d}(z - \Delta z))$$
(S14)

The initial conditions for the total and dissolved oxygen concentrations in the pulmonary arteries were used for  $C_{pc,O_2T}(z=0)$  and  $C_{pc,O_2d}(z=0)$ , respectively. The starting value for the total oxygen in the pulmonary arteries was calculated using Equation S4. As an additional form of validation, the predicted average oxygen partial pressure in the pulmonary arteries ( $P_{pa,O_2} = 41 \text{ mmHg}$ ) approximates the expected physiological value of 40 mmHg (Guyton and Hall (2000)) for a normal subject at rest.

# 3 ASSUMPTION OF PSEUDO-STEADY STATE DIFFUSION ACROSS ALVEOLAR-CAPILLARY MEMBRANE

The molar flux of oxygen across the alveolar-capillary membrane can be represented as (Popel (1989)):

$$J_{O_2,x}(z,t) = -D_{eff} \frac{dC_{d,O_2}}{dx}$$
(S15)

Equation S9a was used as an approximation of the effective diffusion coefficient, which was applied to estimate the diffusion time across the alveolar-capillary membrane:

$$t_d = \frac{l_{mem}^2}{D_{eff}} = \frac{\left(0.6 \times 10^{-4} \,\mathrm{cm}\right)^2}{8 \times 10^{-7} \,\mathrm{cm}^2/\mathrm{s}} = 0.005 \,\mathrm{s}$$
(S16)

The process time (time for boundary changes) was taken to be on the order of the time for one breath. With a normal breathing rate of 12 breaths/min, this would be 5 s, while, with a hyperventilatory rate of 24 breaths/min, the process time would be 2.5 s. For both of these cases, the process time was concluded to be sufficiently larger than the diffusion time, allowing for the pseudo-steady state simplification.

# 4 ESTIMATION OF OSA PATIENT LUNG VOLUME USING RECORDED NASAL PRESSURE



Figure S4. Patient 1 raw and normalized nasal pressure signals over isolated normal breathing region.

For each patient, the recorded pressure signal was observed to have a non-zero mean, which resulted in unphysiological values for the lung volume after conversion. Therefore, to allow for a more realistic representation of the volume, each pressure signal was normalized to a mean of zero by subtracting a moving average taken over 70 seconds for Patient 1 and 50 seconds for Patient 2. The time for each moving average was chosen such that it was on the order of a few breaths, while ensuring that the normalized signal maintained the integrity of the raw pressure signal (Figures S4 and S5).

The following equations were used to simulate normal breathing patterns and corresponding flow rates for the OSA patients, with the tidal volume and breathing rate for each determined using the patient



Figure S5. Patient 2 raw and normalized nasal pressure signals over isolated normal breathing region.



**Figure S6.** Actual and simulated signals for Patient 1. A) Normalized patient nasal pressure signal during isolated normal breathing sequence. B) Simulated normal lung volume and flow rate using breathing rate from isolated patient signal ( $b_r = 20$  breaths/min) and tidal volume from patient height ( $V_T = 0.51$  L).

height-based ideal body weight and normalized pressure signal, respectively:

$$V_A(t) \approx \frac{1}{2} V_T \sin\left(2\pi \cdot b_r \cdot t - \frac{\pi}{2}\right) + \left(\frac{1}{2} V_T + V_{End}\right)$$
(S17)

and

$$\frac{dV_A}{dt} \approx \pi \cdot b_r \cdot V_T \cos\left(2\pi \cdot b_r \cdot t - \frac{\pi}{2}\right)$$
(S18)



**Figure S7.** Actual and simulated signals for Patient 2. A) Normalized patient nasal pressure signal during isolated normal breathing sequence. B) Simulated normal lung volume and flow rate using breathing rate from isolated patient signal ( $b_r = 12$  breaths/min) and tidal volume from patient height ( $V_T = 0.56$  L).

A positive nasal pressure indicated inspiration, while a negative nasal pressure indicated expiration. Therefore, for each patient, the fitting parameter for conversion to nasal flow was determined by setting the average maximum nasal pressure (after normalization) during the isolated normal breathing sequence (Figures S6A and S7A) to the maximum simulated inspiratory flow rate (Figures S6B and S7B):

$$\gamma = \frac{\pi \cdot b_r \cdot V_T}{P_{N\{\text{norm,avg.max}\}}}$$
(S19)

Each normalized nasal pressure signal was converted to nasal flow as:

$$Q_N(t) = \gamma \cdot P_N(t) \tag{S20}$$

The patient alveolar volume, approximated as the lung volume, was determined by integration of the obtained flow signal:

$$V_{A,OSA}(t) = V_{End} + \int Q_N(t) \,\mathrm{d}t \tag{S21}$$



**Figure S8.** Pressure swings during a segment with obstructive events. A) Raw pressure signal during polysomnography study. B) Simulated lung volume after converting normalized pressure using fitting parameter. The sections outlined in red show a sequence with multiple obstructive events and drastic pressure swings, resulting in a low lung volume after conversion. The grayed portions indicate obstructive respiratory events, as labeled in (A).

While analyzing Patient 2, a region with multiple obstructive events and drastic pressure swings was observed (Figure S8A, outlined in red). Although the majority of the volume signal after conversion is reasonable, this section is an example where relying solely on nasal pressure results in values of the simulated lung volume that are much lower than the observed residual volume in OSA patients (Abdeyrim et al. (2015)), with the lowest point dropping close to 1.0 L (Figure S8B). Using RIP chest and abdomen signals, which are available within most clinical polysomnographies, in conjunction with the nasal pressure will likely provide a more accurate representation of patient lung volume in such cases.

# **5 MATLAB IMPLEMENTATION**

# 5.1 Pulmonary Arterial Oxygenation



 $t_i = t_{i+1}$ 

**Figure S9.** Model framework. Breathing and heart rate data (patient cases), physiological and solving parameters, and initial conditions were input to the model. Each equation was run for multiple time iterations to obtain the outputs.

#### All MATLAB codes used to solve the model equations can be found at GitHub:

https://github.com/Cardiovascular-Modeling-Laboratory/OSAModel.git.

Equation S4 was implemented into the MATLAB code as:

$$C_{pa,O_2T}\left(i + \text{floor}\left(\frac{t_{cycle}(i)}{dt(i)}\right) - 1\right) = C_{pv,O_2T}(i-1) - \frac{MR_{O_2}}{Q_s(i-1)}$$
(S22)

$$dt(i) = \frac{t_{cycle}(i) \cdot dt(1)}{t_{cycle}(1)}$$
(S22a)

Here, the for loop index, i, was used to represent a single time iteration. For the patient cases, dt was made to vary proportionally with the heart rate to maintain the number of iterations defining the movement of the control volume through the entire systemic circulation, artery/arteriole system, and systemic capillaries. This was done to avoid any gaps in the output data arrays for  $C_{pa,O_2T}$ ,  $C_{sa,O_2T}$ , and  $C_{sv,O_2T}$ , in the case of a decrease in heart rate between subsequent time iterations, or overwriting of previous data, in the case of an increase in heart rate. In Equation S22a, dt(1) and  $t_{cycle}(1)$  represent the initial conditions for dt and  $t_{cycle}$ , respectively. The floor  $\left(\frac{t_{cycle}(i)}{dt(i)}\right)$  term in Equation S22 was used to determine the number of iterations defining the movement of the control volume through systemic circulation. Due to the variation of dt for the patient cases, this value remains constant. Similarly, Equations S5 and S3 were implemented as:

$$C_{sa,O_2T}\left(i + \text{floor}\left(\frac{t_{sa}(i)}{dt(i)}\right)\right) = C_{pv,O_2T}(i)$$
(S23)

and

$$C_{sv,O_2T}\left(i + \text{floor}\left(\frac{t_{sys,cap}(i)}{dt(i)}\right)\right) = C_{sa,O_2T}(i) - \frac{MR_{O_2}}{Q_s(i)}$$
(S24)

The floor  $\left(\frac{t_{sa}(i)}{dt(i)}\right)$  and floor  $\left(\frac{t_{sys,cap}(i)}{dt(i)}\right)$  terms were used to determine the number of iterations defining the movement of the control volume through systemic artery/arteriole system and systemic capillaries, respectively. These values also remain constant due to the varying dt in the patient cases. For all the simulations,  $Q_s$ , dt,  $t_{sys,cap}$ ,  $t_{cycle}$ , and  $t_{sa}$  were implemented as constants in the code.

#### 5.2 Pulmonary Capillary Mass Transfer

Equation S8 was implemented into the MATLAB code using the following setup:

$$C_{pc,O_2T}(1,i) = C_{pa,O_2T}(i)$$
 (S25)

$$C_{pc,O_2T}(2:\text{end},i) = C_{pc,O_2T}(1:\text{end}-1,i-1) + \frac{k_{pc}}{Q_p(i-1)} \left( C_{A,O_2}(i-1) - C_{pc,O_2d}(1:\text{end}-1,i-1) \right)$$
(S26)

The result of  $C_{pc,O_2T}$  was a matrix, where each column represented the spatial oxygen profile at a specific time point. In addition, the total oxygen concentration in the pulmonary veins was determined as:

$$C_{pv,O_2T}(i) = C_{pc,O_2T}(\text{end}, i)$$
(S27)

For all the simulations,  $Q_p$  was implemented as a constant in the code.

# 5.3 Alveolar Mass Transfer

Equations S12 and S13 for inspiration and expiration, respectively, were implemented into the MATLAB code as:

$$P_{A,O_{2}}(i) = \frac{\left(V_{A}(i) - V_{A}(i-1)\right)\left(P_{I,O_{2}} - P_{A,O_{2}}(i-1)\right)}{V_{A}(i-1)} - \frac{k_{l} \cdot \beta_{p} \cdot dt(i-1)\left(P_{A,O_{2}}(i-1) - P_{c,O_{2}}(i-1)\right)R \cdot T}{V_{A}(i-1)} + P_{A,O_{2}}(i-1)$$
(S28)

and

$$P_{A,O_2}(i) = -\frac{k_l \cdot \beta_p \cdot dt(i-1) \left( P_{A,O_2}(i-1) - P_{c,O_2}(i-1) \right) R \cdot T}{V_A(i-1)} + P_{A,O_2}(i-1)$$
(S29)

These equations were coded into a separate function. For all the simulations, dt was implemented as a constant in the code, but, for the OSA patient cases, it was varied according to Equation S22a.

#### 5.4 Time Step for Simulations and Patient Cases

The initial time step (dt(1)) for the simulations and patient cases was chosen based on the following conditions: ensuring i) model stability over the period of study, ii) model convergence, and iii) maximal computational efficiency. Convergence was tested using the normal breathing simulation. The model was run at values of the time step lower than the selected value of 0.01 s (Table S3), and it was ensured that the solutions were reasonably close for each one. dt(1)>0.01 s was not chosen as the solution began to lose stability and diverge. Although the model can be run at dt(1)<0.01 s, computation time is significantly longer. Therefore, 0.01 s was chosen to maintain a balance between all three conditions. For the patient cases, since dt(1) varies with the heart rate (Equation S22a), the initial time steps of 0.008 s for Patient 1 and 0.007 s for Patient 2 were chosen such that the maximum value would be 0.01 s:

$$\{dt(1) \text{ for patient cases}\} = \frac{0.01 \cdot HR_{\{\min\}}}{HR(1)}$$
(S30)

#### 5.5 Estimation of OSA Patient Lung Volume Using Recorded Nasal Pressure

For Patient 1, the raw nasal pressure signal was normalized as:

$$P_N = P_{N,m} - \operatorname{movmean}(P_{N,m}, 70/dt_m)$$
(S31)

For Patient 2, the raw nasal pressure signal was normalized as:

$$P_N = P_{N,m} - \operatorname{movmean}(P_{N,m}, \ 50/dt_m)$$
(S32)

 $dt_m$  was the time step for measurement. Eq. S21 was implemented into the MATLAB code for each case to determine the time-dependent lung volume using cumulative integration:

$$V_{A,OSA}(1) = V_{End} \tag{S33}$$

$$V_{A,OSA}(2: \operatorname{End}_i - \operatorname{Start}_i + 1) = V_{End} + \operatorname{cumtrapz}(dt_m, Q_N(\operatorname{Start}_i + 1: \operatorname{End}_i))$$
(S34)

Start<sub>i</sub> and End<sub>i</sub> represented the starting and ending time elements for each breathing pattern, respectively, and were chosen to avoid the time period when CPAP was administered to the patients during the sleep studies as well as segments of time with any signal loss in recorded data due to patient movement. In addition, Start<sub>i</sub> was chosen around a point where the nasal pressure was zero, before inspiration, which followed an ideal normal breath with similar inspiratory and expiratory flow rates. The resulting vector of  $V_{A,OSA}$  for each patient was imported into the main code to serve as a column for a reference lookup table.

#### 5.6 Lookup Tables

Interpolation using reference lookup tables was employed to determine the values of alveolar volume, heart rate (for patient data), and dissolved oxygen concentration at each time step. For the OSA simulations, variations of Equation 7 were used to construct breathing patterns. The time and alveolar volume data for each pattern was converted into a .mat file and imported into the main code. Heart rate was kept constant for the simulated cases. A similar conversion process was repeated for the patient data, which also included the variable heart rate input in the .mat file. The data extracted from the .mat files served as reference lookup tables in the main code. Interpolation for alveolar volume and heart rate was carried out using:

$$V_A(i) = \text{interp1}(t_{\text{data}}, V_{\text{data}}, t(i))$$
(S35)

and

$$HR(i) = interp1(t_{data}, HR_{data}, t(i))$$
(S36)

 $t_{data}$  (time) represented the input column of the lookup table, while  $V_{data}$  (alveolar volume) and  $HR_{data}$  (heart rate) were the output columns.

Due to the non-linearity of Equation 3 and to minimize computational effort, a lookup table was constructed to determine the dissolved oxygen concentration at each spatial position. Equation 3 was used to calculate the hemoglobin oxygen saturation for a range of dissolved oxygen concentrations. To ensure accuracy, the dissolved oxygen column in the table ranged from 0 to  $2 \times 10^{-6}$  mol/mL with increments of  $2.5 \times 10^{-10}$  mol/mL. These values were then used with Equation 2 to determine the corresponding total oxygen concentrations. This allowed the use of interpolation:

$$C_{j,O_2d}(i) = \operatorname{interp1}(\operatorname{CT}, \operatorname{Cd}, C_{j,O_2T}(i))$$
(S37)

CT (total oxygen concentration) represented the input column of the lookup table, while Cd (dissolved oxygen concentration) was the output column. j in Equation S37 defines the spatial location. j = pa, pc, pv, sa, and sv for the pulmonary arteries, pulmonary capillary compartment, pulmonary veins, systemic arteries, and systemic veins, respectively.

# 6 MODEL OUTPUTS

#### 6.1 Comparison of Normal Breathing Results with Expected Physiological Values

Expected physiological values for the dissolved oxygen concentration in the blood vessels are not commonly found in literature. Therefore, after converting the wide range of blood oxygen partial pressures in the systemic vessels (Guyton and Hall (2000); Ortiz-Prado et al. (2019); van Faassen et al. (2009)) using  $\beta_p$  (Table S2), values of 119-140  $\mu$ M and 38-63  $\mu$ M were obtained for the systemic arteries and veins, respectively. The average values predicted by the model (Figure 1) for the systemic arteries and veins fall within these ranges. It is, however, important to note that the dissolved oxygen is sensitive to the choice of solubility factor.

#### 6.2 Calculation of Percent Decreases for OSA Simulations

	Percent Decrease (%) in Variable				
Simulation	$S_{sa,O_2}$	$S_{sv,O_2}$	$C_{sa,O_2d}$	$C_{sv,O_2d}$	Mass Transfer
Sim. 1	4.0	5.7	30	7.6	7.0
Sim. 2	4.0	5.6	29	7.5	1.2
Sim. 3	4.9	6.9	33	9.0	13
Sim. 4	5.7	8.0	35	10	19
Sim. 5	1.8	2.6	18	3.6	6.0
Sim. 6	1.7	2.5	17	3.5	7.2
Sim. 7	11	15	47	18	21
Sim. 8	5.4	7.5	34	9.8	20
Sim. 9	3.0	4.4	25	6.0	9.4
Severe OSA	8.0	11	41	14	8.3

Table S5: Percent Decreases for OSA Simulations

Percent decreases in saturation and dissolved oxygen concentration for each simulation were calculated by comparing the average normal values to the absolute minimum points over the time of study:

$$\left\{\% \text{ decrease in } S_{j,O_2}\right\} = \left(\frac{S_{j,O_2\{\text{avg,norm}\}} - S_{j,O_2\{\text{min}\}}}{S_{j,O_2\{\text{avg,norm}\}}}\right) \cdot 100$$
(S38)

$$S_{j,O_{2}\{\text{avg,norm}\}} = \frac{S_{j,O_{2}\{\text{max,norm}\}} + S_{j,O_{2}\{\text{min,norm}\}}}{2}$$
(S38a)

$$\left\{\% \text{ decrease in } C_{j,O_2d}\right\} = \left(\frac{C_{j,O_2d\{\text{avg,norm}\}} - C_{j,O_2d\{\text{min}\}}}{C_{j,O_2d\{\text{avg,norm}\}}}\right) \cdot 100$$
(S39)

$$C_{j,O_2d\{\text{avg,norm}\}} = \frac{C_{j,O_2d\{\text{max,norm}\}} + C_{j,O_2d\{\text{min,norm}\}}}{2}$$
(S39a)

j = sa and sv for the systemic arteries and veins, respectively.

The percent decrease in mass transfer for each simulation was approximated by comparing the average difference in systemic arterial and venous dissolved oxygen for the normal condition to a temporally

averaged difference over the simulated OSA pattern:

{% decrease in mass transfer} = 
$$\left(\frac{\Delta C_{d,norm} - \Delta C_{d,OSA}}{\Delta C_{d,norm}}\right) \cdot 100$$
 (S40)

$$\Delta C_{d,norm} = C_{sa,O_2d\{avg,norm\}} - C_{sv,O_2d\{avg,norm\}}$$
(S40a)

$$\Delta C_{d,OSA} = \frac{1}{t_{OSA}} \int_{360}^{t_{total}} \left( C_{sa,O_2d}(t) - C_{sv,O_2d}(t) \right) dt$$
(S40b)

$$t_{\rm OSA} = t_{\rm total} - 360 \text{ s} \tag{S40c}$$

 $t_{\text{OSA}}$  is the duration of the simulated OSA breathing pattern, while  $t_{\text{total}}$  is the total time for breathing data in each case, both in seconds.

#### 6.3 Calculation of Proposed Burden Scores

Patient	<b>Event Sequence</b>	Total Sequence		
ratient	Area Deviation	Area Deviation	Area Deviation from	
	from Wake	from Wake	Threshold during	
	Sequence (M·s)	Sequence (M·s)	Hypoxia (M·s)	
1	0.006	0.146	0.129	
2	0.009	0.024	0.023	

Table S6: Area Data for Proposed Burden Scores

The average arterial dissolved oxygen for wakefulness was determined as:

$$C_{sa,O_2d\{\text{avg,wake}\}} = \frac{1}{n} \cdot \sum_{k=1}^{n} C_{sa,O_2d\{\text{avg,wake},k\}}$$
(S41)

$$C_{sa,O_2d\{\text{avg,wake},k\}} = \frac{\int_{t_{\{k,s\}}}^{t_{\{k,e\}}} C_{sa,O_2d}(t) \, \mathrm{d}t}{t_{\{k,e\}} - t_{\{k,s\}}}$$
(S41a)

In Equation S41, n was defined as the total number of wake sequences considered (n = 3 for the current analysis). The subscripts s and e in Equation S41a represent the start and end times for each wake sequence, respectively. The proposed hypoxia burden score was determined as:

$$\{\text{Proposed hypoxia burden score}\} = \frac{\int_{t_1}^{t_2} \left( C_{sa,O_2d\{\text{avg,wake}\}} - C_{sa,O_2d}(t) \right) \, \mathrm{d}t}{t_2 - t_1} \tag{S42}$$

In Equation S42,  $t_1$  represents the start time for the analyzed sequence ( $t_1 = 360$  s for the total sequence), and  $t_2$  represents the end time for the analyzed sequence. For the proposed burden score of the hypoxic period over the total patient sequence, the upper threshold was calculated as:

$$C_{sa,O_2d\{\text{hypoxia}\}} = C_{sa,O_2d\{\text{avg,wake}\}} - C_{sa,O_2d\{\text{std,wake}\}}$$
(S43)

 $C_{sa,O_2d\{std,wake\}}$  represents the standard deviation of the arterial dissolved oxygen during wakefulness.



Figure S10. Schematic of area used to calculate proposed burden score for the hypoxic periods over the total sequences.

The proposed burden score for hypoxic period during the total sequence was calculated using the area deviation of the dissolved arterial oxygen from  $C_{sa,O_2d\{hypoxia\}}$  (Figure S10). To determine the score, this area value was normalized by the total time for hypoxia.





**Figure S11.** Patient 1 inputs to model over multi-hour portion of sleep study. A) Recorded heart rate and cardiac output. B) Raw nasal pressure. C) Nasal flow rate obtained from conversion of nasal pressure. D) Lung volume obtained from integration of nasal flow rate.

To evaluate the clinical applicability of the model over longer time periods, data from 3-hour and 2-hour portions of baseline polysomnographies, without any CPAP administration, was fed to the model for Patient 1 and 2, respectively. The heart rate and lung volume were used as direct inputs (Figures S11 and S13), while hemoglobin oxygen saturation and dissolved oxygen concentration in the systemic arteries and veins were output from the model (Figures S12 and S14).



**Figure S12.** Patient 1 outputs from model over multi-hour portion of sleep study. A) Model output hemoglobin oxygen saturation in systemic arteries and veins, along with recorded pulse oximeter data  $(S_{p,O_2})$ . B) Model output dissolved oxygen concentration in systemic arteries and veins.



**Figure S13.** Patient 2 inputs to model over multi-hour portion of sleep study. A) Recorded heart rate and cardiac output.B) Raw nasal pressure. C) Nasal flow rate obtained from conversion of nasal pressure. D) Lung volume obtained from integration of nasal flow rate.



**Figure S14.** Patient 2 outputs from model over multi-hour portion of sleep study. A) Model output hemoglobin oxygen saturation in systemic arteries and veins, along with recorded pulse oximeter data  $(S_{p,O_2})$ . B) Model output dissolved oxygen concentration in systemic arteries and veins.

## 6.5 Statistical Analysis

Variable	<b>Overall Average</b>	Event Series Averages
		0.964
S	0.975	0.971
$O_{sa,O_2}$		0.957
		0.956
	0.762	0.740
S -		0.744
$O_{sv,O_2}$		0.735
		0.738
		64.8
$\Delta C_{\perp}(u\mathbf{M})$	80.7	72.7
$\Delta \mathbf{c}_{\mathbf{d}} (\mu \mathbf{W} \mathbf{I})$		57.7
		56.8

Table S7: Data for Statistical Analysis

The differences for the one-sample t-tests were calculated by subtracting the overall average of each variable from averages of the same variable over identified event series intervals:

$$\left\{\text{Difference in } S_{j,O_2}\right\} = S_{j,O_2\{\text{avg,event}\}} - S_{j,O_2\{\text{avg}\}}$$
(S44)

$$S_{j,O_2\{avg\}} = \frac{1}{t_{study}} \int_{360}^{t_{total}} S_{j,O_2}(t) dt$$
 (S44a)

$$t_{\text{study}} = t_{\text{total}} - 360 \text{ s} \tag{S44b}$$

$$S_{j,O_2\{\text{avg,event}\}} = \frac{1}{t_{\text{event}}} \int_{t_{\text{start}}}^{t_{\text{end}}} S_{j,O_2}(t) \, \mathrm{d}t \tag{S44c}$$

 $t_{\text{event}} = t_{\text{end}} - t_{\text{start}}, \quad t_{\text{start}} = \{\text{Event series start}\}, \quad t_{\text{end}} = \{\text{Event series end}\}$  (S44d) j = sa and sv for systemic arteries and veins, respectively.

$$\{\text{Difference in } \Delta C_d\} = \Delta C_{d\{\text{avg,event}\}} - \Delta C_{d\{\text{avg}\}}$$
(S45)

$$\Delta C_{d\{avg\}} = \frac{1}{t_{study}} \int_{360}^{t_{total}} \left( C_{sa,O_2d}(t) - C_{sv,O_2d}(t) \right) dt$$
(S45a)

$$\Delta C_{d\{avg,event\}} = \frac{1}{t_{event}} \int_{t_{start}}^{t_{end}} \left( C_{sa,O_2d}(t) - C_{sv,O_2d}(t) \right) dt$$
(S45b)

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