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Online supplement

Dynamic CO_2 therapy in periodic breathing – a modeling study to determine optimal timing and dosage regimes

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1. Derivation of the Model Equation

The fundamental equation that determines dc/dt, the rate of change of alveolar CO_2 fraction, can be expressed as shown in Francis et. al. 2000b (reference 12 in the main manuscript):

$$\frac{dc}{dt} \times V_L = \overline{\dot{V}}_A \overline{C} - \left[(\overline{\dot{V}}_A + v)(\overline{C} + c) \right] - \beta \overline{\dot{Q}} c$$

V_L represents alveolar volume. Lower case c is the displacement of CO_2 fraction away from its mean value $\overline{C}$. Likewise lower case v represents the displacement of alveolar ventilation from its mean value $\overline{\dot{V}}_A$. Because of the time delay, the value of v at time t (v_t) depends on the value of c at some time δ previously ($c_{(t-\delta)}$). Near the steady state, therefore, $v_t = S \times c_{(t-\delta)}$, where S represents chemoreflex gain (additional ventilation per unit increase in c). We adopted the convention of using litres for all volumes, and minutes for all times.

The terms in the above equation represent flow of CO_2 into and out of the lung arising from metabolism, ventilation, and exchange with blood stores. Metabolic production of CO_2 by the body is expressed as $\overline{\dot{V}}_A \overline{C}$. The rate of CO_2 removal from the lung by ventilation is expressed as $(\overline{\dot{V}}_A + v)(\overline{C} + c)$. Oscillations in arterial CO_2 necessitate a net transfer of CO_2 from the lung into extra pulmonary stores (in comparison with the steady state) at a rate of $\beta \overline{\dot{Q}} c$, where β indicates the solubility of CO_2 in blood and $\overline{\dot{Q}}$, cardiac output, assuming that pulmonary venous CO_2 is stable.

For the purpose of our numerical model we define the instantaneous alveolar CO_2 fraction and ventilation as upper case C and V respectively, where $C = \overline{C} + c$, and $V = \overline{\dot{V}}_A + v$. We also define the rate of metabolic production of CO_2 as Vco_2, where $Vco_2 = \overline{\dot{V}}_A \overline{C}$. Therefore, the above equation can be rewritten as:

$$\frac{d(C - \overline{C})}{dt} \times V_L = Vco_2 - VC - \beta \overline{\dot{Q}} (C - \overline{C})$$

The mean value of CO_2 fraction $\overline{C}$ is not time-variant, i.e. $d\overline{C}/dt = 0$. Hence, the change in instantaneous alveolar CO_2 fraction over the small time step Δt can be written as Equation 4 in the main manuscript:

$$\Delta C = \frac{\Delta t}{V_L} \times (Vco_2 - VC - \beta \dot{\overline{Q}}(C - \overline{C}))$$

We used 1 second steps for the model. We investigated whether a change in the time step had any effect in the model output, to ensure that the model is not affected by numerical instability instead of system instability (due to large time steps). We ran the simulation with time steps of 0.1, 0.5, 1, 5, and 10 seconds. We found no difference in stability for time steps of 1 second or less. Numerical instability was observed when the time steps were 5 seconds or more.

2. Sensitivity analysis

We further analyzed the sensitivity of the model using extreme (minimum and maximum) values of its parameters as follows: chemoreflex delay (0.28 and 0.67 min), cardiac output (2.5 and 4.5 l/min), chemoreflex gain (1100 and 1800 l/min/atm), metabolic production of CO_2 (0.1 and 0.4 l/min) and lung volume (3 and 6 l). These values were based on previous observations on heart failure patients with periodic breathing (reference 12 in the main manuscript). We ran simulations on all the 32 (= 2^5) possible combinations of these extreme cases using 2% peak concentration and 180 degrees duration of treatment episode within the periodic breathing cycle.

We measured the magnitude of periodic breathing, i.e. standard deviation of ventilation, before treatment in all the combinations. We measured the optimum relative periodic breathing value, i.e. the smallest value of:

$$\frac{\text{Standard deviation of ventilation after treatment}}{\text{Standard deviation of ventilation before treatment}}$$

We measured the optimum phase, i.e. the phase of treatment at which we obtained the optimum relative periodic breathing value. We also measured the margin of error for the optimum phase (the window of treatment phase at which periodic breathing is reduced by at least 30%).

Twenty six of the thirty two combinations were unstable; the remaining six produced a stable or too small ventilatory oscillation pattern to initiate treatment episodes; hence there were no optimum treatment regions in these cases. Nineteen of the twenty six unstable combinations responded to the default treatment regime shape (2% peak concentration and 180 degrees duration of treatment episode within the periodic breathing cycle). The remaining seven of these unstable combinations did not respond significantly to the above treatment regime; a change in peak concentration (other than 2%) and/or a change in *duration* of treatment episode within the periodic breathing cycle (other than 180 degrees) was needed to generate a reduction of >20% in periodic breathing. Even in these cases the region of optimal treatment *phase* was unchanged. For simplicity we have tabulated the results of the simulations that generated oscillations and responded to the default treatment regime shape because these are directly mutually comparable (Table S-1).

We performed factor analysis with these data, using Design-Expert software (revision 7.1.6). We found that the optimum treatment phase is mainly dictated by the chemoreflex delay as shown in Figure S-1. The optimum treatment phase for periodic breathing with shorter chemoreflex delays lay ahead of the peak ventilation whereas periodic breathing with longer delays lay later than peak ventilation. We also noted

that larger lung volumes shifted the optimum treatment phase slightly later in the cycle (by 20 degrees for the variation of 3-6 litres).

Extreme changes in the various physiological parameters can affect how well the model responds to a particular dosing regime (i.e. the optimum relative periodic breathing value and margin of error at the optimum treatment phase), but these outcomes are not directly correlated to any particular physiological variable.

Table S-1: Simulation results using combinations of extreme (Low 'L' and High 'H') cases of the model physiological parameters: chemoreflex delay (0.28 and 0.67 min), cardiac output (2.5 and 4.5 l/min), chemoreflex gain (1100 and 1800 l/min/atm), metabolic production of CO_2 (0.1 and 0.4 l/min) and lung volume (3 and 6 l)

Simulation number	delta	Q	S	Vco_2	V_L	PB untreated (standard deviation of ventilation)	Optimal phase (degrees)	Relative PB at optimum phase	Margin of error at optimum phase (degrees)
1	L	L	L	L	L	2.6929	-30	0.5596	05
2	H	L	L	L	L	3.3789	70	0.4490	15
3	L	H	L	L	L	1.9096	-45	0.0320	60
4	H	H	L	L	L	2.2177	70	0.1912	75
8	H	H	H	L	L	3.2803	40	0.8545	-
9	L	L	L	H	L	9.6474	-40	0.2118	50
10	H	L	L	H	L	13.3839	60	0.1669	65
13	H	H	L	H	L	0.5216	60	0.2656	90
16	H	H	H	H	L	15.3097	50	0.5990	40
18	H	L	L	L	H	2.4360	90	0.2306	55
20	L	L	H	L	H	2.7655	-10	0.6258	10
22	H	H	L	L	H	0.9893	80	0.0402	105
24	H	L	L	H	H	3.8526	90	0.0430	95
25	L	H	H	L	H	2.3798	-10	0.0241	30
27	L	L	H	H	H	10.5568	-20	0.4194	25
28	H	H	H	L	H	2.9465	80	0.2907	30
30	H	L	H	H	H	16.4133	80	0.2469	20
31	L	H	H	H	H	7.9386	-25	0.0209	60
32	H	H	H	H	H	11.8448	70	0.1946	55

5	L	L	H	L	L	3.4310	These did not respond to the standard treatment regime
6	H	L	H	L	L	4.3349	
7	L	H	H	L	L	2.8329	
12	L	L	H	H	L	15.8887	
14	H	L	H	H	L	24.4287	
15	L	H	H	H	L	13.6187	
23	H	L	H	L	H	3.6245	
11	L	H	L	H	L	0.0431	These were either stable or produced too small oscillations
17	L	L	L	L	H	0.0072	
19	L	H	L	L	H	2.24E-04	
21	L	L	L	H	H	4.54E-04	
26	L	H	L	H	H	3.30E-05	
29	H	H	L	H	H	0.0332	

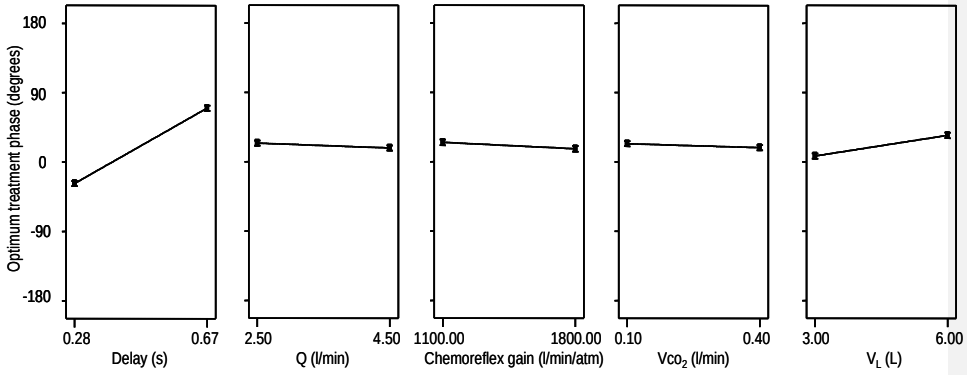

Figure S-1: Physiological parameter dependence of the optimum treatment phase.

The optimum treatment phase is notably affected by the chemoreflex delay and to a lesser extent the lung volume, but not by cardiac output, chemoreflex gain and the metabolic production rate of CO_2.

3. Effect of peak concentration and treatment duration

By varying both duration and concentration, it is possible to produce a 3-dimensional (3D) representation of efficacy of treatment. Figure S-2 demonstrates that the periodic breathing can be exacerbated as well as improved.

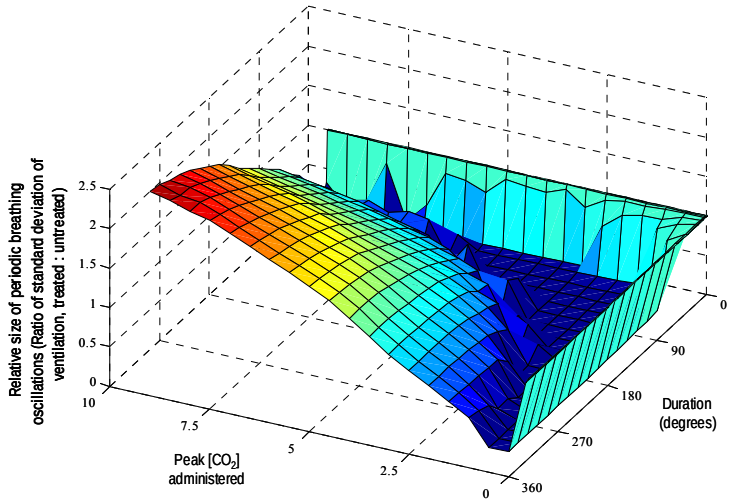

Figure S-2: 3D image of the effect of concentration (%) and treatment duration (degrees)

The periodic breathing can be worsened (areas shaded orange and red) as well as improved (areas shaded green and blue) by varying treatment duration and peak CO_2 concentration.

4. Table of previous studies with calculated values of increase in ventilation due to inspired CO_2

Table S-2

Author	$FiCO_2$	$FetCO_2$	$FetCO_2$-$FiCO_2$	Decrease in $FetCO_2$-$FiCO_2$	Minimum increment in alveolar ventilation that must have occurred with CO_2 treatment
Berssenbrugge *et al.* 1983 (5)	0	-	-	-	49%
	>0 such that $PaCO_2$ increased approx. by 1 mmHg	-	-		
Steens *et al.* 1994 (32)	0 (no treatment)	36.2mmHg (4.76%)	4.76	49%	96%
	3%	41.2mmHg (5.42%)	2.42		

Xie *et al.* 1997 (39)	0 (no treatment)	5.3%	5.3	22%	28%
	1.65%	5.8%	4.15		
Andreas *et al*. 1998 (1)	0 (no treatment)	-	-	-	25% estimated by the authors
	-	+4mmHg	-		
Lorenzi-Filho *et al.* 1999 (24)	0 (no treatment)	4.18%min average	4.18	33%	49%
	1.85%	4.66%min average	2.81		
Szollosi *et al*. 2004 (33)	0 (no treatment)	43.2mmHg (5.6%)	5.6	29%	40%
	2.1%	46.8mmHg (6.1%)	4		
Thomas *et al*. 2005 (35)	0 (no treatment)	35.8mmHg (4.71%)	4.71	between -2% and 19.5%	between -2% and +24%
	0.5-1.5%	40.3mmHg (5.3%)	3.8 - 4.8		