Dynamic CO₂ therapy in periodic breathing: a modeling study to determine optimal timing and dosage regimes

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Mebrate Y, Willson K, Manisty CH, Baruah R, Mayet J, Hughes AD, Parker KH, Francis DP. Dynamic CO₂ therapy in periodic breathing: a modeling study to determine optimal timing and dosage regimes. J Appl Physiol 107: 696–706, 2009. First published July 23, 2009; doi:10.1152/japplphysiol.90308.2008.—We examine the potential to treat unstable ventilatory control (seen in periodic breathing, Cheyne-Stokes respiration, and central sleep apnea) with carefully controlled dynamic administration of supplementary CO₂, aiming to reduce ventilatory oscillations with minimum increment in mean CO₂. We used a standard mathematical model to explore the consequences of phasic CO₂ administration, with different timing and dosing algorithms. We found an optimal time window within the ventilation cycle (covering ~1/6 of the cycle) during which CO₂ delivery reduces ventilatory fluctuations by >95%. Outside that time, therapy is dramatically less effective: indeed, for more than two-thirds of the cycle, therapy increases ventilatory fluctuations >30%. Efficiency of stabilizing ventilation improved when the algorithm gave a graded increase in CO₂ dose (by controlling its duration or concentration) for more severe periodic breathing. Combining gradations of duration and concentration further increased efficiency of therapy by 22%. The (undesirable) increment in mean end-tidal CO₂ caused was 300 times smaller with dynamic therapy than with static therapy, to achieve the same degree of ventilatory stabilization (0.0005 vs. 0.1710 kPa). The increase in average ventilation was also much smaller with dynamic therapy (0.005 vs. 2.015 l/min). We conclude that, if administered dynamically, dramatically smaller quantities of CO₂ could be used to reduce periodic breathing, with minimal adverse effects. Algorithms adjusting both duration and concentration in real time would achieve this most efficiently. If developed clinically as a therapy for periodic breathing, this would minimize excess acidosis, hyperventilation, and sympathetic overactivation, compared with static treatment.

Abolition or reduction of PB would improve this outcome in CHF patients. However, the potential improvement of quality of life alone, from improved sleep, may make the development and investigation of novel therapies worthwhile. Modeling studies can facilitate such developments and inform subsequent clinical investigations to test their relevance.

The use of inhaled CO₂ to stabilize PB has been investigated since the early 1980s (5). Several other papers since then have reported that the administration of constant concentrations of inhaled CO₂ elevates the troughs in CO₂ oscillations (2, 24, 32, 39), preventing apneas, provided that sufficient CO₂ is administered. However, the systemic consequences of the resulting hyperventilation and sympathetic overactivation have made this a less attractive treatment option (1, 24). While this form of static CO₂ delivery reduces the oscillations in ventilatory parameters, the associated arousals are not reduced, with no overall improvement in sleep quality (33). This may be due to the excess CO₂ directly stimulating the cortex or reducing the threshold for cortical arousal.

A fixed increase in inspired CO₂ [inspired CO₂ fraction (FiCO₂)] mandates an increase in ventilation and, therefore, increases the work of breathing. This is often commented on in previous studies (1, 2, 5, 24, 32, 33, 35, 38, 39), but not always quantified. However, it can be easily calculated because, for constant net exhaled volume of CO₂, the narrowed gap between expired and inspired CO₂ must be compensated for by a reciprocal increase in alveolar ventilation (Eq. 1).

\[ \Delta V = \frac{V_{CO_2}}{\Delta(FETCO_2 - FICO_2)} \] (1)

where \( \Delta V \) is the change in alveolar ventilation; \( V_{CO_2} \) is a constant volume of body production of CO₂; and \( \Delta(FETCO_2 - FICO_2) \) is the change in difference of end-tidal CO₂ fraction (FETCO₂) to FiCO₂. Using this calculation, which provides only a lower limit on the increment in ventilation, we see that ventilation is raised by up to 96% (24–96%). We have summarized calculated values of increase in ventilation due to inspired CO₂ in previous studies (Supplementary Table S2; the online version of this article contains supplementary data). In fact, alveolar ventilation would have to have increased by even more than this, because the increase in ventilatory work is likely to increase VCO₂. Lorenzi et al. concluded: “Although CO₂ inhalation abolishes CSR [Cheyne-Stokes respiration]-CSA [central sleep apnea] and reduces the frequency of arousals, it also increases ventilation and would therefore augment the energy and blood flow demands of the respiratory muscles in the face of low cardiac output. Therefore, it is unlikely that
CO₂ inhalation would be a useful long-term therapy for CSR-CSA in patients with CHF” (24).

In this study, we use mathematical modeling to investigate treating PB using optimally graded doses of inspired CO₂ through dynamic delivery.

We aim to deliver targeted CO₂ to counteract the troughs in end-tidal CO₂ oscillations, thereby limiting the total quantity of inspired CO₂ administered. This might minimize the oscillations in the end-tidal CO₂ oscillations, thereby limiting the total quantity of CO₂ administered.

We hypothesized that a small dose of inspired CO₂ would reduce PB, if administered dynamically at an optimal phase and amplitude of ventilatory oscillation. This modeling approach allows a study of the consequences of different algorithms on the resultant control patterns of reproducibly unstable ventilatory control system.

METHODS

Regulation of Ventilation

Ventilation can be considered to be regulated through a feedback control loop of two physiological mechanisms: the chemoreflex and pulmonary gas exchange, which produce the controller and plant gain, respectively. The controller gain is the change in ventilation due to a change in end-tidal CO₂, and plant gain is a change in end-tidal CO₂ as a result of a change in ventilation (20).

Potential Steady State of the Feedback Control System

The dependence of FETCO₂ on steady-state alveolar ventilation (plant gain) is an inversely proportional relationship, because the constant average metabolic production of CO₂ (26). FETCO₂, end-tidal CO₂, is the Potential Steady State of the Feedback Control System.

The constant average metabolic production of CO₂ is determined by the chemoreflex response curve. This is shown as a hyperbolic curve (the isometabolic curve) when CO₂ is plotted against ventilation.

Constant Average Metabolic Production of CO₂ = Ventilation \times FETCO₂  \tag{2}

The dependence of ventilation on end-tidal CO₂ (controller gain) is determined by the chemoreflex response curve. This is shown as a linear relationship (Eq. 3) in Fig. 1, implying a constant value of chemoreflex gain, but can also be nonlinear (26).

\begin{equation} \text{Change in Ventilation} = \text{Chemoreflex gain} \times \text{Change in FETCO₂} \tag{3} \end{equation}

The intercept of these two response curves is where the ventilation control system is potentially in equilibrium (Fig. 1).

The stability of this feedback control system depends on how it responds to small perturbations from the equilibrium state. If, after a small perturbation away from the equilibrium point, the system responds cause it to diverge further away from the equilibrium point, the system is unstable. In contrast, if the system returns to equilibrium, it is stable (26).

The Dynamic Treatment Model

We modified a previously published iterative model (26). In its original form, the model maps system behavior following a small, transient perturbation in CO₂ from a steady-state condition and hence predicts whether the cardiorespiratory control system will be stable or unstable for a wide range of both linear and nonlinear chemoreflex response curves.

The development of the model described here allows the introduction of inspired CO₂ at any desired time and dose during the simulation and allows the effects of this on the ventilation pattern to be quantified. Hence we were able to identify those treatment strategies that are likely to be of clinical benefit.

The Modified Model

The iteration of the model begins with the instantaneous CO₂ value at the steady-state position at time \( t_o \), followed by an introduction of a small, transient, positive perturbation on the CO₂ (Fig. 2). The instantaneous ventilation value \( V \) at time \( t \) (i.e., \( t_o + \Delta t \), where \( \Delta t \) is 1 s in the model) is then calculated from a previous value of CO₂ (\( C_{o2} \)) using a linear function of the chemoreflex gain. The new value of CO₂ for time \( t \) is calculated using a difference equation below (Eq. 4), derived from a previously published analytic equation (13).

\[ \Delta C = \frac{\Delta t}{V} \times [V_{CO₂} - V - \beta Q(\bar{C} - \bar{C})] \tag{4} \]

where \( \Delta C \) is the incremental change in end-tidal CO₂ concentration during the small time increment \( \Delta t \), \( V_l \) is a constant lung volume, \( V \) and \( C \) are instantaneous ventilation and end-tidal CO₂ variables, respectively, at time \( t \), \( \bar{C} \) is the mean alveolar CO₂ fraction, \( Q \) is a constant cardiac output, and \( \beta \) is a constant of solubility of CO₂ in blood.

The new value of \( V \) is then tested according to a configured treatment regime for whether the model should administer CO₂ therapy or not. If ventilation is unstable and the value of \( V \) (both in amplitude and phase of oscillation) is in the configured treatment zone (as described in The Treatment Regime section below), then a corresponding programmed CO₂ treatment dose is added to the new value of the end-tidal CO₂.

In the treatment model, the instantaneous CO₂ at time \( t \) (\( C_t \)) is given by,

\[ C_t = C_{o2-\Delta t} + \Delta C + (\text{CO₂ Therapy}) \tag{5} \]

Here \( C_{o2-\Delta t} \) is the instantaneous CO₂ at the previous time point \( (t-\Delta t) \). \( \Delta C \) is the component of change in CO₂ that is caused by normal gas exchange processes, but assuming zero inspired CO₂, and is obtained from Eq. 4. CO₂ therapy is the component of change in CO₂ that is caused by inspired CO₂ and is calculated from the configured values of “peak concentration” and treatment phase window “duration”. This value is dependent on the amplitude and phase of the ventilation cycle at time \( t \), by an algorithm discussed in more detail below, in The Treatment Regime section.

The new end-tidal CO₂ value is then used to calculate the new value of ventilation.

In the model, the following cardiorespiratory parameters were held constant to standard values for all of our simulations: cardiac output, 3.5 l/min; metabolic production of CO₂, 0.2 l/min; lung volume, 5 liters; linear chemoreflex response curve with slope of 1,200 l/min⁻¹·atm⁻¹, chemoreflex delay, 20 s; solubility of CO₂ in blood, 0.23 l/min·atm·l⁻¹·min⁻¹.
Severity of Ventilatory Oscillations

In this study, the severity of ventilatory oscillations was measured by calculating the relative standard deviation of ventilation over a 15-min simulation period following a 5-min initial transient interval. The smaller the relative standard deviation of ventilation, the more stable the breathing.

The Treatment Regime

Visually, a cycle of ventilation can be represented as a clock face, with peak ventilation (hyperpnea) at 12 o’clock and trough ventilation (hypopnea) at 6 o’clock (Fig. 3). Increasing amplitude of oscillation is represented by an increase in distance away from the center of the clock. The treatment envelope is represented as a sector of the clock, the treatment zone, then it adds the programmed treatment CO2 to give the next instantaneous value of end-tidal CO2 (ETCO2). The derivation of the model was discussed in detail in Manisty et al. (26). See text for definition of acronyms.

5 l·1⁻¹·atm⁻¹; start point of CO2 equal to steady-state CO2, 4%; start point of ventilation equal to steady-state ventilation, 5 l/min; and positive CO2 perturbation, 0.001% 10 s after start. It has been shown that these parameters can be assumed constant near the equilibrium point, since they are not critical in the genesis of ventilatory instability (13). The constant values are based on previously published figures that would be typical for a patient with heart failure and PB (4, 14, 22, 26, 28, 36, 37).

The CO2 therapy is configured to automatically adjust to the amplitude of oscillation and the phase of ventilation during a treatment episode. This allowed us to dynamically configure the therapy (in concentration, duration, and delivery phase) to test the most effective treatment profile.

Use of Real-Time Fourier Analysis to Detect Phase Within the PB Cycle

PB sometimes has a sinusoidal envelope of ventilation, but more often has a nonsinusoidal shape, with the lower part flat, representing apnea.
In our model, we monitor the ratio of instantaneous to mean ventilation. The model uses a Fourier transform method to provide a sinusoidal fit to a wide range of oscillatory ventilation waveforms. The software determines the phase in the cycle of PB. This is achieved by performing a sliding Fourier transform on the preceding ventilation data, acquired during an approximately 1-min period, that can be adjusted to match the observed PB cycle length. The sinusoidal fit to the ventilation is then derived by constructing a sine wave with the amplitude and phase of the lowest frequency oscillatory component in the Fourier transform (i.e., that which is closest in cycle time to the period of ventilation signal transformed). This fitting technique has the advantage that it is not adversely affected by oscillatory cycles containing periods of apnea. It will also be unaffected by breath-to-breath fluctuations of the respiratory signal at frequencies much higher than that of PB.

Figure 6 shows an example of the sinusoidal fitting process satisfactorily applied to simulated noisy PB with periods of apnea. The phase of PB is detected validly.

RESULTS

This model allowed the effect of dynamically timed therapy to be simulated, and the effect of changes in the therapy protocol to be studied. With no treatment programmed, when the model was run, it developed a pattern of PB, as shown in Fig. 7. The period of oscillations was \( \sim 60 \) s.

We then implemented one of a range of treatment regimes and repeated the simulation, from the same starting point as the no-treatment simulation. The resulting ventilatory pattern was documented and compared with the pattern resulting from no-treatment simulation.

The treatment regimes all contained a zone of therapy (duration), which occurred at a certain phase in the PB cycle, and had a certain peak concentration of administered CO\(_2\). The
regimes differed in their 1) timing of center point (midangle) of the treatment episode within the PB cycle (expressed as a “treatment phase”, with 0° representing the time of peak ventilation); 2) duration of treatment episode within the PB cycle (expressed as “duration” an angle within a circle, with, for example, 90° representing treatment for one-fourth of the cycle); and 3) peak concentration of administered CO2 [expressed as “peak concentration” a fraction between 0 and 1 (100% CO2)].

During a treatment episode (i.e., in the therapy zone), the concentration rises from zero to the peak concentration and back to zero again, following a smooth sigmoid distribution of a cosine curve, with peak at the treatment phase, which is the center point of the duration.

**Study 1: Existence of an Optimum Phase Within PB Cycle for CO2 Therapy**

We used the model to vary the phase of ventilation at which the CO2 was delivered, while keeping peak concentration and treatment duration constant. We set the duration of therapy to be one-half the PB cycle (180° out of the 360° cycle), and peak CO2 concentration to be 1%. We repeatedly ran the model from the same baseline starting conditions (Fig. 7) with treatment phases varying in steps of 10° from 180° before peak ventilation to 180° after peak ventilation. To assess efficacy, we measured the ratio of the size of ventilatory oscillations (standard deviation of ventilation) with and without treatment. Values < 1.0 indicate reduced amplitude of PB.

We found that the CO2 therapy is most effective when delivered at a specific range of treatment phases, in this case between −30° and +40° around peak ventilation (0°), as shown in Fig. 8. The severity of PB is sharply reduced (by >95%) when the treatment phase approaches the optimum range from either end. Outside this phase range, the CO2 therapy actually worsens the PB (increased by >30%).

This particular range of optimum treatment phase is dependent on other parameters, and, if these other parameters are changed, the range of optimum treatment phase also changes.

**Study 2: Effect of CO2 Dose on Ventilatory Stability**

We investigated the effect, on the ventilatory pattern, of administering peak concentrations of CO2, ranging from 0 (no treatment) to 10%. The duration of CO2 therapy was kept the same for each simulation at 180°, as in study 1. The treatment phase was also kept at peak ventilation for each simulation; this was shown in study 1 to be within the optimum range of phases for reducing PB for the given baseline conditions.

Initially, we titrated the peak concentration value of administered CO2 from zero in small increments to assess when sufficient CO2 had been delivered to affect the ventilatory pattern. When the concentration of administered CO2 was <0.01%, there was little or no effect on the PB. Small increments of the peak concentration from 0.01% started to affect the ventilatory pattern. Thereafter, peak concentrations between 0.1 and 0.2% reduced the PB sharply. Beyond this point, further increases in concentration resulted in only minimal reductions in PB (Fig. 9).

For any concentration of 0.2% or above, there was a time window during which treatment could be administered and yield a >90% reduction in PB. The most effective abolition of PB was observed with the highest peak CO2 dose (oscillations reduced by >98%). However, this high concentration has
disadvantages: high concentration treatments reduce the margin of error for the optimum treatment phase (−20° to +30° for 10% CO₂ vs. −30° to +40° for 2% CO₂) and would be associated with greater systemic side effects from the CO₂. When higher peak concentration treatment (10% CO₂) is delivered outside the optimum phase window, PB worsens by >300%, whereas at lower peak concentration treatment (2% CO₂) PB worsens by <33%. We, therefore, used 2% CO₂ for subsequent simulations, as it provided the best balance of attenuation of ventilatory oscillations with the widest margin of error. Figure 9 demonstrates how the magnitude of residual PB varies with increasing concentration of administered CO₂ therapy per ventilation cycle (treatment phase = 0°, duration = 180°).

Study 3: Effect of Duration of CO₂ Therapy on Ventilatory Pattern

We studied the effect of duration of treatment on the ventilatory pattern. The simulation was run for various treatment durations between 0° and 360° (where supplemental CO₂ treatment continues throughout the PB cycle, following the cosine curve). For each simulation, the peak concentration and treatment phase of administered CO₂ were kept the same (2% and 0°, respectively). These were shown to be within the optimal range for reducing PB.

We titrated the duration of CO₂ therapy from 0° in small increments to assess when sufficient CO₂ had been delivered to affect the ventilatory pattern. When the duration of CO₂ delivery was <0.5°, there was little or no effect on the PB. Small increments of duration between 0.5° and 12° reduced the PB sharply. Further increase of the duration beyond this point had little further effect (Fig. 10). For any duration of treatment of 12° or above, there was a time window during which treatment could be administered and yield >90% reduction in PB. The most effective abolition of PB was observed with the longest treatment duration of 360° (oscillations reduced by >98%). However, this long duration has disadvantages: it allows a smaller margin of error for the optimum treatment phase (20° less for duration of 360° compared with 180°). Furthermore, treatment with 360° duration worsens PB by ~50%, if delivered outside the optimum treatment phase, compared with <33% increase in degree of PB when applying at 180° duration. In view of these factors, we used a treatment duration of 180° for subsequent simulations, which we felt to be optimal.

Study 4: Interchangeability of CO₂ Therapy Concentration and Duration

We found that a decrease in the concentration of CO₂ administered could be compensated for by an increase in the duration of therapy. In studies 2 and 3, we showed that the effect of peak concentration on PB has a pattern similar to that of the effect of treatment duration. Therefore, it should be possible to use several combinations of peak concentration and duration to deliver a similar dose of CO₂ therapy, to produce an equivalent effect.

We have presented a three-dimensional representation of efficacy of treatment in the online supplement (Supplementary Fig. S2). The relationship between the peak concentration and duration can be expressed as:

$$\text{dose} \propto \text{peak concentration} \times \text{duration} \quad (6)$$

Linear increase or decrease of peak concentration and duration simultaneously will change the resultant dose quadratically. This has its benefits in treating PB with moderate-to-severe amplitude oscillations, as we show below.

Study 5: The Effect of Grading Peak Concentration and Duration Simultaneously When Treating Moderate to Severe (0.6–6.0 l/min) Amplitude Oscillation

Therapy is not administered for low-amplitude PB (<0.6 l/min), while, for high-amplitude PB (severe) (>6.0 l/min), it is more effective to deliver uniform duration and concentration to reduce the amplitude of PB. However, for moderate-to-
severe amplitude (between 0.6 and 6.0 l/min) PB, the optimal dose of CO₂ is no longer uniform but is quadratically related to the amplitude of the PB. The quadratic dose relation is achieved by simultaneously grading the duration and concentration delivery linearly (Fig. 11). This increased the efficacy of therapy by 22%, compared with linearly graded dosing. Grading either parameter linearly in isolation produced a narrower spectrum of optimum treatment range at these moderate-to-severe amplitudes, as shown in Fig. 11 diagrams.

**Study 6: Comparison of the Effectiveness of Static and Dynamic CO₂ Delivery on PB**

We programmed the model to deliver a static CO₂ therapy at all times to the baseline configuration (Fig. 7) and hence established the constant CO₂ concentration that optimally reduced PB (Fig. 12).

We performed the simulation with small increments of CO₂ concentration of 0.05% from 0 to 1% and in increments of 0.5% from 1 to 10%. We found that the optimum concentration for the given configuration with static therapy is ~2%. This therapeutic concentration reduced the PB by >99%. However, this static treatment increased the average end-tidal CO₂ from 4 to 4.3%, and the average ventilation from 5 to 8.4 l/min, over the 20-min treatment period. Therefore, abolishing ventilatory oscillations using static CO₂ delivery is associated with significant increase in average ventilation (Fig. 12).

We studied the effect of using a dynamic treatment at a peak concentration of 2% (the same value as for this static treatment) on the average end-tidal CO₂ and average ventilation. We also found the static concentration that gave the same reduction in PB (97%), as this dynamic treatment, and calculated the effect on the average end-tidal CO₂ and average ventilation. The increases in mean end-tidal CO₂ of the dynamic and static treatments were 0.0005 and 0.1710 kPa, respectively. The increases in mean ventilation of the dynamic and static treatments were 0.005 and 2.015 l/min, respectively.

**Fig. 11. Results comparison of linearly and quadratically graded dose therapy strategies. Both linearly graded dose therapies give narrow optimum treatment option (bottom left and middle) compared with quadratically graded dose treatment (bottom right). Top: duration, either uniform, above a threshold ventilation amplitude (left), or linearly increasing, to a maximum value, with amplitude of ventilatory oscillation (right). Middle: CO₂ concentration, either uniform, above a threshold ventilation amplitude (left), or linearly increasing, to a maximum value, with amplitude of ventilatory oscillation (right). Bottom: results of three possible combinations of therapy strategies: linearly graded dose achieved by uniform duration and graded CO₂ concentration ([CO₂]) (left); linearly graded dose achieved by uniform [CO₂] and graded duration (middle); quadratically graded dose achieved by increasing both duration and [CO₂] with amplitude of ventilatory oscillation (right).**
CO2 had risen to 1.75%, the residual PB oscillations were enough to affect the ventilatory pattern. By the time inspired steadied of the fixed values used in 2.5–4.5 l/min, chemoreflex gain 1,100–1,800 l/min, we introduced a series of 0.25% increments in initial period, during which the PB had become fully developed over 2 hours of simulated time.

We started with the baseline configuration, but, after the initial period, during which the PB had become fully developed and persistent, we introduced a series of 0.25% increments in inspired CO2 at 5-min intervals, from 0.00 to 5.00%.

We found that inspired concentrations >0.75% were large enough to affect the ventilatory pattern. By the time inspired CO2 had risen to 1.75%, the residual PB oscillations were <1/100 of the baseline size. However, this entailed a substantial increase in ventilation. At an optimum inspired CO2 value of 1.75%, average ventilation had already increased by >50%.

Study 7: The Effect of Other Parameters on the Optimum Treatment Phase of Ventilation

We studied the effect of other parameters on the optimum treatment window: cardiac output, chemoreflex gain, lung volume, metabolic production of CO2, and lung volume. For the extremes of chemoreflex gain, metabolic production of CO2, and lung volume.

Chemoreflex delay has a more dramatic effect, as might be expected. As chemoreflex delay ranges from 17 to 40 s, the period of oscillation increases proportionately (by a factor of ∼2.5), and the optimal treatment phase moves from −10 to +80° referenced to peak ventilation. This change in optimal treatment phase corresponds to a change in time of a magnitude similar to the increase in chemoreflex delay. Therefore, in a clinical device, it may be possible to predict the optimum treatment phase region by measuring the period of the ventilatory oscillation and inferring from this the approximate value of the chemoreflex delay.

Further sensitivity analysis of the model is described in the online supplement.

Study 8: Peripheral and Central Chemoreceptors

In the previous sections, we have concentrated on a single chemoreceptor response for clarity in introducing the principles of the dynamic administration of CO2. To investigate the response of the algorithm on multiple chemoreceptors, we reconfigured the model with two notional groups of chemoreceptors with individual group chemoreflex gain and delay. The first set of chemoreceptors was programmed with a gain of 180 l·min⁻¹·atm⁻¹ and had one of three short time delays (15, 20, or 25 s). The second set of chemoreceptors was programmed with a gain of 1,020 l·min⁻¹·atm⁻¹ and had one of three long time delays (80, 100, or 120 s). This corresponds to a split into a ratio of 15 to 85% of the gains used in our simulations using a single chemoreflex gain. This ratio is typical of published values (34). We ran the simulation with various combinations of the individual set chemoreflex delay times. We incorporated a low-pass filter in line with the second set of receptors to account for the sluggish response of central chemoreceptors.

In all cases, we found that, whenever the system is unstable, there turns out to be a window of optimum CO2 administration to effect a reduction in PB. Similar findings were obtained with

![Fig. 12. Response of the model to static therapy. The solid line shows the change in average ventilation (V̇_average) with increasing inspired CO2 values for these parameters lower and higher (cardiac output, metabolic production of CO2, and chemoreflex delay). The total CO2 delivered during the static treatments were >80% more than the amount delivered during dynamic treatment (Table 1).](image)

### Table 1. Comparison of the effect of static and dynamic treatments on the average ventilation and the average end-tidal CO2

<table>
<thead>
<tr>
<th>Type of Treatment Regime</th>
<th>Concentration of Delivered CO2, %</th>
<th>Degree of Attenuation of Periodic Breathing, %</th>
<th>Average End-tidal CO2 Fraction, kPa</th>
<th>Average End-tidal CO2 Fraction Effect of Treatment</th>
<th>Average Ventilation, l/min</th>
<th>Average Ventilation Effect of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dynamic treatment</td>
<td>2 (peak)</td>
<td>97</td>
<td>4.00</td>
<td>+0.0005</td>
<td>5.0</td>
<td>+0.005</td>
</tr>
<tr>
<td>Static treatment with same efficacy as the above</td>
<td>1.4</td>
<td>97</td>
<td>4.17</td>
<td>+0.1700</td>
<td>7.0</td>
<td>+2.000</td>
</tr>
<tr>
<td>Optimum static treatment</td>
<td>2</td>
<td>99</td>
<td>4.30</td>
<td>+0.3000</td>
<td>8.4</td>
<td>+3.400</td>
</tr>
</tbody>
</table>
more equal distribution and when three receptor groups were simulated.

Study 9: Effect on System Stability of Large-amplitude, Long-period Initial Driving Oscillations

To establish whether the results above are peculiar to the particular transient, small-amplitude, initial perturbation that we tried, we repeated the simulations with large-amplitude, long-period initial driving oscillations. The driving oscillations lasted for 5 min, had cycle time of 1 min, and were of a size sufficient to generate apnea at the nadir of ventilation. The treatment was then applied as above, and, after a further 10 min, the resulting size of oscillation was calculated over a 15-min period. An example is shown in Fig. 13A.

The results for optimum treatment phase are shown in Fig. 13B. In general, they are the same as those found with single, transient, small-amplitude, initial perturbations. Figure 13B also shows that the treatment delivered during the apneic phase (close to 180°) did not affect the PB.

DISCUSSION

We have devised and studied a novel mathematical model to deliver optimally timed dynamic CO₂ therapy to ameliorate PB. Using our model, we were able to control the timing, concentration, and duration of CO₂ delivered, as a function of the phase and amplitude of ventilatory oscillations. We have consistently shown that there is an optimum phase window in which a small dose of CO₂ therapy can improve PB. If therapy is delivered outside the optimum range of treatment phase, PB worsens. Importantly, the model allows the prediction of this margin of error.

We considered several factors to determine the optimum treatment values, namely, the maximum PB reduction, with minimum dose delivered and maximum margin of error to remain in the optimum treatment window. For example, in Figs. 9 and 10, a treatment with concentration of 0.8% and duration of 40° may appear as effective as 2% concentration and 180° duration. However, these graphs show the response of the system only when treatment is delivered at the ideal time. In practice, it is useful to have an algorithm that works, even if treatment is not delivered at the ideal time, giving a wider window of opportunity to treat effectively. The window of optimum treatment phase is only one-half the size (−10 to +20°), with the former configuration than with the latter (−30 to +30°). The latter configuration is, therefore, preferable. Furthermore, we have identified that the ideal pattern for this algorithm to work would be with both the concentration and duration (length of treatment episode per ventilation cycle) increasing linearly (quadratic increase of dose), with increasing degree of oscillation.

Most relevant to potential clinical therapies, this study showed that the dynamic treatment increased neither the average end-tidal CO₂, nor the average ventilation, from the baseline value. This is in contrast to the traditional static treatment, where our model shows these parameters to be increased by physiologically significant amounts. Our investigation, in study 6, demonstrates that the dynamic treatment requires a much smaller dose of CO₂, compared with static treatment that reduces PB by the same level.

Previous clinical studies have used static CO₂ to treat PB (1, 5, 24, 32, 33, 35, 39), based on the rationale that patients with PB have arterial CO₂ levels below their apneic threshold. With static supplementary CO₂ administration, the apneas are eliminated, as corroborated by our study 6. However, the mean ventilation increases, as demonstrated in Supplemental Table S2 of the online supplement. In contrast, our dynamic therapy aims to target only the troughs in end-tidal CO₂ that drive hypoventilation. The targeted inspired CO₂ will potentially counteract a transient reduction in arterial PCO₂, preventing it from falling below the apneic threshold, without grossly increasing its mean value. Our proposed system aims not only to prevent apneas, but also to attenuate hypopneas. By minimizing end-tidal CO₂ oscillations, ventilatory oscillations may potentially be reduced or abolished without significantly increasing mean ventilation.

There are some patients in whom mean ventilation is low: in these, our concern to minimize the increment in mean ventilation is not justified, and so the proposed therapeutic model need not be considered particularly advantageous.

We believe that the reason why PB worsens when treatment timing is outside the optimum region is that the inspired CO₂ contributes to augmenting hypercapnia instead of counteracting the transient reduction of CO₂.

One potential advantage of algorithms such as the one we present here is that it has a relatively short “memory”. Sleep is
known to be characterized by discontinuous changes in system characteristics (20, 21, 22), which could be seriously problematic for a therapy strategy that relied on static therapy, or therapy aimed at a particular CO₂ or ventilation target. Our dynamic cycle-detecting approach, however, automatically adjusts to new system characteristics as they arise. Moreover, if system characteristics become stable, therapy automatically ceases.

Previous static CO₂ administration regimes have improved breathing in CSR, but not sleep quality, as reported by Steens et al. (32), Andreas et al. (1) and Szollosi et al. (33). The latter two groups suggested that the main cause for this lack of improvement in sleep quality is elevated sympathetic activity, due to hypercapnia. If this is so, the dynamic treatment suggested by our model may potentially enable reduction of PB without such arousals.

Thomas et al. (35) showed that CO₂ concentrations as low as 0.5% were an effective adjunct to continuous positive airway pressure in the treatment of severe complex sleep apneas, improving sleep quality as well as respiratory disturbances. Although our model corroborates the effectiveness of low-concentration CO₂ therapy, it is not possible, from their work, to determine which proportion of the synergistic effects of CO₂ and continuous positive airway pressure resulted in these beneficial effects. Our baseline simulation differs from this study in that we used levels of cardiac output compatible with those found in CHF patients (as in the clinical studies cited above), whereas they treated patients without heart failure.

Although our simulations showed that the approach of gradual increase in inspired CO₂ abolished PB at low inspired CO₂ level, it also showed that this increased the average ventilation hugely. This demonstrates that we still face similar problems of elevated ventilation with gradual CO₂ increase as we would with static CO₂ administration.

Added dead space has been shown to stabilize PB (19). However, this is achieved at the expense of increased ventilation similar to static CO₂ treatment.

Two previous groups have produced ingenious and simple devices, which arrange to deliver added inspired CO₂ during the patient’s hyperventilation phase to increase end-tidal CO₂ (3, 31). With these systems, therapy always centers around a phase near peak ventilation with a fixed time delay due to (circuit and physiological) dead space. As our model suggests, the period of PB can vary such that significant changes in the phase of optimal CO₂ delivery away from peak ventilation are required for varying chemoreflex delays. Such variation cannot be achieved with these systems, but is obtainable with a model-mediated approach.

In both cited methods, once the fresh gas flow is set in its application to control breathing, the circuit could interpret increases in baseline ventilation as hyperventilation and would deliver CO₂. Our proposed method would treat only periodic fluctuations in ventilations and not changes in the baseline value.

Study Limitations

This study is a mathematical simulation, and not a clinical study. Although this can be considered a limitation, it has the advantage of our being able to guarantee a constant underlying control system instability. This ensures that differences between one run of the simulation and another can be attributed to differences in the therapy algorithm and are not due to random environmental fluctuations. Clinical studies paralleling this one in terms of variety of algorithms tested would be difficult, because biological variability would necessitate large numbers of replicate experiments to give reasonable certainty that observed differences were due to differences between algorithms.

Another limitation of this study is that, to limit the number of simulations to show the aims of the study, we concentrated on the simple linear response of the chemoreflex gain, although the model can be configured to different curve responses, as shown in Manisty et al. (26). In a linear response chemoreflex gain, its slope near the steady-state CO₂ is the predominant factor to determine system stability (27).

In this study, only a single example of an unstable respiratory control system was studied in great depth, i.e., a single set of constant values describing chemoreflex response characteristics, chemoreflex delay, lung volume, cardiac output, and metabolic production of CO₂. However, in study 7, we varied each parameter between its extreme ranges, while maintaining our standard set of values for the others.

We have presented in an online supplement a further sensitivity analysis of the model, in which we have shown how it reacts to combinations of extreme changes to the various physiological parameters that are likely to be found in practice. These sensitivity analyses enable us to appreciate the relative importance of the various physiological parameters as sources of variations to the model outputs. Although these analyses demonstrate that the extreme range of unstable system configurations gives qualitatively similar responses to simulated treatments as those using our standard physiological parameter set, they do not give the detailed behavior of the system for the full spectrum of the input states.

One other limitation of this study is that, for simplicity and brevity, we have not included the possible effect of upper airway resistance in the model. However, in reality, a fall in CO₂ may well result in the rise of upper airway resistance, which will reduce ventilation in a synergistic manner with the same direction of effect as the chemoreceptor-mediated fall in ventilatory effort. Therefore, we generally expect the overall behavior of the system will be similar, although the instability of a system with upper airway resistance sensitive to CO₂ will be more enhanced (29).

In this study, we have used only a limited number of chemoreceptors for simplicity and brevity. Future development of the model should include a large number of chemoreceptors with individual gain and delay times.

This is a “basic science” study, applying respiratory and control system modeling. Previous mathematical models have increased our understanding of the pathophysiology of PB. Similarly, mathematical modeling provides insights into the construction of therapeutic algorithms. This study demonstrates that it is feasible to develop an algorithm that could work in real time (since our CO₂-administering software module uses only real-time input of modeled ventilation and outputs only a desired inspired CO₂ concentration). We recognize that the next stage of this research is to apply this modeling system to some real cases (with various unpredictable apnea-hypopnea patterns) to further tune the timing and dosage of CO₂ delivery and design an experimental study. However, this study gives a good background on the desirable characteristics of the affecting parameters (optimum dose and treatment timing) that an experimental setup would need.
Conclusions

Although static concentrations of CO₂ administration can ameliorate PB, very much smaller quantities of CO₂ can achieve the same degree of amelioration if it can be administered dynamically with careful timing and dosing. Algorithms adjusting both duration and concentration in real time appear to have the greatest potential to do this with minimal unwanted elevation in average CO₂ levels.

With appropriate development of real-time delivery technology, it might be possible to develop clinical therapies for PB diseases, which use such a dynamic approach, with only very minor increments in systemic CO₂ levels and, therefore, essentially avoiding the undesirable physiological effects of CO₂ administration, such as hyperventilation or sympathetic overactivation.

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