Development of respiratory control instability in heart failure: a novel approach to dissect the pathophysiological mechanisms

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Observational data suggest that periodic breathing is more common in subjects with low F_{ETCO_2}, high apnoeic thresholds or high chemoreflex sensitivity. It is, however, difficult to determine the individual effect of each variable because they are intrinsically related. To distinguish the effect of isolated changes in chemoreflex sensitivity, mean F_{ETCO_2} and apnoeic threshold, we employed a modelling approach to break their obligatory *in vivo* interrelationship. We found that a change in mean CO_2 fraction from 0.035 to 0.045 increased loop gain by $70 \pm 0.083\%$ ($P < 0.0001$), irrespective of chemoreflex gain or apnoea threshold. A 100% increase in the chemoreflex gain (from $800\,l\,min^{-1}$ (fraction $CO_2)^{-1}$) resulted in an increase in loop gain of $275 \pm 6\%$ ($P < 0.0001$) across a wide range of values of steady state CO_2 and apnoea thresholds. Increasing the apnoea threshold F_{ETCO_2} from 0.02 to 0.03 had no effect on system stability. Therefore, of the three variables the only two destabilizing factors were high gain and high mean CO_2; the apnoea threshold did not independently influence system stability. Although our results support the idea that high chemoreflex gain destabilizes ventilatory control, there are two additional potentially controversial findings. First, it is high (rather than low) mean CO_2 that favours instability. Second, high apnoea threshold itself does not create instability. Clinically the apnoea threshold appears important only because of its associations with the true determinants of stability: chemoreflex gain and mean CO_2.

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Periodic breathing is self-sustaining oscillations of cardiac and respiratory parameters, with cyclical periods of apnoea and hyperpnoea approximately once per minute. It occurs in some patients with chronic heart failure (Hanly *et al.* 1989*b*; Sin *et al.* 1999; Silva *et al.* 2001), and is an adverse prognostic indicator (Hanly & Zuberi-Khokhar, 1996; Lanfranchi *et al.* 1999; Sin *et al.* 2000; Bradley & Floras, 2003; Corra *et al.* 2006). This unstable pattern of control arises from overshoot of the time-delayed negative feedback mechanisms controlling ventilation (Douglas & Haldane, 1909; Cherniack *et al.* 1979). This results from excessive and/or delayed ventilatory responses to alterations in CO_2 levels, which leads to a vicious circle of inappropriate feedback responses. Physiological variables that are known to interact to determine system stability include chemoreflex delay and gain, alveolar volume and cardiac output (Francis *et al.* 1999*a*; Francis *et al.* 2000*b*).

Many clinical studies both from our group and others have found that accompanying the respiratory oscillations in periodic breathing there are significant haemodynamic oscillations, and that system stability determines both respiratory and cardiac oscillations (Faber *et al.* 1990; Davies *et al.* 2000; Francis *et al.* 2000*a*).

Previously it was thought that these haemodynamic oscillations may have a causative role in periodic breathing (Ben-Dov *et al.* 1992). This was based on the observation that the amplitude of $\dot{V}_{O_2}$ oscillations is larger than

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the amplitude of $\dot{V}_E$ oscillations in periodic breathing, and the $\dot{V}_{O_2}$ oscillations occur earlier in the periodic breathing cycle. This led the authors to conclude that ventilation alone cannot be driving the oscillations in $\dot{V}_{O_2}$, and therefore the cardiac system must have a role (Ben-Dov *et al.* 1992). However, subsequent theoretical work by our group (Francis *et al.* 1999*b*) used a more rigorous mathematical approach to analyse the effect of cyclic fluctuations in ventilation on $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. We reanalysed the data of Ben-Dov *et al.* (1992) using this new mathematical approach, and found that the $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ oscillations could be entirely explained by the fluctuations in alveolar ventilation. Clinical work by our group (Francis *et al.* 1999*a*) which specifically controlled for the confounding factors in the work of Ben-Dov *et al.* (1992) demonstrated that simple oscillations in ventilation in volunteers produce exactly the oscillations in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ that would be expected. Therefore although haemodynamic oscillations may be present in periodic breathing, they are not necessary in the genesis of the instability and therefore it is reasonable in modelling studies to consider cardiac output as broadly stable in the vicinity of the steady state.

There are two opposing hypotheses about the influence of a subject's carbon dioxide levels on ventilatory stability. Observational clinical studies have reported an association between low mean arterial CO_2 or high apnoeic thresholds and unstable ventilatory control (Skatrud & Dempsey, 1983; Modarreszadeh *et al.* 1995; Javaheri & Corbett, 1998). Moreover, since apnoea is preceded by hyperventilation driving arterial CO_2 below an 'apnoea threshold', it has been argued a high apnoea threshold can encourage instability (Cherniack *et al.* 1966; Naughton *et al.* 1993).

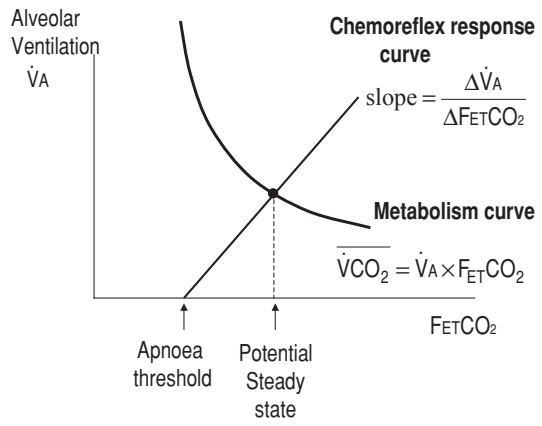


Figure 1. The relationship between the potential steady state, chemoreflex gain and the apnoea threshold
The potential steady state is the point of intercept of the chemoreflex response and the curve of metabolic production of CO_2 (isometabolic curve). If the chemoreflex response curve is constrained to be linear, the intercept (C_{apn}) is determined by the steady state CO_2 ($\overline{C}$) and chemoreflex gain (S): $= \overline{C} - \frac{\overline{V}}{S}$.

An alternative hypothesis is that the apnoeic threshold is not itself an independent determinant of system stability, but that it only appears to be so because it is intimately related to the chemoreflex gain and mean CO_2. In a system with a linear chemoreflex response, the apnoeic threshold is geometrically constrained to be linked to mean F_{ETCO_2} and the chemoreflex gain (Fig. 1). The chemoreflex slope equals the potential steady state ventilation divided by the difference between potential steady state CO_2 and the apnoeic threshold CO_2. This makes it extremely difficult to extricate the influence of each independent variable on ventilatory control by clinical observation.

In contrast to clinical studies, mathematical models allow the effect of individual parameters to be assessed independently. However, although there have been several such models of periodic breathing, these typically include an enforced linear chemoreflex relationship meaning that it is still impossible to examine the independent effect of the apnoeic threshold on ventilatory stability.

We present a mathematical model deliberately designed to allow any combination of potential steady state CO_2 and ventilation, chemoreflex gain and apnoeic threshold. The aim of this study was to apply this model to assess the stability of the resultant control system, separating the relative contributions to ventilatory stability of potential steady state CO_2, chemoreflex slope and apnoeic threshold.

Methods

Chemoreflex control of ventilation

Ventilatory stability depends on the interplay of two physiological mechanisms. The first is chemoreflex gain: the effect that a change in end-tidal CO_2 has on ventilation. This corresponds to controller gain in standard control theory. The second is exhalation gain, corresponding to plant gain – the effect that a change in ventilation has on end-tidal carbon dioxide (F_{ETCO_2}).

The central role of the potential steady state

In ventilatory control the two key variables are ventilation and CO_2. Mean F_{ETCO_2} is linked to ventilation according to a hyperbolic curve (Fig. 1) if $\overline{CO_2}$ exhalation is to match metabolic production of CO_2 ($\overline{\dot{V}_{CO_2}}$) in the body.

If a particular alveolar ventilation rate ($\dot{V}_A$) is maintained in the medium term, F_{ETCO_2} is destined to become $\overline{\dot{V}_{CO_2}}/\dot{V}_A$ (the isometabolic curve). Ventilation in turn depends on F_{ETCO_2} through the chemoreflex response curve. Given these constraints, there is only one combination of F_{ETCO_2} and ventilation which can be sustained: this is called the potential steady state. Regardless of whether the system is stable or unstable, the potential steady state values of F_{ETCO_2} and alveolar ventilation can be defined to be the crossing point of

these two lines. Whether this potential steady state will be achieved is determined by the configuration of the control system.

In general, system stability is dependent on its behaviour around the potential steady state. If the system configuration responds to a small deviation away from the potential steady state by moving progressively closer back to the potential steady state, then the system is stable (Fig. 2*A*).

If, on the other hand, the system configuration is such that its responses to a small deviation cause progressively larger deviations from the potential steady state, then the system will be unstable. In this case the steady state exists only in potential form – i.e. a central point around which system oscillations occur (Fig. 2*B*).

Measurement of system stability

System instability of the model was measured with each potential combination of input parameters by calculating the loop gain (the scale factor by which the amplitude of oscillations increased or decreased on each cycle) in response to a small initial perturbation in ventilation or F_{ETCO_2}. Values greater than 1 indicate spontaneously expanding oscillations characteristic of unstable control, whereas values less than 1 indicate spontaneously decaying oscillations, i.e. stable control.

Loop gain was calculated by dividing the amplitude of one oscillation in ventilation by the amplitude of the previous oscillation. The value that we take for loop gain is an average of the values for loop gain for the second

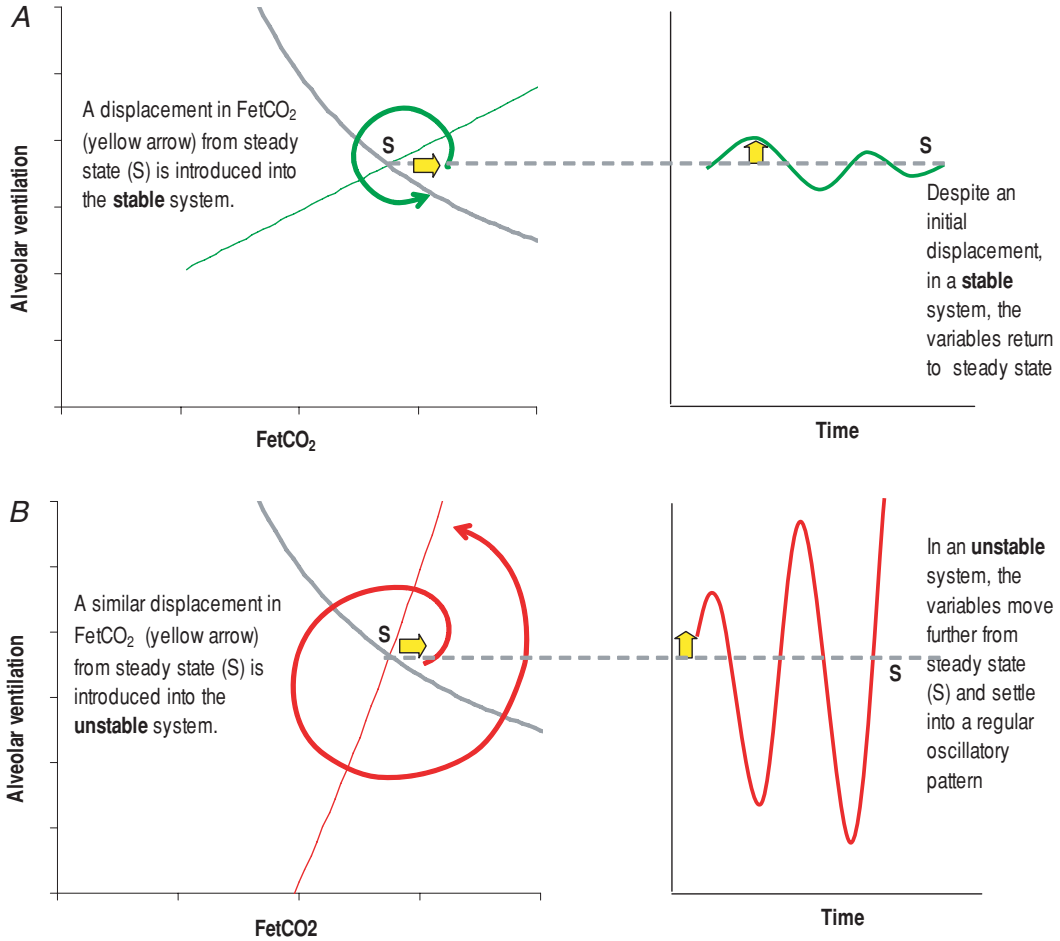


Figure 2. Ventilatory stability
An initial perturbation in ventilation or F_{ETCO_2} away from the steady state leads to oscillations in both of these variables. Whether these oscillations magnify into periodic breathing or decay away back to the steady state depends on system stability. In a stable system (*A*), despite an initial perturbation in F_{ETCO_2} away from the steady state, oscillations decay away and values return to close to the potential steady state. In an unstable system (*B*), with even a small initial perturbation in respiratory parameters, oscillations in F_{ETCO_2} and ventilation increase in amplitude, with resulting periodic breathing.

to fourth oscillations prior to the system reaching its final outcome pattern.

In an unstable system, the presence of apnoeas prevents the size of oscillations increasing beyond a particular amplitude, and therefore eventually the ratio of amplitudes of consecutive oscillations becomes 1.

The model

A simple iterative model can be used to map system behaviour in response to a perturbation (in the form of a small transient change in ventilation or F_{ETCO_2} from potential steady state), and thereby determine whether ventilatory control will be stable. The model creates a chemoreflex response curve using our chosen values of chemoreflex gain, potential steady state F_{ETCO_2} and apnoeic threshold. Since the chemoreflex response is created synthetically in the model, any desired shape of response can be created, which allows us to separately adjust chemoreflex gain and apnoea threshold (Fig. 3).

Clinical data suggest that although the chemoreflex response curve is linear near potential steady state values of F_{ETCO_2}, it is non-linear (concave) near the apnoea threshold (Mohan & Duffin, 1997).

The model plots the response in F_{ETCO_2} and ventilation to the perturbation, given the particular chemoreflex response curve characteristics. The ventilation and F_{ETCO_2} can therefore oscillate with ever-decreasing amplitude back to the potential steady state (loop gain < 1; stable control), or the oscillations can increase in amplitude (loop gain > 1; unstable control).

To prevent unnecessary duplication of entities representing CO_2 levels, in this model we use just two variables. Arterial and end-tidal CO_2 move largely in parallel, so as long as ventilation and cardiac output are close to their potential steady state, one can be used as a proxy for the other, providing we remain aware that there may be an offset between the two. The F_{ETCO_2} has additional meaning as (in combination with alveolar ventilation) it completely determines the amount of CO_2 that is exhaled by the body, and simultaneously (in combination with alveolar volume) it describes the volume of CO_2 stored in the lungs. We therefore choose to use end-tidal CO_2 fraction (F_{ETCO_2}) as the single variable to represent CO_2 status. To describe chemoreflex responses in these terms, we must recognize that chemoreflexes sense not current F_{ETCO_2}, but rather the level of CO_2 in the blood that was in contact with lung CO_2 several seconds previously (equivalent to the chemoreflex delay, δ). We can represent this time-delayed value of CO_2 using a subscript ($c_{t-\delta}$).

We incorporated this information into the equation based on a standard single-compartment model (Francis *et al.* 2000*b*) to describe how the rate of change in F_{ETCO_2}

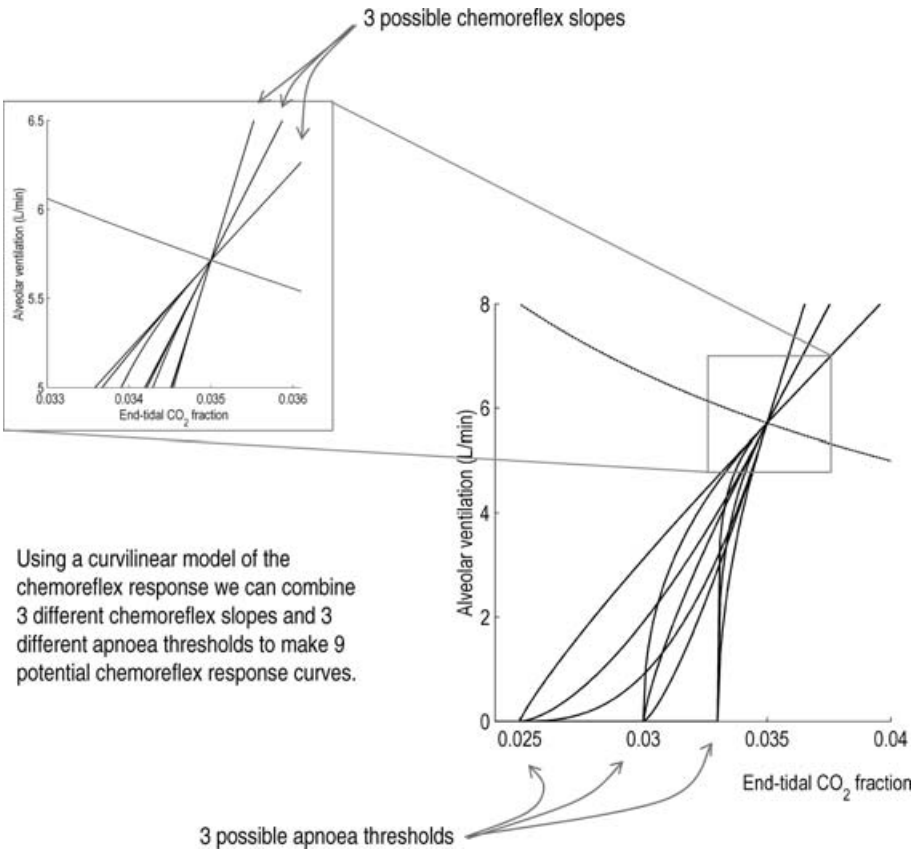


Figure 3. A special curved shape of the chemoreflex response allowing chemoreflex slope and apnoea threshold to be changed independently
The inset shows a magnified region near the potential steady state, indicating 3 chemoreflex slopes. The main figure shows 3 possible apnoea thresholds. Allowing the chemoreflex response to be curved permits any of the chemoreflex slopes to be combined with any of the apnoea thresholds, giving a total of 9 different chemoreflex response curves.

depends on the rate of CO_2 production by metabolism following removal by ventilation and circulatory buffering (Francis *et al.* 2000*b*). The potential steady state F_{ETCO_2} is represented by $\overline{C}$, potential steady state ventilation as $\overline{\dot{V}_A}$, and the current value of CO_2 and ventilation at time t, as v and c, respectively. The buffering of CO_2 by the circulation and extrapulmonary stores depends on β, the solubility of CO_2 in blood, and $\overline{\dot{Q}}$, the mean cardiac output.

The dependency of rate of change of F_{ETCO_2} on the other variables can be derived to be as follows (Francis *et al.* 1999*a*;2000*b*):

$$V_L \frac{dc}{dt} = \overline{\dot{V}_{CO_2}} - vc_{t-\delta} - \beta \overline{\dot{Q}} \left(\overline{C} - c_{t-\delta}\right) \quad (1)$$

We calculated and plotted the fixed curve for the set of potential steady state pairs of CO_2 and alveolar ventilation based on the requirement that their mutual product must equal metabolic production of CO_2 ($\overline{\dot{V}_{CO_2}}$). We created a modifiable function ('chemoreflex function') which described the chemoreflex response: this could be configured to give a large gain (such as in a patient with heart failure), or small gain (such as in a normal subject). Our values for chemoreflex gain were taken from clinical data measured by several different groups, using a range of methodologies (Khoo *et al.* 1995; Mohan *et al.* 1999; Van den Aardweg & Karemaker, 2002; Beecroft *et al.* 2006).

We initialized the model from its potential steady state, and then introduced a small perturbation in CO_2. The model then iteratively calculated successive pairs of values of v (using the chemoreflex function and the appropriate previous value of c) and dc/dt (using eqn (1)). Thus the course of v and c could be plotted for several minutes of simulated time. The details of the model are given as accompanying online Supplemental material.

We used standard values for the cardiorespiratory parameters that were held constant throughout our investigations: cardiac output ($\overline{\dot{Q}}$) = 3.5 l min^{-1}, $\overline{\dot{V}_{CO_2}}$ = 0.2 l min^{-1}, chemoreflex delay (δ) = 0.33 min (Gabrielsen *et al.* 2002; Turner *et al.* 2004).

Results

Study 1. Linear chemoreflex response

The simplest shape of the chemoreflex response is a linear function (Fig. 1). Changing any one of chemoreflex gain (S), $\overline{C}$ or C_{apn} necessitates a change in one of the others.

Study 1A. Changing chemoreflex gain and apnoea threshold. First we assessed the effect of altering the chemoreflex gain programmed into the model, whilst maintaining the potential steady state CO_2 constant. Because in this study the shape of the chemoreflex response is linear, when chemoreflex gain is altered, the apnoea threshold must change (as shown in Fig. 1).

The simulation was run 5 times with chemoreflex gain taking values of 500, 900, 950, 1000 and 1500 (1000 l min^{-1} fraction^{-1} F_{ETCO_2} is equivalent to 1.3 l min^{-1} mmHg^{-1} or 9.9 l min^{-1} kPa^{-1}). These values range from those observed in normal subjects to ones that would be typical for a patient with heart failure and periodic breathing (Javaheri, 1999; Francis *et al.* 2000*b*).

We found that increased chemoreflex gain and apnoeic threshold readily destabilized ventilatory control (Fig. 4*A*). In the unstable systems, chemoreflex slope also determined the amplitude of oscillations in ventilation and CO_2 in the final outcome pattern.

However, from this study in isolation, it is impossible to identify which of these two parameters is responsible for the alterations in ventilatory stability.

Study 1B. Changing the apnoea threshold and potential steady state values of CO_2 and ventilation. We then used the model to investigate the effect of changing both the levels of potential steady state CO_2 and the apnoea threshold, whilst maintaining an unchanging chemoreflex gain. Again, due to the linearity of the model, a higher potential steady state CO_2 at a fixed chemoreflex gain required a higher apnoea threshold.

As the values of apnoea threshold and potential steady state increased, ventilatory control destabilized (Fig. 4*B*).

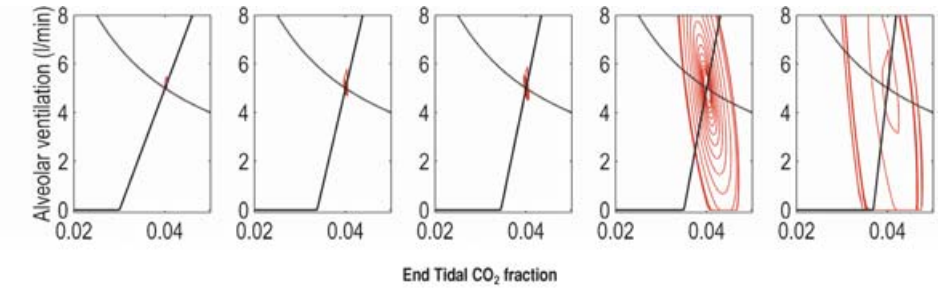
Study 1C. Changing chemoreflex gain and potential steady state values of CO_2 and ventilation. In the third study, we altered the third possible pair of these three physiological variables: potential steady state CO_2 and chemoreflex gain. As the chemoreflex gain was increased and potential steady state CO_2 reduced, the system became more unstable (Fig. 4*C*).

Potential explanations for Studies 1A, 1B and 1C. From studying the results of Study 1, an observer might propose three possible explanations:

an increase in chemoreflex gain is destabilizing, an increase in apnoea threshold is destabilizing, and the level of CO_2 at potential steady state has no effect;
an increase in both the levels of CO_2 at potential steady state and at the apnoea threshold are destabilizing, and the chemoreflex gain has no effect;
an increase in the chemoreflex gain and a decrease in the potential steady state value of CO_2 are destabilizing and the apnoea threshold has no effect.

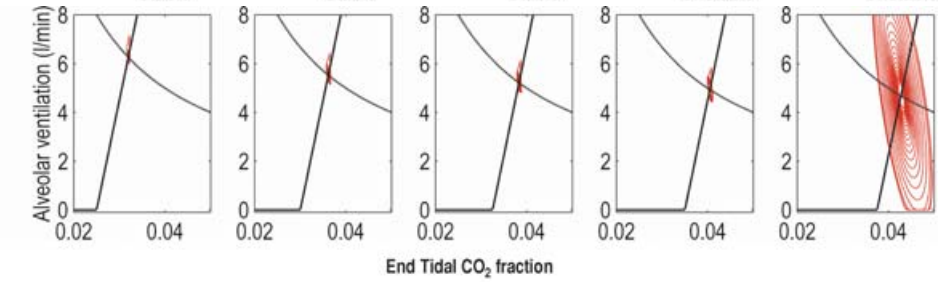
The only way to determine which of these explanations is correct is to study the effect of changing each of the three variables separately. To vary $\overline{C}$, C_{apn} and S independently requires a specially devised model, which we created for Study 2.

A – Changing chemoreflex gain and apnoea threshold



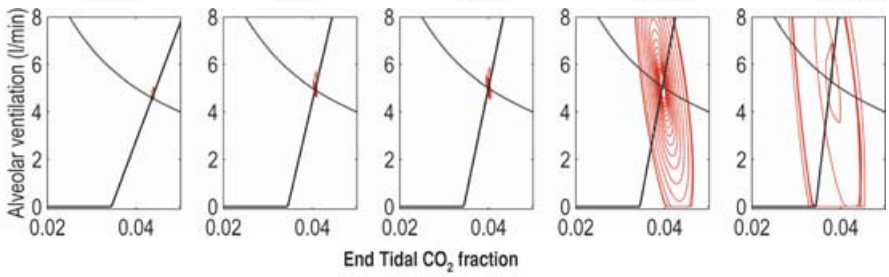
Input parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Chemoreflex gain (L/min/fraction)	500	800	900	1000	1600
Apnoea threshold (FETCO2)	0.030	0.033	0.034	0.035	0.037
Steady state (FETCO2)	0.040	0.040	0.040	0.040	0.040
Results					
Loop gain	**0.26**	**0.67**	**0.94**	**1.24**	**3.09**
Stability	**Stable**	**Stable**	**Stable**	**Unstable**	**Unstable**

B –Changing steady state carbon dioxide and apnoea threshold



Input parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Chemoreflex gain (L/min/fraction)	900	900	900	900	900
Apnoea threshold (FETCO2)	0.025	0.030	0.034	0.035	0.038
Steady state (FETCO2)	0.032	0.038	0.040	0.041	0.047
Results					
Loop gain	**0.32**	**0.74**	**0.94**	**0.97**	**1.13**
Stability	**Stable**	**Stable**	**Stable**	**Stable**	**Unstable**

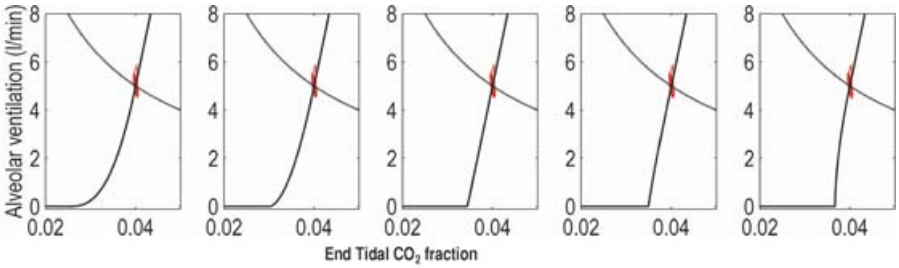
C – Changing steady state carbon dioxide and chemoreflex gain



Input parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Chemoreflex gain (L/min/fraction)	500	800	900	1000	1600
Apnoea threshold (FETCO2)	0.034	0.034	0.034	0.034	0.034
Steady state (FETCO2)	0.044	0.041	0.040	0.039	0.038
Results					
Loop gain	**0.20**	**0.63**	**0.94**	**1.24**	**3.13**
Stability	**Stable**	**Stable**	**Stable**	**Unstable**	**Unstable**

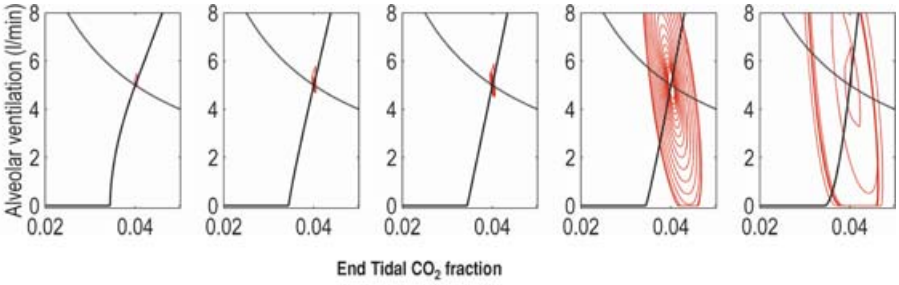
Figure 4. The effect on ventilatory stability of changing apnoea threshold, chemoreflex gain and steady state carbon dioxide in a linear control system
It is impossible to separate the independent effects of these 3 variables on system stability, when the chemoresponse is linear.

A – The effect of isolated changes in apnoea threshold



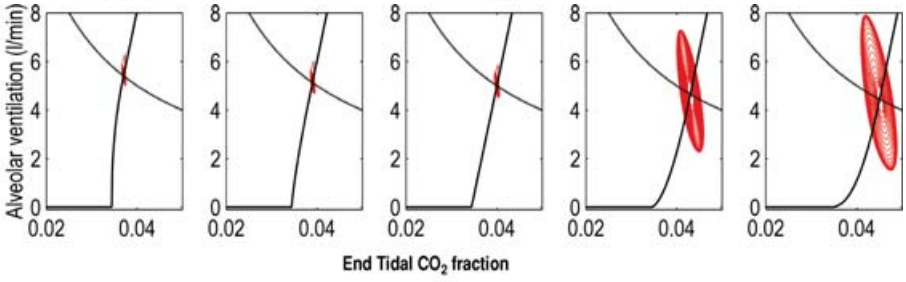
Input parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Chemoreflex gain (L/min/fraction)	900	900	900	900	900
Apnoea threshold (FETCO2)	0.025	0.030	0.034	0.035	0.037
Steady state (FETCO2)	0.040	0.040	0.040	0.040	0.040
Results					
Loop gain	**0.94**	**0.94**	**0.94**	**0.94**	**0.94**
Stability	**Stable**	**Stable**	**Stable**	**Stable**	**Stable**

B – The effect of isolated changes in chemoreflex gain



Input parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Chemoreflex gain (L/min/fraction)	500	800	900	1000	1600
Apnoea threshold (FETCO2)	0.034	0.034	0.034	0.034	0.034
Steady state (FETCO2)	0.040	0.040	0.040	0.040	0.040
Results					
Loop gain	**0.12**	**0.67**	**0.94**	**1.22**	**2.64**
Stability	**Stable**	**Stable**	**Stable**	**Unstable**	**Unstable**

C – The effect of isolated changes in steady state CO_2



Input parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Chemoreflex gain (L/min/fraction)	900	900	900	900	900
Apnoea threshold (FETCO2)	0.034	0.034	0.034	0.034	0.034
Steady state (FETCO2)	0.037	0.039	0.040	0.043	0.045
Results					
Loop gain	**0.74**	**0.87**	**0.94**	**1.12**	**1.24**
Stability	**Stable**	**Stable**	**Stable**	**Unstable**	**Unstable**

Figure 5. The effect on ventilatory stability of changing apnoea threshold, chemoreflex gain and steady state carbon dioxide levels independently
With a curved chemoreflex response, it is possible to demonstate that whilst steady state CO_2 and chemoreflex gain both affect stability, apnoea threshold has no influence on it.

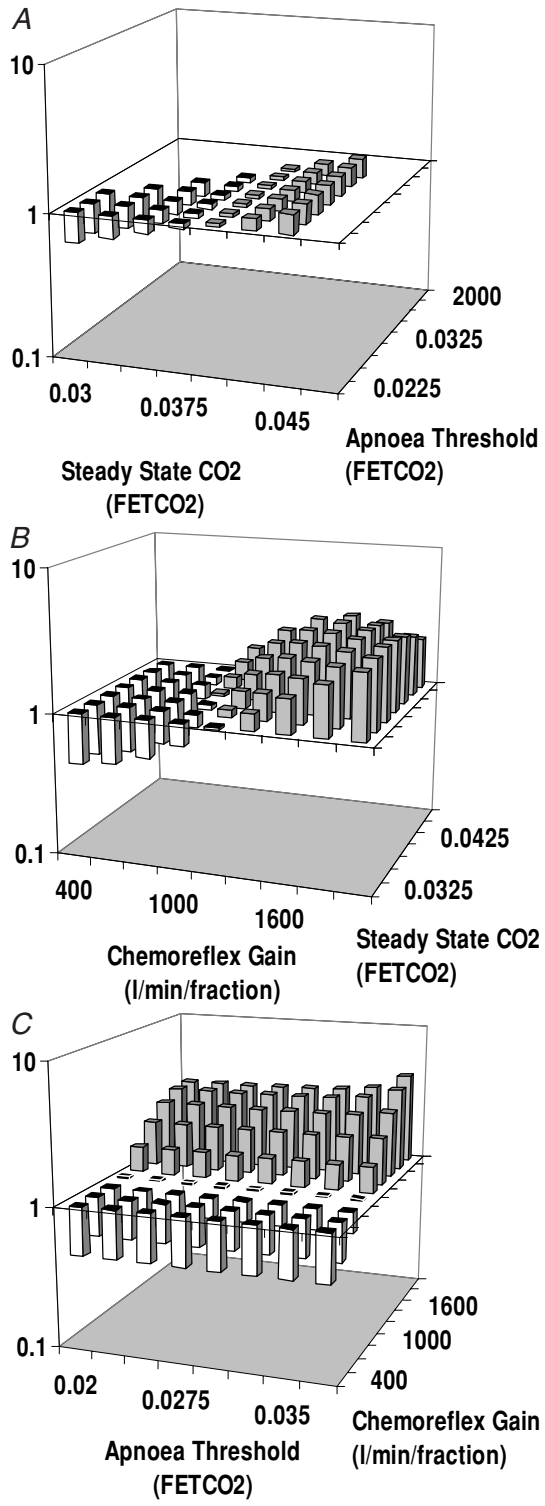


Figure 6. The effect of independently varying two parameters
A, the effect of $\overline{C}$ and C_{apn} on system stability. We maintained the chemoreflex at a fixed value but used different combinations of potential steady state CO_2 ($\overline{C}$) and apnoeic threshold (C_{apn}). This showed that as $\overline{C}$ increased, system stability decreased. C_{apn} however, had no effect on stability. *B*, the effect of $\overline{C}$ and chemoreflex gain on system stability. We maintained the apnoeic threshold at a constant value and found that as either the chemoreflex gain and $\overline{C}$ increase, there is a reduction in system stability. *C*, the effect of C_{apn} and chemoreflex gain on system stability. Again increases in chemoreflex gain were found to increase system instability, and again apnoeic threshold did not affect stability.

Study 2. Separately investigating the independent effects of chemoreflex gain, apnoea threshold and potential steady state

In order to change one of the variables ($\overline{C}$, C_{apn} or S) without altering the others, we introduced curvature into the shape of the chemoreflex response near its lower end. This allows it to pass through any chosen apnoea threshold, while maintaining the chosen value of chemoreflex slope around the potential steady state (Fig. 3).

Study 2A. Effect of the apnoeic threshold in isolation on system stability. We tried a range of values for apnoea threshold fraction (0.0200–0.0375), whilst maintaining the chemoreflex gain at $950\,l\,min^{-1}\,fraction^{-1}$ and the potential steady state fractional CO_2 at 0.04. These values were selected because in the models of Study 1 they were found to be at the borderline of stability, which meant they were most likely to be informative in Study 2: small changes in system stability would be readily detectable.

We found apnoea threshold had no effect on system stability (Fig. 5*A*): $\beta = 0.032$, $P \geq 0.99$.

Study 2B. Effect of chemoreflex gain in isolation on system stability. We then changed chemoreflex sensitivity, maintaining potential steady state CO_2 and apnoea threshold unchanged.

We found that even subtle changes in chemoreflex sensitivities result in large shifts of system stability (Fig. 5*B*): the 25% increase in chemoreflex gain between cases 2 and 4 causes loop gain to increase by 82%. The unstandardized β coefficient on linear regression was 0.02 (standardized $\beta = 0.998$), $P \leq 0.0001$.

Study 2C. Effect of potential steady state CO_2 in isolation on system stability. We set the chemoreflex gain at $900\,l\,min^{-1}\,fraction^{-1}$, and the apnoea threshold at 0.035 whilst changing the potential steady state level of CO_2 (and hence ventilation) over a narrow range. As the potential steady state value of CO_2 increased, respiratory control was found to become more unstable (Fig. 5*C*). The unstandardized β regression coefficient on linear regression was 62.3 (standardized $\beta = 1.0$), $P \leq 0.0001$.

Study 3. Independently varying two parameters

To visualize the independent effects of chemoreflex gain and apnoea threshold, we tested a range of combinations of values of these variables, displaying the resulting loop gains on a 3D plot.

When potential steady state CO_2 fraction increased from 0.035 to 0.045, with constant chemoreflex gain, mean loop gain increased by $70 \pm 0.083\%$, $P < 0.0001$ (Fig. 6*A*). This was true irrespective of the apnoea threshold, giving additional evidence that the apnoea threshold does not influence system stability.

When chemoreflex gain was increased from 800 to $1600\,l\,min^{-1}$ fraction^{-1} with potential steady state CO_2 held constant (Fig. 6*C*), the loop gain increased by $275 \pm 6\%$ ($P < 0.0001$). Again, there was no change in loop gain over a wide range of apnoea thresholds.

In Fig. 6*B* the chemoreflex gain and potential steady state CO_2 were changed in combination, without changing apnoea threshold. Increasing chemoreflex gain from 800 to $1600\,l\,min^{-1}$ (fraction CO_2)$^{-1}$, increased mean loop gain by $248 \pm 24\%$ ($P < 0.0001$). When potential steady state CO_2 fraction increased from 0.035 to 0.045 there was a mean loop gain increase of $44 \pm 26\%$ ($P = 0.03$).

Therefore, supporting our findings in Study 2, we found using multiple combinations of parameters of $\overline{C}$, C_{apn} and chemoreflex gain, only $\overline{C}$ and chemoreflex gain influenced system stability. Apnoea threshold had no independent effect on stability.

Table 1. Value of loop gain for different initial perturbation sizes

	Stable control system	Unstable control system
Loop gain	Loop gain always <1	If initial perturbation larger than oscillations in final outcome pattern, oscillations must initially shrink, i.e. Loop Gain <1.
		If initial perturbation smaller than oscillations in final outcome pattern, oscillations must initially shrink, i.e. Loop Gain >1.

Study 4. The effect of initial perturbation size on ventilatory stability

Although the results of studies 1, 2 and 3 have shown us which of the three variables tested contribute to system stability, the model has also demonstrated that the relevant part of the chemoreflex response is the 'average slope' over the range of F_{ETCO_2} which the patient experiences.

Any steep portions of the chemoreflex response curve, near the central potential steady state point, contribute to instability. What constitutes 'near' the potential steady state is simply the range of F_{ETCO_2} which the patient experiences, and includes values both lower and higher than the steady state F_{ETCO_2}.

Hypothetically therefore if a chemoreflex response curve has a 'convex' shape, it would have an especially steep segment just above the apnoea threshold, and this additional contribution to 'average' slope could make a significant impact on stability. In this hypothetical state, it is conceivable that a system could be just stable if initiated in the shallow-sloped region close to the steady state point, but be unstable if initiated at apnoea (giving the patient exposure to the steep part of the curve near apnoea).

However, real physiological measurements of the chemoreflex response curve performed by several previous workers, using a variety of techniques including modified Read's rebreathing and dynamic end-tidal forcing, have shown no evidence of a steepening of the chemoreflex response near the apnoea threshold. In fact, if there is any curvature of the chemoreflex response, the available data

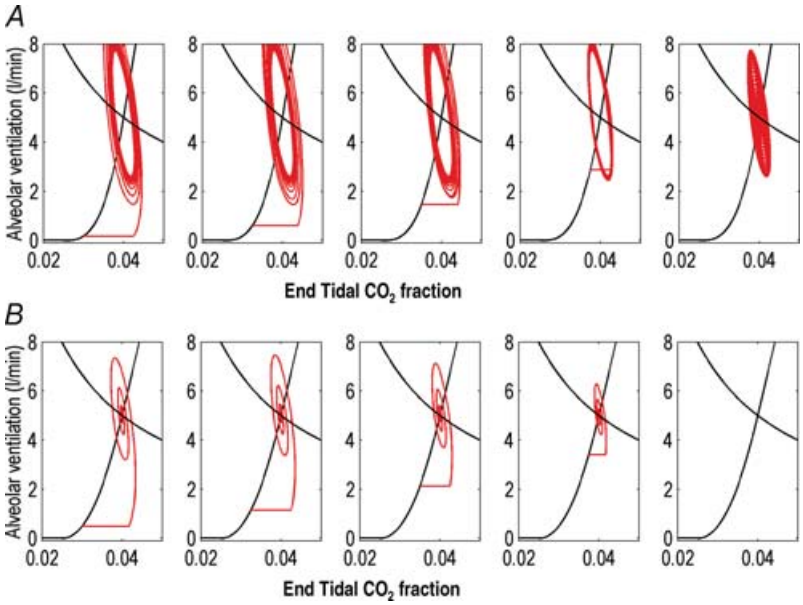


Figure 7. Effect on stability of different initial perturbations sizes in F_{ETCO_2}, with system configuration otherwise kept identical
A, an 'unstable' chemoresponse system: it develops a consistent pattern of oscillations irrespective of the size of the initial perturbation. From a small initial perturbation (top right) the loop gain is clearly initially > 1, while from a large initial oscillation (top left) the loop gain is clearly initially < 1. A system that has loop gain > 1 from a small perturbation definitely cannot be stable. In contrast a loop gain < 1 from large perturbation does not guarantee stability: it might indicate that the system will settle into oscillations of smaller size than the initial perturbation. *B*, a 'stable' chemoresponse system: irrespective of the initial perturbation, ventilation and F_{ETCO_2} revert back towards steady state values. Loop gain is < 1 for all perturbation sizes including the small perturbations which are the type of stimuli that truly distinguish stable from unstable systems. Thus loop gain is only a straightforward indicator of stability when calculated for small disturbances.

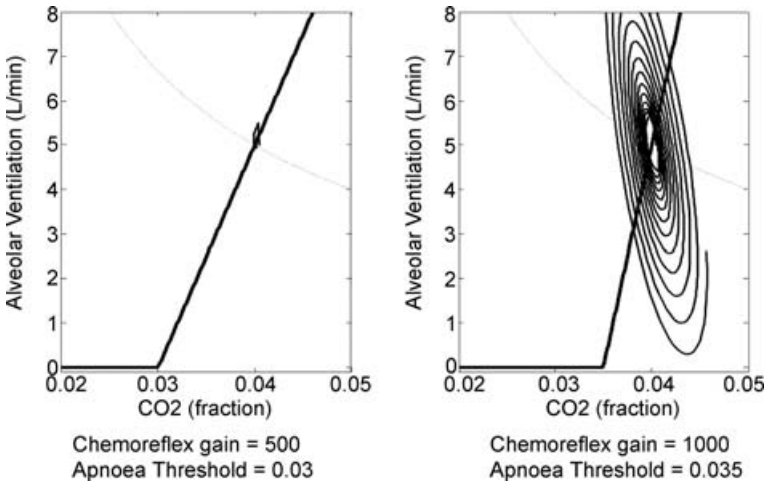


Figure 8. A small change in the apnoeic threshold hides a large change in the chemoreflex gain
If the potential steady state is maintained at a constant value, and only the apnoeic threshold is measured, it would appear that there has only been a small change in the input parameters. Closer inspection, however, shows that although the apnoea threshold has only increased by 14%, the chemoreflex gain doubled.

indicate that the slope at lower F_{ETCO_2} is typically flatter (Mohan *et al.* 1999), as shown in Fig. 1 of Jensen *et al.* (2005).

We therefore tested the effect of different-sized initial perturbations on ventilatory stability, first in a system that was 'unstable' with a small initial perturbation, and subsequently in a 'stable' system.

We found that in an 'unstable' system a small perturbation (Fig. 7*A*, case 1) will result in an initial loop gain > 1, whereas a large perturbation (Fig. 7*A*, case 5) may result in an initial loop gain of < 1. In both situations however, the final outcome pattern of the system is the same.

In the 'stable' system, however, the initial loop gain is always < 1, regardless of perturbation size.

Clearly therefore loop gain is a useful summary of system stability only when measured for small initial perturbations. Perturbation size does not affect the final outcome pattern, but large initial perturbations may settle to smaller long-term oscillations in the final outcome pattern (Table 1).

Discussion

This modelling approach gives a unique opportunity to distinguish individual contributions of different variables which in clinical practice are inextricably linked.

In the first phase of this study, using a model with linear properties, we observed that ventilatory control becomes more unstable if chemoreflex gain increases (with potential steady state CO_2 falling), if chemoreflex gain increases (with the apnoeic threshold also increasing) or if both potential steady state and apnoeic levels of CO_2 rise together. Potentially there might be three contradictory explanations for these data:

high chemoreflex gain and high C_{apn} each destabilize control (with $\overline{C}$ having no effect);
high steady state CO_2 ($\overline{C}$) and high C_{apn} each destabilize control (but chemoreflex gain has no effect);
high chemoreflex gain and $\overline{C}$ each destabilize control (but C_{apn} has no effect).

The only way to separate these possibilities was to modify the chemoreflex function to remove its constraint of a linear chemoreflex slope. Doing so yielded two potentially controversial findings:

- high, rather than low, levels of CO_2 favour system instability;
- apnoea threshold itself has no influence on ventilatory instability.

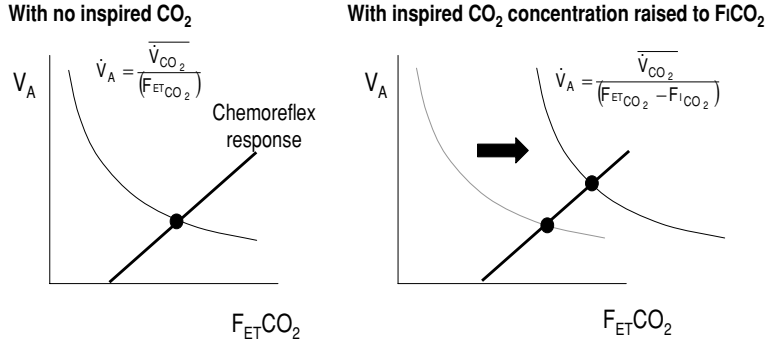


Figure 9. A higher inspired level of CO_2 narrows the gap between end-tidal CO_2 levels and inspired CO_2
The result is that ventilation rises, and so for a constant metabolic production of CO_2 there is a new potential steady state and a fall in plant gain.

Resolving the apparent conflict with clinical studies: chemoreflex measurement may be the key

These findings superficially appear to conflict with widely held clinical opinion, which is that low average CO_2 levels predispose to unstable ventilatory control (Skatrud & Dempsey, 1983; Naughton *et al.* 1993; Xie *et al.* 1994; Javaheri, 1999). For example, it was reported that low arterial CO_2 in heart failure patients is a powerful predictor of central sleep apnoea (Javaheri & Corbett, 1998).

Yet the results of our study indicate that low potential steady state CO_2 is stabilizing rather than destabilizing. We believe this apparent inconsistency between model findings and clinical observations is because the clinical observations rarely include the quantitatively most important determinant of respiratory control stability: chemoreflex gain. Clinical studies more often measure $\overline{C}$ and/or C_{apn} (Modarreszadeh *et al.* 1995; Javaheri & Corbett, 1998). Dempsey *et al.* (2004) and Dempsey (2005) concluded that the key determinants of system stability are plant gain, chemoreflex gain and 'CO_2' reserve (the difference between steady state CO_2 and the apnoea threshold), but clinical data cannot separate these parameters.

If chemoreflex gain is not measured, then the only observable differences between the stable and unstable patients may be small differences in C_{apn} and $\overline{C}$. For example, in Fig. 8, there is a twofold difference in the chemoreflex gain between the subject modelled in the left panel and that in the right, but that this is manifest as only a 14% difference in C_{apn}. This may give the false impression that high C_{apn} is mechanistically important in causing instability, whereas in reality it is the large difference in chemoreflex gain that is important. The apnoeic threshold (C_{apn}) has no independent effect on stability, and indeed, in isolation, low $\overline{C}$ would actually favour stability rather than instability.

This distinction is not simply academic, because incorrect belief in a stabilizing effect of increased potential steady state CO_2 may result in incorrect design of treatment strategies.

Our work and that of others since the beginnings of mathematical modelling of periodic breathing (Mackey & Glass, 1977) have consistently found that $\overline{C}$ levels and chemoreflex gain have a multiplicative effect on stability: a 1% rise in chemoreflex gain has an identical effect on system stability as a 1% increase in $\overline{C}$ (Francis *et al.* 2000*b*). The potential confusion arises because clinically, very large differences in chemoreflex gain may accompany small differences in $\overline{C}$, and therefore the strong destabilizing effect of the high chemoreflex will certainly overcome the small change in $\overline{C}$.

The reason why small changes in $\overline{C}$ can conceal large changes in chemoreflex gain is due to the mandatory relationships between the chemoreflex gain, $\overline{C}$ and the apnoeic threshold under the constraint of a linear chemoreflex response. From the triangular shape of Fig. 1, we can readily derive this relationship:

$$S = \frac{\overline{\dot{V}_{CO_2}}}{\overline{C}\left(\overline{C} - C_{apn}\right)}$$

Small changes in $\overline{C}$, because it is effectively a 'squared' term on the denominator, can be associated with large changes in chemoreflex gain.

How does supplemental inhaled CO_2 assist stability?

A second conundrum is the well recognized observation that raising ambient CO_2 concentration can help to stabilize ventilatory control in some patients (Badr *et al.* 1994; Steens *et al.* 1994; Lorenzi-Filho *et al.* 1999). This would appear to contradict our model results, which indicate that raised levels of potential steady state CO_2 are destabilizing.

This apparent paradox can be readily explained if one considers that an elevation in inspired CO_2 concentration will firstly result in a net reduction in the proportion of CO_2 produced by metabolism that is exhaled with each breath. As inspired CO_2 concentration increases, each litre of alveolar ventilation per minute at the same F_{ETCO_2} excretes less net CO_2 from the body. This is equivalent to a rightward shift of the isometabolic curve by F_{ICO_2}. Quantitatively the curve of metabolically sustainable states changes from

$$\overline{\dot{V}_A} = \frac{\overline{\dot{V}_{CO_2}}}{\left(F_{ETCO_2}\right)}$$

to

$$\overline{\dot{V}_A} = \frac{\overline{\dot{V}_{CO_2}}}{\left(F_{ETCO_2} - F_{ICO_2}\right)}$$

The location of the new potential steady state (the new crossing point of the chemoreflex response curve with the new isometabolic curve) therefore moves rightwards and upwards as shown in Fig. 9. At this new potential steady state, the higher average ventilation means that a 1 l min^{-1} disturbance in ventilation has a smaller absolute effect on F_{ETCO_2}, i.e. the plant gain has fallen. The result is a smaller total loop gain, i.e. a more stable system (Francis *et al.* 2000*b*).

This effect of an increased concentration of inhaled CO_2 has a similar stabilizing effect on ventilatory control to pharmacologically induced hyperventilation (Nakayama *et al.* 2002).

How might supplemental oxygen assist stability?

The administration of oxygen during sleep has been shown to reduce sleep apnoea (Hanly *et al.* 1989*a*; Ponikowski *et al.* 1999). This could be due to a reduction in the net chemoreflex gain. First, the degree of CO_2 sensitivity increases with hypoxia, and therefore one would expect elimination of hypoxia to reduce CO_2 chemoreflex gain. Second, oscillations in arterial oxygen may contribute to some degree to the oscillations in ventilation. Elimination of these oscillations by hyperoxia may therefore further favour stability.

Do our findings conflict with previous modelling studies?

There have been previous modelling studies which also used approaches that allow investigation of the effect of chemoreflex gain and the apnoea threshold on ventilatory stability. For example, our group has previously created an analytical model to identify the causative factors that lead to periodic breathing, and then we performed clinical validation in human subjects (Francis *et al.* 2000*b*). The clinical data identified chemoreflex gain as a powerful destabilizing factor on ventilatory stability, and the theoretical analysis also indicated that high potential steady state levels of CO_2 are a destabilizing factor.

Khoo *et al.* (1982, 1991) have created other mathematical models and also assessed the effects of chemoreflex gain and potential steady state CO_2 levels on ventilatory stability. They found that system instability is increased by hypercapnia and large chemoreflex gain amongst other factors.

Carley & Shannon (1988*b*) developed a mathematical model using a frequency domain approach. This model too indicated that high ventilation enhanced system stability, whereas high CO_2 was destabilizing.

Miyamoto *et al.* (2004) clinically validated the concept of the CO_2 regulatory system being divided into controller gain (the ventilatory response to inspired CO_2), and plant gain (the arterial CO_2 response to changes in ventilation). They were able to measure controller gain and plant gain (the reciprocal of the slope of the hyperbola at the potential steady state), and therefore estimate total loop gain. They too found that at higher ventilation plant gain is lower and the system more stable.

The effect of raised inspired CO_2 on ventilatory stability has also been assessed by Topor *et al.* (2004) using a comprehensive computational model. They deduced that raised F_{ICO_2} stabilizes control by increasing mean ventilation.

The independent role of the apnoeic threshold has less often been studied in mathematical models. Vielle (2000) used a model that could alter both the chemoreflex gain and CO_2 levels, and again found that elevated values of either parameter led to decreased stability. He used C_{apn} threshold as an index for CO_2 levels, but as $\overline{C}$ was not described separately, C_{apn} acted as a proxy for $\overline{C}$. Any change in the apnoeic threshold would therefore be automatically associated with a similar increment in potential steady state CO_2. Therefore his finding that a high apnoeic threshold leads to system instability needs to be qualified as it is related to a joint increase in potential steady state CO_2 and chemoreflex gain. His study does not identify which of the two is the true culprit.

Recently, in a review of the mechanisms of periodic breathing, Cherniack & Longobardo (2006) have warned of the importance of studying the behaviour of the respiratory control system near the potential steady state, rather than just focusing on the apnoea threshold.

Taken together, the results of these previous studies are all consistent with the conclusions that we have found in this modelling study. Increased chemoreflex gain and increased mean F_{ETCO_2} are each able to decrease system stability. Ours is the first model to deliberately assess the *independent* influence of chemoreflex gain, potential steady state CO_2 and the apnoeic threshold on stability. We have aimed to provide a model that is simple to understand, so that the clinical implications can readily be appreciated.

Limitations of the study

For simplicity, we used only a single variable to represent blood gas variation, in keeping with several previous models (Vielle, 2000). During periodic breathing at rest, CO_2 and O_2 oscillations are in almost perfect antiphase (Faber *et al.* 1990) and therefore these oscillations can be satisfactorily treated as a single variable, with tacit recognition that the chemoreflex responds both to a rise in CO_2 and correspondingly to a fall in O_2. Moreover, near the potential steady state, chemoreflex responses to hypoxia are significantly smaller than hypercapnic responses for the same change in partial pressure (Carley & Shannon, 1988*a*; Maayan *et al.* 1992), and therefore the hypoxic contribution should be small.

For simplicity again, we use F_{ETCO_2} levels as a proxy for all CO_2 levels in the body, making the assumption that changes in one are tracked in parallel by changes in the others (in particular, arterial). This simplification is equivalent to assuming no significant physiological dead space. However, even if there is significant physiological dead space, the principal consequence is that the chemoreflex gains expressed in terms of changes in F_{ETCO_2} would be numerically smaller than their conventional expression in terms of arterial CO_2 changes. It would have no impact on the relative contributions of the three parameters to system stability, and therefore no effect on the conclusions of this study. The venous CO_2 is taken to not fluctuate significantly during periodic breathing. This substantially

simplifies the mathematics and is supported by physiological measurements (Vielle & Chauvet, 1998).

Our third simplification is to not separate peripheral and central components of the chemoreflex. Although there are multiple clusters of individual chemosensitive cells located in the aorta, the carotids and the brainstem, we describe the 'net' response, with a single effective delay and gain that represents a summation of the responses of all these individual receptors. Treating each component separately substantially increases the complexity and obscurity of the model, but cannot change the conclusions.

We have intentionally used the simplest possible units for each physical quantity in this study. This eliminates the need for arbitrary constants to convert between units. The simplest measure of end-tidal CO_2 level is its fraction, which is dimensionless. As a result, our unit of chemoreflex gain is '$\mathrm{l\,min^{-1}}$ (fraction of end-tidal CO_2)$^{-1}$', synonymous with '$\mathrm{l\,min^{-1}\,atm^{-1}}$', which is unconventional but fulfils the aim of being the simplest possible unit.

Finally, the purpose of this model is not to examine all cardiac and respiratory influences on system stability, but to extricate the independent effects of chemoreflex sensitivity, apnoea threshold and steady state CO_2, which cannot be separated clinically. This paper therefore adds to previously published clinical studies and mathematical models which aim to comprehensibly identify all influences on system stability – cardiac (including cardiac output and circulation time), respiratory and central (Khoo *et al.* 1982, 1991; Francis *et al.* 2000*b*; Vielle, 2000; Topor *et al.* 2004; Cherniack & Longobardo, 2006).

Conclusions

We have found that in contrast to beliefs arising from clinical observation, cardiorespiratory stability in heart failure is not independently affected by the apnoeic threshold. Moreover, in a second apparent conflict with clinical observation, we have found that it is a high (rather than low) potential steady state level of CO_2 that favours instability. In this paper we have explained both of these apparent paradoxes. They arise from the powerful effect of chemoreflex gain, which is infrequently addressed – perhaps because it is not automatically available from routine clinical data.

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Supplemental material

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