Quantitative General Theory for Periodic Breathing in Chronic Heart Failure and its Clinical Implications

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Background—In patients with chronic heart failure (CHF), periodic breathing (PB) predicts poor prognosis. Clinical studies have identified numerous risk factors for PB (which also includes Cheyne-Stokes respiration). Computer simulations have shown that oscillations can arise from delayed negative feedback. However, no simple general theory quantitatively explains PB and its mechanisms of treatment using widely-understood clinical concepts. Therefore, we introduce a new approach to the quantitative analysis of the dynamic physiology governing cardiorespiratory stability in CHF.

Methods and Results—An algebraic formula was derived (presented as a simple 2D plot), enabling prediction from easily acquired clinical data to determine whether respiration will be unstable. Clinical validation was performed in 20 patients with CHF (10 with PB and 10 without) and 10 healthy normal subjects. Measurements, including chemoreflex sensitivity (S) and delay (δ), alveolar volume (V_L), and end-tidal CO_2 fraction (C_τ), were applied to the stability formula. The breathing pattern was correctly predicted in 28 of the 30 subjects. The principal combined parameter (CS)×(δ/V_L) was higher in patients with PB (14.2±3.0) than in those without PB (3.1±0.5; P=0.0005) or in normal controls (2.4±0.5; P=0.0003). This was because of differences in both chemoreflex sensitivity (1749±235 versus 620±103 and 526±104 L/min per atm CO_2; P=0.0001 and P<0.0001, respectively) and chemoreflex delay (0.53±0.06 vs 0.40±0.06 and 0.30±0.04 min; P=NS and P=0.02).

Conclusion—This analytical approach identifies the physiological abnormalities that are important in the genesis of PB and explicitly defines the region of predicted instability. The clinical data identify chemoreflex gain and delay time (rather than hyperventilation or hypocapnia) as causes of PB. (Circulation. 2000;102:2214–2221.)

Key Words: heart failure ventilation physiology

In congestive heart failure (CHF), periodic breathing (PB) in the daytime1,2 or during sleep3 results in elevated mortality, which may result from the numerous repetitive fluctuations in blood gases, blood pressure, and heart rate.4 These repeated insults may induce chronic sympathetic over-activation, impede exercise capacity,5 and precipitate ventricular arrhythmias.6

It has long been speculated that PB may arise from pathological feedback in ventilatory control.7–10 Clinical studies have identified several possibilities in patients with PB,11,12 particularly hyperventilation or hypocapnia.5,13–16 Prolonged circulation delay8,17 and increased chemoreceptor sensitivity18 have also been implicated. The role of circulation delay is controversial, partly because of animal work19 that had to prolong it to a biologically implausible 2 to 5 minutes to engender PB. Aside from the clinical approach, there are 2 conceptually different mathematical approaches.

Computer simulations, including an ingenious analog electrical circuit7 and numerical iterative models in digital computers,9,20,21 have shown oscillations arising with certain configurations of system physiology. The drawback is that an immediate overview of system behavior across a variety of physiological and pathological states is not gained because computerized resimulation is required for each proposed state. As the number of variables increases, the impact of changes in starting conditions becomes increasingly time-consuming to tabulate and difficult to conceptualize.

The alternative approach is to solve analytically the dynamics of respiratory control in PB. The attraction of this approach is that it should make obvious the range of physiological states that result in PB and predict and explain the mechanisms of effective treatments, while removing the need for computer recalculation for each possible combination of clinical variables. Models have been developed using the frequency domain22 or by seeking critical values of circulation delay,23 but their complexity has limited widespread appreciation. An important step towards a directly clinically applicable model was taken by Mackey and Glass,24 but close examination reveals that the stability criterion proposed is correct only when ventilation and cardiac output are zero.

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2214
The lack of an analytical unified general theory of PB that is both mathematically explicit and comprehensible to clinicians has hindered a deeper understanding of the physiological processes; this understanding would enable rational interventions to be planned. Currently, the underlying delay-differential equations are difficult to solve analytically using the techniques that have hitherto been applied.

We aimed to solve these fundamental equations governing cardiorespiratory stability by applying a new technique that would give a rigorous quantitative basis for understanding the pathophysiology of PB in CHF. This would give rise not only to testable predictions of cardiorespiratory stability from primary clinical data, but also provide a framework for understanding the effect on stability of changes in physiological variables, such as those from therapy.

Methods

Analytical Model

Ventilation is regulated by delayed negative feedback. The chemosensors are located in the aorta, the carotids, and the brainstem and, therefore, they receive information on blood gas status some time after a change occurs in the lung; a further neurological delay may occur before ventilation changes. The purpose of the control system is to regulate blood gases and damp away any small random disturbances. However, the delay before response provides the potential for a vicious circle of increasing stimuli and responses (of alternating signs) to develop; this is PB. The analytical approach seeks to identify explicitly the conditions that cause the oscillations to grow.

What determines whether PB will occur is control system behavior near the steady state. Physiological fluctuations in this region can be described with linear mathematics. Carbon dioxide (CO₂) and oxygen oscillate during PB in antiphase. Therefore, we represent the state of the blood gases by a single variable. It is useful to develop a variable c, which represents the displacement of the alveolar gas stores (nominally CO₂ fraction) away from its mean value, C (Table 1). Likewise v represents the displacement of alveolar ventilation from its mean value Vₐ. Because of the time delay, the value of v at time t (vₜ) depends on the value of c at some time δ previously (cₜ₋δ). Near the steady state, therefore, vₜ = S × cₜ₋δ, where S represents chemoreflex gain (addional ventilation per unit increase in c). Fluxes of CO₂ into and out of the lung arise from metabolism, ventilation, and exchange with blood stores. Metabolic production of CO₂ by the body is expressed as VₐC. The rate of CO₂ removal from the lung by ventilation is expressed as (V/Vₚ)(C+c). Oscillations in arterial CO₂ necessitate a net transfer of CO₂ from the lung to extrapulmonary stores (in comparison with the steady state) at a rate of βQc, where β indicates marginal solubility of CO₂ in blood and...
investigator (L.C.D.). Informed consent and ethical approval were obtained.

Subjects sat and breathed through a calibrated heated pneumotachograph into a metabolic cart that used a mass spectrometer (Innovision) to measure ventilation, CO\textsubscript{2}, and O\textsubscript{2}. Subjects underwent 2 tests. In the first, mean alveolar ventilation (V\textsubscript{A}) and mean end-tidal CO\textsubscript{2} fraction (C\textsubscript{#}) were measured. They then rebreathed from a 6-L bag initially containing 100% oxygen until the end-tidal PCO\textsubscript{2} reached 10 kPa or the test became uncomfortable. The gain (S) of the chemoreflex system was measured as the ratio of the rate of rise of alveolar ventilation to the rate of rise of end-tidal PCO\textsubscript{2} in L/min per atmosphere CO\textsubscript{2}. Effective lung volume (V\textsubscript{L}) for ventilatory exchange was determined by fitting a monoexponential curve to the pattern of increase in end-tidal P\textsubscript{O\textsubscript{2}} when the inspired gas was switched to oxygen.

In the second test, a series of stimuli of 7% inspired CO\textsubscript{2} were applied over 12 to 15 minutes, and the resulting ventilation and end-tidal PCO\textsubscript{2} sequences were resampled at 1 Hz. Chemoreflex time delay (\delta) was determined through cross-correlation analysis as the lag giving the maximal correlation between them. We used values of 0.05 L·L\textsuperscript{-1}·kPa\textsuperscript{-1}26 (and atmospheric pressure of 100 kPa) for \beta\textsubscript{CO\textsubscript{2}} and 0.06 L·kg\textsuperscript{-1}·min\textsuperscript{-1} for resting Q.

### Results

#### General Solution of Analytical Model

Equation 3, on which hinges the stability of cardiorespiratory control in CHF, can be solved by introducing Lambert’s W function\textsuperscript{27} (defined by its inverse, W:ze->ze\textsuperscript{2}), as detailed in the Appendix. The solution is as follows.

\[
\frac{1}{\delta} \text{ln} - \frac{CS\delta}{V_L} e^{(\overline{VA} + \beta Q)\delta/V_L} - \frac{(\overline{VA} + \beta Q)\delta}{V_L}
\]

Although this may at first appear to be a complicated expression, it is constructed from 2 combination variables, CS(\delta/V\textsubscript{L}) and [\overline{VA} + \beta Q](g/V\textsubscript{L}). Inserting values for the 6 physiological variables immediately yields an explicit description of the response to any disturbance in respiration. This response is described by the function e\textsuperscript{r}, which is equal to (e\textsuperscript{g}×e\textsuperscript{jv}), because r contains real and imaginary parts (r=\text{g}+\text{jv}). The rate of growth or decay of oscillations is e\textsuperscript{g}, which depends on the underlying physiological variables in the manner shown in Figure 1. The period of oscillation 2\pi/\omega also varies (as shown in Figure 2); however, for most patients with PB, this period is between 2 and 2.5 times the chemoreflex delay.

Thus, if a patient has (\overline{VA} + \beta Q)(\delta/V\textsubscript{L})=4.5, CS(\delta/V\textsubscript{L})=10.0, and \delta=0.45 minutes, Figure 1 shows that the
response to a small disturbance is an oscillation that grows by a factor of 1.75 every 0.45 minutes, and Figure 2 shows that the period of oscillation will be 1.1 min. The underlying mathematics, which do not to be performed once the 2 plots are available, are done by equation 4, such that 

$$r = \frac{(0.56 + 2.7j)}{d},$$

so the growth factor is $e^{0.56}$ (ie, 1.75 per 0.45 minutes) and the period is $(2\pi/2.7) \times 0.45$ (ie, 1.1 min).

**Generality of Solution**

The solutions plotted in Figures 1 and 2 are completely general: their axes are dimensionless, because all units cancel. The intercept of the stability plot on the $CS(\delta/V_L)$ axis (which at first may appear to be arbitrary) is $\pi/2$, and it, the whole boundary of stability, and indeed the whole shape of the 3D surfaces are independent of all physical constants. The plots will not require recalculation for changes in any variable and are thus applicable to a wide range of situations. Copies are available from the authors.

**Clinical Results**

The observed values of $CS(\delta/V_L)$ and $(VA + \beta Q)(\delta/V_L)$ are plotted in Figure 3. The boundary between oscillatory and steady breathing, predicted by equation 4, is also shown. PB was correctly predicted from primary clinical measurements in 10 of 10 patients with PB, and steady breathing was correctly predicted in 9 of the remaining 10 patients and in 9 of the 10 normal controls.

**Pathophysiologica Components Contributing to PB**

The principal combined parameter $CS(\delta/V_L)$ was much higher in patients with PB (14.2 ± 3.0) than in patients without PB (3.1 ± 0.5; $P = 0.0005$) or in normal controls (2.4 ± 0.5; $P = 0.0003$), as shown in Figure 4. Of its 4 contributory

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**Figure 2.** Effect of $(VA + \beta Q)(\delta/V_L)$ and $CS(\delta/V_L)$ on period of oscillations.

**Figure 3.** Observed values of $(VA + \beta Q)(\delta/V_L)$ and $CS(\delta/V_L)$ in patients with PB (●), patients without PB (△) and normal controls (□). Oblique line indicates the boundary, predicted by equation 5, between oscillatory and steady breathing.
factors, the most important were chemoreflex sensitivity
(1749 ± 235 versus 620 ± 103 and 526 ± 104 L/min per atm
CO$_2$ in patients with PB versus those without PB and normal
controls; $P = 0.0001$ and $P < 0.0001$, respectively) and che-
moreflex delay (0.53 ± 0.06 versus 0.40 ± 0.06 and 0.30 ± 0.04
min; $P = NS$ and $P = 0.02$, respectively). No significant dif-
ference existed between group means for C$_ \#$ (4.9 ± 0.1% versus 4.8 ± 0.1% and 4.8 ± 0.2%; $P > 0.05$ for both compari-
sions) or for V$_L$ (3.5 ± 0.3 versus 3.5 ± 0.2 and 3.2 ± 0.2;
$P > 0.05$ for both comparisons). The second combined param-
eter, $(V_\dot{A} + bQ)(\delta/V_L)$, did not differ between the groups
(5.0 ± 0.9 versus 3.4 ± 0.5 and 3.1 ± 0.5; $P > 0.05$ for both com-
parisons).

**Cycle Time of PB**

For the 10 patients with PB, the observed cycle time averaged
1.2 ± 0.2 min. The prediction from our model, using their
physiological parameters, was for a cycle time of 1.2 ± 0.1
min, the predicted time, using the 40 formula of Mackey and
Glass, was 2.1 ± 0.3 min. The difference between observed
and predicted cycle times are plotted against their means for
our model (Figure 5A) and the model of Mackey and Glass (Figure 5B). With our model, the prediction error averaged
0.0 min, with a SD of 0.4 min (ie, no significant bias; $P = 0.8$).
The Mackey and Glass model showed a significant bias
(prediction error averaging 0.9 min; $P = 0.001$) and a wider
prediction error SD of 0.6 min.

**Discussion**

This new and explicit criterion for stability enables a direct
consideration of the physiological factors that contribute to

![Figure 4](image)

**Figure 4.** Comparison between normal controls, patients without PB, and patients with PB of (A) $C_{\#}d/V_L$; (B) $(V_\dot{A} + \beta Q)(\delta/V_L)$; (C) $S$; (D) $\delta$; (E) $C_{\#}$; and (F) $V_L$.

![Figure 5](image)

**Figure 5.** Comparison between predicted and observed cycle times of periodic breathing, using (A) our analytical model and (B) the formula of Mackey and Glass. Each plot shows the dif-
ference between the predicted and observed values plotted
against the mean of both.
PB and a comparison of their relative importance. The results are general: the stability diagram (Figure 1) is independent of all physical constants, and it does not require recalculation for changes in physiological variables. Moreover, the clinical data show good validity in predicting both instability and period.

This now illuminates clinical controversies regarding pathogenesis and may help in the rational development of therapy. A first step is to simplify Figure 1 to focus on the principal question of whether breathing is doomed to be periodic by showing only the dividing line between stability and instability and by representing the effects of changes in physiological variables by arrows. Figure 6A shows why instability is favored by increased chemoreflex slope (or lag) and by decreased lung volume (or cardiac output). Figure 6B shows how treatment that increases cardiac output, lung volume, ventilation or inspired CO₂ or decreases lag time or effective chemoreflex slope can stabilize ventilation.

**Hyperventilation and Hypocapnia: Red Herrings?**

Chronic hyperventilation and/or hypocapnia are often considered important in the pathogenesis of PB for 2 reasons. First, CHF patients with PB have a lower mean arterial P CO₂ and a higher mean ventilation. Second, the application of inspired CO₂ stabilizes ventilation.

There are also 3 reasons to question the importance of this in causation. First, respiratory control is undoubtedly less stable during sleep when mean ventilation is lower; indeed, even normal subjects frequently develop PB while asleep. Second, exercise, which raises mean ventilation, reliably attenuates PB. Third, and perhaps most importantly, our analysis shows that increased ventilation and decreased P CO₂ each favor stability.

How can these observations be reconciled? The answer lies in an important physiological property infrequently measured in clinical studies: chemoreflex gain.

**Chemoreflex Gain**

The mean value of the product of alveolar ventilation and alveolar CO₂ fraction must match the rate of the metabolic production of CO₂. Thus, for any given metabolic rate, the possible steady-state values of ventilation and alveolar CO₂ fraction form a hyperbola (Figure 7). The position of the respiratory system depends on where the chemoreflex controller response crosses the hyperbola. An increased chemoreflex slope causes it to meet the hyperbola higher.

Clinically, this means that a higher ventilation should always be suspected of concealing a large increase in chemoreflex gain. Elevated hypercapnic gain is associated with respiratory instability in patients with CHF. In one study, the hypercapnic gain was 124% greater in those with central sleep apnea than in those with obstructive sleep apnea, whereas the P CO₂ values were only 16% lower (and, by implication, the alveolar ventilation ≈16% higher). The stability chart shows that these abnormalities in P CO₂ and ventilation both favor stability but are readily overpowered by an underlying large enhancement of chemoreflex gain.

**Lung Volume**

If the association between hyperventilation-hypocapnia and PB seen in observational studies can be explained by an underlying difference in chemoreflex slope, what mechanism can be offered for the therapeutic trials of continuous positive airway pressure, which have found stabilized breathing, increased PCO₂, and decreased mean ventilation? We suggest that continuous positive airway pressure invokes another
The pitch of the resulting unwanted note is independent of the back" phenomena heard when a microphone is accidentally system physiology. It is analogous to the case of the "feed-

No particular pattern of disturbance is necessary to initiate PB. Any disturbance, however small, will become amplified into PB if the scale factor is >1 and damped away if the scale factor is <1. The period of oscillation of the system is also independent of the initial stimulus and depends only on system physiology. It is analogous to the case of the "feedback" phenomena heard when a microphone is accidentally brought too close to a loudspeaker to which it is connected. The pitch of the resulting unwanted note is independent of the initiating sounds. Moreover, attempting to remain silent cannot prevent the squeak. Ultimately, system behavior depends only on the properties of the system. Likewise, if breathing control is in distinctly unstable territory (Figure 1), breathing is doomed to become periodic, with stereotyped period.

Study Limitations
This analytical study and its clinical validation data are principally directed at the critical determinants of cardiore-
toratory stability in PB resulting from CHF. We used a single variable representing blood gas variation. Respiratory stability is determined by system behavior near the steady state, where most patients with CHF have high oxygen saturations. Here, hypoxic chemoreflex responses are much smaller than hypercapnic responses for the same change in partial pressure. Thus, even though swings in PCO2 during the onset phase of PB may be smaller than those of PO2, respiratory stability depends on the CO2 chemoreflex.

There are three aspects, however, in which hypoxia may play a more prominent role. First, any baseline hypoxemia may increase hypercapnic chemoreflex gain. Second, once oscillations become established and episodic desaturations occur, the hypoxic chemoreflex response is steeper and could contribute to determining the size to which oscillations grow (which our model does not study). Third, if the PB is not due to CHF but a different cause, such as altitude hypoxia, deoxygenation may play a pre-eminent role. The model could be re-expressed in terms of hypoxic rather than hypercapnic stimuli: this would affect the measurement of the variables equivalent to C and S but would not affect the general predictions of the model.

Conclusion and Clinical Implications
The 6 principal physiological factors that favor PB are a steep chemoreflex slope, long lag to chemoreflex response, low ventilation, low cardiac output, high alveolar-atmospheric CO2 difference, and small lung volume. Of these, chemoreflex enhancement and prolonged lag to ventilatory response may be the most important factors in CHF. Hyperventilation and hypocapnia, long considered prime factors, may be epiphenomena of increased chemoreflex slope. The beneficial effects of therapies can now be categorized as follows: oxygen reduces effective chemoreflex gain (by removing any enhancement of the hypercapnic chemoreflex gain and attenuating any independent hypoxic chemoreflex component); continuous positive airway pressure increases mean lung volume; and inotropes and corrective surgery reduce circulation delay and increase cardiac output. Inspired CO2 increases ventilation (favoring stability) and also causes the alveolar CO2 to resettle at a slightly higher level. Mathematically, it is the difference between alveolar and inspired CO2 that is represented by C. When this is reduced, it favors stability. Nevertheless, in each case, smaller secondary effects on other parameters cannot be excluded.

In PB, basic elements that are essentially smooth show spontaneous pattern formation because of time-delayed negative feedback. This chemoresponse time delay can be measured using simple clinical equipment as easily as can
chemoreflex gain. An explicitly quantitative framework in terms of clinical concepts is now available with which to consider the mechanisms of therapies at an intellectual level. We hope to stimulate colleagues to consider, measure, and discuss these factors (which exert mathematically independent effects on breathing stability) whenever studying PB or its treatments.

Appendix

There are only two independent unknowns (g and \(\omega\), with \(r = g + j\omega\)), and the equation lies in the complex plane (and is thus equivalent to 2 standard real equations). A general solution might therefore be expected to be readily obtainable. Unfortunately, not only do standard steps fail to reach a general solution, but the general solution is intrinsically so strange that it cannot even be described by conventional mathematical functions. It requires Lambert’s transcendental W function.\(^{27}\) This is the mapping \(W: z \rightarrow z^{1/3} W(z)\)~. For example, because \(3e^{1/3} \approx 60.26\), \(W(60.26) \approx 3.\)

Multiplying equation 3 by the following

\[
\delta e^{\frac{r}{V_L} (V_A + \beta Q)} = \frac{V_L}{\delta} \left( \frac{\delta^2 (V_A + \beta Q)}{V_L} \right) \left( \frac{CS \delta e^{\frac{r}{V_L} (V_A + \beta Q) S}}{V_L} \right)
\]

and rearranging, we obtain equation 6.

\[
\left( r \delta + \frac{(V_A + \beta Q)}{V_L} \right) e^{\frac{r}{V_L} (V_A + \beta Q)} = \frac{CS \delta e^{\frac{r}{V_L} (V_A + \beta Q) S}}{V_L} \left( \frac{V_A + \beta Q}{V_L} \right)
\]

The W function can be applied to both sides as follows.

\[
\frac{1}{\delta} \left( \frac{CS \delta e^{\frac{r}{V_L} (V_A + \beta Q) S}}{V_L} \right) = W \left( \frac{V_A + \beta Q}{V_L} \right)
\]

From this equation, the general solution is as follows.

\[
\delta e^{\frac{r}{V_L} (V_A + \beta Q)} = \frac{V_L}{\delta} \left( \frac{\delta^2 (V_A + \beta Q)}{V_L} \right) \left( \frac{CS \delta e^{\frac{r}{V_L} (V_A + \beta Q) S}}{V_L} \right)
\]

This explicitly yields the predicted growth rate and oscillatory period from primary clinical data. Once Figures 1 and 2 are constructed, however, no further W computation is necessary because they are completely general.

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