Observation and Simulation of the Circulation, Acid-Base Balance, and Response to CO₂ in Cheyne-Stokes Respiration

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SUMMARY

Circulatory, chemical, and ventilatory response factors in Cheyne-Stokes respiration (CSR) were studied by experimental procedures and by mathematical analysis. Hemodynamic, ventilatory, and blood gas patterns in 16 patients with heart disease and CSR (group A) and 16 patients with congestive heart failure (CHF) without CSR (group B) were compared. CO₂ and oxygen were administered to group A. The phenomena exhibited by patients with CSR were simulated by a mathematical model.

The following conclusions were drawn: (1) Reduced blood flow and respiratory alkalosis were similar in both groups; (2) circulation times, lung to artery, were 29 sec greater than normal in patients with CSR but only 8 sec greater than normal in group B patients; (3) the abnormal CO₂ response in CSR, a reduction in threshold and sensitivity, was similar to that in CHF, suggesting that abnormal respiratory mechanisms were responsible; (4) mathematical simulation of CSR was possible by appropriate prolongation of circulation time alone; the CO₂ response (reduction in threshold and sensitivity) had no significant effect on stability; (5) damping of oscillatory ventilation by CO₂ inhalation could be efficiently simulated; (6) CSR with cycle periods less than 50 sec suggests increased neural or chemoreceptor excitability, anemia, or hypoxemia as contributory factors, whereas longer periods suggest primary circulatory factors.

Additional Indexing Words:
Mathematical simulation Congestive heart failure Respiratory center sensitivity
Hemodynamics Ventilation Blood gases

Observations of periodic or Cheyne-Stokes respiration (CSR) in various disease states or under adverse environmental conditions have aroused speculation on the nature of the respiratory control system for more than 50 years. Attention has been directed toward the effects of CO₂ and oxygen and the role of the circulation. Mathematical analysis and modeling have been applied by several workers. Simulation of CSR was possible with normal chemoreceptor responses. Although Douglas and Haldane considered anoxemia an important factor, the observation of consistent hypocapnia led some workers to suggest increased sensitivity to CO₂.

The work reported here is directed toward...
identification of the relative importance of altered hemodynamic state, acid-base balance, and ventilatory response to CO₂ in CSR. Four types of investigation are employed. These are: (1) description of hemodynamic variables in patients with congestive heart failure, with and without CSR; (2) examination of the acid-base equilibria and CO₂ sensitivity in patients with congestive heart failure, with and without CSR; (3) observation of the time course of the effect of CO₂ (and O₂) on CSR; and (4) application of theoretical analysis of the respiratory control system so that the influence of chemical and hemodynamic variables can be assessed.

Methods

Patient Selection and Treatment

A. Patients with Cheyne-Stokes Respiration

The 16 patients selected for study included all patients encountered over a 3-year period in whom CSR was observed and who would consent to the measurement of ventilation and blood gases. The average age was 68 years (range, 50 to 88). All patients presented with symptoms and signs referable to the cardiorespiratory system. Five had associated neurological disease. One was obese with alveolar hypoventilation; one had a small ventricular septal defect secondary to a myocardial infarction; one was mildly azotemic; and one had moderately severe iron-deficiency anemia. Studies were carried out after optimal therapy for orthopnea, edema, and venous and pulmonary congestion. Therapy for congestive heart failure invariably included digitalis, dietary sodium restriction, and thiazide diuretics with potassium supplement and, at times, mercurial diuretics. Patients were free of edema; however, residual mild pulmonary congestion was not infrequent.

B. Control Group

Ventilatory and arterial blood gas measurements were incidental to diagnostic cardiac catheterization in 16 patients with heart disease characterized by pulmonary and systemic venous congestion and reduced cardiac output but without CSR. The mean age was 46 years (range, 22 to 64). The patients, selected in sequence, had received digitalis, dietary salt restriction, and thiazide diuretics with potassium supplements. These patients served as a control group in that therapy for congestive heart failure was similar to that in group A.

Procedure

Patients in the post-absorptive state and without premedication were placed in a supine position with head supported by one or two small pillows. Auditory and visual distractions were minimized in a dimly lighted room. After a 15- to 20-min rest period, a large bore mouthpiece connected to a Rudolf low resistance valve by short length flexible tubing was inserted and the nose gently clamped. Inspired gas could be altered without the patient’s knowledge.

After a 4- to 6-min recording of periodic respiration while breathing room air, administration of a mixture of 2% CO₂ in air was begun, usually at the end of a period of apnea, and continued for 4 to 10 min, whereupon room air ventilation was resumed. Ten to 15 min later the inspired gas was changed to 100% oxygen for 5 to 10 min with subsequent return to room air. An indwelling arterial needle allowed withdrawal of blood samples for analysis of gas tension and hydrogen-ion concentration (Instrumentation Laboratories Model 113) and oxygen saturation by gasometric (Van Slyke) and oximetric methods (Astrup) during apneic and hyperpneic periods throughout the study. When tolerated, higher concentrations of CO₂ in air, up to 5.11%, were administered.

Indicator-dilution curves were recorded via a densitometer sampling system (Waters Model 300) from the femoral artery employing venous or central circulatory injection of 10 to 15 mg of indocyanine green with an 8- to 12-ml saline flush. The Hamilton method was employed for estimation of cardiac output and mean circulation time. The lung to artery circulation time was estimated by subtracting arm to lung time (ether method) when the arm to artery method was employed. In three patients investigated by right heart catheterization in addition to the preceding procedure, direct estimation of lung to artery circulation time was carried out.

The expired gas was led to a wedge spirometer (Medical Science Electronics Model 170) through a spirometer recycler (Medical Science Electronics Model 176). The spirometer was recycled by manual control every 6 to 7 L during the expiratory pause or during inspiration. The recycling was accomplished in less than 1 sec and could not be appreciated by the subject. Gas constantly sampled from the mouthpiece at 100 to 200 ml/min passed through the microcuvette of a Beckman CO₂ analyzer (Model LB-1).

Presentation of Data

Mean ventilation was estimated over two or more cycles if apnea or extreme hypopnea occurred. When CO₂ was administered, ventilation was estimated over the last 2 min of gas exposure.
Maximum and minimum values for ventilation were obtained over a 10-sec period. Corrections for $\text{CO}_2$ sampling were made. Alveolar $\text{CO}_2$ maxima and minima were estimated in the same manner as for ventilation. When apnea was present, maximum values were taken from the immediate post-apneic expired gas. Samples for blood gas analysis were collected anaerobically over a 5- to 10-sec period during the periods of highest and lowest ventilation. When $\text{CO}_2$ was administered, this was usually during the third minute of exposure since frequently cyclic ventilation was not apparent after longer exposure. The period of oscillation, cycle length, was the average time in seconds between the mid-apneic points of several cycles beginning at least 2 min after a change in inspired gas. Ventilation approached a maximum value in 4 to 5 min, even though the mixture could be tolerated for 10 min.

Results

Cardiac Index and Circulation Time

Table 1 provides a summary of mean values. The cardiac index estimated in 12 patients with CSR ranged from 1.65 to 3.1, the mean and se were $2.13 \pm 0.14$. The normal resting cardiac index in the laboratory by similar methods is $3.62 \pm 0.52$. When the cardiac index was estimated after $\text{CO}_2$ or $\text{O}_2$ administration (three patients), no significant changes were noted. For group B (congestive heart failure) the mean cardiac index was $2.25 \pm 0.16$.

The circulation time in CSR, arm to femoral artery, ranged from 23 to 86 sec; the mean lung to femoral arterial circulation time was nearly 40 sec. In three patients, circulation time was estimated from pulmonary artery to femoral artery during right heart catheterization and was 15 sec (obesity and hypoventilation), 18 sec (heart failure and iron-deficiency anemia), and 40 sec (small postinfarction anemia). These times were approximately one-half the cycle length, 30, 38, and 82 sec, respectively. Administration of $\text{CO}_2$ or oxygen did not appreciably affect circulation time (three patients). The mean lung to arterial circulation time, excluding the patients with obesity and anemia, was 45 sec. Patients in group B exhibited a lung to artery circulation time of $18.8 \pm 1.5$ sec.

Cycle Length

While breathing room air, cycle length ranged from 30 sec (obesity and hypoventilation) to 120 sec (mean value, 79 sec). $\text{CO}_2$ breathing caused no change in mean length, 79.6 sec. Oxygen administration, however, prolonged cycle length with a range of 42 to 140 sec. The mean cycle length increased by $19 \pm 3.0$ sec (table 1).

Ventrilation

The typical Cheyne-Stokes respiration on breathing room air was associated with marked hyperpnea at times. All patients exhibited the typical waxing and waning of respiratory efforts. The mean maximum ventilation ($\dot{V}E$) was $20.6 \pm 2.7$ L/min. The average ventilation on room air was $9.4 \pm 0.93$ L/min. Figures 1 and 2 are representative. In patients with congestive heart failure without CSR, $\dot{V}E$ was $6.4 \pm 0.28$ L/min.

### Table 1

<table>
<thead>
<tr>
<th>Hemodynamics: Heart Failure With and Without Periodic Breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Cheyne-Stokes respiration</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>$\text{CO}_2$</td>
</tr>
<tr>
<td>$\text{O}_2$</td>
</tr>
<tr>
<td>$d'(\text{O}_2 - \text{RA})$</td>
</tr>
<tr>
<td>$p$</td>
</tr>
</tbody>
</table>

Abbreviations: N = number of patients studied; PA = pulmonary artery; FA = femoral artery.

*Circulation, Volume XXXVII, March 1968*
Simultaneous ventilation and CO₂ recording. The expired gas is integrated; full-scale is approximately 6 L. Resetting of wedge spirometer is accomplished during an expiratory pause or inspiration. The continuous sampling from the mouthpiece to the CO₂ meter shows inspiratory PICO₂ of room air and 14.2 mm Hg. End tidal PICO₂ was considered Paco₂. The typical gradual dampening of oscillatory ventilation is demonstrated. See text for details.

Figure 1

Effect of CO₂ Inhalation

Inhalation of CO₂ abolished apnea in all patients; in general, cyclic hypopnea and hyperpnea were evident. The mean ventilation in hypopnea was 7.71 ± 1.0 L/min. Hyperpnea was 17.9 ± 2.7 L/min, significantly less than that noted on room air (t = 3.4, P < 0.005). The mean ventilation rose to 13.8 ± 1.8 L/min. The increase was 4.4 ± 0.8 L/min, significantly higher than the room air mean ventilation (t = 5.5, P < 0.001). Table 2 and figures 1 and 2 illustrate these effects.

When O₂ was administered to 12 patients, apnea continued in five (fig. 2), and the remainder showed cyclic variation in ventilation. Mean ventilation during hypopnea was 2.0 ± 0.1 L/min and during maximum ventilation was 16.3 ± 3.0. The difference in mean hyperpnea from that of room air was significant (t = 3.4, P < 0.01). Mean ventilation was 9.6 ± 1.2 L/min, not significantly different from the mean ventilation on room air in the same patients (table 2).

Table 2

Ventilation and Alveolar CO₂: Effects of CO₂ and O₂

<table>
<thead>
<tr>
<th></th>
<th>Ventilation (L/min)</th>
<th>PAO₂ (end-tidal)</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Hypopnea</td>
</tr>
<tr>
<td>Room air</td>
<td>16</td>
<td>20.6 ± 7.4</td>
</tr>
<tr>
<td>CO₂</td>
<td>16</td>
<td>7.71 ± 1.0</td>
</tr>
<tr>
<td>d(CO₂ - RA)</td>
<td>+ 7.7 ± 1.0</td>
<td>- 2.7 ± 0.8</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>O₂</td>
<td>12</td>
<td>2.0 ± 0.7</td>
</tr>
<tr>
<td>d(O₂ - RA)</td>
<td>+ 2.0 ± 0.7</td>
<td>- 7.3 ± 1.9</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.025</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Circulation, Volume XXXVII, March 1968
CHEYNE-STOKES RESPIRATION

Figure 2

(Top panel): Recording as in figure 1. (Left to right): Room air, 2% CO₂, 3.37% CO₂, and 5.11% CO₂. Mean ventilation ranges from 7.6 to 20 L/min, Pa₅₉ from 30 to 48, corresponding to the increase in PaCO₂. The CO₂ response is characterized by a reduced intercept and slope (fig. 3). The maximum Ve on room air exceeds the maximum Ve with 2% and 3.37% CO₂.

(Bottom panel): Prolongation of cycle length with administration of 100% oxygen. PaO₂ was in excess of 300 mm Hg in apnea and hyperpnea.

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Heart disease and CSR</th>
<th></th>
<th>Heart disease and no CSR</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pa₅₉</td>
<td>HCO₃⁻</td>
<td>pH</td>
<td>Pa₅₉</td>
</tr>
<tr>
<td></td>
<td>Apnea</td>
<td>Hyperpnea</td>
<td>Apnea</td>
<td>Hyperpnea</td>
</tr>
<tr>
<td>Mean</td>
<td>33</td>
<td>39.5</td>
<td>24.4</td>
<td>7.485</td>
</tr>
<tr>
<td>N = 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCO₃⁻ &gt; 25</td>
<td>37.3</td>
<td>44.1</td>
<td>27.4</td>
<td>7.48</td>
</tr>
<tr>
<td>N = 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCO₃⁻ &lt; 25</td>
<td>27.2</td>
<td>33.5</td>
<td>20.4</td>
<td>7.49</td>
</tr>
<tr>
<td>N = 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>39</td>
<td>23.5</td>
<td>7.40</td>
<td></td>
</tr>
</tbody>
</table>

Alveolar CO₂ Tension

Expired CO₂ tension is given in table 2. Evidence of hyperventilation may be seen in the rather low levels of alveolar CO₂ (25.2 mm Hg during hyperpnea). This level approaches normality, 37.2 mm Hg, only at the end of the apneic phase as respiration is resumed. The effect of increase in the inspired CO₂ was to minimize the variation in the limits of CO₂ excursion so that the value during hyperpnea fell to only 31.7 and, during the time of lowest ventilation, it rose to only
The mean value for alveolar CO₂ rose. Breathing 100% oxygen had little effect on the mean range of alveolar CO₂ tension. Some patients continued periodic breathing with longer cycles and wider variation in alveolar CO₂ tension compensating for the smaller variations in patients in whom apnea was prevented by 100% oxygen.

Figure 1 is representative of the damping effect of CO₂ on periodic breathing. When the patient breathed room air, the cycle length was 105 sec. Volume of expired gas (Vₑ) ranged from 0 to 17 L/min (mean, 11 L/min). Expired alveolar CO₂ tension (PA⁻CO₂) ranged from 24 to 33, arterial CO₂ tension (PacO₂) from 26 to 29, pH from 7.47 to 7.49, and arterial oxygen tension (PaO₂) from 54 to 66. The introduction of the inspiratory pressure of CO₂ (PICO₂) = 14.2 increased mean ventilation to 14 L/min, but the range decreased to 9 and 16. PACO₂ oscillated between 28 and 32. Figure 2 depicts the ventilatory response to three CO₂ mixtures and also shows that, with 100% O₂ administration, periodic apnea continued but there was progressive prolongation of cycle length.

### Acid-Base Equilibria

Table 3 summarizes the level of serum bicarbonate and blood pH and PaCO₂ in patients with CSR and those with congestive heart failure. Both groups exhibited mild alkalosis and hypocapnia. Although the mean bicarbonate level was not far from normal, a large fraction of both groups (7/12 and 10/16) respectively manifested elevation of pH and bicarbonate suggesting respiratory and metabolic alkalosis. The remaining patterns were those of incompletely compensated respiratory alkalosis.

### Arterial Blood Gases

All patients showed 180° phase shift between PaCO₂ and PaCO₂. As table 4 indicates with room air breathing, the PaO₂ ranged from 75.4 during apnea to 60.1 during hyperpnea. The mean value, while not sufficiently reduced to cause arterial unsaturation, was definitely below normal. CO₂ ventilation...
CHEYNE-STOKES RESPIRATION

337

CHEYNE-STOKES RESPIRATION

337

elevated the \( P_aO_2 \) to 87.1 during the period of reduced ventilation and to 74.3 during the time of maximum ventilation. Arterial \( O_2 \) saturation followed the same pattern as \( P_aO_2 \). Oxygen inhalation increased the oxygen tension to mean values above 300. A similar \( P_aO_2 \) response was seen in patients whether or not apneic periods persisted. The mean \( P_aO_2 \) was 89 ± 2.0 in the patients with congestive heart failure but without CSR.

Arterial \( CO_2 \) tension varied during the ventilatory cycle from 33 mm Hg during the apneic period to 39.5 mm Hg during hyperpnea; the estimated mean was not significantly different from that seen in patients with congestive heart failure. Inhalation of \( CO_2 \) caused a slight rise during the period of reduced ventilation and a slight fall during the hyperpneic phase. Oxygen effects were noted in seven of the 16 patients. This showed a somewhat greater increase in \( CO_2 \) tension during the hyperpneic phase.

\( pH \) determinations indicated mild respiratory alkalosis. The highest \( pH \) values were observed during apnea and the lowest values during the hyperpneic phase. The degree of alkalosis was similar to that seen in congestive heart failure. Administration of \( CO_2 \) to seven of the 16 did not induce any appreciable difference in the range of \( pH \) from that during breathing of room air. Similarly, administration of \( O_2 \) to six patients did not induce a significant variation from the values noted during room air respiration.

Chemoreceptor Response

The reduction in mean \( PaCO_2 \) and increased mean \( VE \) implies an abnormal chemoreceptor response. Periodic breathing precludes description of chemoreceptor by the usual \( CO_2 \) response curves. Therefore, the chemoreceptor characteristics of \( CO_2 \) were estimated by other means.

1. \( VE \) and \( PaCO_2 \) were related during \( CO_2 \) inhalation when apnea was abolished in nine patients. Figure 3 relates the \( VE \) and \( PaCO_2 \) during the hypopnea of \( CO_2 \) inhalation (\( VR \)) with the \( VE \) and \( PaCO_2 \) during hyperpnea. \( VE \) is 7.9 and 18.4; \( PaCO_2 \) is 37.2 and 42.3.

2. A second reflection of chemoreceptor activity was derived from the mean \( VE \) and \( PaCO_2 \) on room air breathing (\( VR \)) and during \( CO_2 \) inhalation (\( VE \) 9.8 and 13.6; \( PaCO_2 \) 36.2 and 39.8; fig. 3). Comparison of the mean resting \( PaCO_2 \) (37.0) in treated congestive heart failure is indicated by X. The normal response is extracted from the report of Alexander and his associates.14

Figure 2 (top) provides an example of the ventilatory response to 2%, 3.37%, and 5.11% \( CO_2 \) in air. Ventilation is shown between the eighth and tenth minutes after change in inspired gas, as is the corresponding \( PaCO_2 \). As in figure 1, \( CO_2 \) eliminates the apnea. The maximum ventilation observed during exposure to 2% and 3.37% \( CO_2 \) is less than the maximum ventilation during the hyperpneic phase of room air breathing (22 L/min). While the mean resting ventilation increased from 7.6 to 20 L/min, the mean \( PaCO_2 \) increased from 30 to 48. The continuous sampling through the \( CO_2 \) meter demonstrates corresponding increases in \( PaCO_2 \).

The mean \( CO_2 \) response characteristics estimated by two indirect methods agree fairly well. The resting \( PaCO_2 \) in congestive heart failure does not differ significantly from the mean \( PaCO_2 \) in periodic breathing on room air. The \( CO_2 \) response curves in CSR differ

Figure 3

Ventilation response curves in patients with CSR (group A) derived as indicated in text. Similar \( VE - PaCO_2 \) relationships are seen in patients with congestive heart failure (CHF) (group B).
from normal in two ways; a shift of the apneic threshold to the left and a decrease in the slope of the sensitivity or responsiveness curve.

**Theoretical Analysis**

**Development of Model**

The mathematical model alluded to previously has successfully simulated the brief cyclic respiration after post-hyperventilation apnea, steady-state responses to changes of $\text{Pa}_{\text{CO}_2}$ and $\text{HCO}_3$ in cerebrospinal fluid, and reproduced periodic breathing when the circulation time is prolonged. The results noted above indicate a uniform response to $\text{CO}_2$ inhalation with a homogeneous pattern. The response to $\text{O}_2$ was, however, variable and—for the present purposes—simulation will be limited to the room air and $\text{CO}_2$ response. The development of the method of simulation has been fully dealt with in the earlier publications and is briefly reviewed in the "Appendix." A diagram of the elements of the control system is shown in figure 4.

The model incorporates two feedback loops for $\text{CO}_2$ and $\text{O}_2$ including: (1) a time invariant chemoreceptor response to $\text{CO}_2$ and $\text{O}_2$ which may reflect the equations of Gray; or may be assigned the average $\text{CO}_2$ response observed in the patients under study; (2) the buffering effects of CSF; and (3) an alveolar to arterial transfer function derived from studies of patients with valvular heart disease and extended to apply to patients with circulatory states resembling those reported herein.

The "Appendix" develops and identifies the relationship between the controlled variable of ventilation and the controlling variables such as metabolic rate, $\text{CO}_2$ stores, functional residual capacity, and the transfer function. In the first example of simulation, all parameters were assigned normal values except the transfer function from lung to artery or lung to chemoreceptor which was assigned a mean transit time of 50 sec with...
the distribution of transit times extrapolated from our previous work.\textsuperscript{12} Figure 5A depicts the instability of ventilation observed by this alteration of a single variable. Figure 5B portrays the combination of prolonged circulation time along with the CO\textsubscript{2} response and reduced PaO\textsubscript{2} derived from the present observations. At the times indicated in figure 5A and B, the value of P\textsubscript{ICO\textsubscript{2}} of equation 3, "Appendix," was changed from 0 to 15. The time course of alveolar ventilation and consequent change in PaCO\textsubscript{2} and PaO\textsubscript{2} is followed for several hundred seconds of computer operation.

The following qualitative similarities between the prototype and the model were considered essential for acceptable simulation. These were as follows:

1. When the mean circulatory delay time (lung to brain) was increased to approximately four times normal, a steady-state oscillation in ventilation with a range from 0 to 2.5 times mean ventilation should be seen.
2. The phasic relationship between PaCO\textsubscript{2} and PaCO\textsubscript{2} as simulated should resemble that observed in the average patient.
3. Introduction of P\textsubscript{ICO\textsubscript{2}} = 15 mm Hg should reduce the amplitude of oscillation and prevent apnea.
4. With CO\textsubscript{2} inhalation, there should be an increase in mean \( \dot{V}_E \) and a decrease in maxima and rise in minima, as in the prototype.
5. The change induced by CO\textsubscript{2} inhalation in PaCO\textsubscript{2} and PaCO\textsubscript{2} of the model should resemble that in the prototype.
6. The PaO\textsubscript{2} should increase as CO\textsubscript{2} inhalation progresses.

**Application of Simulation**

Figure 5A depicts the effect of a 50-sec mean circulation time, lung to chemoreceptor, with all other controlling variables maintained at normal levels. After the initial conditions, a steady-state oscillation evolved. \( \dot{V}_A \) varies from 0 to 10 L/min. PaCO\textsubscript{2} ranges from 35 to 45 mm Hg with a mean of 39. PaO\textsubscript{2} varies from 64 to 110 mm Hg with a mean of 85. Introduction of P\textsubscript{ICO\textsubscript{2}} = 15 mm Hg is shown at 1,000 sec (during apnea). Reduction in amplitude of oscillation occurs with increase in mean value of \( \dot{V}_A \) to 6.5, PaCO\textsubscript{2} to 41.5, PaO\textsubscript{2} to 105. The direction of change in ventilation and blood gases induced by CO\textsubscript{2} fulfills the criteria noted above. Figure 5B depicts the

![Figure 5](http://circ.ahajournals.org/)

**(A):** Controlling variables of figure 3, equations 1 to 8, are all normal except \( T_s = 38, T_f = 4, T_y = 8 \) (eq. 7). This figure is redrawn from the printout of an IBM 7040 digital computer. Flow diagrams are available on request. PaCO\textsubscript{2} at \( V_R = 39 \text{ mm Hg} \); slope of CO\textsubscript{2} sensitivity = 0.45; P\textsubscript{ICO\textsubscript{2}} = 15 at \( t = 1,000 \).

**(B):** Controlling variables as in A except that chemoreceptor response similar to that in figure 3 is introduced. PaCO\textsubscript{2} at \( V_R = 37 \); slope of CO\textsubscript{2} sensitivity = 0.25; \( Ca - V\textsubscript{CO}\textsubscript{2} = 6.5 \text{ vol\%} \); P\textsubscript{ICO\textsubscript{2}} = 15 at \( t = 400 \) to 1,200.
normal variables except prolonged circulation time and the chemoreceptor response deduced from table 4 and figure 3. These variables yield computed ventilation and blood gas values which resemble those of figure 5A.

Since the magnitude of many controlled variables (VA, PaCO2, PaO2) in the model are fixed by the metabolic activity, CO2 stores and cardiac output, the simulated response was normalized for purposes of comparison with the patient group. Figure 6, left, represents a portion of the computer simulation with an ordinal value of 1.0 = control state. The right portion of figure 6 depicts the average relative change in controlled variables induced by CO2 inhalation. These values were obtained from tables 2 and 4.

When computer simulation incorporated the degree of reduced PaO2 (table 4) or the chemoreceptor response from figure 3 but with normal lung to artery circulation time, the system was stable, indicating the importance of prolonged circulation time in system instability.

Discussion

The ventilatory, hemodynamic, and chemical characteristics presented herein resemble those reported earlier.6, 8, 9, 12, 15 The phasic relationship between alveolar and blood gases suggests oscillatory behavior of a negative feedback control system. In the following, the disorders of cardiac function, chemical alterations, and neural responses will be examined in cases of congestive heart failure with and without CSR for information regarding the mechanism of CSR.

Acid-Base Equilibria and CO2 Response

The acid-base and respiratory gas patterns, along with the CO2 response reported herein, resemble the findings of others in cases of heart failure due to valvular heart disease, who reported CO2 and ventilatory relationships characterized by a reduced CO2 threshold and reduced responsiveness.19 We conclude that in CSR the threshold and slope effects tend to cancel and—for this reason—chemoreceptor alterations are not critical to the phenomenon of periodic breathing. This conclusion is supported by simulation results (fig. 5A and B). Brown and Plum13 reported on CSR in patients with heart disease who exhibited acid-base characteristics similar to those in our work. We agree that the threshold to CO2 is reduced; however, we observed reduced CO2 sensitivity rather than the increased sensitivity claimed by the work cited.

The reduced ventilatory response to CO2 may be related to the increased work of breathing for a given level of ventilation in the patients under study. Pauli and associates19 suggested that reduced lung compliance was operative in patients with mitral stenosis who exhibited reduced ventilatory response to CO2, since corrective surgery was followed by a more nearly normal CO2 response. The synergistic effect of lowered PaO2 during hyperpnea on room air (60 mm Hg) is absent with CO2 exposure. This factor, along with the increased work of breathing, may also explain the rapid attainment of maximal ventilatory response (less than that of normal subjects) in the patients reported here.

Mild to severe alkalosis is again noted in all patients with congestive heart failure with and without CSR. However, the degree of alkalosis was variable. Previous work took note of this tendency toward alkalosis and suggested that the nonlinear effect of apnea and hyperpnea would result in mild respiratory alkalosis by a net increase in mean minute ventilation.6 Temporary periodic breathing may be observed in patients who suffer from metabolic acidosis and are rendered alkalotic by excessive bicarbonate administration. We have commented on the occurrence of recurrent tachycardia with apnea in periodic breathing in alkalosis and have found CO2 administration to be of value.20 The basis for the alkalotic state in many of the patients reported herein remains obscure; however, thiazide administration may be incriminated in some.
Results of CO₂ Breathing: Prototype and Model

For many years, the effect of inhalation of low percentage of CO₂ on the prevention of apnea has been known and its effect is rather uniform. Investigators have applied this method in their studies of periodic breathing since the early part of this century.¹

Certain intuitive generalizations regarding the effect of CO₂ may be made. The first is that, although CO₂ could be expected to increase the mean value of arterial CO₂ tension, and thereby to act as a respiratory stimulant, the rate of excretion of CO₂ from the lungs (VA) (PACO₂ - PICO₂) is significantly decreased. As a consequence, the first hyperpneic phase of periodic breathing after an increase in PICO₂ is associated with a reduced rate of CO₂ excretion from the body. Therefore, the conditions which previously had allowed apnea, that is, a combination of PaCO₂ reduced below the threshold point and nearly normal PaO₂, are prevented. These effects would first be expected one-half cycle length after a change in the inspired gas was made. This is well demonstrated in figure 1 in that, after institution of CO₂ inhalation, the initial period of hyperpnea is unchanged. However, the subsequent hypopnea is less marked and apnea may be prevented or greatly abbreviated. One might summarize the expected effects on the control system as being twofold. The first would be a reduction in overall system gain, decreasing the amplitude of oscillation. The second would be an increased DC output level (ventilation). These would combine to produce an increased mean ventilation with reduced oscillation.

Figure 6

(Left): Computer results from figure 5A and B, normalized. (Right) Mean values for cycle length, ventilation, and blood gases. Room air and CO₂ inhalation results are from tables 1 to 3. N = number of patients studied.

*Circulation, Volume XXXVII, March 1968*
The simulation was confined to an investigation of the steady-state oscillation and the effects of CO$_2$ inhalation. We emphasize that the model included normal variables and relationships except prolongation of mean circulation time and appropriate increase in $T_1$ and $T_2$ (figure 5A and B), prolongation of mean circulation time, and inclusion of the Pa$_{O_2}$ and chemoreceptor response from tables 2 to 4. The circulation time would represent an increase in the central blood volume, a decrease in cardiac output, or a combination of both. The reduction in Pa$_{O_2}$ could be due to pulmonary congestion or alteration of ventilation perfusion relationships. We derive the form of transfer function from human and animal studies extrapolated to a mean circulation time of 50 sec.$^{12}$

After steady-state oscillation is well-established, the effects of an increase of Pi$_{CO_2}$ are examined. During the apneic period or early in the hyperpneic state, the Pi$_{CO_2}$ was increased to 15 mm Hg. We have shown in figure 6 that there is fairly good agreement between the computer studies and the average patient response when the mean values of ventilation and blood gases are plotted during the various phases of periodic breathing and expressed as percentages of means for room air. Furthermore, when CO$_2$ is administered, qualitative and quantitative variations are seen in the output from the computer which closely approximates the average patient response. The criteria required for effective simulation as proposed in an earlier section are satisfied. These include the amplitude of steady-state oscillation and ventilation as well as the phasic relationship between arterial and alveolar CO$_2$ with room air breathing. With introduction of Pi$_{CO_2} =$ 15 mm Hg, the increase in mean ventilation with a decrease in oscillation in the model resembles that seen in patients. Similarly, the responses of arterial blood gases and alveolar blood gases show reasonable agreement in both patients and model.

The effect of oxygen is less clear-cut. Cerebral blood flow decreased by oxygen breathing would prolong the lung to central nervous system receptor circulation time. Although we compared mean circulation time from lung to artery in only a few cases, we did not observe any significant prolongation. The work of Ross and associates$^{31}$ on post-tourniquet hyperpnea and oxygen-breathing substantiates our conclusion that the effect of circulation time to the brain is prolonged by a reduction in cerebral blood flow. The constant elevated arterial oxygen tension removes a portion of the chemoreceptor stimulus and thereby further reduces the gain. Since our present model does not include a variable describing alteration in cerebral blood flow nor does it discriminate between central and peripheral chemoreceptors, we do not feel justified in attempting simulation of the effect of oxygen administration. Hypoxia was not a necessary factor in CSR since CSR continued in 5 patients despite Pa$_{O_2} >$ 300 mm Hg.

The above considerations allow certain generalizations regarding the appropriateness and efficiency of simulation. We have endeavored to project from available data accurate representation of model elements which compare closely with the prototype. Gas exchange, FRC, chemoreceptor response, effect of CSF and gas storage volumes were thus derived. A circulatory transfer function was identified and expressed in quantitative terms. We conclude that the proposed model rests upon a firm foundation of physiological information from normal subjects and patients with heart disease. Additional evidence for our conclusions lies in the ability to apply the model without modification to naturally occurring disorders, for example heart failure$^{12}$ as well as experimental manipulations such as post-hyperventilation apnea,$^{8,9}$ response to altered CSF P$_{CO_2}$ and, in the present study, the effect of CO$_2$ inhalation in periodic breathing. The successful application in disease conditions strengthened the conclusion that the mathematical model is efficient, unambiguous, and approaches the unique.

Circulation, Volume XXXVII, March 1968
Determinants of Periodic Respiration

When the disorders of the cardiorespiratory system in all patients with congestive heart failure reported here are compared, certain similarities and differences appear significant. Reduction in cardiac output, alteration of the CO₂ threshold and response and arterial pH and PaCO₂ are similar in the two groups. Minor differences in PaO₂ were noted; however, CSR was observed in the absence of hypoxemia.

The greater prolongation of circulation time (40 sec) in CSR provides the most striking difference between the groups. The cardiac index in group A was only slightly less than that in group B. The longer circulation time in group A could have two causes. 

\[ CvCO₂ - CaCO₂ = 100 VA \left[ (Paco₂ - PICO₂) - FRC \right] \]

The first would be related to the increased central blood volume in group A. A prolongation of the average value would result if patients with the largest central blood volume tended to have the lowest cardiac output. When the significantly longer circulation time in patients with CSR is considered along with the earlier report of oscillatory behavior in the model with a circulatory delay of greater than 25 sec, the conclusion follows that significant prolongation of circulation time is requisite for periodic respiration in heart disease. When CSR is seen with shorter circulatory delays (and periods), increased neural excitability, anemia or hypoxemia, singly or in combination would, by increasing overall system gain, be implicated.

Appendix

The closed-loop system depicted in figure 4 will be represented by the following series of equations. Detailed derivations have been published by Horgan and Lange and associates.12,15 The parameters expressed are based upon reasonable estimates of coefficients and dynamic response characteristics obtained in human and animal investigation. Following the development reported previously,9 the chemoreceptor block relates Pco₂, pH, and Po₂ to alveolar ventilation according to the steady-state equation of Gray.16 Effects of pH are expressed in terms of the associated alteration in Pco₂. The contribution to alveolar ventilation by Pco₂ (VAco₂) is as follows:

\[ VAco₂ = (0.4 \ PaCO₂ - 14.6) Vr \]  

where Vr is 4.0 L/min. The corresponding contribution by Po₂ (VAo₂) is:

\[ VAo₂ = 3.05 \ (10^{-9}) \ (92 - PaO₂)^5 \ Vr. \]  

The effects of alveolar ventilation on the pulmonary capillary blood gases required knowledge of the product of blood flow, Qc = 5.6 L/min, and arteriovenous gas content difference, Cv and Ca. As outlined in earlier work,8,9 consideration must be given the concept of a lung volume time constant because the FRC, assigned a value of 2.5 L, tends to buffer the effects of rapid changes in ventilation. For CO₂ exchange:

\[ Cv \ d (Paco₂)/dt] / Qc \ (Pa - 47). \]  

Similarly for oxygen exchange:

\[ CaO₂ - CvO₂ = 100 VA \left[ (Po₂ - PaO₂) - FRC \right] \]  

Since PaCO₂ is desired, the following expression of the CO₂ dissociation curve is applied:

\[ CaCO₂ = 48 + 0.45 \ (PaCO₂ - 39). \]  

The following mathematical approximation of the oxygen dissociation curve at expected SaO₂ allowed CaO₂ to be expressed as PaO₂.

\[ CaO₂ = 20[1 - \exp (-0.04 \ PaO₂)]. \]  

The time course of PaO₂ and PaCO₂ at the chemoreceptors was obtained by applying the transfer function:

\[ G(s) = \frac{(1 + sT₁)⁻¹(1 + sT₂)⁻¹ \ \exp (-sTa)} \]  

to the time courses of PaCO₂ and PaO₂ of blood leaving the pulmonary capillary as calculated from equations 3 and 4. For oxygen, the contribution to ventilation was calculated directly from equation 2. For CO₂, only 50% of the steady-state effect expressed in equation 1 was considered to be contributed directly by changes in PaCO₂. Consideration of the effects of brain tissue and CSF buffering required that the remaining 50% of VAco₂ be calculated from the change in PaCO₂ modified by a cascaded effect of a 20-sec time constant for brain tissue influenced by CSF and a 300-sec time constant for CSF changes. Thus, for a step input of PaCO₂, the contribution to ventilation VAco₂ would be approximated by:

\[ VAco₂ = 0.4 \ PaCO₂[1 - 0.5 \ \exp (-t/320)]. \]
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Observation and Simulation of the Circulation, Acid-Base Balance, and Response to CO₂ in Cheyne-Stokes Respiration

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Circulation. 1968;37:331-344
doi: 10.1161/01.CIR.37.3.331

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/37/3/331

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