ANALYSES OF BREATH-BY-BREATH RESPONSES
OF VENTILATION TO CO₂ EMPLOYING \( \dot{V} - PCO₂ \) LOOPS

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Abstract. Computer techniques were employed to construct a respiratory control model in which the variables treated were programmed according to a series of mathematical equations, with the purpose of eliciting the relationship of \( \dot{V} - PCO₂ \) (minute ventilation-partial pressure of carbon dioxide) on a transient time basis. It was discovered that the transient \( \dot{V} - PCO₂ \) relationship has the shape of a loop half of which is for on-CO₂ and the other half for off-CO₂. Breath-by-breath ventilation was calculated by means of a home-made computer and the \( \dot{V} - PCO₂ \) relationship was monitored on an XY plotter. The transient \( \dot{V} - PCO₂ \) course also showed a loop which was quite similar in the general shape to the one traced employing theoretical analysis with an analog computer. This \( \dot{V} - PCO₂ \) loop may have potential usefulness to reveal mechanisms of respiratory control which may not be shown by the conventional \( \dot{V} - PCO₂ \) response curves.

INTRODUCTION

One of the areas in respiratory physiology that enjoyed progress in the past 25 years is the regulation of ventilation. Perhaps the beginning of the "rapid" phase of progress in our understanding of the regulatory mechanisms involved in ventilation coincided with the work of Gray (1946, see 1950) who, with a stroke of genius, put forward the first empirical quantitative equation to describe the chemical control of breathing of the "chemostat". Although the equation of Gray (1950) was based on earlier observations made up to that time and although this equation intrinsically and explicitly did not describe the mechanisms, it did stimu-
late much experimental work. Consequently, with more observation, Nielsen and Smith (1951), employing the plot of $\dot{V} - PCO_2$ response curves revealed that $PO_2$ and $PCO_2$ acted not “additively” as stimuli to ventilation.

The work of Nielsen and Smith (1951) was followed by many more observations along the same vein; some were made by the Oxford group who made an attempt to quantitate ventilation as functions of $PO_2$, $PCO_2$ and $H^+$ also with empirical equations (Lloyd and Cunningham 1962, Lloyd et al. 1958).

With the aid of computer techniques, Grodins et al. (1954), Grodins (1959), Grodins and James (1963), Grodins (1964) and Grodins, Buell and Bart (1967) first analysed in a more detailed fashion the effect of $CO_2$ and other stimuli on ventilation. Their work also was followed by many (Defares et al. 1960, Yamamoto 1960, Defares 1964, Edwards and Yamamoto 1965, Milhorn et al. 1965, Yamamoto and Raub 1967, Milhorn and Brown 1970, Yamamoto and Hori 1970). It seems clear and important that with our improving knowledge of respiration on the analytical level, great strides have been made in the quantitation of the respiratory control system.

However, most of the analyses are based on the “steady state” responses or “transient” responses but limited to the behavior of some variables as functions of time.

It occurred to us that if one can perform a “transient” study employing breath-by-breath analysis of ventilation response to, e.g. $CO_2$, perhaps more information can be obtained. This we have tried and the results we obtained dealing with $\dot{V}$ as a function of $PCO_2$ employing breath-by-breath response with both theoretical exposition and experimentation were somewhat “astonishing”. And this communication gives the abbreviated version of our study of the respiratory control employing computer techniques.

**THEORY**

Our respiratory control model has in essence three compartments similar to that of Grodins, Buell and Bart (1967): the brain tissue (the $CO_2$ of which affects ventilation), the non-brain tissue (the metabolic rate of which affects oxygen demand and $CO_2$ production), and the lungs (the function of which is here mainly considered as a $CO_2$ eliminator).

Ten fundamental equations describing the relationships of the variables listed below (Table I) were developed on the bases of previous work done by Grodins et al. (1954), Grodins and James (1963), Defares, Derksen and Duyff (1960) and Defares (1964). Some of the values of the con-
Constants were selected also according to that employed by Grodins et al. (1954), Grodins and James (1963) and Grodins, Buell and Bart (1967) (Table II).

**Table I**

Definition of symbols

\[ A = \text{alveolar} \]
\[ b = \text{brain tissue} \]
\[ B = \text{non-brain tissue} \]
\[ C = \text{concentration, volume/volume} \]
\[ E = \text{expired} \]
\[ J = \text{volume/time (cardiac output)} \]
\[ I = \text{inspired} \]
\[ M = \text{quantity/time (metabolic rate)} \]
\[ \dot{Q} = \text{quantity/time} \]
\[ v = \text{venous} \]
\[ V = \text{volume} \]
\[ \dot{V} = \text{volume/time (ventilation)} \]
\[ \dot{V}_{O_2} = \text{quantity/time (oxygen consumption)} \]

**Table II**

Values of K's used

<table>
<thead>
<tr>
<th>K's</th>
<th>Units</th>
<th>Standard values used</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K_1 )</td>
<td>( \frac{\text{liter CO}_2}{\text{liter blood}} / \frac{\text{liter CO}_2}{\text{liter air}} )</td>
<td>3.20</td>
</tr>
<tr>
<td>( K_2 )</td>
<td>( \frac{\text{liter CO}_2}{\text{liter blood}} / \frac{\text{liter brain tissue}}{\text{liter blood}} )</td>
<td>0.33</td>
</tr>
<tr>
<td>( K_3 )</td>
<td>( \frac{\text{liter air}}{\text{sec}} / \frac{\text{liter CO}_2}{\text{liter brain tissue}} )</td>
<td>980.00</td>
</tr>
<tr>
<td>( K_4 )</td>
<td>( \frac{\text{liter air}}{\text{sec}} / \frac{\text{liter CO}_2}{\text{sec}} )</td>
<td>25.00</td>
</tr>
<tr>
<td>( K_5 )</td>
<td>( \frac{\text{liter blood}}{\text{sec}} / \frac{\text{liter O}_2}{\text{sec}} )</td>
<td>6.50</td>
</tr>
<tr>
<td>( K_6 )</td>
<td>( \frac{\text{liter blood}}{\text{sec}} / \frac{\text{sec}}{\text{(liter blood)}^4} )</td>
<td>4.20</td>
</tr>
<tr>
<td>( K_7 )</td>
<td>( \frac{\text{liter blood}}{\text{sec}} / \frac{\text{(liter CO}_2)^4}{\text{(liter blood)}^4} )</td>
<td>15.00</td>
</tr>
</tbody>
</table>

CO\(_2\) continuity–lung reservoir

\[ C_1 \dot{V} \dot{Q}_E + \dot{Q}_B + \dot{Q}_v - \dot{Q}_a = \dot{Q}_A \quad (1) \]
Alveolar–expired CO$_2$ equilibrium

\[ C_A = \frac{Q_A}{V_A} = \frac{\dot{Q}_E}{V} \]  \hspace{1cm} (2)

Alveolar–arterial equilibrium

\[ C_a = \frac{\dot{Q}_a}{F} = K_1 C_A + K_2 \]  \hspace{1cm} (3)

Brain tissue reservoir CO$_2$ continuity

\[ \dot{Q}_b = M_b + \dot{Q}_a - \dot{Q}_v B \]  \hspace{1cm} (4)

Non-brain tissue reservoir CO$_2$ continuity

\[ \dot{Q}_B = M_B + \dot{Q}_a - \dot{Q}_v B \]  \hspace{1cm} (5)

Brain tissue–venous CO$_2$ equilibrium

\[ C_b = \frac{\dot{Q}_v B}{F_b} = \frac{Q_b}{V_b} \]  \hspace{1cm} (6)

Non-brain tissue venous CO$_2$ equilibrium

\[ C_B = \frac{\dot{Q}_v B}{F_B} = \frac{Q_B}{V_B} \]  \hspace{1cm} (7)

\( \dot{V} \) controller

\[ \dot{V} = K_3 (C_b - C_b(OI)) + K_4 M_B \]  \hspace{1cm} (8)

Cardiac output

\[ \dot{F} = \dot{F}_B + \dot{F}_b = K_5 \dot{V}_O + K_6 \]  \hspace{1cm} (9)

Brain arterial blood flow

\[ F_b = K_7 C_a \]  \hspace{1cm} (10)
Attempts were made to manipulate these equations in order to explicitly depict the behaviour relating $\dot{V}$-PCO$_2$ on the breath-by-breath basis. Since the variation made by a single breath is of a very complex nature, we simplified the situation by solving $\dot{V}$ and CA (concentration of alveolar CO$_2$) as function of time without the breath-by-breath oscillation. Thus, by combining equations 3, 4, 6, 8 and 10 with rearrangements of terms, the following differential equation is obtained:

$$\dot{C}_b + \frac{K_7 C_a^4}{V_b} C_b = \frac{M_b + K_7 C_a^5}{V_b}$$  \hspace{1cm} (11)

The coefficient of $C_b$ makes this equation non-linear. However, since for ordinary purposes, $C_a$ varies not to a great extent (to affect the equation), an average value of $C_a$ can be chosen to calculate this coefficient without altering the results of this equation. This simplification leads to the solution of $\dot{V}$ as follows:

$$\dot{V} = K_3 \left( C_a(\infty) - C_a(0) + \frac{M_b}{K_7} \left( \frac{1}{C_a^4(\infty)} - \frac{1}{C_a^4(0)} \right) \right) \left( 1 - \exp \left( -\frac{K'K_7C_a^4O}{V_b \Delta C_t} t \right) \right) + K_4 M_B$$  \hspace{1cm} (12)

which can be simplified to yield:

$$\dot{V} = K_3 \Delta C_a \left[ 1 - \exp \left( \frac{t}{\tau} \right) \right] + K_4 M_B$$  \hspace{1cm} (13)

where

$$\tau = \frac{V_b \Delta C_t}{K'K_7C_a^4(0)}$$  \hspace{1cm} (14)

Alveolar concentration of CO$_2$ ($C_A$) as a function of time during CO$_2$ inhalation was obtained by combining equations 1, 2, 3, 5 and 7, with rearranging of terms:

$$\ddot{C}_A + \left( \frac{\dot{V}}{V_A} \right) \dot{C}_A + \left( \frac{\ddot{V}}{V_A} \right) C_A = \frac{C_1 \ddot{V} - V_B \dot{C}_B}{V_A}$$  \hspace{1cm} (15)

Both equations 11 and 15 are non-linear.
By linearizing equation 15, we obtain a second order solution for $C_A$ as function of time.

$$C_A = \frac{K_3 \Delta C_a \Delta C_t}{\tau} + \left\{ -\frac{K_3 \Delta C_a \Delta C_t}{\tau} + C_A(0) \right\} \exp -$$

$$- \left(\frac{K_3 \Delta C_a + \tau K_4 M_B}{2K''\tau V_A}\right) \sin \left(\frac{K_3 \Delta C_a}{V_A \tau}\right) t$$  \hspace{1cm} (16)

where \( \tau = \frac{V_b \Delta C_t}{K'K_1C_a(O)} \)  \hspace{1cm} (17)

These two equations of $\dot{V}$ and $C_A$ as functions of time were exposed in graph form as shown in Fig. 1. This was done employing a TR 48 analog computer.

Fig. 1. The time course of $\dot{V}$ and $PACO_2$ traced as a function of time (each square=1 min). The upper three curves are $\dot{V}$'s for 0.07, 0.06 and 0.04 FICO. At the graded X-axis $\dot{V} = 0$, each square = 20 litres/min. The lower three curves are the $PACO_2$ responses. Each square = 10 mm Hg.

The complete diagram of the computer program is depicted in Fig. 2 which treats the system in accordance with the three-compartment concept.

The interesting point was: when $V$ was plotted against $C_A$ (which equals $C_ACO_2$ and with a factor can be changed into $PACO_2$) a loop appeared. Figure 3 shows five $\dot{V}$-$PACO_2$ loops when the $F_1CO_2$ is at 0.02, 0.04, 0.05, 0.06 and 0.07. The loops travel in a counter clockwise direction when CO$_2$ is on. In the graph at one o'clock (Fig. 3), ventilation reached a quasi “steady state”.
Fig. 2. Computer model of the respiratory system constructed from the fundamental equations. $C^2_\alpha$ reads $C^2_\alpha$; $t$ reads $b$; $T$ reads $B$.

Fig. 3. Computer tracing of $\dot{V}$-PCO$_2$ loops with $F_CO_2 = 0.02$ (smallest loop), 0.04, 0.05, 0.06 and 0.07. The graded Y-axis cuts the X-axis at 40 mm Hg PCO$_2$. Each square = 10 mm Hg PCO$_2$; increase to right and decrease to left. Ventilation at rest is 5 litres/min at a PCO$_2$ of 40 mm Hg. Each square of the Y-axis = 10 litres/min. The loop starts at 40 mm Hg PCO$_2$ and travels to right and upward when CO$_2$ is on. At “one o'clock” CO$_2$ is off. The sharp turn at one o'clock indicates a $\dot{V}$-PCO$_2$ loop travels anti-clockwise.
Our experimental design was comparatively simple. Tidal volume was measured by means of a Fleisch-type pneumotachograph, the volume was integrated by a home-made computer (Fig. 4). Respiratory frequency was monitored by recording the duration between the beginning of inspiration of one breath to that of the following breath. The quotient of the tidal volume and the duration to the next breath (Fig. 5) gives the breath-by-breath ventilation. The tracings obtained by this simple computer are shown in Fig. 6 as exposed on a memoscope.

The breath-by-breath changes of ventilation as a function of PCO₂ is exhibited on an XY plotter. One of the experiments is shown in Fig. 7. This experiment was done on one of the authors (FFK) while breathing 5% CO₂ in the inspired air.

There are distinctively four phases (if not more) which can be identified on this V-PCO₂ loop which is in very close agreement to that obtained by means of the computer respiratory control model.
When CO\textsubscript{2} is off, CO\textsubscript{2} decreases sharply while ventilation changes very little (the horizontal portion of the loop). If one connects the sharp bend at one clock of the loops, a usual \( \dot{V}-\text{PCO}_2 \) response curve is obtained.

It can be seen from the graph that when CO\textsubscript{2} is on at zero time (Fig. 7), ventilation changed little while \( \text{PACO}_2 \) increased significantly. This is the first phase: the on-CO\textsubscript{2}-iso-ventilation phase. After 30 sec from the onset of CO\textsubscript{2} administration \( \text{PACO}_2 \) changed little while ventilation changed significantly. This is the second phase: the iso-\( \text{PACO}_2 \) phase. It should be noted that when \( F_1\text{CO}_2 \) is more or less than 0.05, this second phase of the \( \dot{V}-\text{PCO}_2 \) loop may bend inward or outward (see Fig. 3). With the termination of CO\textsubscript{2} inhalation \( \text{PACO}_2 \) decreased significantly while ventilation changed little. This is the third phase: the off-CO\textsubscript{2}-iso-ventilation phase. Then the ventilation travelled roughly along the isometabolic hyperbola and returned to the control value. This is the restitution phase.

There was definitely oscillatory phenomenon. The general direction of this \( \dot{V}-\text{PCO}_2 \) loop is counter-clockwise and it oscillates along this general direction. For example, the ventilation value along phase two at 70 sec
after onset was lower than that at 60 sec and at 170 sec was lower than at 150 sec (Fig. 7).

Figures 8 and 9 show some additional $\dot{V}$-PCO$_2$ loops in sheep during CO$_2$ inhalation. With and without vagotomy, these loops are different from that in man vagotomy in sheep seems to disturb this $\dot{V}$-PCO$_2$ loop. Further experimentation is necessary to reveal the "obscure" shapes, if any, of the $\dot{V}$-PCO$_2$ loops caused by abnormal states. For example, in these sheep on autopsy there was inevitably pulmonary oedema. And during these experiments the sheep were on their backs, it was not impossible that fluid may accumulate in the lungs during experiments. If

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Fig. 7. $\dot{V}$-PACO$_2$ loop in man with $F_1$CO$_2$ = 0.05 (FFK subject). The numbers in the graph are time in seconds after the administration of CO$_2$ in the inspired air (without $-$), and after the termination of CO$_2$ (with $-$). Note the four possible components of this loop for analysis: (i) the on-CO$_2$-iso-ventilation phase (during the mixing of CO$_2$ intrapulmonarily); (ii) the iso-PACO$_2$ phase (during diffusion and mixing of blood, which eventually "saturates" the chemoreceptors); (iii) the off-CO$_2$-iso-ventilation phase (during CO$_2$ evacuation from lungs), and (iv) the restitution phase (blood gas and alveolar PCO$_2$ both returned to the resting point).
Fig. 8. $\dot{V}$-PACO$_2$ loops in sheep with and without bilateral cervical vagotomy. The numbers in the graphs are seconds (") and minutes ('). The numbers with (−) signs in front of them are times after CO$_2$ termination. The lines in the graph are the $\dot{V}$-PCO$_2$ response curves.

so, the slanting path of the second phase could be "attributed" to pulmonary oedema which may impede diffusion.

It can be said, however, that there seems to be potential usefulness in applying the $\dot{V}$-PCO$_2$ loop for experiments in which before we "only" use V-PCO$_2$ curves.
Fig. 9. $\dot{V}$-PCO$_2$ loops in sheep with and without bilateral cervical vagotomy (for details see legend of Fig. 8), with two levels of CO$_2$ inhalation. The second level of CO$_2$ was super imposed on the first one, so there is no restitution phase for the first level of low CO$_2$. The $\dot{V}$-PCO$_2$ response curve is higher after vagotomy.

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REFERENCES


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ERRATA

Page 155, line 11 of Abstract:

instead of \( V/V_T \) should be \( \dot{V}/V_T \)

Page 173 first line from bottom should read:

use \( V-PCO_2 \) curves.

Page 191, line 19 from top:

instead of bandpass 8–1,0000 cycle/sec should be bandpass 8–1,000 cycle/sec