# A MATHEMATICAL MODEL OF THE HUMAN RESPIRATORY CONTROL SYSTEM

HOWARD T. MILHORN, JR., RICHARD BENTON, RICHARD ROSS, *and* ARTHUR C. GUYTON

*From the Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, and the Department of Electrical Engineering, University of Mississippi, University*

ABSTRACT The respiratory system exhibits the properties of a control system of the regulator type. Equations describing this biological control system have been derived. Transient and steady-state solutions for various $CO_2$ and $O_2$ step input disturbances were obtained utilizing a digital computer and are compared with experimental results. The effectiveness of the respiratory system as a regulator is investigated. Further extensions of the model are suggested.

## INTRODUCTION

Basically, two types of control systems exist in the human body. These are (*a*) servo systems and (*b*) regulators. The positioning of a limb in response to a cerebral signal is probably an example of a biological servo system. In this case, the motor cortex is believed to initiate a "step input" for movement of a limb or other part of the body. This limb then, under cerebellar damping, approaches the "final position" designated by the initial signal and reaches it as a steady-state value. The second type, the regulator, finds its biological counterpart in such systems as that for control of respiration. A disturbance, such as a step input of $CO_2$ inhalation, will cause this system to respond in a much different way. Brain tissue $P_{CO_2}$ will rise, but respiration will also increase to "blow off" $CO_2$ so that the new steady-state value reached is much lower than it would have been if respiration had not increased. The respiratory control system can also, under proper conditions, exhibit damped and sustained oscillation. Douglas and Haldane (1908) showed that after a period of voluntary hyperventilation several cycles of damped oscillation often occur, and in the clinical abnormality known as Cheyne-Stoke's respiration, the system continually overshoots and undershoots the regulated level and, thus, exhibits sustained oscillation.

This study was designed to investigate the human respiratory control system. Its purpose has been, first, to derive the basic equations of the system and, secondly, to investigate the system as a biological regulator. This concept is not new; however, the system has been analyzed mathematically only roughly. A simplified analysis was made by Grodins in 1954 in which $CO_2$ was the only controller of ventilation considered; the tissue elements were lumped into a single reservoir, blood flow was held constant, and circulation times were considered to be infinitely short. Horgan and Lange (1963) added circulation times and oxygen control to this basic model in order to study periodic breathing. Defares *et al.* (1960) extended Grodins' model by dividing the tissue reservoir into two distinct compartments, brain and body tissues, and considering cerebral blood flow as a function of arterial $P_{CO_2}$. However, the effects of oxygen as a controller of ventilation and the effect of time delays in the transport of gases from the lungs to the two tissue reservoirs were not considered in this model because of their unimportance to the $CO_2$ inhalation studies with which this model was concerned. These factors have all proved to be very important in describing the respiratory control system. They will be considered in detail in this analysis.

The most important chemical factors regulating respiration are (*a*) carbon dioxide, (*b*) hydrogen ion concentrations, and (*c*) oxygen. That is,

$$\text{alveolar ventilation} = f(CO_2, H^+, O_2). \tag{1}$$

The relationship between pH, $CO_2$ concentration, and the salts of carbonic acid is given by the Henderson-Hasselbalch equation:

$$pH = pK + \log \frac{HCO_3^-}{CO_2} \tag{2}$$

If the blood buffers consisted of a simple bicarbonate system, this equation would give a quantitative measure of the change in pH when the $CO_2$ concentration changes. However, the buffer system is much more complex and, therefore, necessitates a much more complex equation. However, equation (2) does give qualitative indications of the behavior of pH in response to changes in $CO_2$. Thus, carbon dioxide inhalation increases arterial $P_{CO_2}$, and in accordance with equation 2 this decreases the pH. Conversely, voluntary hyperventilation "blows off" $CO_2$ so that the arterial $P_{CO_2}$ falls, which in turn increases the pH. It is evident, then, that an inverse relationship exists between $CO_2$ and pH in respiratory acid-base balance disturbances. Shock and Hastings (1935) have obtained a quantitative relationship between these two stimuli. This is

$$H^+ = a_2 P_{CO_2} + b_2, \tag{3}$$

where $a_2$ and $b_2$ are empirical constants. By combining this equation with equation (1), alveolar ventilation can be reduced to a function of two variables:

$$\text{alveolar ventilation} = f(CO_2, O_2). \tag{4}$$

Our analysis, therefore, will deal directly with these two variables and only indirectly with $H^+$ concentration.

## ASSUMPTIONS AND SYMBOLS

The following assumptions will be used in the analysis:

(*a*) The system consists of three reservoirs (the lungs, the brain tissues, and the body tissues).

(*b*) Blood flow to the brain is dependent upon cerebral-arterial $P_{CO_2}$ and $P_{O_2}$.

(*c*) Minute alveolar ventilation is controlled by both $P_{CO_2}$ and $P_{O_2}$.

(*d*) Circulation times are finite.

(*e*) $O_2$ dissociation curves are equal for arterial and venous blood.

(*f*) Arterial $P_{O_2}$ remains equal to $k_8 \times$ alveolar $P_{O_2}$ at all times where $k_8$ is a constant which is less than unity.

(*g*) Venous $P_{O_2}$ remains equal to tissue $P_{O_2}$ at all times. This applies both to the brain reservoir and the tissue reservoir.

(*h*) $CO_2$ dissociation curves are equal for arterial and venous blood and tissues.

(*i*) Arterial $P_{CO_2}$ remains equal to alveolar $P_{CO_2}$ at all times.

(*j*) Venous $P_{CO_2}$ remains equal to tissue $P_{CO_2}$ at all times.

(*k*) The rapid phasic changes in alveolar and blood gas concentrations with each respiratory cycle are ignored.

(*l*) The respiratory quotient is constant and equal to unity.

Assumptions (*a*) through (*d*) are modifications of the basic assumptions of Grodins. Assumptions (*e*) through (*g*) are new ones encountered when oxygen control is introduced into the system. Assumptions (*h*) through (*l*) were also introduced by Grodins. However, we have fitted the $CO_2$ dissociation curve to an empirical equation and eliminated its assumed linearity. Assumption (*h*) is justifiable only because of lack of experimental data and the belief that the accuracy of the analysis will not be impaired by it.

The following symbols[1] will be used:

| | |
|---|---|
| $CA_{CO_2}$ | Alveolar $CO_2$ concentration (volumetric fraction) |
| $Ca_{CO_2}$ | Alveolar-arterial $CO_2$ concentration (volumetric fraction) |
| $Ca\phi_{CO_2}$ | Brain-arterial $CO_2$ concentration (volumetric fraction) |
| $Ca\alpha_{CO_2}$ | Body-arterial $CO_2$ concentration (volumetric fraction) |
| $CB_{CO_2}$ | Brain tissue $CO_2$ concentration (volumetric fraction) |
| $CT_{CO_2}$ | Body tissue $CO_2$ concentration (volumetric fraction) |
| $CvB_{CO_2}$ | Brain-venous $CO_2$ concentration (volumetric fraction) |
| $CvB\theta_{CO_2}$ | Brain-venous $CO_2$ concentration delayed an amount of time equal to the brain to lung blood gas circulation time |
| $CvT_{CO_2}$ | Body-venous $CO_2$ concentration (volumetric fraction) |
| $CvT\delta_{CO_2}$ | Body-venous $CO_2$ concentration delayed an amount of time equal to the body to lung blood gas circulation time |
| $Cv_{CO_2}$ | Alveolar-venous $CO_2$ concentration (volumetric fraction) |
| $CI_{CO_2}$ | Inspired $CO_2$ concentration (saturated with $H_2O$ vapor at body temperature) |

[1] Standard symbols as set by American Pulmonary Physiologists (*Fed. Proc.*, 1950, 9, 602-605), have been used where possible.

| | |
|---|---|
| $MB_{CO_2}$ | Brain tissue $CO_2$ production (liters/minute) |
| $MT_{CO_2}$ | Body tissue $CO_2$ production (liters/minute) |
| $\dot{Q}B$ | Cerebral blood flow (liters/minute) |
| $\dot{Q}T$ | Body blood flow (liters/minute) |
| $\dot{Q}$ | Cardiac output (liters/minute) |
| $\dot{Q}BN$ | Normal cerebral blood flow (liters/minute) |
| $\dot{V}A$ | Minute alveolar ventilation (liters/minute) |
| $VB_{CO_2}$ | Volume of $CO_2$ in brain reservoir (liters) |
| $VT_{CO_2}$ | Volume of $CO_2$ in body reservoir (liters) |
| $VA_{CO_2}$ | Volume of $CO_2$ in lung reservoir (liters) |
| $VB$ | Brain fluid volume (liters) |
| $VT$ | Body fluid volume (liters) |
| $VA$ | Average alveolar volume (liters) |
| $W$ | Number of 100 gm increments of brain weight divided by 1000 to convert cubic centimeters to liters (gram-liters/cubic centimeter) |
| $S$ | Oxygen solubility coefficient at body temperature ($atm^{-1}$) |
| $PB$ | Sea level barometric pressure (millimeter Hg) |
| $k_5$ | Ratio of normal arterial $Po_2$ to normal alveolar $Po_2$ |
| $\tau_1$ | Lung to brain arterial blood gas circulation time (minute) |
| $\tau_2$ | Lung to body arterial blood gas circulation time (minute) |
| $\tau_3$ | Lung to aortic-carotid bodies arterial blood gas circulation time (min) |
| $\tau_4$ | Brain to lung venous blood gas circulation time (minute) |
| $\tau_5$ | Body to lung venous blood gas circulation time (minute) |
| $Ca\beta_{O_2}$ | Aortic-carotid bodies arterial $O_2$ concentration (volumetric fraction) |
| $MB_{O_2}$ | Brain $O_2$ consumption (liters/minute) |
| $MT_{O_2}$ | Body $O_2$ consumption (liters/minute) |

All remaining symbols referring to oxygen will have the same denotation as the corresponding symbol for carbon dioxide except that the subscript will be $O_2$ instead of $CO_2$. All empirical constants will be defined in the text.

## DERIVATION OF EQUATIONS

A step input to the respiratory system of carbon dioxide in inhaled air causes the arterial and brain tissue $CO_2$ concentrations to rise. In response, both cerebral blood flow and alveolar ventilation increase in an effort to maintain the brain $CO_2$ concentration at the normal level. Similarly, a negative step input of oxygen in inhaled air causes the arterial $Po_2$ to fall. In response, both cerebral blood flow (Kety and Schmidt, 1948) and alveolar ventilation increase in order to maintain an adequate supply of oxygen in the tissues.

From the preceding it is evident that the respiratory system regulates $CO_2$ and $O_2$ levels through negative feedback. That is, a change in $CO_2$ level or a decrease in $O_2$ level brings about regulatory effects through ventilatory and circulatory parameters. With the aid of our previously listed basic assumptions and Fig. 1, we will attempt to derive the equations of this biological regulator.

The rate of change of $CO_2$ volume in the brain reservoir is given by

$$dVB_{CO_2}/dt = MB_{CO_2} + \dot{Q}B(Ca\phi_{CO_2} - CvB_{CO_2}). \tag{5}$$

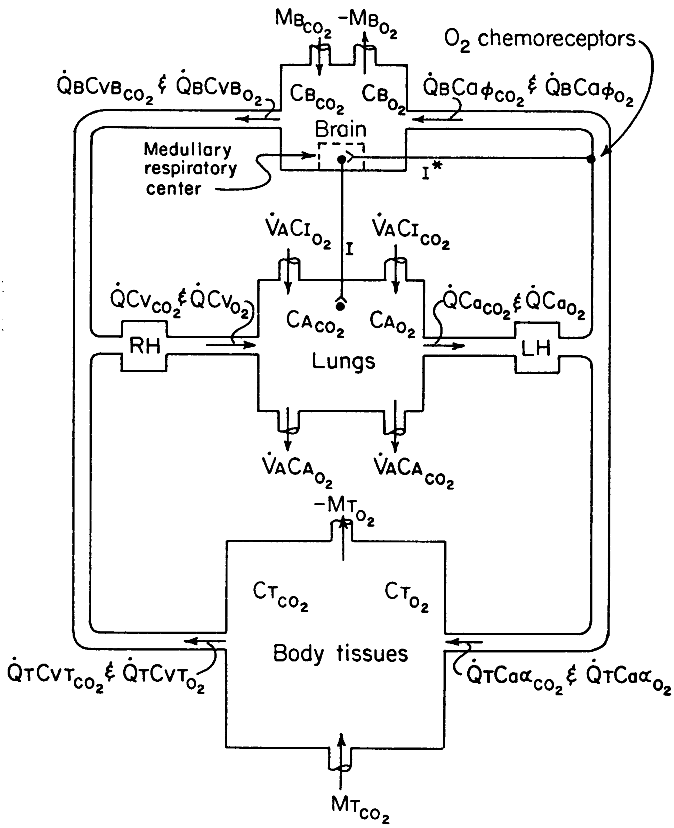


**Figure 1** The respiratory system.

The rate of change of $CO_2$ volume in the body reservoir is given by

$$dVT_{CO_2}/dt = MT_{CO_2} + \dot{Q}T(Ca\alpha_{CO_2} - CvT_{CO_2}). \tag{6}$$

The rate of change of $CO_2$ volume in the lung reservoir is given by

$$dVA_{CO_2}/dt = Q(Cv_{CO_2} - Ca_{CO_2}) + \dot{V}A(CI_{CO_2} - CA_{CO_2}). \tag{7}$$

Similarly, expressions for the time variation of oxygen volume in the three reservoirs can be written as follows:

$$dVB_{O_2}/dt = -MB_{O_2} + \dot{Q}_B(Ca\phi_{O_2} - CvB_{O_2}), \tag{8}$$

$$dVT_{O_2}/dt = -MT_{O_2} + \dot{Q}T(Ca\alpha_{O_2} - CvT_{O_2}), \tag{9}$$

$$dVA_{O_2}/dt = \dot{Q}(Cv_{O_2} - Ca_{O_2}) + \dot{V}A(CI_{O_2} - CA_{O_2}). \tag{10}$$

$MB_{O_2}$ and $MT_{O_2}$ have negative signs in equations (8) and (9) because $O_2$ is used up, whereas in equations (5) and (6) $CO_2$ is produced.

Equations (5) through (10) consist of six equations in twenty eight variables and a solution is, therefore, impossible. The problem, then, is to reduce the number of variables to equal the number of equations. This can be accomplished by using the previously listed assumptions.

Using an empirical equation of the $CO_2$ dissociation curve (Guyton, 1961; accurate within 1 per cent),

$$CO_2 \text{ concentration} = k_1(P_{CO_2})^{k_2}, \tag{11}$$

and the assumption that arterial $P_{CO_2}$ remains equal to alveolar $P_{CO_2}$ (equals $P_B C_{A_{CO_2}}$) at all times, we can obtain a relationship between arterial $CO_2$ concentration and alveolar $CO_2$ concentration. This is

$$Ca_{CO_2} = k_1(P_B CA_{CO_2})^{k_2}. \tag{12}$$

Since $Ca\phi_{CO_2}$ and $Ca\alpha_{CO_2}$ are the same as $Ca_{CO_2}$ delayed by amounts of time equal to the arterial circulation times,

$$Ca\phi_{CO_2} = k_1(P_B CA\phi_{CO_2})^{k_2}, \tag{13}$$

and

$$Ca\alpha_{CO_2} = k_1(P_B CA\alpha_{CO_2})^{k_2}. \tag{14}$$

Assuming that the $CO_2$ dissociation curve is equal for venous blood and tissues yields

$$C_{VB_{CO_2}} = C_{B_{CO_2}}, \tag{15}$$

$$C_{VB}\theta_{CO_2} = C_B\theta_{CO_2}, \tag{16}$$

$$C_{TV_{CO_2}} = C_{T_{CO_2}}, \tag{17}$$

and

$$C_{VT}\delta_{CO_2} = C_T\delta_{CO_2}. \tag{18}$$

Since oxygen is present in physical solution in the tissues,

$$\text{brain } P_{O_2} = P_B C_{B_{O_2}}/S, \tag{19}$$

and

$$\text{body } P_{O_2} = P_B C_{T_{O_2}}/S. \tag{20}$$

Using equations (19) and (20), an empirical equation of the oxygen dissociation curve (Guyton, 1961; accurate within 1 per cent)

$$O_2 \text{ concentration} = k_3(1 - \exp(-k_4 P_{O_2}))^2, \tag{21}$$

and the assumption that venous $P_{O_2}$ remains equal to tissue $P_{O_2}$ at all times, we obtain

$$C_{VB_{O_2}} = k_3(1 - \exp(-k_4 P_B C_{B_{O_2}}/S))^2, \tag{22}$$

$$C_{VB}\theta_{O_2} = k_3(1 - \exp(-k_4 P_B C_B\theta_{O_2}/S))^2, \tag{23}$$

$$Cv_{T_{O_2}} = k_3(1 - \exp(-k_4 P_B C_{T_{O_2}}/S))^2, \quad (24)$$

and

$$Cv_{T\delta_{O_2}} = k_3(1 - \exp(-k_4 P_B C_{T\delta_{O_2}}/S))^2. \quad (25)$$

Also, using equation (21) and the assumption that arterial $P_{O_2}$ remains equal to $k_5 \times$ alveolar $P_{O_2}$ (equals $k_5 P_B C_{A_{O_2}}$) at all times, we obtain

$$Ca_{O_2} = k_3(1 - \exp(-k_4 k_5 P_B C_{A_{O_2}}))^2, \quad (26)$$

$$Ca\phi_{O_2} = k_3(1 - \exp(-k_4 k_5 P_B C_{A\phi_{O_2}}))^2, \quad (27)$$

and

$$Ca\alpha_{O_2} = k_3(1 - \exp(-k_4 k_5 P_B C_{A\alpha_{O_2}}))^2. \quad (28)$$

We can arrive at some more useful relationships if we take concentrations as our variables. Therefore,

$$C_{B_{CO_2}} = V_{B_{CO_2}}/V_B, \quad (29)$$

$$C_{T_{CO_2}} = V_{T_{CO_2}}/V_T, \quad (30)$$

$$C_{A_{CO_2}} = V_{A_{CO_2}}/V_A, \quad (31)$$

$$C_{B_{O_2}} = V_{B_{O_2}}/V_B, \quad (32)$$

$$C_{T_{O_2}} = V_{T_{O_2}}/V_T, \quad (33)$$

and

$$C_{A_{O_2}} = V_{A_{O_2}}/V_A. \quad (34)$$

Cerebral blood flow is regulated by both arterial $P_{CO_2}$ and $P_{O_2}$. Kety and Schmidt (1948) obtained the experimental curve which describes the relationship between arterial $P_{CO_2}$ and cerebral blood flow (Fig. 2*a*). It can be fitted empirically by

$$(\Delta\dot{Q}_B)_{CO_2} = W[h_1(P_{CO_2})^5 + i_1(P_{CO_2})^4 + j_1(P_{CO_2})^3 + p_1(P_{CO_2})^2 + q_1 P_{CO_2} + r], \quad (35)$$

where $h_1$, $i_1$, $j_1$, $p_1$, $q_1$, and r are empirical constants and the term on the left of the equal sign is the change from normal in cerebral blood flow due to a change in arterial $P_{CO_2}$.

Similarly, cerebral blood flow is regulated by arterial $P_{O_2}$ (Kety and Schmidt, 1948), but no experimental curve can be found in the existing literature. We can, however, determine an approximate curve from a couple of existing points and a few assumptions. We can assume that increasing alveolar-arterial $P_{O_2}$ to the right of the normal point produces no significant change since oxygen up to almost three times its normal concentration in air causes no measurable increase in cerebral blood flow. Breathing 10 per cent oxygen, however, causes the $P_{O_2}$ to fall so that cerebral blood flow increases about 35 per cent. Since the cerebral blood flow is about 50 cc/100 gm/min. at the normal point (see Fig. 2), we have two points through which our curve must pass. A thorough search of the existing literature has failed to produce any other points, so that we must make an assumption as to the exact shape

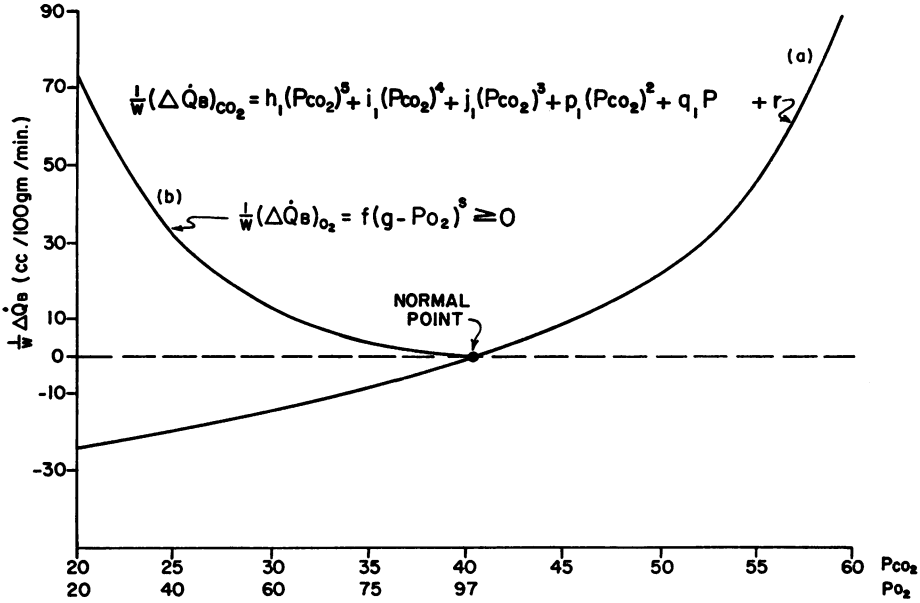


FIGURE 2 Cerebral blood flow *vs.* arterial $P\text{co}_2$ and $P\text{o}_2$.

of the curve. We are probably safe to assume that cerebral blood flow about doubles when 5 per cent $O_2$ is breathed. Since breathing low $O_2$ also causes the $CO_2$ to be low, we must add the $CO_2$ inhibition to the actual blood flow in order to obtain the $O_2$ curve alone. This can be accomplished with the aid of Fig. 2*a*. The resulting curve (Fig. 2*b*) can be fitted empirically by an equation of the form

$$(\Delta\dot{Q}_B)_{O_2} = Wf(g - P\text{o}_2)^s \geq 0, \tag{36}$$

where $f$, $g$, and $s$ are empirical constants and the term on the left of the equal sign is the change from normal in cerebral blood flow due to a change in arterial $P\text{o}_2$.

Combining equations (35) and (36), using the assumptions that arterial $P\text{co}_2$ and $P\text{o}_2$ remain equal to alveolar $P\text{co}_2$ and $k_5 \times$ alveolar $P\text{o}_2$ respectively, and converting to concentrations yield the cerebral circulatory controller equation:

$$\dot{Q}_B = (\Delta\dot{Q}_B)_{CO_2} + (\Delta\dot{Q}_B)_{O_2} + \dot{Q}_{BN} = W\Big[h(C_A\phi_{CO_2})^5 + i(C_A\phi_{CO_2})^4 + j(C_A\phi_{CO_2})^3 + p(C_A\phi_{CO_2})^2 + qC_A\phi_{CO_2} + r + f\Big(g - \frac{1}{k_5}C_A\phi_{O_2}\Big)^s\Big] + \dot{Q}_{BN}, \tag{37}$$

where $h = h_1P_B{}^5$, $i = i_1P_B{}^4$, $j = j_1P_B{}^3$, $p = p_1P_B{}^2$, and $q = q_1P_B$.

Body tissue blood flow is cardiac output minus cerebral blood flow:

$$\dot{Q}_T = \dot{Q} - \dot{Q}_B \tag{38}$$

Two more useful relationships, from Fig. 1, are

$$\dot{Q}Cv_{CO_2} = \dot{Q}_BCv_B\theta_{CO_2} + \dot{Q}_TCv_T\delta_{CO_2}, \quad (39)$$

and

$$\dot{Q}Cv_{O_2} = \dot{Q}_BCv_B\theta_{O_2} + \dot{Q}_TCv_T\delta_{O_2}. \quad (40)$$

Substituting equations (16) and (18) in equation (39), and equations (23) and (25) in equation (40) yields

$$\dot{Q}Cv_{CO_2} = \dot{Q}_B(C_B\theta_{CO_2} - C_T\delta_{CO_2}) + \dot{Q}C_T\delta_{CO_2}, \quad (41)$$

and

$$\dot{Q}Cv_{O_2} = k_3\{\dot{Q}_B[(1 - \exp(-k_4P_BC_B\theta_{O_2}/S))^2 - (1 - \exp(-k_4P_BC_T\delta_{O_2}/S))^2] + \dot{Q}(1 - \exp(-k_4P_BC_T\delta_{O_2}/S))^2\}. \quad (42)$$

Alveolar ventilation can be expressed as functions of alveolar-arterial $P_{CO_2}$, $H^+$, and $P_{O_2}$ independently as follows (Gray, 1952):

$$(\dot{V}_A)_{CO_2} = a_1P_{CO_2} - b_1, \quad \text{(Fig. 3}a\text{)} \quad (43)$$

$$(\dot{V}_A)_{H^+} = c_1H^+, \quad \text{(Fig. 3}b\text{)} \quad (44)$$

and

$$(\dot{V}_A)_{O_2} = d_1(m_1 - P_{O_2})^n \geq 0, \quad \text{(Fig. 3}c\text{)} \quad (45)$$

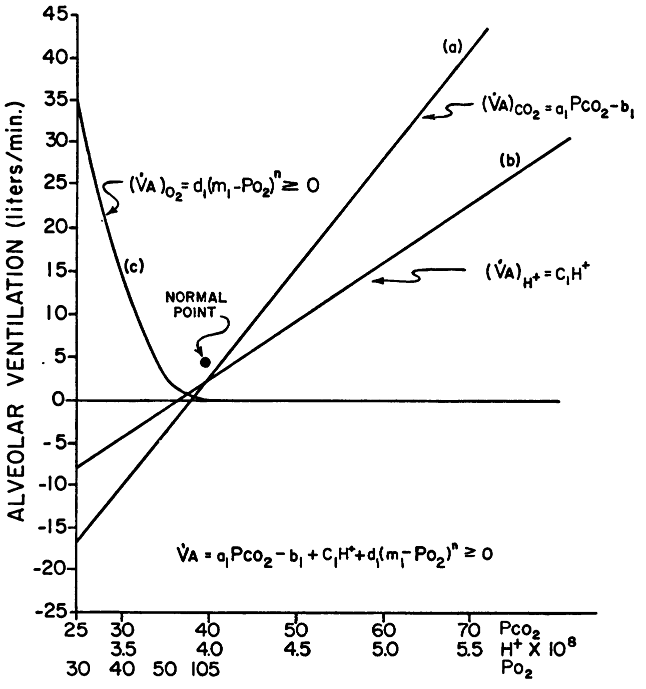


**Figure 3** Alveolar ventilation as independent functions of alveolar-arterial $P_{CO_2}$, $H^+$ concentration, and $P_{O_2}$.

where $a_1$, $b_1$, $c_1$, $d_1$, $m_1$, and $n$ are empirical constants and the terms on the left of the equal signs are the partial alveolar ventilations resulting from the independent effects of $P_{CO_2}$, $H^+$ concentration, and $P_{O_2}$, respectively. Alveolar ventilation, therefore, becomes

$$\begin{aligned} \dot{V}_A &= (\dot{V}_A)_{CO_2} + (\dot{V}_A)_{H^+} + (\dot{V}_A)_{O_2} \\ &= a_1 P_{CO_2} - b_1 + c_1 H^+ + d_1(m_1 - P_{O_2})^n \geq 0. \end{aligned} \tag{46}$$

Although recent developments have indicated that these three stimuli do not act entirely independently, equation (46) will suffice for our purpose.

Substituting equation (3) in equation (44) and adding the result to equation (43) yields

$$(\dot{V}_A)_{CO_2} = a_3 P_{CO_2} - b_3, \tag{47}$$

where $a_3 = a_1 + c_1 a_2$ and $b_3 = -c_1 b_2 + b_1$.

It has been shown that changes in ventilation lag behind rapid changes in arterial pH and thus $P_{CO_2}$ (Hesser, 1949). Since we have assumed that venous $P_{CO_2}$ remains equal to tissue $P_{CO_2}$ at all times, it seems likely that the brain tissue $P_{CO_2}$ is the regulated variable and not arterial $P_{CO_2}$. We will, therefore, have to devise a new curve to fit this condition. We are probably justified in assuming that our new curve, relating brain tissue $P_{CO_2}$ to alveolar ventilation, will have the same form as equation (47). We may, then, give our new curve the equation

$$(\dot{V}_A)_{CO_2} = a_4(\text{brain tissue } P_{CO_2}) - b \tag{48}$$

where $a_4$ and $b$ are constants having one set of values for excitatory $CO_2$ effects and another for inhibitory $CO_2$ effects. This will be discussed later in more detail. The assumption that brain tissue $P_{CO_2}$ is the regulated variable was also made in the previously mentioned models.

Since we have decided to express our equations in terms of concentrations, we must convert $P_{CO_2}$ in equation (48) to concentration. Therefore, we obtain

$$(\dot{V}_A)_{CO_2} = a(C_{B_{CO_2}})^{1/k_2} - b, \tag{49}$$

where $a = a_4/(k_1)^{1/k_2}$.

Equation (45) states that alveolar ventilation is a function of alveolar-arterial $P_{O_2}$. However, it is actually the arterial blood bathing the aortic and carotid bodies rather than alveolar-arterial blood. We must adapt equation (45) to this condition. Therefore, using the assumption that arterial $P_{O_2}$ remains equal to $k_5 \times$ alveolar $P_{O_2}$ we obtain

$$(\dot{V}_A)_{O_2} = d(m - k_5 P_B C_A \beta_{O_2})^n \geq 0, \tag{50}$$

where $d = d_1/k^n_5$, and $m = k_5 m_1$.

Using equations (49) and (50), equation (46) becomes

$$\dot{V}_A = a(C_{B_{CO_2}})^{1/k_2} - b + d(m - k_5 P_B C_A \beta_{O_2})^n \geq 0. \tag{51}$$

This is our ventilatory controller equation and represents a combination of the steady-state transfer functions of the medullary respiratory center, carotid and aortic bodies, and mechanical portion of the lungs. Since Grodins *et al.* (1954), Defares *et al.* (1960), and Lange and Horgan (1963) have previously considered both steady-state and transient transfer functions to be identical, we shall do the same, but we will discuss the probable effects of this later in the paper.

Substituting equations (13), (15), and (29) in equation (5), we obtain

$$dCB_{CO_2}/dt = (1/VB)\{MB_{CO_2} + \dot{Q}B[k_1(PBCA\phi_{CO_2})^{k_2} - CB_{CO_2}]\}. \tag{52}$$

Substituting equations (14), (17), (30), and (38) in equation (6), we obtain

$$dCT_{CO_2}/dt = (1/VT)\{MT_{CO_2} + (\dot{Q} - \dot{Q}B)[k_1(PBCA\alpha_{CO_2})^{k_2} - CT_{CO_2}]\}. \tag{53}$$

Substituting equations (12), (31), and (41) in equation (7), we obtain

$$dCA_{CO_2}/dt = (1/VA)\{\dot{Q}B(CB\theta_{CO_2} - CT\delta_{CO_2}) + \dot{Q}[CT\delta_{CO_2} - k_1(PBCA_{CO_2})^{k_2}] + \dot{V}A(CI_{CO_2} - CA_{CO_2})\}. \tag{54}$$

Substituting equations (22), (27), and (32) in equation (8), we obtain

$$dCB_{O_2}/dt = (1/VB)\{-MB_{O_2} + k_3\dot{Q}B[(1 - \exp(-k_4k_5PBCA\phi_{O_2}))^2 - (1 - \exp(-k_4PBCB_{O_2}/S))^2]\}. \tag{55}$$

Substituting equations (24), (28), (33), and (38) in equation (9), we obtain

$$dCT_{O_2}/dt = (1/VT)\{-MT_{O_2} + k_3(\dot{Q} - \dot{Q}B)[(1 - \exp(-k_4k_5PBCA\alpha_{O_2}))^2 - (1 - \exp(-k_4PBCT_{O_2}/S))^2]\}. \tag{56}$$

Substituting equations (26), (34), and (42) in equation (10), we obtain

$$dCA_{O_2}/dt = (1/VA)\{k_3\dot{Q}B[(1 - \exp(-k_4PBCB\theta_{O_2}/S))^2 - (1 - \exp(-k_4PBCT\delta_{O_2}/S))^2] + k_3\dot{Q}[(1 - \exp(-k_4PBCT\delta_{O_2}/S))^2 - (1 - \exp(-k_4k_5PBCA_{O_2}))^2] + \dot{V}A(CI_{O_2} - CA_{O_2})\}. \tag{57}$$

Equations (52) through (57), in addition to equations (37) and (51), are the equations of the normal human respiratory control system. Under the following conditions these equations can be reduced to an equal number of variables:

(*a*) Metabolism remains constant

(*b*) Cardiac output remains constant

(*c*) Such variables as $CA\phi_{CO_2}$, $CB\Theta_{O_2}$, etc., are actually the same variables as $CA_{CO_2}$, $CB_{O_2}$, etc., delayed in time an amount equal to the various circulation times.

Our eight variables are now $\dot{Q}B$, $\dot{V}A$, $CB_{CO_2}$, $CT_{CO_2}$, $CA_{CO_2}$, $CB_{O_2}$, $CT_{O_2}$, and $CA_{O_2}$.

## STEADY-STATE ANALYSIS

In the steady-state all derivatives are constant. This constant is zero for brain, body, and lung gas concentrations. Such variables as $CA\phi_{CO_2}$, $CB\Theta_{O_2}$, etc. reduce to $CA_{CO_2}$, $CB_{O_2}$, etc. The steady-state equations of the normal human respiratory system are therefore

$$MB_{CO_2} + \dot{Q}B[k_1(PBCA_{CO_2})^{k_2} - CB_{CO_2} = 0 \tag{58}$$

$$MT_{CO_2} + (\dot{Q} - \dot{Q}B)[k_1(PBCA_{CO_2})^{k_2} - CT_{CO_2}] = 0 \tag{59}$$

$$\dot{Q}B(CB_{CO_2} - CT_{CO_2}) + \dot{Q}[CT_{CO_2} - k_1(PBCA_{CO_2})^{k_2}] + \dot{V}A(CI_{CO_2} - CA_{CO_2}) = 0, \tag{60}$$

$$-MB_{O_2} + k_3\dot{Q}B[(1 - \exp(-k_4k_5PBCA_{O_2}))^2 - (1 - \exp(-k_4PBCB_{O_2}/S))^2] = 0, \tag{61}$$

$$-MT_{O_2} + k_3(\dot{Q} - \dot{Q}B)[(1 - \exp(-k_4k_5PBCA_{O_2}))^2 - (1 - \exp(-k_4PBCT_{O_2}/S))^2] = 0, \tag{62}$$

$$-k_3\dot{Q}B[(1 - \exp(-k_4PBCB_{O_2}/S))^2 - (1 - \exp(-k_4PBCT_{O_2}/S))^2 + k_3\dot{Q}[(1 - \exp(-k_4PBCT_{O_2}/S))^2 - (1 - \exp(-k_4k_5PBCA_{O_2}))^2] + \dot{V}A(CI_{O_2} - CA_{O_2}) = 0, \tag{63}$$

$$\dot{V}A = a(CB_{CO_2})^{1/k_2} - b + d(m - k_5PBCA_{O_2})^n \geq 0, \tag{64}$$

and

$$\dot{Q}_B = W[h(CA_{CO_2})^5 + i(CA_{CO_2})^4 + j(CA_{CO_2})^3 + p(CA_{CO_2})^2 + qCA_{CO_2} + r + f(g - 1/k_5(PBCA_{O_2}))^s] + \dot{Q}BN. \tag{65}$$

In addition, if we wish to solve for the steady-state arterial and venous concentrations, equations (12), (15), (17), (22), (24), and (26) may be used as they stand.

The next step is to determine the values of all the constants used in the steady-state equations. Most of these are readily found in various sources of the literature and pose no real problem. The $CO_2$ production of the entire body is 0.263 liters/min (Grodins *et al.*, 1954). The brain $CO_2$ production is equal to 0.003 liters/100 gm/min (Guyton, 1961). Since the normal brain weighs 1400 gms (Guyton, 1961), this ($MB_{CO_2}$) amounts to 14 × 0.003 = 0.042 liters/min. The body tissue $CO_2$ production ($MT_{CO_2}$) is, therefore, 0.263 − 0.042 = 0.221 liters/min. The brain respiratory quotient remains close to unity so that $MB_{O_2} = MB_{CO_2} = 0.042$ liters/min. Since we have assumed a respiratory quotient of unity for the entire body, $MT_{O_2} = MT_{CO_2} = 0.221$ liters/min. The normal sea level barometric pressure ($PB$) is 760 mm Hg. The constants $k_1$, $k_2$, $k_3$, and $k_4$ can be determined from the $CO_2$ and $O_2$ dissociation curves. These are 0.107, 0.415, 0.2, and 0.05, respectively. The constant $k_5$ can be determined by dividing the normal arterial $Po_2$ by the normal alveolar $Po_2$. This is 97/105 = 0.92. Cardiac output is 6.0 liters/min (Grodins *et al.*, 1954). The constants $h$, $i$, $j$, $p$, $q$, $r$, $f$, and $s$ can be determined from the curves of Fig. 3. These are $(760)^5 \times (3.23431 \times 10^{-6})$, $-(760)^4 (4.46082 \times 10^{-4})$, $(760)^3 (2.25409 \times 10^{-2})$, $-(760)^2 (4.79044 \times 10^{-1})$, (760) (4.36567), 43.0, 0.003, and 2.3, respectively. The value of $g$ is our normal arterial $Po_2$ of 98 mm Hg. The constant $W$ is the number of 100 gm increments in the normal brain weight divided by 1000 to convert cubic centimeters to liters and is equal to 0.014 gm-liters/cc (Guyton, 1961). Normal cerebral blood flow is equal to approximately 50 cc/100 gm/min (Guyton, 1961). This yields a value of $0.014 \times 50 = 0.7$ liters/min. The value of $CI_{CO_2}$ is normally zero, and the concentration of inspired oxygen (saturated with water vapor at body temperature), $CI_{O_2}$, is 0.1967 (Guyton, 1961). $S = 0.024 \text{ atm}^{-1}$.

The only remaining constants are those of the ventilatory controller equation. It will be these values that determine the steady-states for different values of $CI_{CO_2}$ and $CI_{O_2}$. An analysis of several steady-state conditions has shown that the excitatory value of $a$ is 810. By arbitrarily choosing a normal alveolar ventilation of 4.75 liters/-min, we set the excitatory value of $b$ at 194.5. There is no reason to believe that the inhibitory value of $a$ is equal to the excitatory value. In fact, the experimental data of Gray (1952) shows a break in the slope at about the normal alveolar ventilation. By picking an inhibitory value for $a$, we set the inhibitory value of $b$, as well as $d$ and $n$, since the correct steady-state values must be maintained. By varying the inhibitory value of $a$ (and thus the values of the other three dependent constants), the best possible agreement with experimental transients was reached. This yielded inhibitory values for $a$ and $b$ of 99.0 and 19.6, respectively. The values of $d$ and $n$ are determined from the above procedure to be $8.0 \times 10^{-4}$ and 3.0, respectively. The value of $m$ is our normal arterial $Po_2$ of 98 mm Hg.

By use of an IBM 1620 digital computer the normal steady-state values of the system variables were obtained. These are listed in Fig. 4 where they are compared with the normal human male values from several sources of the literature.

By giving $CI_{CO_2}$ different values, new steady-state alveolar ventilation values were

| | Man | Computed values |
|---|---|---|
| Alveolar $CO_2$ | 5.3 vol. per cent | 5.6 vol. per cent |
| Brain $CO_2$ | | 55.9 |
| Tissue $CO_2$ | 51.0 | 54.0 |
| Artérial $CO_2$ | 48.0 | 49.5 |
| Cerebral venous $CO_2$ | 54.8 | 55.9 |
| Tissue venous $CO_2$ | 51.0 | 54.0 |
| Alveolar $O_2$ | 13.8 | 14.1 |
| Brain $O_2$ | | 0.110 |
| Tissue $O_2$ | 0.128 | 0.134 |
| Arterial $O_2$ | 19.6 | 19.7 |
| Cerebral venous $O_2$ | 12.9 | 13.6 |
| Tissue venous $O_2$ | 15.0 | 15.4 |
| Cerebral bloodflow | 0.70 liter/min. | 0.70 liter/min. |
| Alveolar ventilation | 4.7 liters/min. | 4.75 liters/min. |

FIGURE 4 Normal steady-state values.

obtained for different inhaled $CO_2$ concentrations. These are shown in Fig. 5 where they are compared to values in man by Comroe *et al.* (1962).

By giving the constant $C_{I_{O_2}}$ different values, new steady-state alveolar ventilation values were obtained for different inhaled $O_2$ concentrations. These are shown in Fig. 6 where they are compared to values in man by Comroe *et al.* (1962).

The steady-state values are in good agreement with experimental data.

One of the values of this type of study can be demonstrated by Fig. 7. Fig. 7*a* is a

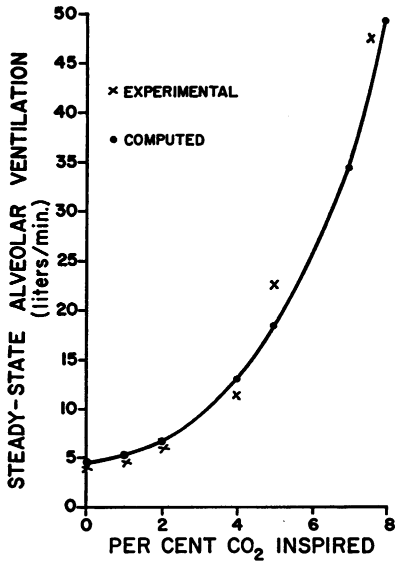


FIGURE 5 Alveolar ventilation steady-state values *vs.* per cent inspired $CO_2$.

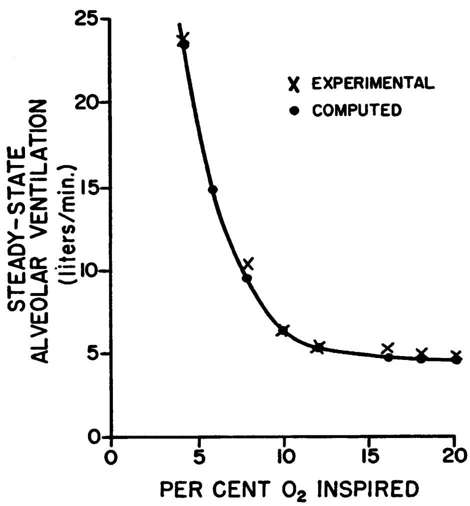


FIGURE 6 Alveolar ventilation steady-state values *vs.* per cent inspired $O_2$.

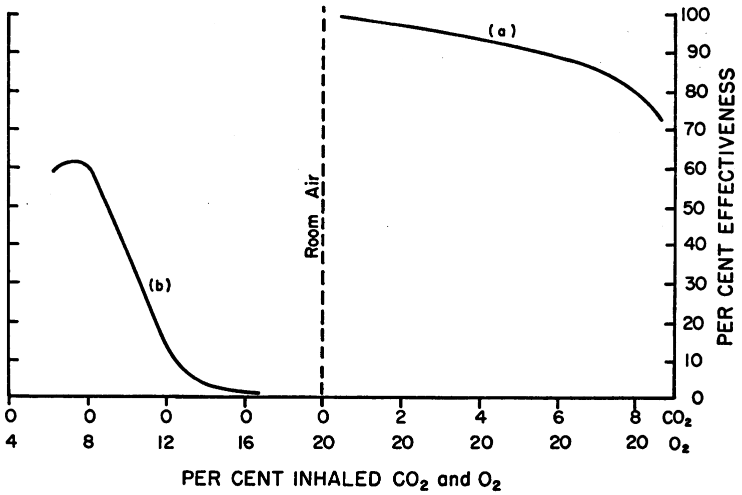


FIGURE 7 The effectiveness of the respiratory control system as a regulator.

plot of per cent inhaled $CO_2$ *vs.* per cent effectiveness of the respiratory control system as a regulator. The curve was calculated from

$$\text{per cent effectiveness} = [(CBO_{CO_2} - CB_{CO_2})/(CBO_{CO_2} - CBN_{CO_2})] \times 100, \quad (66)$$

where $CBO_{CO_2}$ is the brain $CO_2$ concentration with no regulation, $CBN_{CO_2}$ is the normal brain $CO_2$ concentration (while breathing room air), and $CB_{CO_2}$ is the steady-state brain $CO_2$ concentration with regulation. It is interesting to note that at $CO_2$ concentrations above 7.5 per cent, the regulatory effectiveness declines rapidly. From this, one might postulate that the inability of human beings to exist for long periods of time in $CO_2$ concentrations greater than 8 per cent is due to a decrease in regulatory ability of the respiratory system. This sharp decline would allow a rapid increase in brain $CO_2$ concentration and result in a more rapid desensitization of respiratory center tissue to increasing inhaled $CO_2$ concentrations.

Fig. 7*b* is a plot of per cent inhaled $O_2$ *vs.* per cent regulatory effectiveness as calculated from

$$\text{per cent effectiveness} = [(Ca_{O_2} - Cao_{O_2})/(CaN_{O_2} - Cao_{O_2})] \times 100, \quad (67)$$

where the symbols refer to arterial oxygen concentrations and are defined as previous ones were for $CO_2$. The minute amount of regulation that exists for inhaled $O_2$ concentrations near normal values can be explained teleologically by the shape of the oxygen dissociation curve. Inhaled $O_2$ concentrations change the alveolar $Po_2$, and thus the arterial $Po_2$, proportionately, but because of the small slope of the oxygen dissociation curve in this range, little hemoglobin desaturation occurs when the alveolar $P_{O_2}$ falls; the tissues still receive an abundant supply of oxygen; and as a result little regulation is necessary. As the concentrations of inhaled $O_2$ are decreased still further, significant amounts of hemoglobin desaturation occur, and greater percentages of effectiveness become necessary. It is interesting to note that at 7 per cent oxygen the effectiveness ceases its increase and at about 6 per cent begins a rapid decline. This could help to explain the inability of human beings to exist for long periods of time in oxygen concentrations less than 6 per cent. The human respiratory control system would undoubtedly be a better $O_2$ regulator if it were not for the $CO_2$ "braking" action on ventilation.

From the preceding, it would appear that man would be able to survive at much higher $CO_2$ concentrations and much lower $O_2$ concentrations if the respiratory control system did not suffer a decrease in regulatory function past critical concentrations.

## TRANSIENT ANALYSIS

First, we must define several more constants. These are the reservoir volumes $V_B$, $V_T$, and $V_A$ and the circulation times $\tau_1$, $\tau_2$, $\tau_3$, $\tau_4$, and $\tau_5$. Since the normal tissue fluid volume is 40 liters (Grodins *et al.*, 1954) and the normal brain fluid volume ($V_B$) is 0.9 liters (Guyton, 1961), we obtain a volume ($V_T$) of $40 - 0.9 = 39.1$ liters for our body reservoir. The average alveolar volume ($V_A$) is 3 liters (Grodins *et al.*, 1954). It will be noted that these three volumes do not appear in the steady-state equation and, hence, have no influence on the steady-state values.

The circulation times $\tau_1$, $\tau_2$, $\tau_3$, $\tau_4$, and $\tau_5$ were calculated to be 10, 20, 15, 30, and 5 seconds, respectively, in the normal human being.

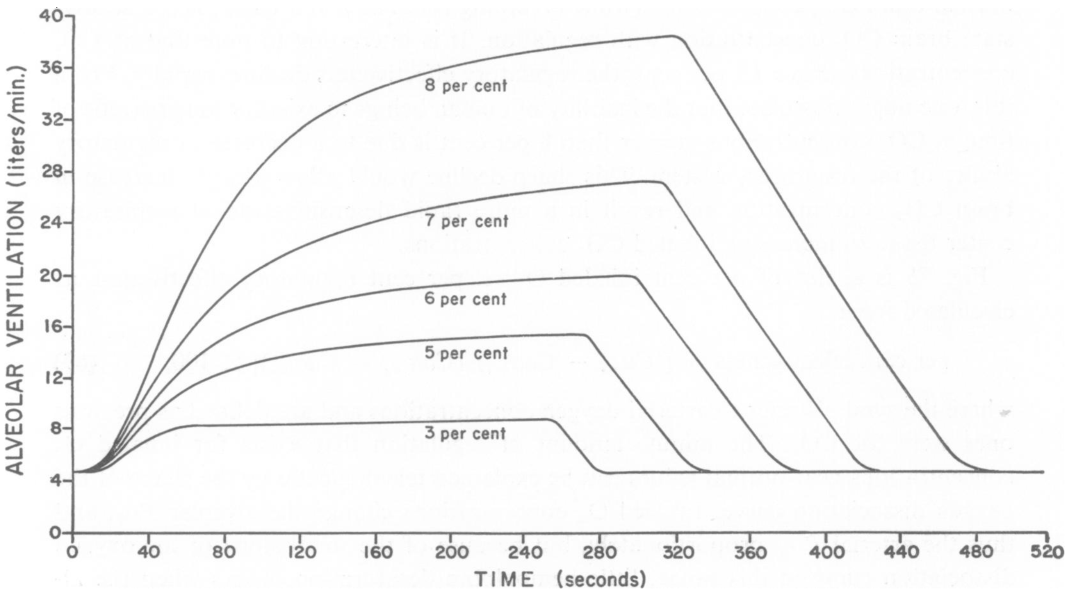


**FIGURE 8** Theoretical alveolar ventilation transients for 3, 5, 6, 7, and 8 per cent $CO_2$ steps in inspired air.

Fig. 8 shows the response of the model to several positive and negative step input disturbances of $CO_2$ in inhaled air. The "on" transient is the result of a positive $CO_2$ step input disturbance and was initiated by suddenly changing the value of $CI_{CO_2}$ (by means of a computer sense switch) from the normal value of zero to the desired concentration. The system responds to this disturbance by passing through a transient state in an attempt to reach a new equilibrium state. The "off" transient is the result of a negative $CO_2$ step input disturbance and was initiated by suddenly changing the value of $CI_{CO_2}$ from the previous concentration back to zero. The system responds to this disturbance by passing through another transient state in an attempt to reach the initial equilibrium state.

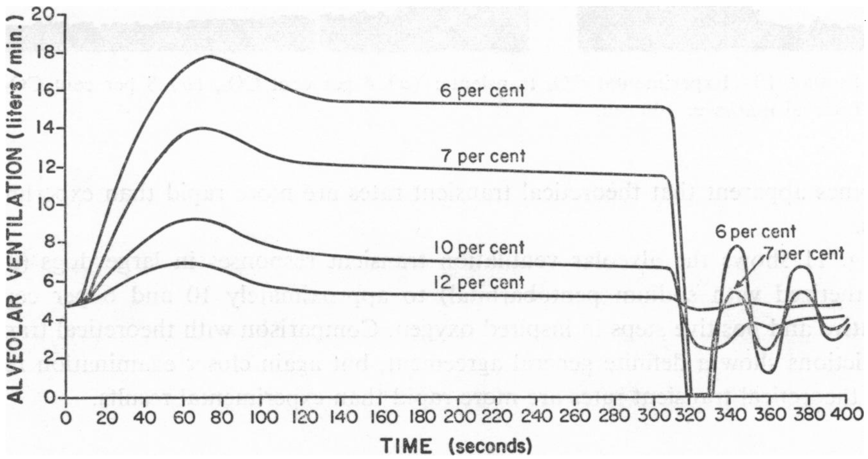


**FIGURE 9** Theoretical alveolar ventilation transients for 6, 7, 10, and 12 per cent $O_2$ steps in inspired air.

Fig. 9 shows the transient response of the model to several negative and positive step input disturbances of $O_2$ in inhaled air. The on transient is the result of a negative $O_2$ step input disturbance and was initiated by suddenly changing the value of $CI_{O_2}$ from the normal value of 0.1967 to the desired concentration. The off transient is the result of a positive $O_2$ step input disturbance and was initiated by suddenly changing the value of $CI_{O_2}$ from the previous concentration back to 0.1967.

The theoretical transients were obtained with the aid of a digital computer.

## EXPERIMENTAL RESULTS

Fig. 10 shows the alveolar ventilation transient responses in man to approximately 4 and 8 per cent $CO_2$ positive and negative step input disturbances in inspired air (reprinted from Defares *et al.*, 1960). Comparison with theoretical transient predictions (Fig. 9) shows a definite general agreement, but upon closer examination it

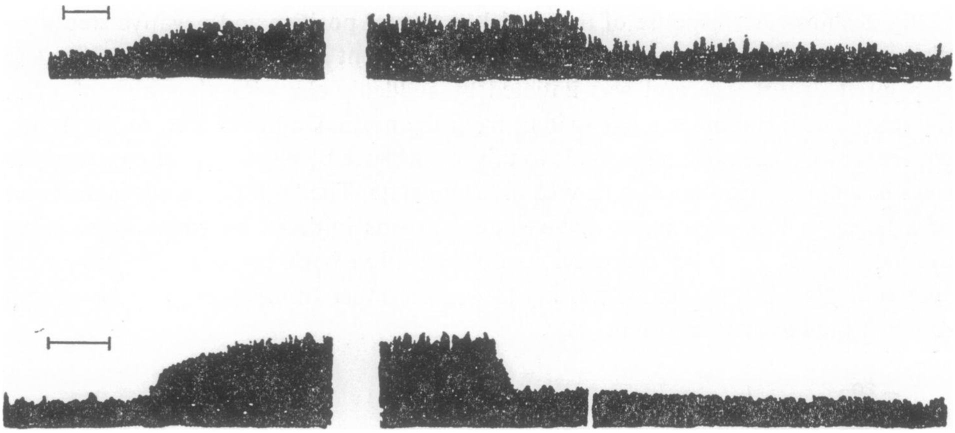

FIGURE 10 Experimental $CO_2$ transients: (*a*) 4 per cent $CO_2$, (*b*) 8 per cent $CO_2$. Interval marks = 100 sec.

becomes apparent that theoretical transient rates are more rapid than experimental ones.

Fig. 11 shows the alveolar ventilation transient responses in large dogs (lightly anesthetized with sodium pentobarbital) to approximately 10 and 6 per cent $O_2$ negative and positive steps in inspired oxygen. Comparison with theoretical transient predictions show a definite general agreement, but again closer examination reveals that theoretical transient rates are more rapid than experimental results.

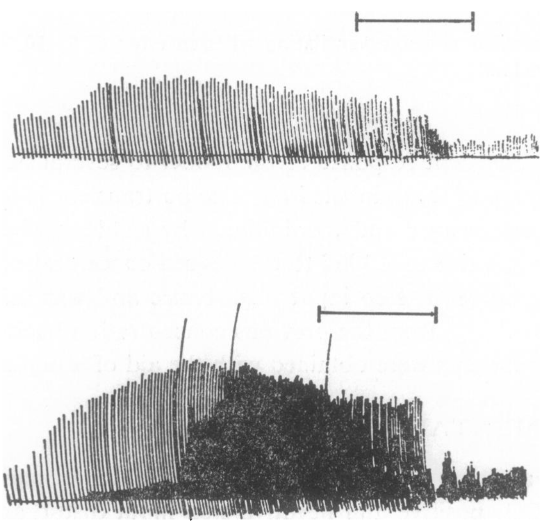

FIGURE 11 Experimental $O_2$ transients: (*a*) 10 per cent $O_2$, (*b*) 6 per cent $O_2$. Interval marks = 100 sec.

## DISCUSSION

The purpose of this paper has been to derive the basic equations for respiratory control in the human being and to obtain transient and steady-state solutions for both positive and negative step input disturbances of inspired $CO_2$ and $O_2$ concentrations. An insight into the importance of this type of analysis is given by the study of the effectiveness of the respiratory system as a regulator.

The carbon dioxide part of the system originated with Grodins in 1954 and was extended by Defares in 1960. This part of the system has been further extended in this paper by the addition of finite circulation times, fitting Kety and Schmidt's data for cerebral blood flow to an empirical equation, and breaking the slope of the $CO_2$ controller equation at the normal brain tissue $CO_2$ concentration as indicated by the experimental data of Gray (1952). The last serves a twofold function: first, it eliminates the $CO_2$ "off" undershoot in alveolar ventilation, which is otherwise present in the computer solution but not in actual experiments, and, secondly, it dampens the $O_2$ "on" oscillation so that it resembles more closely that of experimental results.

Comparison of computer transients to $CO_2$ step inputs in man shows that the former are more rapid than those found experimentally. Grodins *et al.* (1954) did not encounter this problem since his controlled variable was located in a lumped tissue reservoir ($V_B + V_T$) of 40 liters, whereas our controlled variable is located in the brain reservoir having a volume ($V_B$) of 0.9 liters. The value of these volumes, along with blood flow to the reservoir and metabolic rate are the factors which determine the rate of change of alveolar ventilation. It is apparent, then, that our model is incomplete and we must look for the missing part. The obvious place to look first is at the $CO_2$ controller equation since, as stated before, this is a steady-state transfer function and there is no reason to believe that the equation holds during transient states, in fact, to do so would be highly improbable. Our dilemma may be solved if we introduce rate control into our model as well as the existent proportional control. No experimental attempts whatsoever have ever been made to determine this part of the transfer function. The actual equation may be of the form:

$$(\dot{V}_A)_{CO_2} = a_1 P_{CO_2} - b_1 - f_1(dP_{CO_2}/dt), \qquad (68)$$

where the function $f_1(dP_{CO_2}/dt)$ has one form for on transients and another for off transients.

Comparison of computer transients with negative and positive step inputs in animals has shown that the former are also much faster than those found experimentally. The answer to this problem may be found also by introducing rate control into the $O_2$ controller equation. The actual equation may be of the form:

$$(\dot{V}_A)_{O_2} = d_1(m_1 - P_{O_2})^n - f_2(dP_{O_2}/dt), \qquad (69)$$

where the function $f_2(dP_{O_2}/dt)$ may also have two forms.

At any rate, the actual forms of equations (68) and (69) need to be determined before a final transient analysis of the system, including variation of parameters, can be undertaken.

This investigation was supported by a research grant-in-aid from the National Heart Institute, United States Public Health Service.

*Received for publication, January 16, 1964.*

## REFERENCES

COMROE, J. H., JR., FORSTER, R. E., II, DUBOIS, A. B., BRISCOE, W. A., and CARLSON, E., 1962, The Lung, Chicago, Year Book Publishers, 2nd edition.

DEFARES, J. G., DERKSON, H. E., and DUYFF, J. W., 1960, *Acta Physiol. et Pharmacol. Neerl.*, **9**, 327.

DOUGLAS, C. G., and HALDANE, J. S., 1908, *J. Physiol.*, **38**, 401.

GRAY, J. S., 1952, Pulmonary Ventilation and Its Physiological Regulation, Springfield, Illinois, Charles C Thomas.

GRODINS, F. S., GRAY, J. S., SCHROEDER, K. R., NORINS, A. L., and JONES, R. W., 1954, *J. Appl. Physiol.*, **7**, 283.

GUYTON, A. C., 1961, Textbook of Medical Physiology, Philadelphia, W. B. Saunders Company.

HESSER, C. M., 1949, *Acta Physiol. Scand.*, **18**, suppl. 64.

HORGAN, J. D., and LANGE, R. L., 1963, Institute of Electrical and Electronic Engineers Convention Record, pt. 9, 149.

KETY, S. S., and SCHMIDT, C. F., 1948, *J. Clin. Inv.*, **27**, 484.

SHOCK, N. W., and HASTINGS, A. B., 1935, *J. Biol. Chem.*, **112**, 239.